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Effect of prehospital epinephrine on out-of-hospital cardiac arrest: a report from the national out-of-hospital cardiac arrest data registry in Japan, 2011–2012

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Abstract
Purpose The effect of prehospital epinephrine on neurological outcome in out-of-hospital cardiac arrest (OHCA) is still controversial. We sought to determine whether prehospital epinephrine administration was associated with improved outcomes in adult OHCA.
Methods A nationwide, population-based, propensity score-matched study of OHCA patients from January 1, 2011, to December 31, 2012, in Japan was conducted. We included adult OHCA patients treated by emergency medical service personnel without an excessive delay. The primary outcome was neurologically favorable survival 1 month after OHCA.
Results A total of 237,068 patients (16,616 with a shockable rhythm and 220,452 with a non-shockable rhythm) were included in the final cohort. A total of 4024 out of the 16,616 shockable OHCAs and 29,393 out of the 220,452 non-shockable OHCAs received prehospital epinephrine. In the propensity score-matched cohort, prehospital epinephrine was associated with a decreased chance of neurologically favorable survival (shockable OHCA 7.6 vs. 17.9 %, OR 0.38 [95%CI 0.33–0.43]; non-shockable OHCA 0.6 vs. 1.2 %, OR 0.47 [95%CI 0.39–0.56]). In the subgroup analyses, prehospital epinephrine was significantly associated with poor neurological outcome in all subgroups. In the ancillary analyses, although the neurological outcome was worse as the number of epinephrine doses increased or the time to epinephrine increased, patients had a greater chance of a favorable neurological outcome only when a single dose of epinephrine was administered within 15 min of the emergency call in shockable OHCA.
Conclusions Among adult OHCA patients, prehospital epinephrine was associated with a decreased chance of neurologically favorable survival. Situations in which prehospital epinephrine is effective may be extremely limited.

Keywords Cardiac arrest · Cardiopulmonary resuscitation · Epinephrine · Adrenaline · Epidemiology

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Introduction

Although recommendations on epinephrine for out-of-hospital cardiac arrest (OHCA) have been weakened with each revision of the international guidelines on cardiopulmonary resuscitation (CPR), standard-dose epinephrine (1 mg every 3 to 5 min) is nevertheless still recommended in the 2015 guidelines [1, 2]. While numerous studies have shown that epinephrine administration in OHCA increases prehospital return of spontaneous circulation (ROSC) and

hospital admission, they conversely suggest that it may also result in adverse survival and neurological outcomes [3–6]. However, epinephrine may have a favorable effect on survival and neurological outcome depending on initial cardiac rhythm or bystander witness status [7]. Additionally, its effect may differ depending on the timing or frequency of administration [8–10]. Thus, while it may be that the weak recommendation of epinephrine in the resuscitation algorithm was retained due to numerous remaining uncertainties, providing an epinephrine recommendation as a simple, standardized method may not be reasonable. Moreover, many studies on the effects of epinephrine reflect the resuscitation practices prior to 2010, and their applicability to current circumstances (after 2010) is questionable.

We therefore investigated the effects of epinephrine using national administrative data from 2011 to 2012. Because prior studies have suggested that the effects of epinephrine depend on differences in initial cardiac rhythm, we investigated the effects of epinephrine in both shockable and non-shockable rhythms. We furthermore examined the effects of the timing and frequency of administration on patient outcome.

Materials and methods

Study design, setting, and participants

We used the All-Japan Utstein Registry database. The database is managed by the Fire and Disaster Management Agency (FDMA). The details of the registry and the emergency medical service (EMS) system in Japan have been described previously [6, 7, 11–13]. In brief, the All-Japan Utstein Registry database is a nationwide, population-based, prospective registry of all OHCAs. All patients with OHCA (defined as pulselessness, apnea, and unresponsiveness) for whom resuscitation was attempted by EMS personnel were identified and followed, including patients with do-not-resuscitate (DNR) orders. In Japan, EMS personnel are legally obliged to attempt resuscitation, except in specific situations, such as decapitation, rigor mortis, livor mortis, and decomposition. Therefore, almost all OHCA patients are transported to an emergency hospital.

The registry uses standardized Utstein-style templates for OHCA to facilitate uniform reporting with precisely defined variables and outcomes [14, 15]. The data are collected from three sources: 119 dispatch centers, fire stations, and receiving hospitals. The data forms are completed by EMS personnel, and the data are integrated into the All-Japan Utstein Registry system on the FDMA database server. The integrity of data is ensured through rigorous certification by a data entry specialist, and the completeness and accuracy of the data are checked by standardized software.

The cohort included data submitted to the All-Japan Utstein Registry from January 1, 2011, to December 31, 2012. We included adult patients aged 18 years or older. Patients with a delay in treatment (the time from call to contact with patient or epinephrine administration >60 min and the time from contact with patient to hospital arrival >120 min) were excluded because they may had abnormal prehospital setting and outcomes. In addition, patients with missing, incomplete, inconsistent, or unknown data on time, first documented rhythm, etiology of cardiac arrest, or prehospital advanced life support were excluded from the analysis. Patients with missing or unknown data accounted for approximately 5.3 % of the total patients (Fig. 1).

This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review board of the University of Tokyo approved the study with a waiver of informed consent because of the anonymous nature of the data (no. 10096).

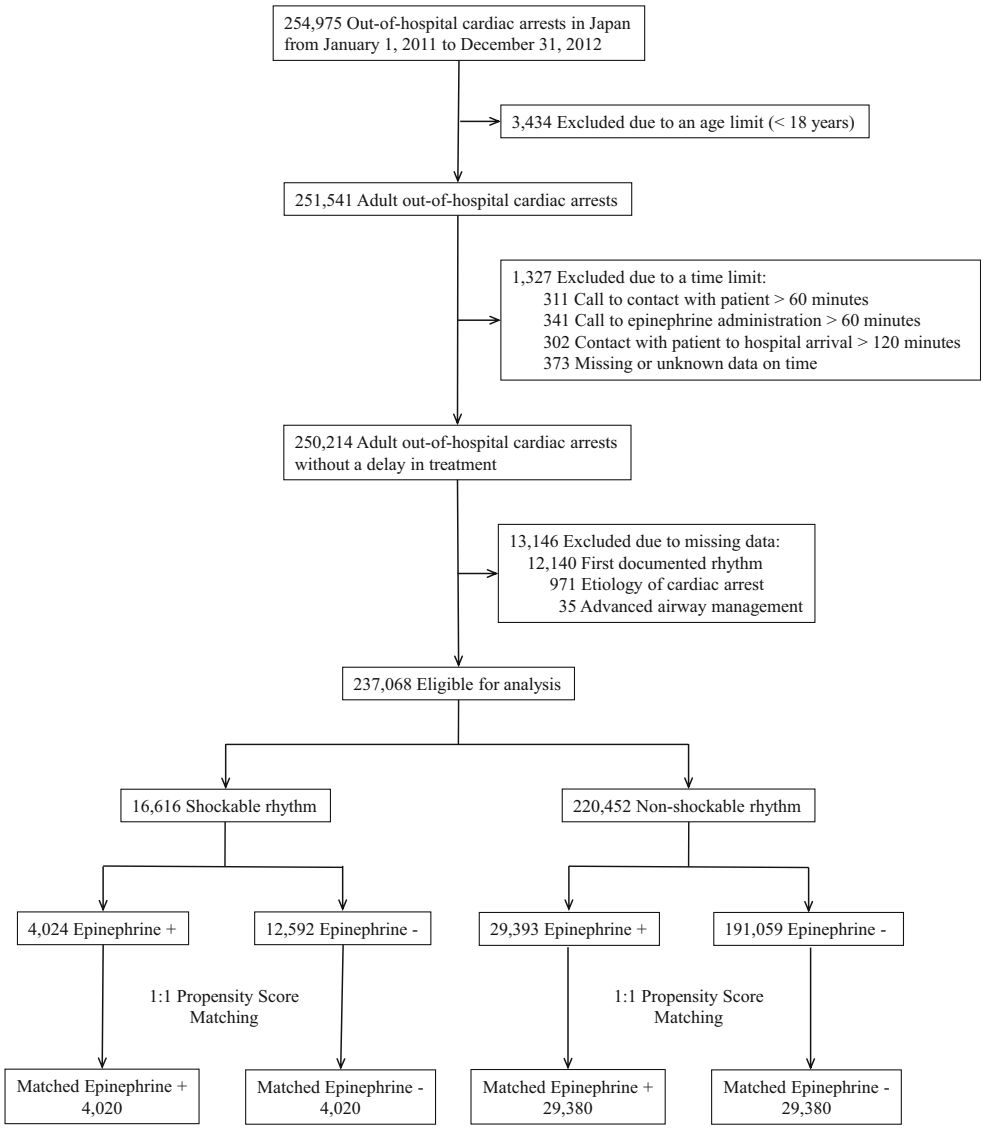
Data collection

Data concerning sex, age, bystander witness, bystander CPR, public-access automated external defibrillator (AED), first documented rhythm, etiology of cardiac arrest, and prehospital advanced life support (i.e., information on epinephrine administration and advanced airway management) were collected. A series of EMS times (call receipt, vehicle arrival at the scene, contact with patient, initiation of CPR, epinephrine administration, prehospital ROSC, and hospital arrival) were also recorded. The etiology of cardiac arrest for patients admitted to the hospital was probed during the hospital stay. On the other hand, for patients who died without hospital admission, the etiology of cardiac arrest was determined by the attending physicians at the emergency department in collaboration with the EMS personnel or coroners based on the witness information, clinical course, medical history, physical findings, examination findings, imaging, and autopsy. If there were no evidence that suggested a noncardiac etiology, then the etiology was presumed to be cardiac [15].

Patients were followed up at 1 month by the EMS personnel to collect data on 1-month survival and neurological status and to reconfirm the etiology of cardiac arrest. The medical control director of the hospital provided information on the patient unless the patient was transferred to another hospital within 1 month. If transferred, then the EMS personnel conducted the follow-up investigation.

The primary outcome was favorable neurological status at 1 month after OHCA. The secondary outcomes were 1-month survival, prehospital ROSC, and time from contact with patient to hospital arrival. The neurological status was assessed with the Glasgow-Pittsburgh cerebral performance category (CPC) scores by the attending physician in charge of the patient. A CPC score of 1 or 2 (good performance or moderate

Fig. 1 Patient flow chart



disability, respectively) was defined as a favorable neurological outcome, and a CPC score of 3, 4, or 5 (severe disability, vegetative state, or death, respectively) as a poor neurological outcome [15, 16].

Statistical analysis

The baseline characteristics were described as counts with proportions for categorical variables and means with standard deviations for continuous variables. The *t* test was used to compare continuous variables, and the χ^2 test was used to compare categorical variables.

Because the data lacked randomization, a propensity score approach was used to control for selection bias and confounding. A propensity score for prehospital epinephrine administration for each patient was estimated by using a multivariable logistic regression model. The following variables were included in the model: sex, age, bystander witness, bystander CPR, public-access AED (PAD), first documented rhythm, etiology of cardiac arrest, prehospital advanced airway management, and time from call to contact with patient. The *c* statistic was used to assess goodness-of-fit. A 1:1 nearest-neighbor matching was performed on the propensity score with a caliper ≤0.2 and without replacement between patients who received and did not receive prehospital epinephrine [17]. We assessed the success of the propensity-matching procedure by comparing the distribution of patient characteristics in the matched cohort.

In the propensity score-matched cohort, we used a univariable logistic regression model to compare the frequency of each outcome for patients who received and did not receive prehospital epinephrine and to estimate odds ratios (OR) with 95 % confidence intervals (CI). We further examined the association between prehospital epinephrine

administration and the outcomes of various subgroups based on sex (male or female), age (18–64 or ≥65 years), bystander witness (presence or absence), bystander CPR (presence or absence), etiology of cardiac arrest (cardiac or noncardiac), cardiac rhythm (VF or VT for shockable rhythm, and PEA or asystole for non-shockable rhythm), and time from call to contact with patient (< 7 or ≥7 min). For each subgroup, the association of epinephrine administration with each outcome was estimated in a logistic regression model that included a treatment variable (with or without prehospital epinephrine administration) and the same covariates listed previously for the estimation of the propensity score, and adjusted ORs with 95 % CIs were reported.

In addition, we performed ancillary analyses that focused on the frequency of epinephrine administration and the time to epinephrine administration. We calculated the ORs with 95 % CIs for each outcome depending on the number of epinephrine doses, with no epinephrine administration as the reference. For patients who received epinephrine, the ORs for a 1-min increment of time to epinephrine administration and their 95 % CIs for each outcome were calculated for the total cohort and for subgrouped cohorts with and without witness. In addition, to estimate the time limit for successful epinephrine administration, we evaluated the association of time to epinephrine administration (0–15, 16–20, 21–25, 26–30, or ≥31 min after emergency call) with favorable outcomes, depending on the number of epinephrine doses (1, 2, ≥3 times). No adjustments were made for ancillary analyses, and thus, the findings from those analyses were exploratory.

All of the tests were two sided at a significance level of 0.05. All of the statistical analyses were performed with JMP Pro 11.0.0 software (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, we identified 237,068 adult OHCA patients who received treatment without a delay (Fig. 1); 16,616 (7.0 %) had a shockable initial rhythm, and 220,452 (93.0 %) had a non-shockable initial rhythm. Of the 16,616 shockable OHCAs, 4024 (24.2 %) received epinephrine and 4020 patients who received epinephrine were matched with 4020 patients who did not. Of the 220,452 non-shockable OHCA, 29,393 (13.3 %) received epinephrine and 29,380 patients who received epinephrine were matched with 29,380 who did not receive.

The baseline characteristics of the total cohort and the propensity score-matched cohort in the shockable OHCA group are shown in Table 1, and those in the non-shockable OHCA group are in Table 2. In both shockable and non-shockable OHCA, there were imbalances between the groups with and without epinephrine administration in the unmatched cohort. In the propensity score-matched cohorts, the baseline characteristics were similar between the two groups.

The clinical outcomes of patients who received and did not receive epinephrine in the propensity score-matched cohort are summarized in Table 3. Although prehospital epinephrine administration was associated with increased prehospital ROSC after non-shockable OHCA, patients who received epinephrine had a poorer 1-month neurological outcome than those who did not (0.6 vs. 1.2 %, OR 0.47 [95%CI 0.39–0.56]). In shockable OHCA, prehospital epinephrine administration was associated with a decreased 1-month survival (16.4 vs. 27.0 %, OR 0.53 [95%CI 0.47–0.59]) and a poorer neurological survival (7.6 vs. 17.9 %, OR 0.38 [95%CI 0.33–0.43]) compared with those who had no prehospital epinephrine administration, and not associated with prehospital ROSC ($P = 0.0524$). In addition, patients with prehospital epinephrine administration had approximately a 5-min delay in hospital arrival compared with those without.

In the subgroup analyses, prehospital epinephrine administration was significantly associated with poor neurological outcome in all subgroups (online-only supplemental Tables 1, 2, and 3). Prehospital epinephrine administration was associated with increased 1-month survival only in unwitnessed non-shockable OHCA cases and asystole cases.

In the ancillary analysis that focused on the number of epinephrine doses, an increased dose was generally associated with a stepwise decrease in 1-month survival and neurologically favorable survival (online-only supplemental Figure). In shockable OHCA, patients with single dose of epinephrine had a better chance of prehospital ROSC than those without epinephrine (OR 1.28, 95%CI 1.12–1.46). In non-shockable OHCA, compared with no epinephrine administration, epinephrine administration was associated with increased prehospital ROSC, regardless of the number of doses. In addition, a single dose of epinephrine for non-shockable OHCA was associated with improved 1-month survival (OR 1.67, 95%CI 1.51–1.84). In another ancillary analysis that focused on patients with prehospital epinephrine, all of the outcomes were better as the time from call to epinephrine administration was shorter, regardless of cardiac rhythm or bystander witness (online-only supplemental Table 4).

As an additional analysis, we investigated the association of the timing of epinephrine administration with 1-month survival and neurologically favorable survival, depending on the number of epinephrine doses (Table 4). Only when the time interval from call to epinephrine was up to 15 min, patients who received a single dose of epinephrine had a more favorable neurological outcome than those who did not receive epinephrine in shockable OHCA (OR 1.95, 95%CI 1.37–2.72). In addition, a single dose of epinephrine administered within 20 min in a shockable OHCA case and within 25 min in a non-shockable OHCA case was associated with increased 1-month survival.

Table 1 Baseline characteristics of patients with shockable OHCA

	Total (shockable OHCA)			Propensity score-matched cohort (shockable OHCA)		
	Epinephrine (+) $n = 4024$	Epinephrine (−) $n = 12{,}592$	*P* value	Epinephrine (+) $n = 4020$	Epinephrine (−) $n = 4020$	*P* value
Sex (male)	3249 (80.7)	9492 (75.4)	<0.0001	3245 (80.7)	3263 (81.2)	0.6092
Age (years), mean (SD)	66.1 (15.3)	66.7 (15.6)	0.0275	66.1 (15.3)	66.3 (15.2)	0.6794
(1) 18≤ , <35	152 (3.8)	428 (3.4)		151 (3.8)	149 (3.7)	
(2) 35≤ , <45	241 (6.0)	761 (6.0)		241 (6.0)	218 (5.4)	
(3) 45≤ , <55	441 (11.0)	1364 (10.8)		441 (11.0)	436 (10.9)	
(4) 55≤ , <65	868 (21.6)	2756 (21.9)		868 (21.6)	878 (21.8)	
(5) 65≤ , <75	1035 (25.7)	2931 (23.3)		1032 (25.7)	1061 (26.4)	
(6) 75≤ , <85	883 (21.9)	2824 (22.4)		883 (22.0)	875 (21.8)	
(7) 85≤	404 (10.0)	1528 (12.1)		404 (10.1)	403 (10.0)	
Witness	2948 (73.3)	9085 (72.2)	0.1697	2944 (73.2)	2959 (73.6)	0.7049
Bystander CPR	2031 (50.5)	5901 (46.9)	<0.0001	2027 (50.4)	1993 (49.6)	0.7212
Public-access AED	168 (4.2)	475 (3.8)	0.2489	166 (4.1)	144 (3.6)	0.2025
First documented rhythm				210 (1.8)	220 (1.9)	0.6264
(1) VF	3938 (97.9)	12,131 (96.3)	<0.0001	3934 (97.9)	3951 (98.3)	0.1679
(2) VT	86 (2.1)	461 (3.7)	<0.0001	86 (2.1)	69 (1.7)	0.1679
Cardiac etiology	3604 (89.6)	10,908 (86.6)	<0.0001	3600 (89.6)	3630 (90.3)	0.2663
Noncardiac etiology	420 (10.4)	1684 (13.4)	<0.0001	420 (10.5)	390 (9.7)	0.2663
(1) Cerebrovascular disease	73 (1.8)	308 (2.5)		73 (1.8)	69 (1.7)	
(2) Respiratory disease	51 (1.3)	192 (1.5)		51 (1.3)	51 (1.3)	
(3) Malignant tumor	18 (0.5)	143 (1.1)		18 (0.5)	31 (0.8)	
(4) External causes	106 (2.6)	394 (3.1)		106 (2.6)	102 (2.5)	
(5) Other	172 (4.3)	647 (5.1)		172 (4.3)	137 (3.4)	
Time from call to contact with patient (min), mean (SD)	8.7 (3.4)	8.4 (3.5)	<0.0001	8.7 (3.4)	8.7 (3.4)	0.4134
(1) 0≤ ,< 4	47 (1.2)	278 (2.2)		47 (1.2)	47 (1.2)	
(2) 4≤ , <7	942 (23.4)	3463 (27.5)		942 (23.4)	953 (23.7)	
(3) 7≤ , <10	1778 (44.2)	5355 (42.5)		1777 (44.2)	1777 (44.3)	
(4) 10≤ , <13	828 (20.6)	2347 (18.6)		826 (20.6)	834 (20.8)	
(5) 13≤	429 (10.7)	1149 (9.1)		428 (10.7)	409 (10.2)	
Time from call to epinephrine administration (min), mean (SD)	23.3 (8.1)			23.3 (8.1)		
(1) 0–15	586 (14.6)			585 (14.6)		
(2) 16–20	1127 (28.0)			1126 (28.0)		
(3) 21–25	986 (24.5)			985 (24.5)		
(4) 26–30	634 (15.8)			634 (15.8)		
(5) 31≤	691 (17.2)			690 (17.2)		
No. of epinephrine doses						
(1) 1	1471 (36.6)			1471 (36.6)		
(2) 2	1198 (29.8)			1198 (29.8)		
(3) 3	706 (17.5)			703 (17.5)		
(4) 4	323 (8.0)			322 (8.0)		
(5) 5	326 (8.1)			326 (8.1)		
Advanced airway management	2513 (62.5)	4151 (33.0)	<0.0001	2509 (62.4)	2502 (62.2)	0.8720

The data are expressed as the number (%) of patients or the mean (SD) unless otherwise indicated

OHCA out-of-hospital cardiac arrest, *SD* standard deviation, *CPR* cardiopulmonary resuscitation, *AED* automated external defibrillator, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Table 2 Baseline characteristics of patients with non-shockable OHCA

	Total (non-shockable OHCA)			Propensity score-matched cohort (non-shockable OHCA)		
	Epinephrine (+) *n* = 29,393	Epinephrine (−) *n* = 191,059	*P* Value	Epinephrine (+) *n* = 29,380	Epinephrine (−) *n* = 29,380	*P* value
Sex (male)	17,514 (59.6)	104,099 (54.5)	<0.0001	17,505 (59.6)	17,487 (59.5)	0.8797
Age (years), mean (SD)	75.2 (14.9)	75.5 (15.7)	0.0009	75.2 (14.9)	75.3 (14.9)	0.5084
(1) 18≤ , <35	617 (2.1)	5062 (2.7)		616 (2.1)	609 (2.1)	
(2) 35≤ , <45	846 (2.9)	6175 (3.2)		846 (2.9)	834 (2.8)	
(3) 45≤ , <55	1378 (4.7)	9059 (4.7)		1375 (4.7)	1408 (4.8)	
(4) 55≤ , <65	3185 (10.8)	18,295 (9.6)		3182 (10.8)	3193 (10.9)	
(5) 65≤ , <75	5187 (17.7)	31,451 (16.5)		5184 (17.6)	5170 (17.6)	
(6) 75≤ , <85	9587 (32.6)	59,941 (31.4)		9585 (32.6)	9578 (32.6)	
(7) 85≤	8593 (29.2)	61,076 (32.0)		8592 (29.2)	8588 (29.2)	
Witness	16,018 (54.5)	64,548 (33.8)	<0.0001	16,005 (54.5)	16,118 (54.9)	0.3491
Bystander CPR	13,653 (46.5)	83,287 (43.6)	<0.0001	13,642 (46.4)	13,639 (46.4)	0.9802
Public-access AED	384 (1.3)	1488 (0.8)	<0.0001	380 (1.3)	340 (1.2)	0.1336
First documented rhythm						
(1) PEA	11,183 (38.1)	40,988 (21.5)	<0.0001	11,171 (38.0)	11,201 (38.1)	0.7988
(2) Asystole	18,210 (62.0)	150,071 (78.6)	<0.0001	18,209 (62.0)	18,179 (61.9)	0.7988
Cardiac etiology	17,003 (57.9)	105,106 (55.0)	<0.0001	16,994 (57.8)	17,042 (58.0)	0.6883
Noncardiac etiology	12,390 (42.2)	85,953 (45.0)	<0.0001	12,386 (42.2)	12,338 (42.0)	0.6883
(1) Cerebrovascular disease	1301 (4.4)	6814 (3.6)		1300 (4.4)	1026 (3.5)	
(2) Respiratory disease	1834 (6.2)	12,028 (6.3)		1834 (6.2)	1991 (6.8)	
(3) Malignant tumor	657 (2.2)	7556 (4.0)		657 (2.2)	970 (3.3)	
(4) External causes	4983 (17.0)	34,304 (18.0)		3613 (12.3)	4853 (16.5)	
(5) Other	3615 (12.3)	25,251 (13.2)		172 (4.3)	3498 (11.9)	
Time from call to contact with patient (min), mean (SD)	9.2 (3.9)	9.1 (4.2)	0.0002	9.2 (3.9)	9.3 (4.2)	0.1249
(1) 0≤ , <4	282 (1.0)	2204 (1.2)		282 (1.0)	261 (0.9)	
(2) 4≤ , <7	5903 (20.1)	42,037 (22.0)		5899 (20.1)	5911 (20.1)	
(3) 7≤ , <10	12,664 (43.1)	80,584 (42.2)		12,661 (43.1)	12,712 (43.3)	
(4) 10≤ , <13	6403 (21.8)	40,860 (21.4)		6399 (21.8)	6373 (21.7)	
(5) 13≤	4141 (14.1)	25,374 (13.3)		4139 (14.1)	4123 (14.0)	
Time from call to epinephrine administration (min), mean (SD)	24.9 (8.5)			24.9 (8.5)		
(1) 0–15	3111 (10.6)			3108 (10.6)		
(2) 16–20	7010 (23.8)			7007 (23.9)		
(3) 21–25	7259 (24.7)			7257 (24.7)		
(4) 26–30	5449 (18.5)			5445 (18.5)		
(5) 31≤	6564 (22.3)			6563 (22.3)		
No. of epinephrine doses						
(1) 1	11,207 (38.1)			11,201 (38.1)		
(2) 2	8769 (29.8)			8764 (29.8)		
(3) 3	5064 (17.2)			5064 (17.2)		
(4) 4	2464 (8.4)			2463 (8.4)		
(5) 5	1889 (6.4)			1888 (6.4)		
Advanced airway management	20,791 (70.7)	70,570 (36.9)	<0.0001	20,778 (70.7)	20,781 (70.7)	0.9783

The data are expressed as the number (%) of patients or the mean (SD) unless otherwise indicated

OHCA out-of-hospital cardiac arrest, *SD* standard deviation, *CPR* cardiopulmonary resuscitation, *AED* automated external defibrillator, *PEA* pulseless electrical activity

Table 3 Primary and secondary outcomes of those in the propensity score-matched cohort

	Shockable OHCA				Non-shockable OHCA			
	Epinephrine (+) n = 4020	Epinephrine (−) n = 4020	OR (95%CI)	P value	Epinephrine (+) n = 29,380	Epinephrine (−) n = 29,380	OR (95%CI)	P value
Time from contact with patient to hospital arrival (min), mean (SD)	28.9 (10.8)	24.7 (12.2)		<0.0001	29.0 (10.8)	24.9 (11.1)		<0.0001
Prehospital ROSC	995 (24.8)	1071 (26.6)	0.91 (0.82–1.00)	0.0524	5692 (19.4)	1635 (5.6)	4.08 (3.85–4.32)	<0.0001
1-month survival	659 (16.4)	1086 (27.0)	0.53 (0.47–0.59)	<0.0001	1100 (3.7)	1098 (3.7)	1.00 (0.92–1.09)	0.9653
Favorable neurological outcome (CPC 1 or 2)	305 (7.6)	719 (17.9)	0.38 (0.33–0.43)	<0.0001	164 (0.6)	348 (1.2)	0.47 (0.39–0.56)	<0.0001

The data are expressed as the number (%) of patients or the mean (SD) unless otherwise indicated

OHCA out-of-hospital cardiac arrest, *OR* odds ratio, *CI* confidence interval, *SD* standard deviation, *ROSC* return of spontaneous circulation, *CPC* Glasgow-Pittsburgh cerebral performance category

Discussion

In this nationwide, population-based study of OHCA, prehospital epinephrine administration was associated with a decreased chance of neurological favorable survival, regardless of the initial cardiac rhythm. In addition, prehospital epinephrine administration was associated with a poor neurological outcome in all subgroups. The neurological outcome became worse as the number of epinephrine doses increased or the time to epinephrine increased. Patients had greater chance of favorable neurological outcome only when single-dose epinephrine was administered within 15 min of the emergency call in shockable OHCA.

To our knowledge, this is the first and largest cohort study to assess in detail the effect of prehospital epinephrine administration on the outcomes of OHCA after the 2010 CPR guideline update. Our findings were robust due to the population-based study design, the use of propensity score matching and regression modeling to control for selection bias and potential confounding, and the subgroup analyses. Therefore, although this was an observational study, our findings strongly suggest that prehospital epinephrine may be harmful in OHCA, with the exception of an early single dose of epinephrine in a shockable OHCA case.

Although epinephrine is known to increase ROSC, there are some concerns about its detrimental effect on survival and neurological outcome [3–6]. Epinephrine can contribute to ROSC through strong alpha-adrenergic actions that result in macrovascular coronary and cerebral perfusion. On the other hand, its beta-adrenergic actions may be involved in poorer survival and neurological outcomes. Inotropic and chronotropic effects may cause an imbalance between the oxygen supply and the demand from the myocardium, which may result in post-cardiac arrest myocardial dysfunction [18, 19]. In addition, epinephrine is also reported to impair microvascular perfusion, including cerebral microcirculation [20, 21]. The majority of our findings also showed positive effects on ROSC and negative effects on survival and neurological outcomes. In the subgroup analysis, while there was no subgroup in which neurological outcome improved due to epinephrine administration, in the unwitnessed, non-shockable OHCA and asystole subgroups, 1-month survival increased (online-only supplemental Tables 1 and 2). Yet for such subgroups where lifesaving would not be possible without the use of epinephrine, these results suggest the discomfiting possibility that epinephrine may lead to undue futile salvage. Considering that the mere increase in 1-month survival without a favorable neurological status means failure of cerebral resuscitation in spite of successful cardiopulmonary resuscitation, we might have to refrain from reckless epinephrine administration.

The optimal dose of epinephrine is not known, although increasing the cumulative dose of epinephrine may worsen survival and neurological outcomes [8, 10]. However, repeated doses signified the prolonged time needed for resuscitation. Moreover, the adverse effects of epinephrine are possibly stronger post-resuscitation. Therefore, we must ascertain when, during the course of cumulative administration, the harms begin to overweigh the benefits. On the other hand, the time to administration is also important. Indeed, some studies suggested the possibility that the earlier epinephrine is administered in cardiac arrest, particularly in non-shockable OHCA, the greater its effect [9, 22–24]. Therefore, we conducted ancillary analyses to probe the boundaries of timing and frequency that should be considered in epinephrine administration (online-only supplemental Figure, online-only supplemental Table 4, and Table 4). Compared with cases where epinephrine was not administered, only shockable OHCA cases in which epinephrine was administered within 15 min of the emergency call had an improved neurological outcome. In cases of shockable OHCA and non-shockable OHCA in which epinephrine was administered only once

Table 4 Boundary line of the number of epinephrine doses and the time to epinephrine administration

No. of epinephrine doses and time to epinephrine	Shockable OHCA				Non-shockable OHCA			
	1-month survival (%)	OR (95%CI)	Neurologically favorable survival (%)	OR (95%CI)	1-month survival (%)	OR (95%CI)	Neurologically favorable survival (%)	OR (95%CI)
(I) Single dose								
Time from call to epinephrine								
(1) No epinephrine	27.0	Reference	17.9	Reference	3.7	Reference	1.2	Reference
(2) 0–15 min	47.6	2.46 (1.80–3.35)	29.8	1.95 (1.37–2.72)	13.1	3.87 (3.09–4.81)	2.0	1.72 (0.98–2.80)
(3) 16–20 min	33.6	1.37 (1.08–1.73)	16.4	0.90 (0.66–1.20)	10.3	2.96 (2.53–3.45)	1.6	1.38 (0.95–1.95)
(4) 21–25 min	23.2	0.81 (0.63–1.04)	8.1	0.41 (0.28–0.58)	6.6	1.81 (1.54–2.12)	1.2	1.03 (0.71–1.43)
(5) 26–30 min	13.1	0.41 (0.28–0.58)	4.4	0.21 (0.11–0.36)	4.3	1.17 (0.95–1.43)	0.5	0.41 (0.22–0.69)
(6) ≥31 min	11.3	0.35 (0.24–0.49)	5.3	0.26 (0.15–0.42)	2.6	0.68 (0.54–0.86)	0.4	0.30 (0.15–0.52)
(II) Twice								
Time from call to epinephrine								
(1) No epinephrine	27.0	Reference	17.9	Reference	3.7	Reference	1.2	Reference
(2) 0–15 min	32.0	1.27 (0.92–1.75)	15.2	0.82 (0.53–1.22)	4.5	1.22 (0.89–1.64)	1.0	0.85 (0.42–1.51)
(3) 16–20 min	18.4	0.61 (0.45–0.80)	9.9	0.51 (0.35–0.72)	4.5	1.21 (0.97–1.49)	0.6	0.48 (0.25–0.81)
(4) 21–25 min	11.9	0.36 (0.25–0.52)	4.9	0.24 (0.13–0.39)	3.4	0.90 (0.70–1.14)	0.3	0.24 (0.10–0.50)
(5) 26–30 min	9.1	0.27 (0.16–0.44)	1.1	0.05 (0.01–0.16)	2.5	0.66 (0.47–0.89)	0.3	0.26 (0.09–0.57)
(6) ≥31 min	4.9	0.14 (0.07–0.25)	1.5	0.07 (0.02–0.18)	1.8	0.48 (0.34–0.66)	0.3	0.25 (0.10–0.52)
(III) ≥3 times								
Time from call to epinephrine								
(1) No epinephrine	27.0	Reference	17.9	Reference	3.7	Reference	1.2	Reference
(2) 0–15 min	17.2	0.56 (0.39–0.78)	9.2	0.47 (0.29–0.71)	1.3	0.34 (0.21–0.53)	0.0	0.00 (0.00–0.12)
(3) 16–20 min	10.3	0.31 (0.22–0.42)	4.9	0.24 (0.15–0.36)	1.7	0.45 (0.33–0.59)	0.4	0.29 (0.15–0.52)
(4) 21–25 min	8.9	0.26 (0.17–0.38)	3.3	0.16 (0.08–0.28)	1.8	0.48 (0.34–0.64)	0.3	0.25 (0.11–0.50)
(5) 26–30 min	3.5	0.10 (0.04–0.20)	1.7	0.08 (0.02–0.21)	0.7	0.19 (0.09–0.33)	0.2	0.12 (0.02–0.38)
(6) ≥31 min	2.2	0.06 (0.02–0.14)	1.6	0.08 (0.02–0.20)	0.9	0.23 (0.12–0.37)	0.0	0.00 (0.00–0.11)

The number of epinephrine doses was categorized into three dose categories: single, twice, and ≥3 times. The time from emergency call to epinephrine administration was categorized into five interval categories: 0–15, 16–20, 21–25, 26–30, and ≥31 min. The ORs for each interval category and their 95 % CIs for each outcome were calculated by a univariable logistic regression model with the no epinephrine group as the reference

OHCA out-of-hospital cardiac arrest, *OR* odds ratio, *CI* confidence interval

within 20 and 25 min, respectively, 1-month survival increased without any significant deterioration in neurological outcome. Contrary to the recommendations from the guidelines (1 mg epinephrine every 3 to 5 min), our study results suggest that epinephrine is effective only in an extremely limited number of situations in OHCA: that is to say that (1) repeated epinephrine administration may be harmful, (2) a delay in initial administration of epinephrine may be harmful even with a single dose, and (3) epinephrine may only lead to undo futile salvage without a favorable neurological outcome. Whether early single-dose epinephrine in shockable OHCA improves neurological outcome is inconclusive because the findings from the ancillary analyses were exploratory. Therefore, further studies that focused on these issues are needed.

Our study results also indicated that prehospital epinephrine administration delayed hospital arrival. Delayed hospital arrival may be fatal. Resuscitation practices have changed dramatically over the past several decades. Not only have there been increases in prehospital AED and bystander CPR implementation rates [25, 26], but also there have been striking advancements in in-hospital and post-resuscitation care (e.g., cardiovascular intervention, targeted temperature management, and extracorporeal life support) [27, 28]. A delay in in-hospital and post-resuscitation care may have a great impact on outcomes after OHCA [29].

Although this study, which focused on OHCA patients who were treated with recent CPR practices, has extreme importance, there could be selection bias and potential confounding in spite of propensity score matching and regression modeling. An RCT comparing epinephrine and a placebo for OHCA is ongoing and may provide further clarification (PARAMEDIC 2: ISRCTN73485024).

This study has several limitations. First, this is an observational study. Although we tried to control for selection bias and potential confounding by performing propensity score matching and regression modeling, the possibility of residual confounding remains. Therefore, the findings of this study might only indicate association and not causality. Second, the generalizability of our findings is uncertain. Although the All-Japan Utstein Registry data includes mostly people of Japanese ethnicity, the effect of epinephrine might differ in different ethnic groups. In addition, we excluded a small number of patients based on missing, incomplete, inconsistent, or unknown data. Although only 5.3 % of the total patients were excluded, that might also decrease the generalizability of our findings. Third, our study cohort included patients with DNR orders. These patients might distort the findings of our study. However, it is impossible to distinguish patients with DNR orders from those without DNR orders in this national registry. Further studies that collect data on DNR orders are needed. Fourth, we were unable to assess the quality of CPR. Although prehospital CPR should be provided in accordance to Japanese CPR guidelines, there might be variability among EMS personnel. In addition, information on the interruption of CPR during epinephrine administration was unavailable. Fifth, the All-Japan Utstein Registry data does not collect information on in-hospital/post-resuscitation care. Such care might have a critical impact on the outcomes, and therefore, it could be an unmeasured confound.

Conclusion

In conclusion, prehospital epinephrine administration was associated with a decreased chance of neurologically favorable survival in OHCA, although prehospital epinephrine might have positive effects only when early single-dose epinephrine is administered in shockable OHCA. In addition, neurological outcome became worse as the number of epinephrine doses increased or the time to epinephrine increased.

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Compliance with ethical standards This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review board of the University of Tokyo approved the study with a waiver of informed consent because of the anonymous nature of the data (no. 10096).

Conflict of interest The authors declare that they have no competing interests.

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