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Rate of intra-arrest epinephrine administration and early post-arrest organ failure after in-hospital cardiac arrest

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Abstract

Introduction: Data supporting epinephrine administration during resuscitation of in-hospital cardiac arrest (IHCA) are limited. We hypothesized that more frequent epinephrine administration would predict greater early end-organ dysfunction and worse outcomes after IHCA.

Methods: We performed a retrospective cohort study including patients resuscitated from IHCA at one of 67 hospitals between 2010 and 2019 who were ultimately cared for at a single tertiary care hospital. Our primary exposure of interest was rate of intra-arrest epinephrine bolus administration (mg/min). We considered several outcomes, including severity of early cardiovascular failure (modeled using Sequential Organ Failure Assessment (SOFA)

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cardiovascular subscore), early neurological and early global illness severity injury (modeled as Pittsburgh Cardiac Arrest Category (PCAC)). We used generalized linear models to test for independent associations between rate of epinephrine administration and outcomes.

Results: We included 695 eligible patients. Mean age was 62±15 years, 416 (60%) were male and 172 (26%) had an initial shockable rhythm. Median arrest duration was 16 [IQR 9–25] min, and median rate of epinephrine administration was 0.2 [IQR 0.1–0.3] mg/min. Higher rate of epinephrine predicted worse PCAC, and lower survival in patients with initial shockable rhythms. There was no association between rate of epinephrine and other outcomes.

Conclusion: Higher rates of epinephrine administration during IHCA are associated with more severe early global illness severity.

Keywords

Cardiac arrest; resuscitation; cardiopulmonary resuscitation; epinephrine

Introduction

Consensus guidelines for resuscitation of cardiac arrest include intravenous or intraosseous epinephrine administration every 3 to 5 minutes. [1] A recent trial of epinephrine versus placebo during out-of-hospital cardiac arrest (OHCA) showed no difference in long-term outcomes between treatment arms. [2] Epinephrine administration during cardiopulmonary resuscitation (CPR) may reduce cerebral blood flow, cause stress cardiomyopathy, or have other adverse effects that attenuate any survival benefit conferred by promoting ROSC. [3–5]

Demographics and arrest characteristics among patients suffering in-hospital cardiac arrest (IHCA) differ from OHCA. [6,7] An observational study from the Get With the Guidelines–Resuscitation (GWTG-R) registry found decreased probability of ROSC and functionally favorable survival with delayed epinephrine administration. [8] In contrast, another study from the same database found less frequent epinephrine administration may be associated with improved survival compared to guideline-recommended dosing. [9] We hypothesized that higher rate of epinephrine administration during ICHA would predict greater early post-arrest organ failure. We tested this hypothesis by exploring the association between the rate of epinephrine administration during IHCA with measures of early post-arrest brain injury and cardiovascular dysfunction, as well as hospital survival to discharge and discharge neurological function.

Methods

Patient Population and Care

This work was approved by the University of Pittsburgh Human Research Protection Office. We performed a retrospective observational cohort study including adult patients resuscitated from IHCA at one of 67 hospitals in Pennsylvania, Ohio and West Virginia between January 2010 and August 2019. All patients arrested at or were ultimately transferred to a single high-volume academic medical center (UPMC Presbyterian Hospital).

We maintain a prospective registry of all patients treated by our Post-Cardiac Arrest Service (PCAS) from which we identified cases for inclusion.

All patients at the tertiary care hospital were managed by a member of the PCAS, as we have previously described. [10] We obtain a baseline head CT imaging as standard of care unless hemodynamic instability precludes imaging, or the patient is following two-step commands after arrest. We treat all comatose patients with targeted temperature management for 24 hours, regardless of initial rhythm or arrest location. We target a mean arterial pressure of >80mmHg post-arrest to optimize cerebral perfusion, unless patients awaken sooner. Nurses document vital signs and infusion rates at least hourly, and typically obtain blood gas studies every 6–8 hours during initial stabilization.

We excluded patients under 18 years of age and those who arrested secondary to trauma or a primary neurological event. Arrests less than 5 minutes total duration were excluded, because rate of epinephrine administration in these cases reflects short arrest duration rather than more rapid medication administration. We considered arrests occurring in the emergency department (ED) to be IHCA.

Data Collection

We performed a structured chart review examining the original IHCA code documentation. Time to achieve ROSC was defined as the total time from confirmed pulselessness until return of sustained pulses, rounded to the nearest minute. If there were multiple re-arrests, then total CPR duration was recorded as a summation. We recorded the number of epinephrine doses as the summation of 1mg intravenous or intraosseous 1:10,000 epinephrine doses administered during CPR. We calculated the rate of administration by dividing the number of epinephrine doses by the total duration CPR duration (mg/min). We log-transformed this predictor for regression analyses.

We abstracted age, sex, and arrest location (ED, intensive care unit (ICU), general floor, cardiac catheterization lab, operative room (OR), or other location. We classified initial electrocardiogram (ECG) rhythm and arrest etiology as previously described. [7] We also recorded the most advanced airway used during arrest, and number of rearrests during initial resuscitation.

Exposures and Outcome Measures

Our primary exposure of interest was rate of epinephrine administration. Our primary outcomes of interest were measures of early neurological and cardiovascular dysfunction. These included the ratio of grey matter to white matter density in Hounsfield units (GWR) at the level of the basal ganglia obtained on CT brain imaging; [11] sequential organ failure assessment cardiovascular (SOFA-CV) subscale scores [12] and Pittsburgh Cardiac Arrest Category (PCAC). By definition, assignment of PCAC is based on the best available neurological examination in the first 6 hours after arrest. We considered only clinical data available within 6 hours of collapse for models predicting outcomes assessed prior to hospital discharge. [13] Late outcomes were survival and Cerebral Performance Category (CPC) at hospital discharge among survivors, dichotomized as good (CPC 1 or 2) or poor (3 or 4). [14]

Study Data Analysis

We summarized cohort characteristics and outcomes using descriptive statistics and present raw numbers with corresponding percentages, means with standard deviations if normally distributed or median with interquartile ranges if not normally distributed. We used multiple imputations with chained equations to handle missing data and inspected Monte Carlo errors to determine the appropriate number of imputations. We used generalized linear models to test the association of log-transformed rate of epinephrine with outcomes, with and without adjustment for other covariates. Covariates included for adjustment were a priori for biological plausibility and included age, number of shocks, sex, arrest duration, most advanced airway placed intra-arrest, arrest location, transfer status, number re-arrests, and initial rhythm. Coronary angiography was included, only considering catheterization occurring within 6 hours of arrest for PCAC and SOFA outcomes. We included TTM strategy into models predicting discharge outcomes.

We excluded total number of epinephrine doses from adjusted models because of collinearity. As a sensitivity analysis, we repeated regression models limited to complete cases. As an exploratory analysis, we tested for an interaction between presenting rhythm and rate of epinephrine administration. We conducted all analyses using Stata Version 15 (StataCorp, College Station, TX).

Results

Patient Profile

Of 968 IHCA patients screened for eligibility, 273 met exclusions; 232 CPR duration <5 minutes, 1 age <18, 23 arrest etiology was either neurologic or trauma related, and 17 never actually lost pulses. This left 695 (72%) remaining subjects. Median number of subjects per referring hospital was 2 [IQR 1–6]. Most subjects (279, 60%) were male, mean age was 62±15 years, and most arrests occurred on a general hospital floor (211, 30%) or in the ED (255, 37%) (Table 1). Median survivor arrest duration was 16 [IQR 9–25] minutes, and median rate of epinephrine administration was 0.2 [IQR 0.1–0.3] mg/min (Table 1). Overall, 5.4% of data were missing and we performed 10 imputations prior to regression analysis.

Predictors of Morbidity and Mortality

Subjects receiving higher cumulative doses of epinephrine, and longer cumulative CPR had worse outcomes. Illness severity indices are summarized in Table 2. Higher rate of epinephrine administration was independently associated with worse PCAC (OR 5.14 [95% CI 1.24–21.38)], but not GWR, SOFA-CV, or discharge CPC (Table 3). Rate of epinephrine was not associated with overall survival to discharge, but we observed a significant interaction between presenting rhythm and rate of epinephrine administration. Specifically, higher rate of epinephrine was independently associated with worse survival among patients presenting with VT/VF (adjusted OR 0.02 [95% CI 0.00–0.51]), with no significant association with survival in patients presenting with PEA or asystole.

Discussion

In this cohort of resuscitated IHCA patients, higher rate of epinephrine administration was associated with increased early global illness severity, as well as worse survival among patients with shockable initial rhythms. Vasoconstrictive effects of epinephrine promote ROSC by augmenting coronary blood flow, myocardial oxygen delivery and diastolic pressure. Despite these beneficial effects, beta-adrenergic myocardial stimulation during resuscitation may increase the risk of rearrest due to ventricular dysrhythmia, cause catecholamine-induced cardiomyopathy and impair cerebral blood flow. [3–5,15,17] Thus, it is biologically plausible that excessive epinephrine may worsen early illness severity. Patients presenting with VT/VF, a subgroup enriched for cardiac etiologies of arrest, may be particularly susceptible to adverse effects of epinephrine. Outcomes in this subgroup may also be worsened if early defibrillation is delayed because rapid epinephrine administration is instead priorities.

There are several limitations to this study. Our population is limited to patients with ROSC. Thus, while the observed associations may be due to direct deleterious effects of epinephrine, it may also be that epinephrine administration allows sicker patients to achieve ROSC. Moreover, our exposure did not compare epinephrine use to no epinephrine use. Thus, we cannot comment directly on the utility of including epinephrine in IHCA resuscitation. Although patients came from many hospitals of varying characteristics, they were all ultimately transferred to a single center, which limits generalizability. Further, we did not have data on time to epinephrine or shock administration, which predict ROSC and survival to hospital discharge. [7, 17] While guidelines recommend epinephrine administration every 3–5 minutes, there is a paucity of data to support this dosing interval. Nevertheless, rate of epinephrine administration in this cohort may be a proxy for overall adherence to guidelines for resuscitation of IHCA. Thus, the relationships we observed may be biased by this unmeasured confounder.

While epinephrine improves ROSC and short-term survival in OHCA, we find higher rate of epinephrine administration is associated with higher early post-arrest illness severity. Further randomized control trials may explore optimal timing and dosing of epinephrine during IHCA.

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Table 1:

Clinical characteristics and intra-arrest care

Characteristic	Patient Cohort (n=695)
Mean age (SD)	62 (15)
Female sex	279 (40)
Interfacility transfer	370 (53)
Shockable initial rhythm	172 (25)
Arrest Location	
Cath lab	28 (4)
ED	255 (37)
Floor	211 (30)
ICU	132 (19)
Operating room	18 (3)
Other/Unknown	51 (7)
Arrest Etiology	
Cardiac	176 (25)
Distributive shock	43 (6)
Exsanguination	30 (4)
Metabolic derangement	30 (4)
Respiratory	180 (26)
Toxicological	25 (4)
Unknown/Other	211 (30)
CPR duration, min	12 (8 – 20)
Epinephrine doses, mg (IQR)	2 (1 – 4)
Rate of epinephrine dosing, mg/min (IQR)	0.2 (0.1 – 0.3)
Coronary angiography performed	125 (18)
Time to CT scan, hours (IRQ)	4.8 (3.2 – 7.8)
Time to angiography, hours (IQR)	4.2 (2.4 – 15)
Airway management	
Bag valve mask	71 (10)
Supraglottic airway	7 (1)
Endotracheal intubation	404 (58)
Preexisting advanced airway	153 (22)
Other	60 (9)

Age is expressed in mean years ± SD, while the remainder of clinical variables are shown as number and (%) of cases for demographic data, and median and (IQR) for intra-arrest parameters.

Table 2:

Illness severity, survival and discharge outcomes

Early organ dysfunction	**Patient Cohort (n=695)**
PCAC	
I	213 (31)
II-III	159 (23)
IV	206 (30)
Not assessable[^]	117 (17)
GWR (IQR)	1.35 (1.28 – 1.43)
SOFA-CV	
0	44 (8)
I	65 (11)
II	5 (1)
III	93 (16)
IV	360 (63)
Discharge Characteristics	
Survival to discharge	285 (41)
Survivor length of stay (IQR)	16 (9 – 25)
Survival Disposition	
Acute rehabilitation	63 (23)
Home	93 (34)
Hospice	8 (3)
Long-term acute care	24 (9)
Skilled nursing facility	204 (75)
Other	14 (5)
Discharge CPC	
I-II	71 (10)
III-IV	213 (31)
Deceased	410 (59)

Markers of early organ dysfunction are displayed as raw numbers with percentages among cardiac arrest survivors. Survivor length of stay and GWR are displayed as median and (IQR) and remainder of discharge characteristics are listed as number and corresponding percentage of cases.

[^]Scoring of Pittsburgh Cardiac Arrest Category includes assessment of neurological examination, so cannot be assessed in the context of neuromuscular blockade or other confounders such as refractory shock or hypoxemia. GWR – grey to white ratio.

Table 3:

Analysis of density of epinephrine on morbidity and mortality outcome for both adjusted and unadjusted multivariate models

Outcome	Unadjusted Model		Adjusted Model	
	OR	95% CI	OR	95% CI
PCAC	1.28	1.00–1.64	5.14	1.24 – 21.38
GWR	1.98	0.56–1.21	1.03	0.93 – 1.14
SOFA-CV	0.41	0.68–1.24	4.06	0.64 – 25.87
Survival	0.78	0.62–0.99		
VT/VF			0.02	0.00 – 0.51
PEA			0.61	0.86 – 4.27
Asystole			5.19	0.23 – 115.38
CPC	1.79	0.77–1.45	0.21	0.00 – 9.03

Adjusted models predicting PCAC, GWR and SOFA-CV control for age, number shocks, sex, arrest duration, most advanced airway placed intra-arrest, arrest location, transfer status, number re-arrests, initial rhythm, and coronary angiography if performed within 6 hours of arrest. TTM strategy was additionally included into models predicting discharge outcomes.

CI- Confidence Interval; GWR- grey to white ratio; OR- Odds Ratio.