Prehospital Epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac Arrest

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Context Epinephrine is widely used in cardiopulmonary resuscitation for out-of-hospital cardiac arrest (OHCA). However, the effectiveness of epinephrine use before hospital arrival has not been established.

Objective To evaluate the association between epinephrine use before hospital arrival and short- and long-term mortality in patients with cardiac arrest.

Design, Setting, and Participants Prospective, nonrandomized, observational propensity analysis of data from 417 188 OHCAs occurring in 2005-2008 in Japan in which patients aged 18 years or older had an OHCA before arrival of emergency medical service (EMS) personnel, were treated by EMS personnel, and were transported to the hospital.

Main Outcome Measures Return of spontaneous circulation before hospital arrival, survival at 1 month after cardiac arrest, survival with good or moderate cerebral performance (Cerebral Performance Category [CPC] 1 or 2), and survival with no, mild, or moderate neurological disability (Overall Performance Category [OPC] 1 or 2).

Results Return of spontaneous circulation before hospital arrival was observed in 2786 of 15 030 patients (18.5%) in the epinephrine group and 23 042 of 402 158 patients (5.7%) in the no-epinephrine group ($P < .001$); it was observed in 2446 (18.3%) and 1400 (10.5%) of 13 401 propensity-matched patients, respectively ($P < .001$). In the total sample, the numbers of patients with 1-month survival and survival with CPC 1 or 2 and OPC 1 or 2, respectively, were 805 (5.4%), 205 (1.4%), and 211 (1.4%) with epinephrine and 18 906 (4.7%), 8903 (2.2%), and 8831 (2.2%) without epinephrine (all $P < .001$). Corresponding numbers in propensity-matched patients were 687 (5.1%), 173 (1.3%), and 178 (1.3%) with epinephrine and 944 (7.0%), 413 (3.1%), and 410 (3.1%) without epinephrine (all $P < .001$). In all patients, a positive association was observed between prehospital epinephrine and return of spontaneous circulation before hospital arrival (adjusted odds ratio [OR], 2.36; 95% CI, 2.22-2.50; $P < .001$). In propensity-matched patients, a positive association was also observed (adjusted OR, 2.51; 95% CI, 2.24-2.80; $P < .001$). In contrast, among all patients, negative associations were observed between prehospital epinephrine and long-term outcome measures (adjusted ORs: 1-month survival, 0.46 [95% CI, 0.42-0.51]; CPC 1-2, 0.31 [95% CI, 0.26-0.36]; and OPC 1-2, 0.32 [95% CI, 0.27-0.38]; all $P < .001$). Similar negative associations were observed among propensity-matched patients (adjusted ORs: 1-month survival, 0.54 [95% CI, 0.43-0.68]; CPC 1-2, 0.21 [95% CI, 0.10-0.44]; and OPC 1-2, 0.23 [95% CI, 0.11-0.45]; all $P < .001$).

Conclusion Among patients with OHCA in Japan, use of prehospital epinephrine was significantly associated with increased chance of return of spontaneous circulation before hospital arrival but decreased chance of survival and good functional outcomes 1 month after the event.

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EPINEPHRINE IS WIDELY USED IN cardiopulmonary resuscitation (CPR) for patients with out-of-hospital cardiac arrest (OHCA).[1-3] However, its effectiveness in CPR has not been established. Epinephrine is associated with increased myocardial oxygen consumption and ventricular arrhythmias during the period after resuscitation.[4] Concern has been raised regarding increased myocardial dysfunction[5,6] and disturbed cerebral microcirculation after cardiac arrest.[7] Findings in support of epinephrine use include animal studies that show a beneficial short-term effect of epinephrine,[8,9] and evidence of increased cerebral and coronary perfusion by redirected peripheral blood flow has been reported.[10,11]

To verify the effectiveness of epinephrine in CPR, the influences of other factors, such as patients, bystanders, CPR by bystanders, life support by emergency medical service (EMS) personnel, and time from call to the scene or hospital arrival, need to be controlled. To control for the effects of covariates, a randomized controlled trial needs to be performed. However, such a study is not easily performed because of ethical reasons.

For editorial comment see p 1198.

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As for the effectiveness of epinephrine use in CPR, a large, retrospective registry study in Sweden reported that epinephrine is an independent predictor of mortality.[12] A large, observational before-after study in Singapore showed that epinephrine is not beneficial for immediate or 1-month survival.[13] Recently, 2 randomized controlled trials showed that patients receiving adrenaline during cardiac arrest had no statistically significant improvement in survival to hospital discharge, although there was a significantly improved likelihood of achieving return of spontaneous circulation (ROSC).[14,15] These studies were limited by several methodological problems, such as the use of samples from a single center, type II errors, and imperfect randomization.[14] In view of these previous studies, the findings are not consistent and the effectiveness of epinephrine in CPR has not been established. We thus performed a propensity analysis that sought to determine how epinephrine use in CPR before hospital arrival was associated with immediate and 1-month survival using national data from a whole sample of OHCAs between 2005 and 2008 in Japan.

METHODS

EMS System and Data Collection

The EMS system in Japan has been described previously.[16-18] Briefly, in Japan, municipal governments provide EMS through about 800 fire stations with dispatch centers. Because the Japanese guidelines do not allow EMS providers to terminate resuscitation in the field, all patients with OHCA who are treated by EMS personnel are transported to hospitals.[19] Based on the standardized Utstein style template, registry of all OHCA cases in Japan is performed in a prospective, nationwide, and population-based manner by the Fire and Disaster Management Agency (FDMA). In particular, time from call to the scene or hospital arrival is measured using dispatch records at the fire station and an emergency lifesaving technician watch. Data concerning bystander CPR administration, automated external defibrillator use, and the characteristics of CPR by EMS personnel (eg, initial rhythm, defibrillation, intubation, epinephrine use) are collected using EMS records. To collect 1-month follow-up data, the EMS person in charge of each patient with OHCA has a face-to-face meeting with the physician who treated that patient at the hospital. If the patient is not at the hospital, the EMS personnel conducts a follow-up search. These data are initially handwritten. Then, in cooperation with the physicians in charge of patients with OHCA, the EMS personnel summarize the data of each OHCA case in standardized Utstein style.[20,21] The data at the 807 fire stations with dispatch centers in the 47 prefectures are then electronically integrated into the national registry system on the FDMA database server.

In most cases, an ambulance crew consists of 3 emergency personnel, including at least 1 emergency lifesaving technician. Emergency lifesaving technicians have undergone extensive training in the provision of emergency care until arrival at the hospital. These technicians are permitted to insert an intravenous line and an adjunct airway and to use semiautomated external defibrillators.[16] Specially trained emergency lifesaving technicians have been permitted to insert an intravenous line since July 2004, and certified emergency lifesaving technicians have been permitted to administer intravenous epinephrine since April 2006.[16]

Epinephrine use is implemented according to the FDMA resuscitation guidelines for emergency lifesaving technicians.[22] Specifically, during the resuscitation of patients with OHCA, after checking the initial rhythm and using defibrillation when appropriate, along with CPR, emergency lifesaving technicians perform tracheal intubation and/or insert an intravenous line with approval from an online emergency physician. Then, after verifying the absence of impulse in the carotid artery, the emergency lifesaving technicians administer epinephrine with the approval of the emergency physician.[22]

Study Design and Patients

This was a prospective observational study using national registry data. The study was approved by the ethics committee at Kyushu University Graduate School of Medicine. The requirement for written informed consent was waived.

Patients were aged 18 years or older, had an OHCA before arrival of EMS personnel, were treated by EMS personnel, and were then transported to medical institutions between January 1, 2005, and December 31, 2008, in Japan.

Variables

The collected data included information on OHCA patients, CPR initiated by bystander, life support by EMS personnel, and patient outcome. When patients survived cardiac arrest, they were followed up for as long as 1 month after the event, and information on survival and neurological and physical status 1 month after the event was collected. Neurological outcomes 1 month after successful resuscitation were evaluated using the Glasgow-Pittsburgh Cerebral Performance Category (CPC) scale, which has 5 categories: (1) good cerebral performance; (2) moderate cerebral disability; (3) severe cerebral disability; (4) coma or vegetative state; and (5) death; and using the Overall Performance Category (OPC) scale, also with 5 categories: (1): no or mild neurological disability; (2) moderate neurological disability; (3) severe neurological disability; (4) coma or vegetative state; and (5) death.[20,21,23] At 1 month after the event, the EMS person in charge of the patient with OHCA contacted the physician in charge of that patient at the medical facility and collected CPC and OPC data by chart review and an in-person interview. These data were entered into the national database.

The etiology of cardiac arrest (ie, cardiac or noncardiac) was determined clinically by the physician in charge with the aid of the EMS personnel. Regarding first documented rhythm, because an automated external defibrillator analyzes a patient's rhythm automatically and delivers a shock only when it detects ventricular fibrillation

(VF), the patient's first recorded rhythm was regarded as VF when laypersons delivered shocks with the use of a public-access automated external defibrillator. Additionally, the category of VF included ventricular tachycardia. Only epinephrine was used during prehospital CPR for patients with OHCA, following the FDMA resuscitation guideline for emergency lifesaving technicians.[22]

End Points

The 4 end points were ROSC before hospital arrival, survival at 1 month after cardiac arrest, 1-month survival with CPC category 1 or 2, and 1-month survival with OPC category 1 or 2.[20,21,23]

Statistical Analysis

Data that met the criteria concerning patient age, time course, and epinephrine use were analyzed. Using data for all cases, 3 unconditional logistic regression models were fit using one of the end points as a dependent variable. With an actual 1-month survival rate of 5.4% in the intravenous epinephrine group and 4.7% in the no-epinephrine group, 15 030 samples for each group provided a power level of 92.0% with a type I error of .05.[24]

Epinephrine use before hospital arrival was not randomly assigned in the patient population; therefore, we developed a propensity score for epinephrine use before hospital arrival and controlled for potential confounding and selection bias.[25] By multivariable logistic regression analysis not taking patient outcome into account, the propensity score for prehospital epinephrine use was determined. Specifically, a full nonparsimonious logistic regression model was fit with prehospital epinephrine use as a dependent variable, which included every variable in TABLE 1 (ie, 20 variables, including 3 dummy variables for cases per year) plus dummy variables for the 47 prefectures in Japan (ie, 46 variables) as independent variables. A propensity score for epinephrine use before hospital arrival was calculated from the logistic regression equation for each patient. This propensity score represented the probability that a patient with OHCA would be given epinephrine before hospital arrival. Using the SAS macro program by Parsons et al,[26] based on propensity score, patients with OHCA who were given epinephrine were matched with unique control patients who were not given epinephrine before hospital arrival. Using data for the propensity-matched patients, 4 types of conditional logistic regression models were fit with one of the end point variables as a dependent variable. With an actual 1-month survival rate of 5.1% in the intravenous epinephrine group and 7.0% in the no-epinephrine group, 13 401 samples for each group provided a power level of 94.1% with a type I error of .01.[24]

The 2-sided significance level for all tests was $P < .05$. All analyses were performed using SAS software, version 8.2 (SAS Institute Inc).

RESULTS

Patient Characteristics

Between January 1, 2005, and December 31, 2008, 431 968 OHCAs occurred. Of these cases, 417 188 met the inclusion criteria (FIGURE 1 and Table 1). The mean age of all patients was 72 (SD, 16) years, and no significant difference existed between the mean ages of the 2 groups ($P = .86$). There was a significant difference between those who were given epinephrine and those who were not before hospital arrival. The number of OHCA cases who received epinephrine increased over the study period from 190 in 2005 to 8124 in

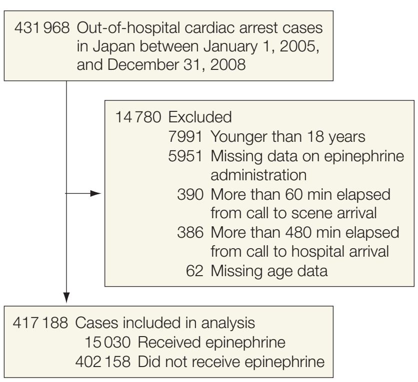
Table 1. Baseline Characteristics of Patients With Out-of-Hospital Cardiac Arrest According to Epinephrine Administration, 2005-2008, Japan (N = 417 188)[a]

Characteristics	Epinephrine (n = 15 030)	No Epinephrine (n = 402 158)
Cases per year		
2005	190 (1.3)	100 514 (25.0)
2006	1764 (11.8)	102 250 (25.4)
2007	4947 (32.9)	96 310 (24.0)
2008	8124 (54.1)	103 017 (25.6)
Age, mean (SD), y	72.38 (15.5)	72.41 (16.4)
Male	9546 (63.5)	236 366 (58.8)
Bystander eyewitness	8938 (59.5)	159 304 (39.6)
Family member bystander eyewitness	5250 (34.9)	82 812 (20.6)
Origin of cardiac arrest		
Cardiac	9088 (60.5)	220 597 (54.9)
Noncardiac	5942 (39.5)	181 561 (45.2)
Cardiopulmonary resuscitation initiated by bystander		
Chest compression	6627 (45.1)	143 975 (36.0)
Rescue breathing	2458 (16.9)	60 691 (15.2)
Use of public-access automated external defibrillator	113 (0.8)	1449 (0.4)
Life support by emergency medical service personnel		
Emergency lifesaving technician present in ambulance	14 929 (99.4)	374 818 (93.2)
Physician present in ambulance	1079 (7.2)	9176 (2.3)
Advanced life support performed by physician	2558 (17.0)	61 302 (15.3)
Time from call to arrival at scene, mean (SD), min	7.54 (4.0)	7.18 (3.8)
Time from call to arrival at hospital, mean (SD), min	38.15 (13.5)	31.68 (13.3)
First documented rhythm		
Ventricular fibrillation/pulseless ventricular tachycardia	2054 (13.7)	29 103 (7.2)
Pulseless electrical activity/asystole	12 975 (86.3)	373 049 (92.8)
Defibrillation by emergency medical service personnel	3117 (20.9)	42 348 (10.5)
Use of advanced life support devices (eg, laryngeal mask/adjunct airway/tracheal tubes)	11 496 (76.5)	172 673 (42.9)
Insertion of intravenous line	14 420 (96.0)	64 246 (16.0)

[a] Data are expressed as No. (%) unless otherwise indicated. All baseline characteristic comparisons between the 2 groups were statistically significant at $P < .001$ except age ($P = .86$). Values were missing for 5 to 10 998 individuals across all variables.

2008, whereas the number of OHCA cases who did not receive epinephrine remained at the same level ($P<.001$) (Table 1). Additionally, we checked the effects of prehospital epinephrine use by VF/non-VF status. Among patients with VF, 432 patients (21.1%) in the epinephrine group and 6478 (22.3%) in the no-epinephrine group had ROSC before hospital arrival ($\chi^2=1.59$; $P=.21$). The numbers of patients with 1-month survival, CPC category 1 or 2, and OPC category 1 or 2, respectively, were 316 (15.4%), 126 (6.1%), and 127 (6.2%) in the epinephrine group and 6209 (21.3%), 3927 (13.5%), and 3920 (13.5%) in the no-epinephrine group ($\chi^2=41.02$, 91.82, and 90.13, respectively; all $P<.001$). Among patients without VF, 2354 (18.2%) in the epinephrine group and 16 564 (4.4%) in the no-epinephrine group had ROSC before hospital arrival ($\chi^2=5052.66$; $P<.001$). The numbers of patients without VF with 1-month survival, CPC category 1 or 2, and OPC category 1 or 2, respectively, were 489 (3.8%), 79 (0.6%), and 84 (0.7%) in the epinephrine group and 12 696 (3.4%), 4975 (1.3%), and 4910 (1.3%), in the no-epinephrine group ($\chi^2=5.08$; $P=.02$; $\chi^2=50.96$; $P<.001$; and $\chi^2=43.91$; $P<.001$, respectively) (eAppendix and eTable 1; available at http://www.jama.com).

Figure 1. Study Participant Selection



Epinephrine Use Before Hospital Arrival and Patient Survival

TABLE 2 and FIGURE 2 summarize survival outcomes based on epinephrine use among all patients. With respect to the 4 end-point variables, in the initial unadjusted model, there was a significant difference between those who were administered epinephrine and those who were not before hospital arrival (all $P<.001$) (Figure 2). A positive association was detected between prehospital epinephrine use and the outcome measure in patients with ROSC before hospital arrival in the 3 models. A significant positive association in the crude model (OR, 1.15; 95% CI, 1.07-1.23; $P<.001$) and a significant negative association in the adjusted model using selected variables (OR, 0.43; 95% CI, 0.39-0.46; $P<.001$) or all variables (OR, 0.46; 95% CI, 0.42-0.51; $P<.001$) were observed for 1-month survival with respect to an association between prehospital epinephrine use and the outcome measures. A significant negative association was detected between prehospital epinephrine use and CPC and OPC in the 3 models.

Table 2. Unconditional Logistic Regression Analyses of Outcomes in Epinephrine Group (vs No-Epinephrine Group) Among All Patients With Out-of-Hospital Cardiac Arrest

	Odds Ratio (95% CI)[a]			
Analysis	ROSC	1-Month Survival	CPC 1 or 2	OPC 1 or 2
Unadjusted (n = 417 155)	3.75 (3.59-3.91)	1.15 (1.07-1.23)	0.61 (0.53-0.70)	0.63 (0.55-0.73)
Adjusted for selected variables (n = 412 078)[b]	3.06 (2.93-3.21)	0.43 (0.39-0.46)	0.21 (0.18-0.24)	0.22 (0.19-0.25)
Adjusted for all covariates (n = 391 046)[c]	2.36 (2.22-2.50)	0.46 (0.42-0.51)	0.31 (0.26-0.36)	0.32 (0.27-0.38)

Abbreviations: CPC, Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation.
[a] For all odds ratios, $P<.001$.
[b] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.
[c] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

Prehospital Epinephrine Use and Survival in Propensity-Matched Patients

To calculate the propensity score, a full nonparsimonious logistic regression model was fit. This model yielded a C statistic of 0.96, which indicated a very strong ability to differentiate between those who used epinephrine before hospital arrival and those who did not. The propensity score ranged from 0.007 to 1.000, which indicated that the probability of epinephrine use before hospital arrival by a patient with OHCA would be between 0 and 1. In the study, 13 401 patients who were given epinephrine were matched with 13 401 patients who were not given epinephrine (TABLE 3). With respect to every predictor variable, no significant difference was detected between patients who were given epinephrine and patients who were not given epinephrine, which showed that these propensity-matched patients were well matched.

TABLE 4 and FIGURE 3 summarize survival outcomes based on epinephrine use among propensity-matched patients. With respect to the 4 end-point variables, in the initial unadjusted model, there was a significant difference between those who were administered epinephrine and those who were not before hospital arrival (all $P<.001$) (Figure 3). For ROSC, a positive association was detected between prehospital epinephrine use and the outcome measures in the 4 models. The positive association became increasingly more evident after adjustment for selected variables and after adjustment for all variables. Inversely, for 1-month survival and survival with minimal neurological impairment (ie, CPC category 1 or 2, OPC category 1 or 2), a significant negative association was observed between epinephrine use before hospital arrival and the outcome measures. These negative associations became increasingly more evident after adjustment for selected variables and after adjustment for all variables (eAppendix and eTable 2).

COMMENT

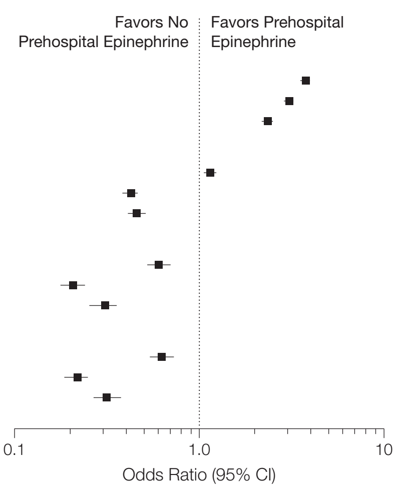
Our findings, based on propensity-matched analyses using 4 different models, clearly show that intravenous epinephrine administration before hospital arrival is independently associated with reduced 1-month survival (Table 4). As for the effectiveness of prehospital epinephrine use in cardiopulmonary resuscitation, 1 large observational study supported effectiveness[12] while others did not.[13,27] Although recent randomized controlled trials showed that epinephrine use before hospital arrival was not associated with long-term survival, there were several methodological problems with these trials.[15,25] Previous findings are inconsistent, so the effectiveness of epinephrine in CPR has not been established. Our findings are derived from national registry data, and sample size for propensity analysis posed no problem. Based on a valid propensity analysis controlling for the effects of selection bias and confounding factors, we observed that intravenous epinephrine use before hospital arrival was a significant predictor of poor long-term outcome. We believe that the present findings are important both theoretically and practically. As noted previously, epinephrine is reportedly associated with increased myocardial dysfunction, disturbed cerebral microcirculation after cardiac arrest, and ventricular arrhythmias during the period after resuscitation.[4-7] The adverse long-term effect might be due to these pharmacological effects of epinephrine.

Epinephrine use before hospital arrival was consistently a significant and positive predictor of ROSC before hospital arrival in the 4 different models, and the ORs ranged from 1.91 to 2.51 (all $P < .001$) (Table 4). Our results are based on propensity-matched data and are consistent with previous findings.[14,15,27] Several results have been reported that can explain the biological or pharmacological aspects of intravenous epinephrine administration leading to improved short-term outcomes, including animal studies showing short-term effects of epinephrine[8,9] and evidence to indicate increased cerebral and coronary perfusion by redirected peripheral blood flow.[10,11] Thus, the short-term effect might be attributable to these pharmacological effects of epinephrine.

A major confounder in this analysis is that patients who did not receive epinephrine in the prehospital setting may have received epinephrine after hospital arrival. Therefore, the differences may reflect changes in the type of care after hospital arrival and may not be attributable to the drug itself. Thus, we conducted a sensitivity analysis. In matched subsets of patients who had ROSC prior to hospital arrival, there would be no indication to receive epinephrine in the hospital, so the pure effect of the drug could be determined. Thus, we compared long-term survival between these patients. The numbers of 1-month survivors in the epinephrine and no-

Figure 2. Results of Unconditional Logistic Regression Analyses Comparing Prehospital Epinephrine Use vs No Prehospital Epinephrine Use in Patients With Out-of-Hospital Cardiac Arrest

Model	Total No. of Cases	No. (%) With Outcome: Epinephrine	No. (%) With Outcome: No Epinephrine	Odds Ratio (95% CI)
ROSC				
Unadjusted	417 155	2786 (18.5)	23 042 (5.7)	3.75 (3.59-3.91)
Adjusted for selected variables[a]	412 078	2692 (18.6)	22 804 (5.7)	3.06 (2.93-3.21)
Adjusted for all covariates[b]	391 046	2556 (18.6)	21 629 (5.7)	2.36 (2.22-2.50)
1-Month survival				
Unadjusted	417 186	805 (5.4)	18 906 (4.7)	1.15 (1.07-1.23)
Adjusted for selected variables[a]	412 078	772 (5.3)	18 637 (4.7)	0.43 (0.39-0.46)
Adjusted for all covariates[b]	391 046	733 (5.3)	17 677 (4.7)	0.46 (0.42-0.51)
CPC 1 or 2				
Unadjusted	417 187	205 (1.4)	8903 (2.2)	0.61 (0.53-0.70)
Adjusted for selected variables[a]	412 078	197 (1.4)	8781 (2.2)	0.21 (0.18-0.24)
Adjusted for all covariates[b]	391 046	187 (1.4)	8329 (2.2)	0.31 (0.26-0.36)
OPC 1 or 2				
Unadjusted	417 187	211 (1.4)	8831 (2.2)	0.63 (0.55-0.73)
Adjusted for selected variables[a]	412 078	202 (1.4)	8710 (2.2)	0.22 (0.19-0.25)
Adjusted for all covariates[b]	391 046	192 (1.4)	37 732 (2.2)	0.32 (0.27-0.38)



CPC indicates Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation. Different sample sizes in the 3 models result from increasing numbers of cases with missing data as the number of independent variables increased.
[a] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.
[b] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

epinephrine groups were 438 (18.0%) and 661 (46.8%), respectively ($P<.001$). The numbers of patients with CPC category 1 or 2 in the epinephrine and no-epinephrine groups were 113 (4.7%) and 354 (25.0%), respectively ($P<.001$). The numbers of patients with OPC category 1 or 2 in the epinephrine and no-epinephrine groups were 115 (4.7%) and 351 (24.8%), respectively ($P<.001$). Additionally, we compared time from call to scene arrival or hospital arrival between the epinephrine and no-epinephrine groups. The mean times from call to scene arrival in the epinephrine and no-epinephrine groups were 7.37 (SD, 3.73) minutes and 6.72 (SD, 3.05) minutes, respectively ($P<.001$). The mean times from call to hospital arrival in the epinephrine and no-epinephrine groups were 40.01 (SD, 14.19) minutes and 40.43 (SD, 21.84) minutes, respectively ($P=.53$). Because the no-epinephrine group was not transported more quickly to the emergency department, improved long-term outcomes might not reflect more rapid delivery to definitive care. In summary, the sensitivity analysis showed that the use of epinephrine might be related to decreased 1-month survival.

There are several notable findings of this study. First, the number of patients with OHCA who were given epinephrine increased dramatically from 190 in 2005 to 8123 in 2008. Since April 2006, certified emergency lifesaving technicians have been permitted to administer intravenous epinephrine.[16] The large increase in the number of patients who were administered epinephrine might be due to this change in the Japanese guidelines. In 2005, epinephrine was administered in 190 cases. Physicians were in ambulances in 2.5% of the 417 168 cases occurring during the study period. Thus, physicians likely administered intravenous epinephrine to the 190 patients in 2005. Second, in the total sample, only 1.4% of patients in the epinephrine group had good neurological outcomes, despite a 5.4% survival rate (Table 1). Thus, only about 25% of survivors had good neurological outcomes. The same basic pattern was found among propensity-matched patients (Table 3). This rate is substantially lower than those reported in most OHCA studies, in which the majority of long-term survivors had good outcomes.[12,13,15,25,27] This finding implies that epinephrine administration might save the heart but not the

Table 3. Baseline Characteristics of Patients With Out-of-Hospital Cardiac Arrest According to Epinephrine Administration in Propensity-Matched Patients[a]

Characteristics	Epinephrine (n = 13 401)	No Epinephrine (n = 13 401)
Cases per year		
2005	183 (1.4)	174 (1.3)
2006	1704 (12.7)	1664 (12.4)
2007	4124 (30.8)	4183 (31.2)
2008	7390 (55.2)	7380 (55.1)
Age, mean (SD), y	72.43 (15.5)	72.40 (15.7)
Male	8480 (63.3)	8427 (62.9)
Bystander eyewitness	7729 (57.7)	7866 (58.7)
Family member bystander eyewitness	4519 (33.7)	4533 (33.8)
Origin of cardiac arrest		
Cardiac	8039 (60.0)	7984 (59.6)
Noncardiac	5362 (40.0)	5417 (40.4)
Cardiopulmonary resuscitation initiated by bystander		
Chest compression	5854 (43.7)	5918 (44.2)
Rescue breathing	2205 (16.5)	2243 (16.7)
Use of public-access automated external defibrillator	102 (0.8)	99 (0.7)
Life support by emergency medical service personnel		
Emergency lifesaving technician present in ambulance	13 316 (99.4)	13 308 (99.3)
Physician present in ambulance	811 (6.1)	873 (6.5)
Advanced life support performed by physician	2122 (15.8)	2233 (16.7)
Time from call to arrival at scene, mean (SD), min	7.50 (4.0)	7.47 (4.0)
Time from call to arrival at hospital, mean (SD), min	37.92 (13.2)	37.66 (18.3)
First documented rhythm		
Ventricular fibrillation/pulseless ventricular tachycardia	1758 (13.1)	1781 (13.3)
Pulseless electrical activity/asystole	11 643 (86.9)	11 620 (86.7)
Defibrillation by emergency medical service personnel	2610 (19.5)	2602 (19.4)
Use of advanced life support devices (eg, laryngeal mask/adjunct airway/tracheal tubes)	10 294 (76.8)	10 290 (76.8)
Insertion of intravenous line	12 868 (96.0)	12 865 (96.0)

[a] Data are expressed as No. (%) unless otherwise indicated. All baseline characteristic comparisons between the 2 groups were not statistically significant.

Table 4. Conditional Logistic Regression Analyses of Outcome in Epinephrine Group (vs No-Epinephrine Group) Among Propensity-Matched Patients With Out-of-Hospital Cardiac Arrest (n = 26 802)

	Odds Ratio (95% CI)[a]			
Analysis	ROSC	1-Month Survival	CPC 1 or 2	OPC 1 or 2
Unadjusted	1.91 (1.78-2.05)	0.71 (0.64-0.79)	0.41 (0.34-0.49)	0.43 (0.36-0.51)
Adjusted for propensity	2.01 (1.83-2.21)	0.71 (0.62-0.81)	0.41 (0.33-0.52)	0.43 (0.34-0.54)
Adjusted for propensity and selected variables[b]	2.24 (2.03-2.48)	0.60 (0.49-0.74)	0.40 (0.26-0.63)	0.43 (0.28-0.66)
Adjusted for propensity and all covariates[c]	2.51 (2.24-2.80)	0.54 (0.43-0.68)	0.21 (0.10-0.44)	0.23 (0.11-0.45)

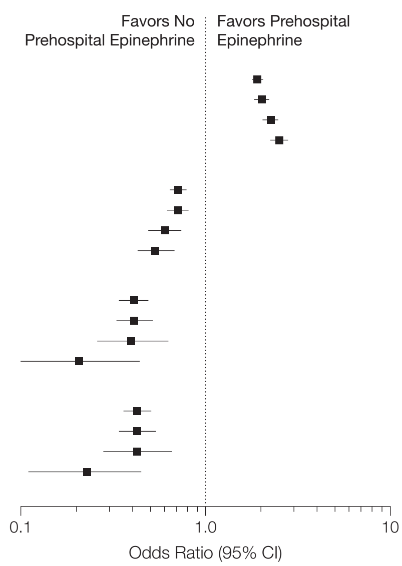
Abbreviations: CPC, Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation.
[a] For all odds ratios, $P<.001$.
[b] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.
[c] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

brain, which is worth further study. Third, we also conducted an analysis of the association between prehospital epinephrine use and outcomes in the total sample (Table 2). Analyses of CPC and OPC both yielded ORs less than 1 for the association between prehospital epinephrine use and long-term neurological outcome, which was consistent with the results obtained for propensity-matched patients (Table 4). A crude analysis revealed a significant positive association between prehospital intravenous epinephrine administration and 1-month survival (OR, 1.15; $P<.001$). However, after adjusting for the effects of the selected variables, a significant negative association between prehospital epinephrine use and 1-month survival emerged (OR, 0.43; $P<.001$); this association remained significant after adjusting for all variables in the third model (OR, 0.46; $P<.001$). Generally, an observational study cannot be free from selection bias and confounding factors.[25] Concomitant with this theoretical expectation, inconsistent associations between epinephrine administration before hospital arrival and the 1-month survival rate were observed.

Several limitations and caveats to our study must be acknowledged. First, the major limitation was that epinephrine use before hospital arrival was not assigned by random allocation. We performed propensity analysis and made a rigorous adjustment for selection bias and confounding factors, which would be expected with a standard multivariable analysis.[25] Nevertheless, we must acknowledge that observational studies can only partially control and adjust for factors actually measured, whereas randomized allocation can control both known and unknown confounding factors and avoid the introduction of bias. Second, data on in-hospital CPR after arrival were not included in the analysis. Long-term survival cannot be achieved without first restoring circulation. A positive association was observed between epinephrine use before hospital arrival and short-term survival, whereas a negative association was detected between epinephrine use before hospital arrival and long-term survival. It is possible that these findings might have been due to a difference in in-hospital resuscitation modes, such as induced hypothermia[28] and mechanical chest compression devices,[29] between those who were administered epinephrine and those were not. Specifically, hypothermia is not a routine treatment for in-hospital CPR patients with OHCA in Japan. Additionally, no standard regimen of care after hospital arrival has been established. Thus, the use of induced hypothermia, cardiac catheterization, or epinephrine or other pressors (eg, vasopressin) may differ among hospitals. In summary, although the quality of in-hospital resuscitation might influence 1-month survival, we could not control for the effects of such factors. Third, some variables were problematic. The etiology of OHCA was determined clinically by the physician in charge with the aid of EMS personnel. However, we must recognize that

Figure 3. Results of Conditional Logistic Regression Analyses Comparing Prehospital Epinephrine Use vs No Prehospital Epinephrine Use in Propensity-Matched Patients With Out-of-Hospital Cardiac Arrest

Model	Total No. of Cases	No. (%) With Outcome: Epinephrine	No. (%) With Outcome: No Epinephrine	Odds Ratio (95% CI)
ROSC	26 802	2446 (18.3)	1400 (10.5)	
Unadjusted				1.91 (1.78-2.05)
Adjusted for propensity				2.01 (1.83-2.21)
Adjusted for propensity and selected variables[a]				2.24 (2.03-2.48)
Adjusted for all covariates[b]				2.51 (2.24-2.80)
1-Month survival	26 802	687 (5.1)	944 (7.0)	
Unadjusted				0.71 (0.64-0.79)
Adjusted for propensity				0.71 (0.62-0.81)
Adjusted for propensity and selected variables[a]				0.60 (0.49-0.74)
Adjusted for all covariates[b]				0.54 (0.43-0.68)
CPC 1 or 2	26 802	173 (1.3)	413 (3.1)	
Unadjusted				0.41 (0.34-0.49)
Adjusted for propensity				0.41 (0.33-0.52)
Adjusted for propensity and selected variables[a]				0.40 (0.26-0.63)
Adjusted for all covariates[b]				0.21 (0.10-0.44)
OPC 1 or 2	26 802	178 (1.3)	410 (3.1)	
Unadjusted				0.43 (0.36-0.51)
Adjusted for propensity				0.43 (0.34-0.54)
Adjusted for propensity and selected variables[a]				0.43 (0.28-0.66)
Adjusted for all covariates[b]				0.23 (0.11-0.45)



CPC indicates Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation.
[a] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.
[b] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

the determination of a noncardiac etiology is highly atypical and problematic except among arrests due to trauma, drowning, strangulation, or drug overdose.[30] Epinephrine dosage has been reported to influence the outcome of patients with OHCA.[31] According to our interviews with emergency medicine physicians, a single dose of epinephrine was administered in the majority of cases. However, because of lack of data, we could not consider the number of epinephrine doses used in the cases included this study.

In summary, despite the limitations to the study, the associations between epinephrine use before hospital arrival and short- and long-term outcomes were strong and consistent. Specifically, our data show that intravenous epinephrine use before hospital arrival was associated with decreased 1-month survival on the basis of propensity-matched national data. Epinephrine use before hospital arrival was a positive predictor of short-term survival, which is in line with previous findings. Our findings need to be verified by studies that include in-hospital resuscitation data.

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Study concept and design: Hagihara, Hasegawa.
Acquisition of data: Hagihara, Hasegawa.
Analysis and interpretation of data: Hagihara, Hasegawa, Abe, Nagata, Wakata, Miyazaki.
Drafting of the manuscript: Hagihara, Wakata.
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Statistical analysis: Hagihara, Abe.
Administrative, technical, or material support: Hagihara, Hasegawa, Abe, Nagata, Wakata, Miyazaki.
Study supervision: Hagihara.

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Online-Only Material: eTables 1 and 2 and the eAppendix are available at http://www.jama.com.

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