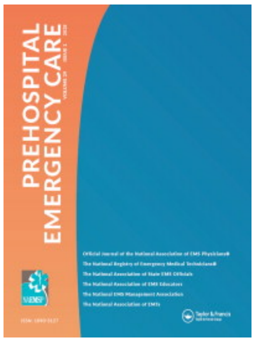

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Does Single Dose Epinephrine Improve Outcomes for Patients with Out-of-Hospital Cardiac Arrest and Bystander CPR or a Shockable Rhythm?

Tyler S. George[a], Nicklaus P. Ashburn[a], Anna C. Snavely[a,b], Bryan P. Beaver[c], Michael A. Chado[d], Harris Cannon[a], Casey G. Costa[e], James E. Winslow[a], R. Darrell Nelson[a], Jason P. Stopyra[a], and Simon A. Mahler[a,f,g]

[a]Department of Emergency Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [b]Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [c]Department of Emergency Medicine, University of Kansas School of Medicine, Kansas City, Kansas; [d]Department of Emergency Medicine, The Ohio State University, Columbus, Ohio; [e]Department of Emergency Medicine, Virginia Commonwealth University, Richmond, Virginia; [f]Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [g]Department of Implementation Science, Wake Forest University School of Medicine, Winston-Salem, North Carolina

ABSTRACT

Background: A single dose epinephrine protocol (SDEP) for out-of-hospital cardiac arrest (OHCA) achieves similar survival to hospital discharge (SHD) rates as a multidose epinephrine protocol (MDEP). However, it is unknown if a SDEP improves SHD rates among patients with a shockable rhythm or those receiving bystander cardiopulmonary resuscitation (CPR).

Methods: This pre-post study, spanning 11/01/2016-10/29/2019 at 5 North Carolina EMS systems, compared pre-implementation MDEP and post-implementation SDEP in patients $\geq$18 years old with non-traumatic OHCA. Data on initial rhythm type, performance of bystander CPR, and the primary outcome of SHD were sourced from the Cardiac Arrest Registry to Enhance Survival. We compared SDEP vs MDEP performance in each rhythm (shockable and non-shockable) and CPR (bystander CPR or no bystander CPR) subgroup using Generalized Estimating Equations to account for clustering among EMS systems and to adjust for age, sex, race, witnessed arrest, arrest location, AED availability, EMS response interval, and presence of a shockable rhythm or receiving bystander CPR. The interaction of SDEP implementation with rhythm type and bystander CPR was evaluated.

Results: Of 1690 patients accrued (899 MDEP, 791 SDEP), 19.2% (324/1690) had shockable rhythms and 38.9% (658/1690) received bystander CPR. After adjusting for confounders, SHD was increased after SDEP implementation among patients with bystander CPR (aOR 1.61, 95%CI 1.03-2.53). However, SHD was similar in the SDEP cohort vs MDEP cohort among patients without bystander CPR (aOR 0.81, 95%CI 0.60-1.09), with a shockable rhythm (aOR 0.96, 95%CI 0.48-1.91), and with a non-shockable rhythm (aOR 1.26, 95%CI 0.89-1.77). In the adjusted model, the interaction between SDEP implementation and bystander CPR was significant for SHD ($p = 0.002$).

Conclusion: Adjusting for confounders, the SDEP increased SHD in patients who received bystander CPR and there was a significant interaction between SDEP and bystander CPR. Single dose epinephrine protocol and MDEP had similar SHD rates regardless of rhythm type.

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Introduction

Each year there are more than 350,000 out-of-hospital cardiac arrests (OHCAs) in the United States. Despite efforts to improve OHCA survival, the survival rate for OHCA remains approximately 10% (1,2). The American Heart Association's Advanced Cardiovascular Life Support and the International Liaison Committee on Resuscitation guidelines recommend epinephrine administration every 3 to 5 min for OHCA (3). However, emerging evidence suggests epinephrine may not improve rates of survival to hospital discharge (SHD) despite epinephrine being associated with higher rates of return of spontaneous circulation (ROSC) (4–6). Epinephrine has been shown to increase myocardial demand and increase the chances of cardiac arrhythmias, which could be drivers of worse outcomes (7–9).

Given the equipoise regarding epinephrine dosing for OHCA, our team recently completed an evaluation of a prehospital "one and done" single dose epinephrine protocol (SDEP) compared to a traditional multidose epinephrine protocol (MDEP). Results of this study demonstrated that SDEP was associated with similar SHD but decreased ROSC rates (10), which was consistent with prior studies (4–6). However, none of these studies have evaluated whether the

CONTACT Tyler S. George tsgeorge@wakehealth.edu

Supplemental data for this article can be accessed online at https://doi.org/10.1080/10903127.2024.2348663.

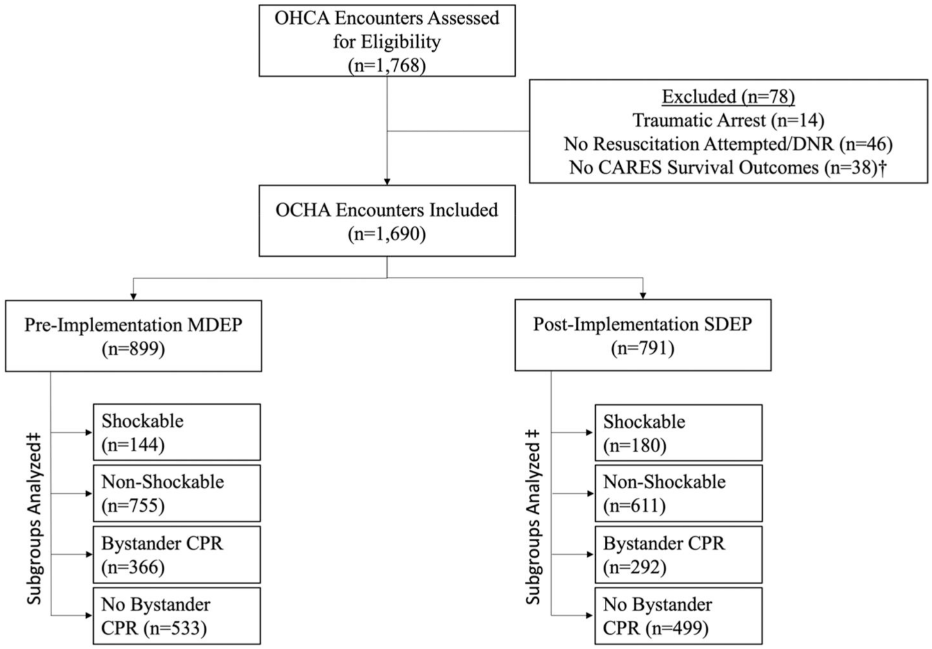

Figure 1. The study flow diagram.
OHCA – out-of-hospital cardiac arrest, DNR – do not resuscitate; CARES – Cardiac Arrest Registry to Enhance Survival.
†: While 38 total encounters were without CARES outcomes, only 18 additional encounters were excluded once encounters for traumatic arrest and those with no resuscitation attempted/DNR were excluded.
‡: Subgroups are overlapping and not mutually exclusive.

SDEP or MDEP approach is favored in key patient subgroups, among patients with a shockable rhythm or who received bystander cardiopulmonary resuscitation (CPR), which are well known to be associated with SHD (11–13).

To address this critical evidence gap, we conducted a pre-planned secondary analysis of our single dose epinephrine pre-post implementation study comparing adult OHCA patients receiving resuscitation guided by a SDEP vs. MDEP. Our objectives were to determine if SHD, ROSC, and favorable neurologic outcome rates differed for patients receiving a SDEP vs. MDEP resuscitation strategy among: 1) patients with a shockable or non-shockable heart rhythm and 2) those receiving or not receiving bystander CPR. In addition, we aimed to explore differences in SHD, ROSC, and favorable neurologic outcome rates among patients presumed to have arrested from a primary cardiac etiology.

Methods

Study design and Oversight

We conducted a preplanned secondary analysis of the single dose epinephrine pre-post implementation study, which was carried out among five emergency medical services (EMS) systems in North Carolina (NC) from November 1, 2016 to October 31, 2019. The study protocol was approved by the Wake Forest University Health Sciences Institutional Review Board, and a waiver of informed consent was granted. The research and reporting process adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (14). The single dose epinephrine implementation study methods have been previously described (10).

Study Setting and Population

The study was conducted in a region of NC encompassing urban, suburban, and rural communities across five counties with a combined population of nearly 850,000 people (Online Supplemental Table 1). Each county operated an advanced life support (ALS) EMS system with medical direction provided by an emergency physician with subspecialty board certification in EMS. The study included patients who were 18 years of age or older and had undergone attempted resuscitation for non-traumatic OHCA. In the pre-implementation period, patients received a multidose epinephrine protocol (MDEP) of 1 mg of 1:10,000 intravenous (IV) or intraosseous (IO) epinephrine every 3–5 min. In the post-implementation period, patients received a single dose epinephrine protocol (SDEP) of 1 mg of IV/IO epinephrine, with no provision for additional doses as per the protocol. During the post-implementation period, the NC Office of EMS also began permitting the use of ketamine for CPR-induced consciousness. Two patients received ketamine for this indication over the study period. No other changes were made to the cardiac arrest protocol. The OCHA protocols are available in Online Supplemental Appendix 1.

Data Collection and Variables

Data were collected from 11/1/2016-10/29/2019 one year before and after SDEP implementation. Online Supplemental Table 1 provides initiation dates of the SDEP in each county EMS system. The prehospital electronic medical records were queried for information on patient demographics and EMS response interval. The Cardiac Arrest Registry to Enhance Survival (CARES) database was used to determine the initial

Table 1. Cohort characteristics pre vs. post implementation categorized by shockable vs. non-shockable heart rhythms.

	Pre-Implementation MDEP ($n = 899$), n (%)		Post-Implementation SDEP ($n = 791$), n (%)		Total ($n = 1690$), n (%)	
RHYTHM	Shockable $n = 144$ (%)	Non-Shockable $n = 755$ (%)	Shockable $n = 180$ (%)	Non-Shockable $n = 611$ (%)	Shockable $n = 324$ (%)	Non-Shockable $n = 1366$ (%)
Age - median (IQR) (years)	66 (53-75)	64 (50-76)	64 (53.5-75)	66 (54-78)	65 (53-75)	65 (52-77)
Sex						
Female	41 (28.5)	323 (42.8)	56 (31.1)	237 (38.8)	97 (29.9)	560 (41.0)
Race						
White	104 (72.2)	569 (75.4)	138 (76.7)	451 (73.8)	242 (74.7)	1020 (74.7)
Black	36 (25.0)	177 (23.4)	39 (21.7)	140 (22.9)	75 (23.2)	317 (23.2)
Other	4 (2.78)	9 (1.19)	3 (1.7)	20 (3.27)	7 (2.2)	29 (2.1)
Ethnicity						
Hispanic/Latino	1 (0.7)	4 (0.5)	3 (1.7)	11 (1.8)	4 (1.2)	15 (1.1)
County						
Forsyth	81 (56.3)	380 (50.3)	82 (45.6)	289 (47.3)	163 (50.3)	669 (49.0)
Iredell	28 (19.4)	105 (13.9)	41 (22.8)	94 (15.4)	69 (21.3)	199 (14.6)
Randolph	20 (13.9)	159 (21.1)	32 (17.8)	146 (23.9)	52 (16.1)	305 (22.3)
Stanly	4 (2.8)	24 (3.2)	11 (6.1)	23 (3.8)	15 (4.6)	47 (3.4)
Surry	11 (7.6)	87 (11.5)	14 (7.8)	59 (9.7)	25 (7.7)	146 (10.7)
Presumed cardiac arrest etiology						
Cardiac	133 (92.4)	578 (76.6)	170 (94.4)	480 (78.6)	303 (93.5)	1058 (77.5)
Non-cardiac	11 (7.6)	177 (23.4)	10 (5.6)	131 (21.4)	21 (6.5)	308 (22.5)
Respiratory	6 (4.2)	97 (12.9)	6 (3.3)	91 (14.9)	12 (3.7)	188 (13.8)
Overdose	4 (2.8)	70 (9.3)	1 (0.6)	36 (5.9)	5 (1.5)	106 (7.8)
Drowning	0 (0.0)	2 (0.26)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Electrocution	1 (0.7)	0 (0.0)	2 (1.1)	0 (0.0)	3 (0.9)	0 (0.0)
Other	0 (0.0)	8 (1.1)	1 (0.6)	4 (0.65)	1 (0.3)	12 (0.9)
Initial cardiac rhythm						
Shockable	144 (100.0)	0 (0.0)	180 (100.0)	0 (0.0)	324 (100.0)	0 (0.0)
Ventricular fibrillation	96 (66.7)	0 (0.0)	113 (62.8)	0 (0.0)	209 (64.5)	0 (0.0)
Ventricular tachycardia	11 (7.6)	0 (0.0)	6 (3.3)	0 (0.0)	17 (5.3)	0 (0.0)
Other shockable rhythm	37 (25.7)	0 (0.0)	61 (33.9)	0 (0.0)	98 (30.3)	0 (0.0)
Non-shockable	0 (0.0)	755 (100.0)	0 (0.0)	611 (100.0)	0 (0.0)	1366 (100.0)
Asystole	0 (0.0)	482 (63.8)	0 (0.0)	365 (59.7)	0 (0.0)	847 (62.0)
Pulseless electrical activity	0 (0.0)	182 (24.1)	0 (0.0)	171 (28.0)	0 (0.0)	353 (25.8)
Other non-shockable rhythm	0 (0.0)	91 (12.1)	0 (0.0)	75 (12.3)	0 (0.0)	166 (12.2)
Witnessed cardiac arrest	109 (75.7)	408 (54.0)	136 (75.6)	331 (54.2)	245 (75.6)	739 (54.1)
Bystander CPR	70 (48.6)	296 (39.2)	78 (43.3)	214 (35.0)	148 (45.7)	510 (37.3)
AED available	73 (50.69)	13 (1.7)	95 (52.8)	9 (1.5)	168 (51.9)	22 (1.6)
Response interval (median, IQR) (minutes)	7.3 (5.4-9.9)	8.4 (6.0-10.9)	7.7 (5.5-10.3)	7.9 (5.6-10.6)	7.5 (5.5-10.0)	8.1 (5.8-10.7)

	Pre-Implementation MDEP ($n = 899$), n (%)		Post-Implementation SDEP ($n = 791$), n (%)		Total ($n = 1690$), n (%)	
BYSTANDER CPR	Bystander CPR $n = 366$ (%)	No Bystander CPR $n = 533$ (%)	Bystander CPR $n = 292$ (%)	No Bystander CPR $n = 499$ (%)	Bystander CPR $n = 658$ (%)	No Bystander CPR $n = 1032$ (%)
Age (median, IQR) (years)	65 (51-77)	64 (51-76)	66 (55-75.5)	65 (53-78)	66 (54-76)	64 (52-76)
Sex						
Female	141 (38.5)	223 (41.8)	104 (35.6)	189 (37.9)	245 (37.2)	412 (39.9)
Race						
White	278 (76.0)	395 (74.1)	217 (74.3)	372 (74.6)	495 (75.2)	767 (74.3)
Black	81 (22.1)	132 (24.8)	63 (21.6)	116 (23.3)	144 (21.9)	248 (24.0)
Other	7 (1.9)	6 (1.1)	12 (4.1)	11 (2.2)	19 (7.8)	17 (1.6)
Ethnicity						
Hispanic/Latino	2 (0.6)	3 (0.6)	8 (2.7)	6 (1.2)	10 (1.5)	9 (0.9)
County						
Forsyth	159 (43.4)	302 (56.7)	87 (29.8)	284 (56.9)	246 (37.4)	586 (56.8)
Iredell	68 (18.6)	65 (12.2)	75 (25.7)	60 (12.0)	143 (21.7)	125 (12.1)
Randolph	81 (22.1)	98 (18.4)	73 (25.0)	105 (21.0)	154 (23.4)	203 (19.7)
Stanly	11 (3.0)	17 (3.2)	20 (6.9)	14 (2.8)	31 (4.7)	31 (3.0)
Surry	47 (12.8)	51 (9.6)	37 (12.7)	36 (7.2)	84 (12.8)	87 (8.4)
Presumed cardiac arrest etiology						
Cardiac	302 (82.5)	409 (76.7)	253 (86.6)	397 (79.6)	555 (84.3)	806 (78.1)
Non-cardiac	64 (17.5)	124 (23.3)	39 (13.4)	102 (20.4)	103 (15.7)	226 (21.9)
Respiratory	38 (10.4)	65 (12.2)	25 (8.6)	72 (14.4)	63 (9.6%)	137 (13.3)
Overdose	24 (6.6)	50 (9.4)	10 (3.4)	27 (5.4)	34 (5.2%)	77 (7.5)
Drowning	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Electrocution	0 (0.0)	1 (0.2)	2 (0.7)	0 (0.0)	2 (0.3)	1 (0.1)
Other	1 (0.3)	7 (1.3)	2 (0.7)	3 (0.6)	3 (0.5)	10 (1.0)
Initial cardiac rhythm						
Shockable	70 (19.1)	74 (13.9)	78 (26.7)	102 (20.4)	148 (22.5)	176 (17.1)
Ventricular fibrillation	41 (11.2)	55 (10.3)	44 (15.1)	69 (13.8)	85 (12.9)	124 (12.0)
Ventricular tachycardia	4 (1.1)	7 (1.3)	0 (0.0)	6 (1.2)	4 (0.6)	13 (1.3)
Other shockable rhythm	25 (6.8)	12 (2.3)	34 (11.6)	27 (5.4)	59 (9.0)	39 (3.8)

(*continued*)

Table 1. Continued.

	Pre-Implementation MDEP ($n = 899$), n (%)		Post-Implementation SDEP ($n = 791$), n (%)		Total ($n = 1690$), n (%)	
BYSTANDER CPR	Bystander CPR $n = 366$ (%)	No Bystander CPR $n = 533$ (%)	Bystander CPR $n = 292$ (%)	No Bystander CPR $n = 499$ (%)	Bystander CPR $n = 658$ (%)	No Bystander CPR $n = 1032$ (%)
Non-shockable	296 (80.9)	459 (86.1)	214 (73.3)	397 (79.6)	510 (77.5)	856 (82.9)
Asystole	207 (56.6)	275 (51.6)	129 (44.2)	236 (47.3)	336 (51.1)	511 (49.5)
Pulseless electrical activity	51 (13.9)	131 (24.6)	46 (15.8)	125 (25.1)	97 (14.7)	256 (24.8)
Other non-shockable rhythm	38 (10.4)	53 (9.9)	39 (13.4)	36 (7.2)	77 (11.7)	89 (8.6)
Witnessed cardiac arrest	199 (54.4)	318 (59.7)	167 (57.2)	300 (60.1)	366 (55.6)	618 (59.9)
Bystander CPR	366 (100.0)	0 (0.0)	292 (100.0)	0 (0.0)	658 (100.0)	0 (0.0)
AED available	51 (13.9)	35 (6.6)	52 (17.8)	52 (10.4)	103 (15.7)	87 (8.4)
Response interval (median, IQR) (minutes)	8.0 (5.8-10.5)	8.3 (5.9-10.9)	7.6 (5.2-10.3)	7.9 (5.7-10.6)	7.7 (5.1-10.4)	8.1 (5.9-10.7)

IQR – interquartile range, CPR – cardiopulmonary resuscitation, AED – automatic external defibrillator. All rows show n, % unless otherwise indicated.

heart rhythm, whether bystander CPR was performed, whether the arrest was witnessed, and whether an AED was available. CARES defines shockable rhythms as ventricular fibrillation, ventricular tachycardia, and unknown shockable rhythm. Non-shockable rhythms are defined as asystole, pulseless electrical activity, and unknown unshockable rhythm. The CARES registry was also used to ascertain the cause of arrest, as determined by EMS personnel (15). Arrests were presumed to be from a cardiac etiology unless death was likely from respiratory/asphyxia, drowning, electrocution, etc. When available, CARES used additional information from hospital records and/or medical examiners' reports were used to clarify arrest etiology. Patient outcomes including SHD, ROSC, and neurologic status at the time of hospital discharge were also extracted from the CARES registry.

Outcomes

The primary outcome was survival to hospital discharge (SHD). Consistent with CARES and prior investigations, this was defined as leaving the hospital alive, regardless of neurologic or functional status (10, 15, 16). The secondary outcome was return of spontaneous circulation (ROSC), which CARES defines as the presence of a palpable pulse or blood pressure for ≥ 20 min without the need for additional chest compressions (15). An exploratory outcome was discharge with a favorable neurologic outcome, defined as a Cerebral Performance Category (CPC) of "good" or "moderate" (CPC category 1 or 2 out of 4) (15, 17). According to the CARES definitions, CPC 1 corresponds to a state of being "conscious, capable of working, and leading a normal life," while CPC 2 suggests being "conscious and able to function independently but with hemiplegia, seizures, or permanent memory or mental changes." Cerebral Performance Category 3 indicates that the patient is "dependent on others due to impaired brain function," and CPC 4 indicates that the patient "is not conscious or aware" (15). Discharge with a favorable neurologic outcome was assessed among all patients and among survivors only.

Statistical Analysis

Counts and percentages were utilized to present categorical variables such as sex, race, EMS system, rhythm types, if bystander CPR was performed, as well as SHD and ROSC rates. Median and interquartile ranges (IQR) were used to describe continuous variables such as age and EMS response interval. The OHCA encounter was the unit of analysis and analysis was by intention to treat (i.e., all patients in the pre-implementation period were analyzed as being in the MDEP cohort and all patients in the post-implementation period were analyzed as being in the SDEP cohort). A per protocol analysis was not possible because the CARES registry does not collect the number of epinephrine doses administered and this information was unable to be obtained from the prehospital EHRs. SHD, ROSC, and favorable neurologic outcome rates were compared between the SDEP and MDEP cohorts using Generalized Estimating Equations (GEE) with a logit link to account for clustering within EMS systems. Models were fit within each subgroup, defined by rhythm type (shockable and non-shockable) and bystander CPR (bystander CPR or no bystander CPR). The interaction of SDEP implementation with rhythm type and bystander CPR was also evaluated. Multivariable models were adjusted for age, sex, race, witnessed arrest, location of the arrest, AED availability, EMS response interval, and the presence of a shockable rhythm or receiving bystander CPR. These covariates were selected based on existing OHCA resuscitation research (1, 18–25). Race was categorized as a two-level variable for modeling purposes (White and non-White). Location was considered a three-level variable (home, medical facility, and other). Unadjusted and adjusted odds ratios (aOR) with corresponding 95% confidence intervals (95%CI) were calculated from the GEE models. We also conducted a prespecified analysis among only those patients who experienced OHCA from a presumed primary cardiac etiology. This subset underwent the same analysis methods described above.

Results

During the five-year study period, there were 1,690 OHCA encounters (899 pre-implementation, 791 post-implementation). The overall cohort was 38.9% female (657/1690) and 25.3% non-white (428/1690) with a median age of 65 years (IQR 53-76). Among all patients, 19.2% (324/1690) presented with an initial shockable rhythm and 38.9% (658/1690) received bystander CPR. The study flow diagram is

Table 2. Bystander CPR subgroups.

	Bystander CPR				No Bystander CPR				
	Pre-implementation MDEP ($n=366$), n (%)	Post-implementation SDEP ($n=292$), n (%)	Odds Ratio (95%CI)		Pre-implementation MDEP ($n=533$), n (%)	Post-implementation SDEP ($n=499$), n (%)	Odds Ratio (95%CI)		Interaction (Implementation cohort x bystander CPR)
			Unadjusted	Adjusted[1]			Unadjusted	Adjusted[1]	
ROSC	129 (35.2)	95 (32.5)	0.91 (0.73-1.15)	0.90 (0.70-1.17)	251 (47.1)	162 (32.5)	0.54 (0.37-0.79)	0.46 (0.32-0.65)	<0.001
SHD	43 (11.7)	47 (16.1)	1.47 (0.99-2.19)	1.61 (1.03-2.53)	79 (14.8)	75 (15.0)	1.02 (0.89-1.17)	0.81 (0.60-1.09)	0.002
Favorable Neurologic Outcome (all)	37 (10.1)	35 (12.0)	1.13 (0.66-1.96)	NA[2]	62 (11.6)	50 (10.0)	0.85 (0.69-1.04)	NA[2]	0.24
Favorable Neurologic Outcome (survivors)	37/43 (86.1)	35/47 (74.5)	0.51 (0.23-1.13)	NA[2]	62/79 (78.5)	50/75 (66.7)	0.50 (0.37-0.69)	NA[2]	0.29

[1]Adjusted for age, sex (male vs. female), race (white vs. non-white), witnessed arrest (yes/no), location of the arrest (home, medical facility, other), AED availability (yes/no), EMS response interval, and the presence of a shockable rhythm (yes/no).
[2]Unable to adjust due to the small number of events.

presented in Figure 1 and cohort characteristics based on rhythm type and bystander CPR are summarized in Table 1.

Rates of bystander CPR were similar pre- vs. post SDEP-implementation, with 40.7% (366/899) in the MDEP and 36.9% (292/791) in the SDEP groups receiving bystander CPR ($p = 0.11$). Among those with bystander CPR, there was a 4.4% absolute increase in the rate of SHD in the SDEP group compared to the MDEP group, but this unadjusted comparison was not statistically significant (16.1% [47/292] vs. 11.7% [43/366]; $p = 0.057$). However, after adjustment for confounders, the SDEP was significant for improved SHD among patients with bystander CPR (aOR 1.61, 95%CI 1.03-2.53). Among patients without bystander CPR, SHD rates were similar in the SDEP and MDEP groups in unadjusted (15.0% [75/499] vs. 14.8% [79/533]; $p = 0.77$) and adjusted analyses (aOR 0.81, 95%CI 0.60-1.09). In patients with bystander CPR, ROSC rates were similar in the SDEP group compared to the MDEP group (32.5% [95/292] vs. 35.2% [129/366]; $p = 0.43$). Among those without bystander CPR, ROSC rates were decreased in the SDEP group (32.5% [162/499] vs. 47.1% [251/533]; $p = 0.002$). After adjustment, the SDEP implementation remained non-significant for ROSC rates among patients who received bystander CPR (aOR 0.90, 95%CI 0.70-1.17) and remained significant for decreased ROSC rates among patients without bystander CPR (aOR 0.46, 95%CI 0.32-0.65). In the adjusted model, the interaction between the SDEP implementation and bystander CPR was significant for SHD ($p = 0.002$) and ROSC ($p < 0.001$). Table 2 shows the study outcomes based on receiving bystander CPR and Figure 2 presents the odds ratios for study outcomes in the bystander and no bystander CPR groups. The exploratory outcome of favorable neurologic outcomes among all patients and just survivors are described in Table 2.

There were fewer patients with an initial shockable rhythm in the pre-implementation MDEP cohort than in the post-implementation SDEP cohort (16.0% [144/899] vs. 22.8% [180/791]; $p < 0.001$). Among those with a shockable rhythm, SHD rates were similar in the SDEP and MDEP groups in unadjusted (30.0% [54/180] vs. 29.9% [43/144]; $p = 0.95$) and adjusted analyses (aOR 0.96, 95%CI 0.48-1.91). Survival to hospital discharge rates were also similar among patients with a non-shockable rhythm in the SDEP and MDEP groups in unadjusted (11.1% [68/611] vs. 10.5% [79/755]; $p = 0.71$) and adjusted analyses (aOR 1.26, 95%CI 0.89-1.77). Return of spontaneous circulation rates were significantly lower in the SDEP group as compared to the MDEP group for both patients with a shockable rhythm (54.4% [98/180] vs. 63.2% [91/144]; $p = 0.005$) and non-shockable rhythm (26.0% [159/611] vs. 38.3% [289/755]; $p = 0.007$). In the adjusted analyses, ROSC rates remained significantly decreased in the SDEP group, regardless of rhythm type (shockable: aOR 0.65 [95%CI 0.50-0.84], non-shockable: aOR 0.57 [95%CI 0.34-0.97]). In the adjusted model, the interaction between SDEP implementation and rhythm type was not significant for SHD ($p = 0.65$) or ROSC ($p = 0.68$). Table 3 shows the study outcomes based on rhythm type and Figure 3 presents adjusted odds ratios

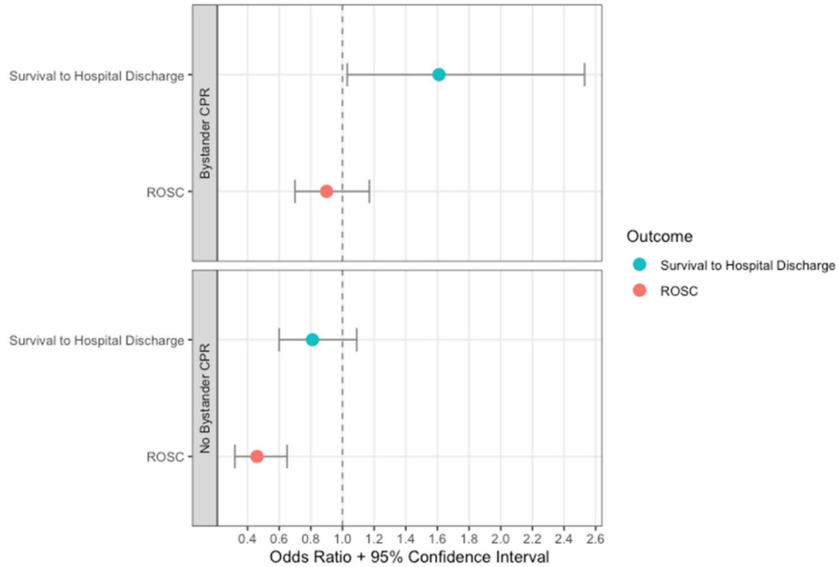

Figure 2. SDEP vs. MDEP adjusted odds ratios for study outcomes among all patients with bystander CPR or without bystander CPR.
Models were adjusted for age, sex, race, witnessed arrest, location of the arrest, AED availability, EMS response interval, and the presence of a shockable rhythm or receiving bystander CPR. ROSC – return of spontaneous circulation.

for study outcomes for each rhythm type. Favorable neurologic outcomes among all patients and survivors are described in Table 3. Findings of the SDEP implementation across bystander CPR subgroups and heart rhythm subgroups were consistent among patients thought to have arrested from a primary cardiac etiology in both unadjusted and adjusted models (Supplemental Tables 2 and 3).

Discussion

The key finding of this subgroup analysis is the association between the single dose epinephrine protocol (SDEP) implementation and increased SHD in patients who received bystander CPR after accounting for potential confounders. Survival to hospital discharge rates were similar for the SDEP and MDEP regardless of rhythm type and among those who did not receive bystander CPR. The effect of SDEP on SHD was consistent, regardless of whether the arrest was due to presumed cardiac causes or non-cardiac causes such as respiratory/asphyxia, drowning, electrocution, etc., underscoring the SDEP's reliable effectiveness across various OHCA presentations.

In the adjusted model, the SDEP was associated with significantly higher SHD compared to MDEP among patients who received bystander CPR. In the unadjusted model, patients who received bystander CPR had a 4.4% absolute increase in survival to hospital discharge in the SDEP group compared to the MDEP group, this effect estimate was not statistically significant. Prior studies have consistently established that early bystander CPR improves survival in OHCA (12, 13, 24), but little data exists exploring the effect that epinephrine administration has on patients who received bystander CPR. To our knowledge, this analysis is the first to quantify the combined effect of bystander CPR and single dose epinephrine administration. The higher rate of SHD for the SDEP among patients receiving bystander CPR may be explained by the SDEP allowing greater time for EMS crews to focus on tasks other than drug administration, such as high-quality chest compressions and defibrillation. Additionally, fewer doses of epinephrine may lead to less opportunity for cardiac arrhythmias or an increase in myocardial demand (25). These factors may explain why the SDEP leads to improved rates of SHD, especially in patients that have already benefited from bystander CPR during their OHCA. Given our findings, more research is needed to validate the effect of a SDEP on SHD among patients who receive bystander CPR and to further elucidate drivers of improved outcomes in this population.

Survival to hospital discharge was similar for the SDEP and MDEP regardless of rhythm type. A recent meta-analysis of 18 randomized trials found that epinephrine improved SHD among those with a non-shockable rhythm but not those with a shockable rhythm (26). Similarly, the PARAMEDIC-2 trial compared epinephrine to placebo in OHCA and found that epinephrine significantly improved survival at 30 days for patients with a non-shockable rhythm, but did not cause a significant difference in survival at 30 days for those with a shockable rhythm (6). These findings suggest that patients with a shockable heart rhythm might not benefit from epinephrine administration. However, our findings did not find a difference in SHD based on single or multiple doses of epinephrine regardless of initial rhythm. While our findings did not find a notable difference in outcomes based on initial rhythm, further work may be needed to explore these details further. For example, the forthcoming EpiDOSE randomized controlled trial will assess the use of a low dose epinephrine (up to 2 mg total) protocol for patients with an initial shockable OHCA (27).

Discharge with a favorable neurologic outcome was an exploratory endpoint. Our findings showed that among all patients, the rates of favorable neurologic outcomes in the SDEP and MDEP protocols were similar regardless of

Table 3. Rhythm subgroups.

	Shockable				Non-shockable				
	Pre-implementation MDEP	Post-implementation SDEP	Odds Ratio (95%CI)		Pre-implementation MDEP	Post-implementation SDEP	Odds Ratio (95%CI)		Interaction (Implementation cohort x rhythm type)
	($n = 144$), n (%)	($n = 180$), n (%)	Unadjusted	Adjusted1	($n = 755$), n (%)	($n = 611$), n (%)	Unadjusted	Adjusted1	
ROSC	91 (63.2)	98 (54.4)	0.69 (0.54-0.90)	0.65 (0.50-0.84)	289 (38.3)	159 (26.0)	0.56 (0.37-0.86)	0.57 (0.34-0.97)	0.68
SHD	43 (29.9)	54 (30.0)	0.98 (0.58-1.66)	0.96 (0.48-1.91)	79 (10.5)	68 (11.1)	0.91 (0.69-1.80)	1.26 (0.89-1.77)	0.65
Favorable Neurologic Outcome (all)	34 (23.6)	43 (23.9)	1.01 (0.63-1.60)	NA[2]	65 (8.6)	42 (6.9)	0.78 (0.38-1.61)	NA[2]	0.67
Favorable Neurologic Outcome (suvivors)	34/43 (79.1)	43/53 (79.6)	1.04 (0.90-1.19)	NA[2]	65/79 (82.3)	42/68 (61.8)	0.18 (0.07-0.50)	NA[2]	<0.001

[1]Adjusted for age, sex (male vs. female), race (white vs. non-white), witnessed arrest (yes/no), location of the arrest (home, medical facility, other), AED availability (yes/no), EMS response interval, and bystander CPR (yes/no).
[2]Unable to adjust due to the small number of events.

whether they received bystander CPR or not or whether they had a shockable heart rhythm or not. However, when neurologic outcomes were analyzed among just survivors, we did detect improved rates of favorable neurologic outcomes among those who received care guided by the MDEP and did not have a shockable heart rhythm or receive bystander CPR. However, these unadjusted results should be interpreted cautiously given they are exploratory and that the small number of events precluded adjustment for potential confounders.

Given our findings, the relationship between epinephrine administration and OHCA outcomes appears nuanced and is affected by numerous factors such as bystander CPR. The outcomes observed between the SDEP and bystander CPR emphasizes the crucial role of community education in optimizing outcomes for OHCA patients. It is important to acknowledge that OHCA interventions do not function in a vacuum. The broader system of pre-hospital care, including bystander CPR and access to early defibrillation, sets the stage for EMS interventions. Considering the limited improvement in OHCA outcomes over the last three decades, our findings indicate a pressing need to reassess existing guidelines and further explore additional resuscitation strategies. While EMS medical directors continue evaluating their OHCA resuscitation protocols and the prior single dose epinephrine implementation study findings, this subgroup analysis provides further evidence that a SDEP might improve patient outcomes, especially among those who received bystander CPR.

Limitations

There were several limitations to the study. Given the pre-post implementation study design, patients were not randomized to the SDEP or MDEP, potentially exposing the study to unknown confounders and maturation effects. This subgroup analysis makes multiple comparisons, thus increasing the chance of finding a random difference between subgroups. Although data collection ended in 2019, our study findings are still relevant as there have not been any widely implemented, major changes in OHCA care regarding epinephrine dosing. Given changes in local medical directors, obtaining additional data for this analysis was not feasible. Further, this study occurred in a geographically limited area of NC, limiting generalizability. However, the five participating EMS systems care for rural, suburban, and urban patients and transport to a variety of hospital types, including critical access, community, and academic tertiary care centers. This study relied on the CARES database, which does not adjudicate patient outcomes, record the number of doses of epinephrine, or the time to epinephrine administration (28, 29). While EMS systems agreed to a limited data use agreement, this data did not include further information regarding how many doses of epinephrine or time to first dose of epinephrine. As such, a per protocol analysis was not possible. Finally, the relatively modest sample sizes within our subgroups may have limited the statistical power of the analysis. This potentially affected our ability to detect meaningful differences between groups.

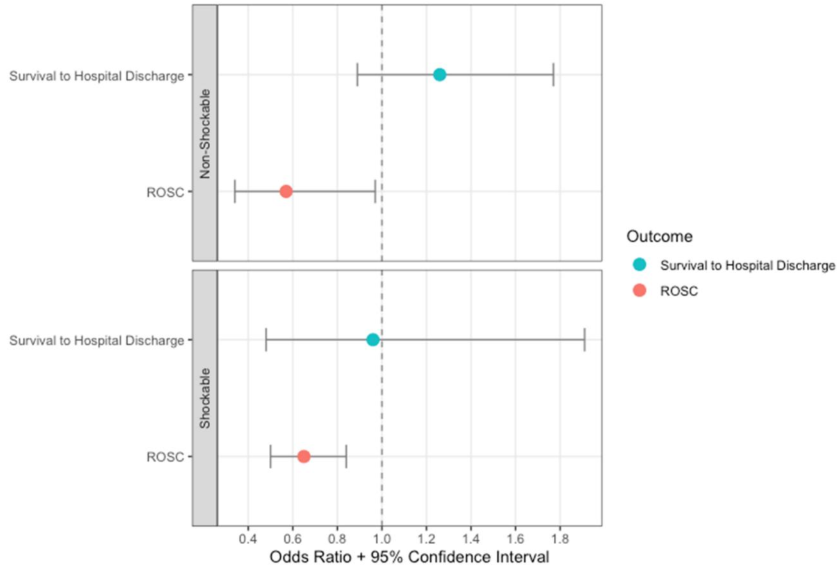

Figure 3. SDEP vs. MDEP adjusted odds ratios for study outcomes among all patients with shockable or non-shockable heart rhythms.
Models were adjusted for age, sex, race, witnessed arrest, location of the arrest, AED availability, EMS response interval, and the presence of a shockable rhythm or receiving bystander CPR. ROSC – return of spontaneous circulation.

Conclusion

A SDEP was associated with an improved SHD rate in those who received bystander CPR. Survival to hospital discharge rates were similar between the SDEP and MDEP strategies among patients who did not receive bystander CPR and among patients with both shockable and non-shockable rhythms. Our findings also demonstrate that patients exposed to a SDEP had similar rates of ROSC when they received bystander CPR. However, the rates of ROSC decreased among those who did not receive bystander CPR and among patients with both shockable and non-shockable rhythms. These findings suggest that EMS medical directors might further consider a single-dose epinephrine protocol, especially among patients receiving bystander CPR.

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Author Contributions

TSG and NPA conceived the study idea. NPA and JPA coordinated data management. ACS, TSG, and NPA performed data analysis. BPB, JTW, RDN, and JPS provided prehospital expertise. TSG and NPA drafted the manuscript. All authors contributed to the manuscript and substantially to its revision. TSG takes responsibility for the manuscript as a whole.

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ORCID

Tyler S. George http://orcid.org/0000-0002-6777-038X
Nicklaus P. Ashburn http://orcid.org/0000-0002-3466-8813
Anna C. Snavely http://orcid.org/0000-0001-6916-4255
James E. Winslow http://orcid.org/0009-0009-7557-9989
R. Darrell Nelson http://orcid.org/0000-0002-9830-4461
Jason P. Stopyra http://orcid.org/0000-0001-7457-3969

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