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Epinephrine Dosing Period and Survival after In-Hospital Cardiac Arrest

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Abstract

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Background—Expert guidelines for treatment of cardiac arrest recommend administration of epinephrine every three to five minutes. However, different dosing periods of epinephrine have not been systematically assessed.

Objective—We evaluated the association between epinephrine dosing frequency and survival to hospital discharge in adults with an in-hospital cardiac arrest (IHCA).

Methods—Using data from 2000–2009 in the Get With the Guidelines(GWTG)-Resuscitation IHCA registry (formerly the National Registry of Cardiopulmonary Resuscitation [NRCPR]), we examined the association between epinephrine dosing period and survival to hospital discharge. Epinephrine dosing period was defined as the time between the first epinephrine dose and the resuscitation endpoint, divided by the total number of epinephrine doses received subsequent to the first epinephrine dose. Generalized estimating equations were used to construct multivariable logistic regression models, adjusted for patient and arrest characteristics.

Results—Included were 20,909 eligible IHCA events from 505 GWTG-Resuscitation participating hospitals. Compared to an epinephrine dosing period of 4 to <5 minutes per dose, survival to hospital discharge was significantly higher in patients with an epinephrine dosing period of 6 to <10 minutes per dose: for 6 to <7 min/dose, adjusted odds ratio [OR], 1.41 (95% CI: 1.12, 1.78); for 7 to <8 min/dose, adjusted OR, 1.30 (95%CI: 1.02, 1.65); for 8 to <9 min/dose, adjusted OR, 1.79 (95%CI: 1.38, 2.32); for 9 to <10 min/dose, adjusted OR, 2.17 (95%CI: 1.62, 2.92). This pattern was consistent for both shockable and non-shockable cardiac arrest rhythms. Moreover, for the majority (87%) of cardiac arrests due to non-shockable rhythms, an epinephrine dosing period of 1 to <3 minutes/dose was associated with lower rates of survival.

Conclusion—In this large, observational, national registry of in-hospital cardiac arrest, we found that epinephrine dosing at a less frequent dosing period than recommended by consensus guidelines was associated with improved survival of in-hospital cardiac arrest. Our findings suggest that clinical trials may be needed to determine the role and dose frequency of epinephrine in the treatment of in-hospital cardiac arrest.

INTRODUCTION

More than 200,000 in-hospital cardiac arrests (IHCA) occur annually in the U.S. with a survival rate of less than 20%.^(1–4) Despite being a common and high risk problem, several recommended therapies in resuscitation guidelines lack a supportive evidence base. For example, the recommendation to use epinephrine as a vasopressor agent in cardiopulmonary resuscitation (CPR), for all presenting cardiac rhythms, has remained largely unchanged in resuscitation guidelines despite unproven survival benefit.^(5, 6)

The rationale for recommending epinephrine use in CPR is based on its ability to augment blood pressure and increase coronary perfusion through systemic vasoconstriction. However, epinephrine also stimulates cardiac adrenoreceptors and therefore may have detrimental effects on the heart during ischemia and upon reperfusion after return of spontaneous circulation (ROSC).^(5, 7) The appropriate epinephrine dosing regimen to balance these opposing effects remains unclear. Administration of high dose epinephrine (5–10X standard dose) has not been shown to improve survival compared with the standard one milligram dose.^(8, 9) However, little is known about the effect of the frequency of

epinephrine dosing and survival after cardiac arrest. This gap in knowledge is important because current guidelines recommend the administration of epinephrine every three to five minutes, based primarily on expert opinion. Accordingly, we sought to examine the association between epinephrine dosing frequency and survival to hospital discharge in adults with an IHCA.

METHODS

Study Design

We used data submitted to the Get With the Guidelines (GWTG)-Resuscitation registry (formerly the National Registry of Cardiopulmonary Resuscitation [NRCPR]), a prospective, multicenter registry of patients with IHCA. The study design and data collection of GWTG-Resuscitation have been previously described.⁽¹⁾ Briefly, an IHCA was defined as any patient with unresponsiveness, apnea, and absence of a central pulse. Standardized Utstein definitions are employed within GWTG-Resuscitation to ensure uniform reporting for cardiac arrest variables.⁽¹⁰⁾ Data accuracy within GWTG-Resuscitation is ensured by testing and certification of data entry personnel, use of case-study methods for newly enrolled hospitals before submission of data, data entry software with numerous built in data checks for missing or outlying values, and a reabstraction process that has demonstrated a mean error rate of 2.4% of all data.^(1, 11)

Patient Population

Our study included IHCA events from January 1, 2000 through November 23, 2009 among adult inpatients in a general hospital ward bed or an intensive care unit bed at the time of cardiac arrest. For an admission containing multiple cardiac arrest events, only the index (first) cardiac arrest was included. We focused our analysis on patients in the general hospital ward and intensive care units and therefore excluded 28,331 arrests occurring in other hospital areas (Figure 1). Because our study sought to evaluate the association between epinephrine dosing frequency and survival, we excluded 22,212 arrests without at least two epinephrine doses, as dosing period could not be calculated (see below). To avoid confounding with use of vasopressin and other vasopressors, we excluded 31,117 arrests in which a vasopressor infusion was in place at the time of cardiac arrest, and 18,703 arrests during which a vasopressor other than epinephrine was administered. We excluded 9,006 arrests for which our independent variable of interest, epinephrine dosing period, could not be determined, owing to missing or inconsistent times for epinephrine administration or unknown epinephrine dose count (earlier versions of the GWTG-Resuscitation data fields did not include dose count). Finally, we excluded 6,831 arrests with outlier epinephrine dosing periods (i.e., <1 minute or ≥ 10 minutes per dose). Our final study cohort was comprised of 20,909 IHCA for whom epinephrine dosing period could be determined.

Epinephrine Dosing Period

Epinephrine dosing period was defined as the amount of time between the first epinephrine dose and the resuscitation endpoint (either death or return of spontaneous circulation [ROSC] for at least 20 minutes), divided by the total number of epinephrine doses received subsequent to the first epinephrine dose. Epinephrine dosing period was classified in pre-

specified categories: 1 to <3 minutes/dose, 3 to <4 minutes/dose, 4 to <5 minutes/dose, 5 to <6 minutes/dose, 6 to <7 minutes/dose, 7 to <8 minutes/dose, 8 to <9 minutes/dose, and 9 to <10 minutes/dose. Epinephrine dosing period is meant to estimate the epinephrine dosing pattern *intended* by the prescribing physician leading the resuscitation efforts. That physician is apt to verbally prescribe an amount of time, in minutes, between epinephrine doses (e.g., 3 minutes, 4 minutes or 5 minutes per guideline recommendation). The time period prior to the first dose of epinephrine was not considered in the epinephrine dosing period because this initial phase of resuscitation is inherently less organized and likely to have included time when the lead physician was not present to prescribe medications. However, for purpose of secondary analysis, an alternate independent variable, “total epinephrine dosing period”, was used and was defined more simply as the total cardiac arrest duration divided by total number of epinephrine doses administered.

Statistical Analysis

Baseline characteristics among categories of epinephrine dosing period are described. To evaluate the association between epinephrine dosing period and survival to hospital discharge, we constructed multivariable logistic regression models. Generalized estimating equations (GEE) with a logit link, an exchangeable correlation matrix, and a robust variance estimator, were used to examine the association between epinephrine dosing period and survival to hospital discharge, adjusted for patient and event characteristics and for clustering of cardiac arrest cases within hospitals.(12, 13) For our independent variable, we chose an epinephrine dosing period of 4 to <5 minutes/dose as our reference category, as this is the recommended dosing frequency of current resuscitation guidelines.

Covariates included in the adjusted models were chosen *a priori* based on their association with survival from prior studies of IHCA and biologic plausibility. These included: age, sex, race, patients' preadmission status of home/self care, admission illness category, pre-arrest comorbidities (congestive heart failure [CHF] this admission, prior CHF, myocardial infarction [MI] this admission, prior MI, acute cerebrovascular accident [CVA], baseline central nervous system deficits, respiratory insufficiency, pneumonia, renal insufficiency, hepatic insufficiency, diabetes, septicemia, metastatic or hematologic cancer, major trauma), coexisting requirement for mechanical ventilation during the cardiac arrest, hospital location of the cardiac arrest (intensive care, ward, ward telemetry), whether the arrest was witnessed, initial pulseless rhythm (asystole, pulseless electrical activity [PEA], ventricular fibrillation [VF], pulseless ventricular tachycardia [VT], whether the arrest occurred on a weekend or at night, cardiac arrest duration, and time to first epinephrine dose.

Covariates missing more than 0.5% of values were assessed for differential distribution of missing data among categories of the primary predictor epinephrine dosing period. Hypothermia treatment was left out of the regression model as most hospitals did not submit information on its use. For continuous variables, assumptions of linearity were tested with partial residual plots.(14) Because the associations between cardiac arrest duration and time to first epinephrine dose with survival to discharge were non-linear, cubic splines with five knots were used to transform these variables for model inclusion.(15)

As a secondary analysis, we repeated the above analyses, stratified by whether the first identifiable rhythm was shockable (VF or pulseless VT) or non-shockable (asystole or PEA). For the analyses with the subgroup of shockable rhythms, time to defibrillation was added to the model as a continuous variable. We also examined the association between epinephrine dosing period and survival using the alternate independent variable, total epinephrine dosing period. Sensitivity analyses were conducted on the primary and secondary analyses. First, the analyses were repeated sequentially after culling cardiac arrests of greater durations (>60, >50, >40, >30, >20 minutes), since patients with transient ROSC are potentially overrepresented among cardiac arrests of greater duration. Second, the analyses were repeated sequentially after culling cardiac arrests with greater duration of time-to-first-epinephrine-dose (>30, >20, >10 minutes). All analyses were performed using Stata/IC 11.1 (StataCorp, College Station, TX). All analyses were specified *a priori*, with the exception of a *post-hoc* exploratory analysis where we removed the cardiac arrest duration covariate from our model in order to better understand the difference of the unadjusted and adjusted outcomes.

RESULTS

Of 20,909 IHCA, 1100 (5.3%) patients received epinephrine every 1 to <3 minutes, 2381 (11.4%) every 3 to <4 minutes, 3712 (17.8%) every 4 to <5 minutes, 4184 (20.0%) every 5 to <6 minutes, 3373 (16.1%) every 6 to <7 minutes, 2676 (12.8%) every 7 to <8 minutes, 1961 (9.4%) every 8 to <9 minutes, and 1522 (7.3%) every 9 to <10 minutes (Figure 2). Baseline characteristics of IHCA events among categories of epinephrine dosing period are presented in Table 1. There were no significant differences in the pattern of missing data among categories. In the overall study population, the mean age was 68 ± 16 years, 61% of patients were male, 68% were white and 23% were of black race. The most common admission illness category was medical noncardiac (53%) followed by medical cardiac (27%). Thirty percent of the IHCA events occurred in general hospital beds unmonitored by telemetry, 34% in general hospital beds monitored by telemetry, and 36% in intensive care beds. The most common presenting cardiac rhythm was asystole (46%), followed by PEA (39%), while shockable rhythms comprised less than 13% of events. The mean cardiac arrest duration was 19 ± 10 minutes.

Return of spontaneous circulation occurred in 7558 (36.2%) patients and survival to hospital discharge occurred in 1470 (7.0%) patients. The proportion of patients surviving to hospital discharge by category of epinephrine dosing period is presented in Figure 3. Compared to a reference epinephrine dosing period of 4 to <5 minutes/dose, an epinephrine dosing period of 6 to <10 minutes/dose was associated with higher rates of survival to discharge: for 6 to <7 min/dose, adjusted odds ratio [OR], 1.41 (95% CI: 1.12, 1.78); for 7 to <8 min/dose, adjusted OR, 1.30 (95% CI: 1.02, 1.65); for 8 to <9 min/dose, adjusted OR, 1.79 (95% CI: 1.38, 2.32); for 9 to <10 min/dose, adjusted OR, 2.17 (95% CI: 1.62, 2.92); test for linear trend $p < 0.001$. For cardiac arrests due to shockable rhythms, a similar pattern was observed between epinephrine dosing period and survival (Appendix I, $p < 0.001$). For cardiac arrests due to non-shockable rhythms, the overall pattern of association was similar ($p < 0.001$) and an epinephrine dosing frequency of 1–3 minutes/dose was associated with lower survival (adjusted OR, 0.63 [95% CI: 0.47, 0.85], Appendix II).

The results of the secondary analysis that assessed the alternate predictor, total epinephrine dosing period, are presented in Figure 4. A pattern of increasing survival with increasing total epinephrine dosing period was similarly observed when the total epinephrine dosing period was used ($p<0.001$).

In the sensitivity analysis performed to understand the potential confounding of longer cardiac arrest duration, the sequential culling of cardiac arrests of greater duration did not alter the pattern of association between epinephrine dosing period and survival to hospital discharge. The pattern of association between epinephrine dosing period and survival to hospital discharge for cardiac arrests of duration less than 20 minutes yielded similar results (Figure 5). Furthermore, when we removed the cardiac arrest duration covariate from our primary regression model, the associations between epinephrine dosing period and survival to hospital discharge reverted to be in general alignment with the overall unadjusted model.

DISCUSSION

In this large, national registry of IHCA, we found that epinephrine dosing at higher dosing period (i.e., less frequent dosing) than recommended by consensus guidelines was associated with improved survival. This pattern was consistent for both shockable and non-shockable cardiac arrest rhythms. Moreover, for the majority (87%) of cardiac arrests due to non-shockable rhythms, an epinephrine dosing period of 1 to <3 minutes/dose was associated with lower rates of survival.

The primary predictor, epinephrine dosing period, was designed as a marker of the epinephrine dosing pattern intended by the prescribing physician leading the resuscitation effort. Our findings remained consistent when total epinephrine dosing period over the full duration of cardiac arrest was used as an alternate predictor. It remains unclear if the association of improved survival with increased epinephrine dosing period was caused by the potential harmful effects of epinephrine or if another unmeasured factor, such as interrupted CPR, was at play.

An appropriate strategy against confounding by indication was a major emphasis in our study design process.⁽¹⁶⁾ We anticipated that longer cardiac arrest durations would be associated with differing epinephrine dosing periods, but it came as some surprise that this association was a negative and graded one (Table 1, $p<0.001$). In other words, on average, epinephrine was dosed less frequently when cardiac arrests were of greater duration, despite the lower survival potential of prolonged cardiac arrest. Less surprising, the primary outcome, survival to hospital discharge, was negatively and non-linearly associated with cardiac arrest duration. In anticipation of such complex observations, cubic splines were pre-specified as the flexible form in which to model two important time covariates, overall duration of cardiac arrest and time to first epinephrine dose.⁽¹⁵⁾

In the context of current treatment guidelines for IHCA, our results are consistent with those to be expected were the recommended epinephrine dosing period of every 3 minutes, 4 minutes or 5 minutes to be harmful compared with less frequent epinephrine dosing.

Our work should be interpreted in the context of the following limitations. First, confounding by indication may be present if treating providers used epinephrine more sparingly for patients who were immeasurably less sick (e.g., patients with intermittent return of pulse without meeting ROSC definition). If this were the case, however, we would expect that the sensitivity analyses performed after the sequential culling of cardiac arrests of greater duration would have affected our inference, and they did not. Second, time data were self-reported by hospitals and inaccuracies may exist. However, any inaccuracies in the time variables would be expected to be nondifferential and to bias our observations toward the null hypothesis. Third, we were unable to account for epinephrine dose amount in addition to dose frequency. However, the highest dose of epinephrine administered was recorded and <4% were greater than one milligram. Fourth, we were unable to adjust for post resuscitation hypothermia treatment even though two trials have suggested its clinical utility in out-of-hospital cardiac arrest.(17, 18) Fifth, our results may not be generalizable to other populations (e.g., children) or hospital locations. Finally, although data from 505 different facilities were included in our work, observations made among hospitals that participate in the NRCPR may not generalize to other hospitals.

In summary, we found that less frequent epinephrine dosing than recommended by consensus guidelines was associated with improved survival of in-hospital cardiac arrest. Our findings suggest that clinical trials may be needed to determine the role and dose frequency of epinephrine in the treatment of in-hospital cardiac arrest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Study Cohort. Of the initial 141,324 in-hospital cardiac arrest events in the Get With the Guidelines(GWTG)-Resuscitation, 20,909 eligible patients were included in the final study population.

Figure 2. Frequency distribution of in-hospital cardiac arrest events eligible for analysis, by category of epinephrine dosing period.

Figure 3.

Survival to discharge by category of epinephrine dosing period (the amount of time between the first epinephrine dose and the resuscitation endpoint, divided by the total number of epinephrine doses received subsequent to the first epinephrine dose).

Figure 4.

Survival to discharge by category of total epinephrine dosing period (total cardiac arrest duration divided by total number of epinephrine doses administered).

Figure 5.
Survival to discharge by category of epinephrine dosing period for in-hospital cardiac arrests of duration less than 20 minutes.

Table 1

Baseline characteristics of 20,909 in-hospital cardiac arrest events by categories of epinephrine dosing period.

Characteristic	Epinephrine Dosing Intensity (minutes/dose)*									
	1-3 min/dose (n=1100)	3-1 min/dose (n=2381)	4-5 min/dose (n=3712)	5-6 min/dose (n=4184)	6-7 min/dose (n=3373)	7-8 min/dose (n=2676)	8-9 min/dose (n=1961)	9-10 min/dose (n=1522)		
Age, mean (SD), y	67.0 (16.1)	67.6 (15.8)	67.6 (15.9)	67.4 (15.8)	67.7 (16.0)	67.5 (15.7)	68.9 (14.8)	68.2 (15.1)		
Male sex, no.(%)	674 (61.3)	1443 (60.6)	2277 (61.3)	2544 (60.8)	2071 (61.4)	1642 (61.4)	1165 (59.4)	882 (58.0)		
Race/ethnicity, no.(%)										
White	760 (69.1)	1597 (67.1)	2479 (66.8)	2850 (68.1)	2362 (70.0)	1799 (67.2)	1374 (70.1)	1015 (66.7)		
Black	223 (20.3)	571 (24.0)	850 (22.9)	967 (23.1)	740 (21.9)	612 (22.9)	411 (21.0)	367 (24.1)		
Other	117 (10.6)	213 (9.0)	383 (10.3)	367 (8.8)	171 (8.0)	265 (9.9)	176 (9.0)	141 (9.2)		
Preadmission = home/self care, no.(%)	796 (72.4)	1676 (70.4)	2660 (71.7)	3048 (72.9)	2452 (72.7)	1995 (74.6)	1470 (75.0)	1115 (73.3)		
Preadmission Cerebral Performance Category, no.(%)**										
1 (normal)	458 (42.8)	979 (42.4)	1596 (44.4)	1837 (45.3)	1482 (45.2)	1186 (45.5)	875 (45.8)	646 (44.1)		
2 (disability, independent ADLs)	300 (28.0)	648 (28.1)	D73 (27.0)	1107 (27.3)	883(26.9)	761 (29.2)	523 (27.4)	422 (28.8)		
3 (disability, not independent ADLs)	127 (11.9)	312 (13.5)	476 (13.2)	510 (12.6)	423 (12.9)	299 (11.5)	230 (12.0)	188 (12.8)		
4 (coma)	47 (4.4)	65 (2.8)	87 (2.4)	127 (3.1)	75 (2.3)	66 (2.5)	50 (2.6)	42 (2.9)		
Unknown	138 (12.9)	304 (13.2)	467 (13.0)	477 (11.8)	417 (12.7)	295 (11.3)	252 (12.2)	167 (11.4)		
Admission Illness category, no.(%)										
Medical cardiac	317 (28.8)	605 (25.4)	999 (26.9)	1068 (25.5)	928 (27.5)	745 (27.8)	557 (28.4)	443 (29.1)		
Surgical cardiac	52 (4.7)	109 (4.6)	138 (3.7)	166 (4.0)	134 (4.0)	110 (4.1)	84 (4.1)	57 (3.8)		
Medical noncardiac	558 (50.8)	1265 (53.1)	2008 (54.1)	2282 (54.6)	1803 (53.5)	1432 (53.5)	1017 (51.9)	796 (52.4)		
Surgical noncardiac	136 (12.4)	347 (14.6)	474 (12.8)	577 (13.8)	445 (13.2)	332 (12.4)	265 (13.5)	196 (12.9)		
Trauma	36 (3.3)	54 (2.3)	87 (2.4)	87 (2.1)	61 (1.8)	56 (2.1)	36 (1.8)	27 (1.8)		
Pre-arrest comorbidity, no.(%)**										
CHF this admission	182 (17.5)	338 (15.4)	624 (18.0)	651 (16.7)	580 (18.2)	463 (18.3)	325 (17.7)	252 (17.6)		
Prior CHF (before admission)	216 (20.8)	476 (21.6)	731 (21.1)	779 (19.9)	708 (22.2)	519 (20.5)	423 (23.1)	320 (22.4)		
MI this admission	126 (12.1)	232 (106)	403 (11.6)	455 (11.7)	403 (12.7)	328 (13.0)	229 (12.5)	184 (12.9)		
Prior MI before admission	177 (17.0)	317 (14.4)	532 (15.4)	592 (15.2)	537 (16.9)	390(154)	306 (16.7)	245 (17.1)		

Characteristic	Epinephrine Dosing Intensity (minutes/dose)*									
	1-3 min/dose (n=1100)	3-1 min/dose (n=2381)	4-5 min/dose (n=3712)	5-6 min/dose (n=4184)	6-7 min/dose (n=3373)	7-8 min/dose (n=2676)	8-9 min/dose (n=1961)	9-10 min/dose (n=1522)		
Acute CVA	60 (5.8)	92 (4.2)	139 (4.0)	182 (4.7)	138 (4.3)	123 (4.9)	86 (4.7)	72 (5.0)		
Baseline CNS deficits	146 (14.0)	306 (13.9)	473 (13.6)	548 (14.0)	420 (13.2)	336 (13.3)	248 (13.5)	201 (14.1)		
Respiratory insufficiency	446 (42.9)	854 (38.8)	1308 (37.8)	1448 (37.1)	1158 (36.4)	974 (38.5)	687 (37.5)	532 (37.2)		
Pneumonia	165 (15.9)	362 (16.5)	522 (15.1)	589 (15.1)	475 (14.9)	408 (16.1)	258 (14.1)	219 (15.3)		
Renal insufficiency	330 (31.7)	687 (31.2)	1126 (32.5)	1212 (31.0)	1077 (33.5)	872 (34.5)	613 (33.4)	487 (34.0)		
Hepatic insufficiency	79 (7.6)	166 (7.6)	246 (7.1)	283 (7.2)	240 (7.5)	197 (7.8)	125 (6.8)	92 (6.4)		
Diabetes	324 (31.2)	672 (30.6)	1083 (31.3)	1237 (31.7)	1006 (31.6)	841 (33.3)	613 (33.4)	467 (32.6)		
Septicemia	139 (13.4)	338 (15.4)	480 (13.9)	537 (13.7)	458 (14.4)	374 (14.8)	241 (13.3)	194 (13.6)		
Cancer (metastatic or hematologic)	150 (14.4)	339 (15.4)	536 (15.5)	616 (15.8)	501 (15.7)	365 (14.4)	276 (15.1)	209 (14.6)		
Major Trauma	46 (4.4)	80 (3.6)	115 (3.3)	122 (5.1)	81 (2.5)	78 (3.1)	56 (3.1)	58 (2.7)		
Interventions already in place, No.(%)										
Mechanical ventilation	212 (19.3)	422 (17.7)	594 (16.0)	647 (15.5)	496 (14.7)	408 (15.3)	244 (12.4)	247 (16.2)		
IHCA location, no.(%)										
Intensive care	476 (42.5)	878 (36.9)	1324 (35.7)	1481 (35.4)	1218 (36.1)	969 (36.2)	699 (35.7)	543 (35.7)		
Inpatient, monitored by telemetry	264 (24.0)	585 (24.6)	902 (24.3)	1015 (24.3)	855 (25.4)	699 (26.1)	509 (26.0)	387 (25.4)		
Inpatient, unmonitored by telemetry	369 (33.6)	918 (38.6)	1486 (40.0)	1688 (40.3)	1300 (38.5)	1008 (37.7)	753 (38.4)	592 (38.9)		
Arrest characteristics, no.(%)										
Unwitnessed	321 (29.2)	789 (33.1)	1262 (34.0)	1448 (34.6)	1114 (33.0)	879 (32.9)	628 (32.0)	495 (32.5)		
First pulseless rhythm										
VF	96 (8.7)	205 (8.6)	284 (7.7)	340 (8.1)	269 (8.0)	222 (8.3)	188 (9.6)	140 (9.2)		
VT	56(5.1)	84 (3.5)	136 (3.7)	174 (4.2)	133 (3.90)	130 (4.9)	86 (4.4)	62 (4.1)		
PEA	405 (36.8)	850 (35.7)	1425 (38.4)	1650 (39.4)	1282 (38.0)	1089 (40.7)	793 (40.4)	651 (42.8)		
Asystole	509 (46.3)	1164 (48.9)	1764(47.5)	1903 (45.5)	1589 (47.1)	1150 (43.0)	827 (42.2)	620 (40.7)		
Unknown	34 (3.1)	78 (3.3)	103(2.8)	117 (2.8)	100(3.0)	85 (3.2)	67 (3.4)	49 (3.2)		
Night time, 11pm to 6am, no(%)	367(33.4)	940 (39.5)	1534(41.3)	1690 (40.4)	1317 (39.1)	1034 (38.6)	811 (41.4)	617 (40.5)		
Weekend, Fri 11p – Mon 7a, no.(%)**	336(33.7)	757 (35.3)	1221 (36.5)	1444 (38.0)	1165 (38.2)	913 (37.8)	678 (39.0)	515 (37.6)		
Treatment characteristics										

Characteristic	Epinephrine Dosing Intensity (minutes/dose)*							
	1–3 min/dose (n=1100)	3–1 min/dose (n=2381)	4–5 min/dose (n=3712)	5–6 min/dose (n=4184)	6–7 min/dose (n=3373)	7–8 min/dose (n=2676)	8–9 min/dose (n=1961)	9–10 min/dose (11=1522)
Time to 1 st Cpi dose, mean(SD)	3.5(4.7)	3.1 (3.3)	3.1 (3.4)	3.2 (3.5)	3.1 (3.3)	3.1 (3.6)	3.0 (3.5)	3.0 (3.5)
Arrest duration, mean(SD), min	11.1(8.1)	15.2 (8.2)	17.2 (8.5)	18.6 (9.6)	20.4 (10.4)	21.4 (11.4)	22.5 (12.2)	23.0 (12.4)
Arrest duration after 1 st Epi, mean(SD)	7.6 (6.6)	12.0 (7.9)	14.1(8.1)	15.4 (9.3)	17.3 (10.0)	18.3 (10.8)	19.5 (11.9)	19.9 (12.2)
Hypothermia after ROC, no.(%)**	10(1.7)	16 (1.8)	25(2.1)	31 (2.3)	31 (2.6)	17 (1.8)	10(1.3)	14 (2.2)

* Epinephrine dosing period categories are inclusive of lower bound, not-inclusive of upper bound

** Missingness less than 0.5% except for the following: pre-arrest comorbidity (6.3%), weekend (Fri 11p – Mon 7a, 9.8%), admission cerebral performance score (14.9%), and hypothermia (treatment) after ROC (63.8%)