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Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: An observational cohort study

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Abstract

Introduction: Few clinical trials have provided evidence that epinephrine administration after out-of-hospital cardiac arrest (OHCA) improves long-term survival. Here we determined whether prehospital epinephrine administration would improve 1-month survival in OHCA patients.

Methods: We analyzed the data of 209,577 OHCA patients; the data were prospectively collected in a nationwide Utstein-style Japanese database between 2009 and 2010. Patients were divided into the initial shockable rhythm (n=15,492) and initial non-shockable rhythm (n=194,085) cohorts. The endpoints were prehospital return of spontaneous circulation (ROSC), 1-month survival, and 1-month favorable neurological outcomes (cerebral performance category scale, category 1 or 2) after OHCA. We defined epinephrine administration time as the time from the start of cardiopulmonary resuscitation (CPR) by emergency medical services personnel to the first epinephrine administration.

Results: In the initial shockable rhythm cohort, the ratios of prehospital ROSC, 1-month survival, and 1-month favorable neurological outcomes in the non-epinephrine group were significantly higher than those in the epinephrine group (27.7% vs. 22.8%, 27.0% vs. 15.4%, and 18.6% vs. 7.0%, respectively; all $p<0.001$). However, in the initial non-shockable rhythm cohort, the ratios of prehospital ROSC and 1-month survival in the epinephrine group were significantly higher than those in the non-epinephrine group (18.7% vs. 3.0% and 3.9% vs. 2.2%, respectively; all $p<0.001$) and there was no significant difference between the epinephrine and non-epinephrine groups for 1-month favorable neurological outcomes ($p=0.62$). Prehospital epinephrine administration for OHCA patients with initial non-shockable rhythms was independently associated with prehospital ROSC (adjusted odds ratio [aOR], 8.83, 6.18, 4.32; 95% confidence interval [CI], 8.01-9.73, 5.82-6.56, 3.98-4.69; for epinephrine

administration times ≤9 min, 10-19 min, and ≥20 min, respectively), with improved 1-month survival when epinephrine administration time was <20 min (aOR, 1.78, 1.29; 95% CI, 1.50-2.10, 1.17-1.43; for epinephrine administration times ≤9 min and 10-19 min, respectively), and with deteriorated 1-month favorable neurological outcomes (aOR, 0.63, 0.49; 95% CI, 0.48-0.80, 0.32-0.71; for epinephrine administration times 10-19 min and ≥20 min, respectively).

Conclusions: Prehospital epinephrine administration for OHCA patients with initial non-shockable rhythms was independently associated with achievement of prehospital ROSC and had association with improved 1-month survival when epinephrine administration time was <20 min.

Key Words: cardiac arrest; cardiopulmonary resuscitation; epinephrine; non-shockable rhythm; pulseless electrical activity; asystole.

Introduction

Out-of-hospital cardiac arrest (OHCA) is an increasing public health concern in industrial countries with aging populations [1-4]. Survival after OHCA has not significantly improved in almost 3 decades, despite enormous research spending and the development of novel drugs and devices [5]. In Japan, more than 100,000 OHCA cases occur every year [1, 2, 6, 7] and nationwide improvements in favorable neurological outcomes following cardiac arrest have been observed after connecting the links in the "chain of survival" [1, 8]. Epinephrine has been a cornerstone of cardiac resuscitation therapy and advanced cardiac life support since the 1960s [9]. Epinephrine increases aortic blood pressure and coronary perfusion pressure during chest compression in animals [10, 11]. In humans, high-dose epinephrine has been shown to raise the coronary perfusion pressure and may improve rates of return of spontaneous circulation (ROSC) [12]. The most recent advanced life support guidelines for the treatment of cardiac arrest due to ventricular fibrillation (VF) recommend the administration of either epinephrine or vasopressin as the first drug after defibrillation [13]. And also epinephrine is the recommended first-line drug for the resuscitation of patients with both asystole and pulseless electrical activity (PEA) [13]. However, there is little evidence from clinical trials that epinephrine administration after OHCA improves long-term survival [6, 14, 15]. Increased myocardial dysfunction [16, 17] and disturbed cerebral microcirculation [18] after epinephrine administration may contribute importantly to the poor long-term outcomes.

A recent randomized controlled trial (RCT) [14] showed that patients with an initial non-shockable rhythm had higher ratios of short-term survival when intravenous therapy was administered, while no differences in outcomes were found for patients with a shockable rhythm. Moreover, as some patients do recover after administration of epinephrine, there would be subsets of patients for whom epinephrine administration is

in fact beneficial [9]. Therefore, the first objective of the present study was to examine whether initial cardiac rhythm would be considered a key factor for predicting survival and favorable neurological outcomes at 1 month. The second objective was to determine whether prehospital epinephrine administration would improve 1-month survival in patients who had experienced OHCA with initial non-shockable rhythms.

Materials and methods

Study design and data source

The present investigation was a nationwide population-based observational study of all adult patients (age, ≥18 years) for whom resuscitation had been attempted after OHCA in Japan from January 1, 2009, to December 31, 2010. Cardiac arrest was defined as the cessation of cardiac mechanical activities, as confirmed by the absence of signs of circulation [1]. The cause of arrest was presumed to be cardiac unless evidence suggested external causes (trauma, hanging, drowning, drug overdose, and asphyxia), respiratory diseases, cerebrovascular diseases, malignant tumors, or any other non-cardiac cause. Attribution of non-cardiac or cardiac cause was made by the physicians in charge in collaboration with the emergency medical services (EMS) personnel. This study was approved by the Ethical Committee of Kanazawa University. The requirement for written informed consent was waived.

Emergency medical services system in Japan

Japan has approximately 127 million residents in an area of 378,000 km^2, approximately two-thirds of which is uninhabited mountainous terrain [1, 19]. Details of the Japanese EMS system have been described previously [1, 2, 6, 7, 19, 20, 21]. Briefly, municipal governments provide EMS through about 800 fire stations with dispatch centers. The Fire and Disaster Management Agency (FDMA) of Japan supervises the

nationwide EMS system [1, 6, 7, 19, 20], while each local EMS system is operated by the local fire station. Generally, an ambulance crew includes 3 EMS staff members, including at least 1 emergency life-saving technician (ELST) [1]. ELSTs are allowed to use several resuscitation methods, including semi-automated external defibrillators, insertion of a supraglottic airway device (laryngeal mask airway, laryngeal tube, and esophageal-tracheal twin-lumen airway device), insertion of a peripheral intravenous line, and administration of Ringer lactate solution [1]. Since July 2004, only specially trained ELSTs are permitted to insert a tracheal tube, and since April 2006, they have been permitted to administer intravenous epinephrine in the field under online physician instruction [1, 2, 6, 7]. All EMS providers perform cardiopulmonary resuscitation (CPR) according to the Japanese CPR guidelines [21], based on the 2005 American Heart Association guidelines [4], since October 2006. As EMS personnel in Japan are legally prohibited from terminating resuscitation in the field, most OHCA patients undergo CPR by EMS providers and are transported to hospitals, except in cases where fatality is certain [1]. Epinephrine use is implemented according to the FDMA resuscitation guidelines for ELST [21, 22]. The guidelines allow ELSTs to attempt intravenous access only twice, and each attempt must take no longer than 90 sec. The allowable dosage of epinephrine is 1 mg per attempt, and repeated doses may be administered under physician instruction.

Data collection and quality control

The FDMA launched a prospective population-based observational study involving all OHCA patients who received EMS in Japan [1]. EMS personnel at each center recorded data for OHCA patients with the cooperation of the physician in charge, using an Utstein-style template [23]. All data were transferred and stored in the nationwide database developed by the FDMA for public use. We analyzed this database with the permission of the FDMA, who provided all the anonymous data to our research group.

The main items included in the dataset were as follows: sex, age, causes of arrest (presumed cardiac origin or not), bystander witness status, bystander CPR with or without automated external defibrillator use, initial identified cardiac rhythm, bystander category (i.e., if there was a bystander, whether the bystander was a layperson or EMS personnel), whether epinephrine was administered, whether advanced airway management techniques (including endotracheal tube, laryngeal mask airway, and esophageal-tracheal tube) were used, whether ROSC was attained before arrival at the hospital, time of the emergency call, time of vehicle arrival at the scene, time of ROSC, time of vehicle arrival at the hospital, time of epinephrine administration, 1-month survival, and neurological outcome at 1 month after cardiac arrest. The neurological outcome was defined using the Cerebral Performance Category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death [23]. CPC categorization was determined by the physician in charge. The call-to-response time was calculated as the time from the emergency call to the time of vehicle arrival at the scene. The call-to-hospital-arrival time was calculated as the time from the emergency call to the time of vehicle arrival at the hospital.

End points

The primary study end point was survival at 1 month. The secondary end points were ROSC before arrival at the hospital and survival at 1 month with favorable neurological outcome (defined as a CPC of 1 or 2) [23].

Statistical analysis

Kolmogorov-Smirnov Lilliefors tests were performed to evaluate the distributions of continuous variables, and we found that all continuous variables were not normally distributed (all $p < 0.01$). Therefore, the Wilcoxon and Kruskal–Wallis tests for

continuous variables and the chi-square test for categorical variables were performed to compare the characteristics or outcomes between the cohorts in each initial cardiac rhythm. Multivariate logistic regression analyses including 12 variables were performed to assess the factors contributing to 1-month survival and 1-month CPC 1–2 for all eligible patients. The 12 selected variables included year, age, gender, witnessed arrest, bystander CPR, arrest presumed cause, initial cardiac rhythm, prehospital shock delivery, advanced airway management, call-to-response time, call-to-hospital arrival time, and prehospital epinephrine administration for the model as an independent variable. These analyzing models yield concordance statistics of 0.81 for 1-month survival and 0.89 for 1-month CPC 1–2, respectively, which indicated good discrimination.

Moreover, multivariate logistic analysis including 11 variables was used to determine the impact of prehospital epinephrine administration for prehospital ROSC, 1-month survival, and 1-month CPC 1–2 in each initial cardiac rhythm. The 11 selected variables included year, age, gender, witnessed arrest, bystander CPR, arrest presumed cause, initial cardiac rhythm, prehospital shock delivery, advanced airway management, call-to-response time, and prehospital epinephrine administration for the model as an independent variable.

In these multivariate logistic regression analyses for outcomes, we classified the following 2 continuous variables into 4 categories, respectively: age ($\leq$ 39 years, 40–59 years, 60–79 years, $\geq$ 80 years) and call-to-response time ($\leq$ 4 min, 5–9 min, 10–14 min, $\geq$ 15 min). We defined epinephrine administration time as the time interval from the start of CPR by EMS personnel to the first epinephrine administration. In order to associate the epinephrine administration time with whether or not epinephrine was received, we classified prehospital epinephrine administration variables into 4 categories: No, Yes ($\leq$ 9 min), Yes (10–19 min), and Yes ($\geq$ 20 min), where the figures in parentheses are the epinephrine administration times.

Continuous variables have been expressed as means and standard deviations. Categorical variables have been expressed as percentages. As an estimate of effect size and variability, we report odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using the JMP statistical package version 10 (SAS Institute Inc., Cary, NC, USA). All tests were 2 tailed, and a value of p <0.05 was considered statistically significant.

Results

During the 2-year study period, details of 238,345 patients were documented in the database. We considered 209,577 (87.9%) patients eligible for enrolment into this study. Figure 1 depicts the inclusion/exclusion criteria for subjects in the present study. Overall prehospital ROSC, 1-month survival, and 1-month CPC 1–2 were 6.3% (n = 13,237), 4.0% (n = 8,434), and 1.8% (n =3,419), respectively. Of these arrests, 15,492 (7.4%) were of an initial shockable rhythm and 194,085 (92.6%) were of an initial non-shockable rhythm. The ratios of both short-term and long-term outcomes in the initial shockable rhythm cohort were significantly higher than those in the initial non-shockable rhythm cohort (26.7% vs. 4.7% for prehospital ROSC, 24.7% vs. 2.4% for 1-month survival, and 16.3% vs. 0.6% for 1-month CPC 1–2; all p < 0.001). Table 1 shows baseline characteristics of study patients and the results of multivariate logistic regression analyses for 12 prehospital factors in predicting 1-month outcomes after OHCA. Initial shockable rhythm was an independently contributing factor in both survival (adjusted OR, 4.59; 95 % CI, 4.13–5.10) and CPC 1–2 (adjusted OR, 5.46; 95 % CI, 4.67–6.42) at 1 month after OHCA with the highest adjusted OR among variables. Although prehospital epinephrine administration had no significant factors for 1-month survival, it was independently associated with deteriorated neurological outcomes at 1 month.

Table 2 shows baseline characteristics of study patients according to the initial cardiac rhythm and the presence of prehospital epinephrine administration. Among patients who received prehospital epinephrine, call-to-response time and epinephrine administration time in the initial shockable rhythm cohort were significantly shorter than those in the initial non-shockable rhythm cohort (all p <0.0001). Table 3 shows both short-term and long-term outcomes according to the initial cardiac rhythm and the presence of prehospital epinephrine administration. In the initial shockable rhythm cohort, the ratios of both short-term and long-term outcomes in the non-epinephrine group were significantly higher than those in the epinephrine group (27.7% vs. 22.8% for prehospital ROSC, 27.0% vs. 15.4% for 1-month survival, and 18.6% vs. 7.0% for 1-month CPC 1–2; all $p < 0.001$). However, in the initial non-shockable rhythm cohort, the ratios of prehospital ROSC and 1-month survival in the epinephrine group were significantly higher than those in the non-epinephrine group (18.7% vs. 3.0% and 3.9% vs. 2.2%, respectively; all $p < 0.001$). No significant difference between the epinephrine and non-epinephrine groups for 1-month CPC 1–2 was found in the initial non-shockable rhythm cohort (0.59% vs. 0.62%, $p = 0.605$).

The results of multivariate logistic analyses including 11 variables to determine the factors associated with prehospital ROSC, 1-month survival, and 1-month CPC 1–2 in the initial shockable rhythm cohort are shown in Table 4. Prehospital epinephrine administration, of which time was $\leq$ 9 min, was only positively associated with prehospital ROSC (adjusted OR, 1.45; 95% CI, 1.20–1.75). There was no significant difference in 1-month survival between no epinephrine and epinephrine administration with an administration time of $\leq$ 9 min (adjusted OR, 0.95; 95% CI, 0.77–1.16). However, a negative association with prehospital epinephrine administration was observed in 1-month survival where epinephrine administration time was $\geq$ 10 min (adjusted OR, 0.51, 0.33; 95% CI, 0.44–0.59, 0.25–0.42; for epinephrine administration times 10–19 min and $\geq$ 20 min, respectively). Moreover, prehospital epinephrine

administration was independently associated with deteriorated neurological outcomes at 1 month (adjusted OR, 0.71, 0.34, 0.21; 95% CI, 0.54–0.92, 0.28–0.42, 0.14–0.31; for epinephrine administration times ≤ 9 min, 10–19 min, and ≥ 20 min, respectively).

Table 5 shows the results of multivariate logistic analyses including 11 variables to determine the factors associated with the short-term and long-term outcomes in the initial non-shockable rhythm cohort. Prehospital epinephrine administration was independently associated with prehospital ROSC (adjusted OR, 8.83, 6.18, 4.32; 95% CI, 8.01–9.73, 5.82–6.56, 3.98–4.69; for epinephrine administration times ≤ 9 min, 10–19 min, and ≥ 20 min, respectively). Moreover, prehospital epinephrine administration was independently associated with 1-month survival when the first epinephrine administration was performed for < 20 min (adjusted OR, 1.78, 1.29; 95% CI, 1.50–2.10, 1.17–1.43; for epinephrine administration times ≤ 9 min and 10–19 min, respectively). There was no significant difference in 1-month CPC 1–2 between no epinephrine and epinephrine administration when the administration time was ≤ 9 min (adjusted OR, 0.95; 95% CI, 0.62–1.37). However, prehospital epinephrine administration was independently associated with deteriorated neurological outcomes at 1 month when epinephrine administration time was ≥ 10 min (adjusted OR, 0.63, 0.49; 95% CI, 0.48–0.80, 0.32–0.71; for epinephrine administration times 10–19 min and ≥ 20 min, respectively).

Discussion

The present analyses using a large population-based nationwide database of Japanese patients who had experienced OHCA show that initial shockable rhythm is associated with both 1-month survival and 1-month favorable neurological outcomes and is considered a crucial key variable for CPR. This finding is consistent with a previous meta-analysis study by Sasson et al. [5]. They conclusively affirm the critical

importance of shockable rhythm for outcomes along with bystander CPR and ROSC in the prehospital setting. On the basis of these results, we have further investigated the effectiveness of prehospital epinephrine administration for OHCA patients with each initial cardiac rhythm. In the initial shockable rhythm cohort, the ratios of both short-term and long-term outcomes in the non-epinephrine group were significantly higher than those in the epinephrine group. However, in the initial non-shockable rhythm cohort, the ratios of prehospital ROSC and 1-month survival in the epinephrine group were significantly higher than those in the non-epinephrine group and no significant difference between the epinephrine and non-epinephrine groups for 1-month CPC 1–2 was found.

Although there were no beneficial effects of prehospital epinephrine administration on 1-month outcomes in patients with initial shockable rhythms after OHCA, prehospital epinephrine administration for OHCA patients with non-shockable initial rhythms is independently associated with 1-month survival, when the epinephrine administration time was < 20 min. To our knowledge, this is the first study to show that prehospital epinephrine administration significantly improves 1-month survival after OHCA in patients with initial non-shockable rhythms associated with its administration time. Unlike previous observational studies [2, 3] underpowered to show this crucial association, our study is sufficiently large enough to identify the important beneficial effect of epinephrine on 1-month survival after OHCA with initial non-shockable rhythms. We have also demonstrated that prehospital epinephrine administration is independently associated with deterioration in neurological outcomes at 1 month after cardiac arrest with both initial shockable and non-shockable rhythms when the epinephrine administration time was $\geq$ 10 min.

Epinephrine hydrochloride produces beneficial effects in patients during cardiac arrest, primarily because of its α-adrenergic receptor-stimulating properties [13, 24]. The α-adrenergic effects of epinephrine can increase both coronary and cerebral

perfusion pressures during CPR [13]. The value and safety of the β-adrenergic effects of epinephrine are controversial because they may increase myocardial work and reduce subendocardial perfusion [13]. Laboratory data suggested that harmful epinephrine-induced reductions in microvascular blood flow during and after CPR may offset the beneficial epinephrine-induced increase in arterial blood pressure during CPR [16, 17, 18]. However, epinephrine is the recommended first-line drug for the resuscitation of patients with both shockable and non-shockable initial rhythms [13].

A recent RCT by Olasveengen et al. [14] showed higher ratios of short-term survival (any ROSC during resuscitation, hospital admission, or intensive care unit admission) in the drug administration (epinephrine, 79%; atropine, 46%; amiodarone, 17%) cohort than in the control cohort but failed to show improvements in long-term survival (hospital discharge and 1 year after cardiac arrest). In their subgroup analysis, non-shockable rhythm had 3-fold higher ratios for achievement of ROSC with intravenous treatment. Although there may be some confounding factors, the same tendency was found in our current study. The ROSC achievement ratio in our non-shockable rhythm cohort was 6-fold higher with prehospital epinephrine treatment (Table 3, $p < 0.001$). Multivariate logistic regression analysis in the non-shockable rhythm cohort clearly indicated the effectiveness of prehospital epinephrine for prehospital ROSC with a high adjusted OR (Table 5). However, unlike their report that showed no differences in outcomes between with and without intravenous treatment for patients with shockable rhythms, our study indicated that shockable rhythms had significant differences in outcomes for administration of epinephrine (Table 3, $p < 0.001$). Multivariate logistic regression analyses in our study have revealed that epinephrine administration for shockable rhythms worsened neurological outcomes at 1 month (Table 4). As epinephrine did not have a deteriorative effect on 1-month survival for shockable rhythms when epinephrine administration time was $\leq$ 9 min (Table 4), this harmful effect of epinephrine on neurological outcomes for initial shockable rhythms

may be related to the administration time of epinephrine and indication bias for epinephrine administration after the shock delivery. Others have found detrimental effects of epinephrine in patients with VF [15, 25]. Moreover, the majority of survivors are VF patients who respond to the first 1–2 defibrillations and hence have no need for subsequent drug administration during resuscitation; these patients show a higher survival rate than those who require drug intervention [26]. Therefore, comparisons of the effects of epinephrine on long-term survival after OHCA in patients with VF are likely to be biased, and it is difficult to determine whether epinephrine provides long-term benefit for such patients.

Another RCT by Jacobs et al. [15] demonstrated that epinephrine resulted in a statistically significant increase in ROSC but not in the primary outcome of survival to hospital discharge. Their study also suggested that short-term survival following epinephrine administration after OHCA differed by cardiac rhythm. The treatment effect of epinephrine on prehospital ROSC was more marked in patients with non-shockable rhythms than it was in patients with shockable rhythms. The results for achievement of ROSC were consistent with our current results. Moreover, we have demonstrated that prehospital epinephrine administration for OHCA patients with initial non-shockable rhythms was independently associated with improved 1-month survival when epinephrine administration time < 20 min (Table 5; adjusted OR, 1.78, 1.29; 95% CI, 1.50–2.10, 1.17–1.43; for epinephrine administration times $\leq$ 9 min and 10–19 min, respectively).

Hagihara et al. [6] conducted an observational study with a nationwide database in Japan. Using a propensity score analysis, they indicated that prehospital epinephrine use may be associated with poorer 1-month survival and worse neurologic outcomes at 1 month after cardiac arrest. Their results are inconsistent with our present results. Unlike our current study, they did not include the epinephrine administration time variable as an important key confounding factor. Moreover, although certified ELSTs in Japan have

been permitted to administer intravenous epinephrine in the field under online physician instruction since April 2006, they selected the data from 2005 to 2008. This database selection may have bias for the indication of epinephrine. We have selected the data from 2009 to 2010 for our analysis under the Japanese CPR guidelines [21] based on the 2005 American Heart Association guidelines [4].

Another observational study in Osaka showed that prehospital epinephrine administration had no significant effect on 1-month survival in bystander-witnessed non-traumatic OHCA adults with initial non-VF/ventricular tachycardia rhythms [3]. These results are also inconsistent with our present results. This may be due mainly to differences in study subjects. Of 209,577 patients in the large nationwide database, 194,085 patients with initial non-shockable rhythms after OHCA including any cardiac arrest causes were evaluated in our study. On the other hand, they evaluated only selected 3,161 patients with witnessed non-traumatic OHCA from the Osaka Utstein registry database with exclusion of shock-responded VF/ventricular tachycardia patients. Of those cardiac arrest patients, 2,655 patients with initial non-shockable rhythms were studied using multivariate logistic regression analysis for 9 variables. We have analyzed eligible data using multivariate logistic analysis for 11 variables to reduce known confounding factors.

Recently, Nakahara et al. [2] analyzed a nationwide Japanese database between 2007 and 2008 and reported that cardiac origin OHCA patients who received early epinephrine administration (epinephrine administration time $\leq$ 10 min) had significantly higher ratios of intact neurological survival. As they analyzed only 49,165 of 212,088 adult OHCA patients (23.2%) for the study after excluding no witnessed arrest (59.2%), OHCA due to external causes, and early ROSC without epinephrine administration, there would be some selection bias. Their results were inconsistent with our current results. We could not indicate the beneficial effect of prehospital epinephrine on neurological outcome at 1 month in both shockable and non-shockable rhythms, even if

the epinephrine administration time was received < 9 min. These differences may derive mainly from subject selection bias.

In our present results, initial PEA rhythm was a crucial independent factor for prehospital ROSC, 1-month survival, and 1-month CPC 1–2 in the non-shockable rhythm cohort (Table 5). These results may reflect time-dependent effects of epinephrine administration in patients with cardiac arrest with PEA. Nordseth et al. investigated the time-dependent effects of epinephrine on clinical state transition in patients with initial PEA and found that epinephrine has notable clinical effects, including “speeding up” the rate of transition and extending the time window for ROSC development [27]. PEA is categorized into the following 3 clinical states: “normotensive PEA” with baseline cardiac contractions; “pseudo-PEA” with decreased cardiac contractions; and “true-PEA” with no cardiac contractions [28]. Intravenous epinephrine seems appealing in the latter 2 categories to promote ROSC [27]. These effects of epinephrine may ultimately contribute to 1-month survival. Arrich et al. [29] reported that total epinephrine dose during asystole and PEA cardiac arrests was associated with an unfavorable neurological outcome and increased in-hospital mortality. This implies that another drug combination or a new protocol is required if prehospital epinephrine is not effective in OHCA patients with initial non-shockable rhythms. Experimental data suggest that simultaneous administration of epinephrine and nitroglycerin or atenolol may lead to a better outcome, compared with the administration of epinephrine alone [30, 31]. However, there are no definitive data from human studies.

Study limitations

The potential limitations of the current analyses are as follows. First, the major limitation was that patients with prehospital epinephrine administration were not assigned by randomized selection. As limited certified ELSTs have been permitted to

administer intravenous epinephrine under online medical control in Japan, the EMS personnel organization or their individual skills may have influenced the current results. In our current study, epinephrine use was indicated only for non-shockable rhythm refractory to chest compression or shock delivery after shockable rhythm. This would tend to bias the epinephrine patients toward worse outcomes and diminish the ROSC, 1-month survival, and CPC 1–2 improvements. Second, unmeasured confounding factors in our study might have influenced our results. As we did not evaluate in detail the in-hospital treatments such as induced hypothermia [32], extracorporeal CPR [33], and drugs other than epinephrine, which may impact the results. We assumed that OHCA patients received standard advanced life support according to the Japanese CPR guidelines [21] based on the 2005 American Heart Association guidelines [4]. Additionally, we did not have sufficient data for patients with OHCA such as underlying disease, the place where the cardiac arrest occurred, and the quality of bystander CPR. Although the nationwide database has used the Utstein-style guidelines for reporting cardiac arrest, we had no such detailed data and could not include that data in our analyses. Third, we did not evaluate the relation between the total dosages of epinephrine and outcomes. Repeated dosages of epinephrine were administered under physician instruction after refractory of the first epinephrine administration in this study. This instruction itself may be influenced by a judgement of the physician in charge. Moreover, one important confounder in this analysis is that patients without prehospital epinephrine administration may have received epinephrine after arrival to hospitals. Total cumulative epinephrine dosage of $\geq$ 15 mg has been reported to influence the outcome of OHCA patients [34]. And this is considered to be associated with impaired tissue oxygen utility and impaired lactate clearance for hours after CPR. However, we did not have the detailed cumulative dose of epinephrine including in-hospital dosages for each patient. Consequently, we could not analyze the administration dosages of epinephrine mainly due to lack of sufficient data. Fourth, it is not known whether our

results are applicable to other communities with different emergency care characteristics. It may be necessary for researchers in other countries to validate our results.

Conclusions

Prehospital epinephrine administration for OHCA patients with initial non-shockable rhythms was independently associated with achievement of prehospital ROSC and had association with improved 1-month survival when epinephrine administration time was < 20 min.

Key messages

We analyzed nationwide Utstein-style Japanese data collected over 2 years and found that initial cardiac rhythm was a crucial prehospital factor for predicting both survival and favorable neurological outcomes at one month.

In the initial shockable rhythm cohort, the ratios of prehospital ROSC, 1-month survival, and 1-month CPC 1–2 in the non-epinephrine group were significantly higher than those in the epinephrine group. However, in the initial non-shockable rhythm cohort, the ratios of prehospital ROSC and 1-month survival in the epinephrine group were significantly higher than those in the non-epinephrine group. No significant difference between the epinephrine and non-epinephrine groups for 1-month CPC 1–2 was found in the initial non-shockable rhythm cohort.

In OHCA patients with initial shockable rhythms, only prehospital epinephrine administration with an administration time of < 9 min was independently associated with increased odds of prehospital ROSC.

Prehospital epinephrine administration for OHCA patients with initial non-shockable rhythms was independently associated with prehospital ROSC and had association with improved 1-month survival when epinephrine administration

time was < 20 min.

Prehospital epinephrine administration for OHCA patients with initial non-shockable rhythms was independently associated with deteriorated neurological outcomes at 1 month when the epinephrine administration time was ≥ 10 min.

Abbreviations

CI: confidence interval; CPC: Cerebral Performance Category; CPR: cardiopulmonary resuscitation; ELST: emergency life-saving technician; EMS: emergency medical services; FDMA: Fire and Disaster Management Agency; OHCA: out-of-hospital cardiac arrests; OR: odds ratio; PEA: pulseless electrical activity; RCT: randomized controlled trial; ROSC: return of spontaneous circulation; VF: ventricular fibrillation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YG and TM designed the study. YG, TM and YNG conducted data cleaning. YG and YNG analysed the data. YG drafted the manuscript, and YNG and TM contributed substantially to its revision. YG takes responsibility for the paper as a whole. All authors approved the manuscript before submission.

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Figure Legends:

Figure 1 Study profile showing participant selection. EMS, emergency medical services; ROSC, return of spontaneous circulation; CPC, cerebral performance category.

Table 1. Characteristics of patients and contributing factors to 1-month outcomes after out-of-hospital cardiac arrest

Characteristics	All patients (n = 209,577)		Adjusted OR (95% CI)			
			1-month survival		1-month CPC 1–2	
Year, 2010	107,952	(51.5)	1.06	(1.01–1.11)	1.07	(1.00–1.15)
Age*, years	74.0	± 16.1	0.24	(0.21–0.28)	0.97	(0.97–0.98)
Male	120,784	(57.6)	0.99	(0.94–1.04)	1.06	(0.97–1.15)
Witnessed arrest	74,788	(35.7)	3.34	(3.17–3.52)	3.31	(3.04–3.61)
Bystander CPR	95,672	(45.7)	1.14	(1.09–1.19)	1.31	(1.23–1.42)
Presumed cardiac cause	118,908	(56.7)	0.85	(0.81–0.90)	1.59	(1.45–1.75)
Shockable initial cardiac rhythm	15,492	(7.4)	4.59	(4.13–5.10)	5.46	(4.67–6.42)
Prehospital actual shock delivery	21,653	(10.3)	1.97	(1.77–2.18)	3.00	(2.55–3.53)
Use of advanced airway management	90,892	(43.3)	0.83	(0.79–0.87)	0.48	(0.44–0.52)
Call-to-response time*, min	7.6	± 3.8	0.003	(0.001–0.004)	0.87	(0.86–0.88)
Call-to-hospital arrival time*, min	32.8	± 12.1	0.45	(0.35–0.59)	1.00	(0.99–1.00)
Prehospital epinephrine administration	23,676	(11.3)	0.98	(0.92–1.05)	0.47	(0.42–0.54)

Values are reported either as n (%) or mean ± standard deviation. Values were missing for 492 to 590 individuals across time variables. * Adjusted odds ratios are reported for unit odds. CPR, cardiopulmonary resuscitation; CPC, cerebral performance category; OR, odds ratio; CI, confidence interval.

Table 2. Characteristics of patients according to the initial rhythm and prehospital epinephrine administration

Characteristic	Initial shockable rhythm (n = 15,492)		Initial non-shockable rhythm (n = 194,085)	
	Epinephrine (n = 3,136)	Non-epinephrine (n = 12,356)	Epinephrine (n = 20,540)	Non-epinephrine (n = 173,545)
Year				
2009	1,423 (45.4)	6,410 (51.9)	9,075 (44.2)	84,717 (48.8)
2010	1,713 (54.6)	5,946 (48.1)	11,465 (55.8)	88,828 (51.2)
Age, years	66.2 ± 15.0	66.3 ± 15.4	74.4 ± 15.0	74.6 ± 16.1
Male	2,542 (81.1)	9,411 (76.2)	12,344 (60.1)	96,487 (55.6)
Witnessed arrest	2,237 (71.3)	8,581 (69.5)	10,796 (52.6)	53,174 (30.6)
Bystander CPR	1,610 (51.3)	6,323 (51.2)	9,825 (47.8)	77,914 (44.9)
Presumed cardiac cause	2,794 (89.1)	10,743 (87.0)	11,702 (57.0)	93,669 (54.0)
Initial cardiac rhythm				
Ventricular fibrillation	3,077 (98.1)	12,037 (97.4)	NA	NA
Pulseless ventricular tachycardia	59 (1.9)	319 (2.6)	NA	NA
Pulseless electrical activity	NA	NA	7,460 (36.3)	34,153 (19.7)
Asystole	NA	NA	13,080 (63.7)	139,392 (80.3)
Prehospital actual shock delivery	3,003 (95.8)	11,685 (94.6)	1,719 (8.4)	5,246 (3.0)
Use of advanced airway management	2,035 (64.9)	4,695 (38.0)	15,011 (73.1)	69,151 (39.9)
Call-to-response time, min	7.4 ± 3.3	7.0 ± 3.2	8.0 ± 4.1	7.6 ± 3.8

Epinephrine administration time*, min	15.5	± 6.9	NA	17.0	± 7.8	NA
Total dose of prehospital epinephrine, mg						
1	1,213	(38.7)		8,163	(39.7)	
2	970	(30.9)	NA	6,329	(30.8)	NA
3 ≤	953	(30.4)		6,048	(29.4)	

Values are reported either as n (%) or mean ± standard deviation. Values were missing for 26 to 539 individuals across time variables. *Time from the start of CPR by EMS personnel to the first epinephrine administration. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; NA, not available.

Table 3. Outcomes of patients according to the initial rhythm and prehospital epinephrine administration

Outcomes	Initial shockable rhythm (n = 15,492)			Initial non-shockable rhythm (n = 194,085)		
	Epinephrine (n = 3,136)	Non-epinephrine (n = 12,356)	*p* value	Epinephrine (n = 20,540)	Non-epinephrine (n = 173,545)	*p* value
Prehospital ROSC	716 (22.8)	3,426 (27.7)	< 0.0001	3,847 (18.7)	5,248 (3.0)	< 0.0001
1-month survival	482 (15.4)	3,338 (27.0)	< 0.0001	795 (3.9)	3,819 (2.2)	< 0.0001
1-month CPC 1–2	219 (7.0)	2,301 (18.6)	< 0.0001	121 (0.59)	1,078 (0.62)	0.605

Values are reported as n (%). ROSC, return of spontaneous circulation; CPC, cerebral performance category.

Table 4. Results of multivariate logistic regression analyses for outcomes in the initial shockable rhythm cohort

Variables	Adjusted OR (95% CI)		
	Prehospital ROSC	1-month survival	1-month CPC 1–2
Year			
2009	Reference	Reference	Reference
2010	1.04 (0.97–1.12)	1.07 (0.99–1.16)	1.08 (0.99–1.19)
Age, years			
≤ 39	1.87 (1.58–2.21)	4.48 (3.74–5.36)	7.58 (6.10–9.43)
40 – 59	1.53 (1.36–1.73)	3.33 (2.91–3.82)	4.73 (3.97–5.67)
60 – 79	1.64 (1.47–1.82)	2.58 (2.28–2.93)	3.26 (2.76–3.88)
80 ≤	Reference	Reference	Reference
Male	0.87 (0.80–0.96)	0.89 (0.80–0.98)	0.90 (0.80–1.00)
Witnessed arrest	1.96 (1.80–2.14)	1.98 (1.80–2.17)	2.27 (2.02–2.56)
Bystander CPR	1.42 (1.31–1.53)	1.43 (1.32–1.54)	1.64 (1.49–1.80)
Presumed cardiac cause	1.39 (1.23–1.57)	2.16 (1.88–2.51)	2.50 (2.08–3.03)
Initial cardiac rhythm			
Ventricular fibrillation	0.58 (0.44–0.76)	0.72 (0.54–0.98)	0.75 (0.52–1.10)
Pulseless ventricular tachycardia	Reference	Reference	Reference
Prehospital actual shock delivery	1.95 (1.57–2.43)	1.92 (1.52–2.46)	2.52 (1.85–3.50)
Use of advanced airway management	0.54 (0.50–0.58)	0.59 (0.54–0.64)	0.43 (0.39–0.47)
Call-to-response time, min			

≤ 4	3.19 (2.39–4.33)	5.88 (4.09–8.75)	5.76 (3.72–9.40)
5 – 9	2.33 (1.77–3.14)	3.89 (2.73–5.74)	3.42 (2.23–5.54)
10 – 14	1.32 (0.98–1.80)	1.95 (1.34–2.93)	1.61 (1.02–2.67)
15 ≤	Reference	Reference	Reference
Prehospital epinephrine administration*			
No	Reference	Reference	Reference
Yes (≤ 9 min)	1.45 (1.20–1.75)	0.95 (0.77–1.16)	0.71 (0.54–0.92)
Yes (10 min – 19 min)	0.88 (0.78–1.00)	0.51 (0.44–0.59)	0.34 (0.28–0.42)
Yes (20 min ≤)	0.63 (0.52–0.77)	0.33 (0.25–0.42)	0.21 (0.14–0.31)

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; CPC, cerebral performance category; OR, odds ratio; CI, confidence interval. * If prehospital epinephrine was received, variables were divided into 3 categories according to the time from the start of CPR by emergency medical services personnel to the first epinephrine administration (epinephrine administration time) which are indicated in parentheses.

Table 5. Results of multivariate logistic regression analyses for outcomes in the initial non-shockable rhythm cohort

Variables	Adjusted OR (95% CI)		
	Prehospital ROSC	1-month survival	1-month CPC 1–2
Year			
2009	Reference	Reference	Reference
2010	1.04 (0.99–1.09)	1.06 (0.99–1.12)	1.10 (0.98–1.23)
Age, years			
≤ 39	1.12 (0.99–1.25)	1.53 (1.32–1.76)	2.53 (1.91–3.29)
40 – 59	1.37 (1.27–1.48)	1.57 (1.42–1.73)	2.84 (2.37–3.41)
60 – 79	1.26 (1.19–1.32)	1.50 (1.40–1.61)	2.12 (1.85–2.44)
80 ≤	Reference	Reference	Reference
Male	0.96 (0.92–1.01)	0.97 (0.91–1.03)	1.11 (0.98–1.25)
Witnessed arrest	2.23 (2.12–2.34)	2.48 (2.32–2.65)	2.37 (2.08–2.70)
Bystander CPR	1.09 (1.04–1.14)	1.00 (0.94–1.06)	0.95 (0.84–1.07)
Presumed cardiac cause	0.50 (0.48–0.52)	0.66 (0.62–0.70)	1.19 (1.06–1.34)
Initial cardiac rhythm			
Pulseless electrical activity	3.72 (3.55–3.90)	3.61 (3.39–3.85)	6.05 (5.31–6.92)
Asystole	Reference	Reference	Reference
Prehospital actual shock delivery	1.22 (1.11–1.34)	1.68 (1.49–1.89)	2.60 (2.15–3.11)
Use of advanced airway management	0.94 (0.90–0.98)	0.96 (0.91–1.02)	0.55 (0.48–0.62)
Call-to-response time, min			

≤ 4	1.45 (1.28–1.66)	2.90 (2.33–3.65)	2.98 (1.95–4.81)
5 – 9	1.35 (1.20–1.52)	2.38 (1.93–2.98)	2.28 (1.52–3.64)
10 – 14	1.11 (0.98–1.27)	1.56 (1.24–1.98)	1.35 (0.87–2.22)
15 ≤	Reference	Reference	Reference
Prehospital epinephrine administration*			
No	Reference	Reference	Reference
Yes (≤ 9 min)	8.83 (8.01–9.73)	1.78 (1.50–2.10)	0.95 (0.62–1.37)
Yes (10 min – 19 min)	6.18 (5.82–6.56)	1.29 (1.17–1.43)	0.63 (0.48–0.80)
Yes (20 min ≤)	4.32 (3.98–4.69)	0.79 (0.66–0.93)	0.49 (0.32–0.71)

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; CPC, cerebral performance category; OR, odds ratio; CI, confidence interval. * If prehospital epinephrine was received, variables were divided into 3 categories according to the time from the start of CPR by emergency medical services personnel to the first epinephrine administration (epinephrine administration time) which are indicated in parentheses.

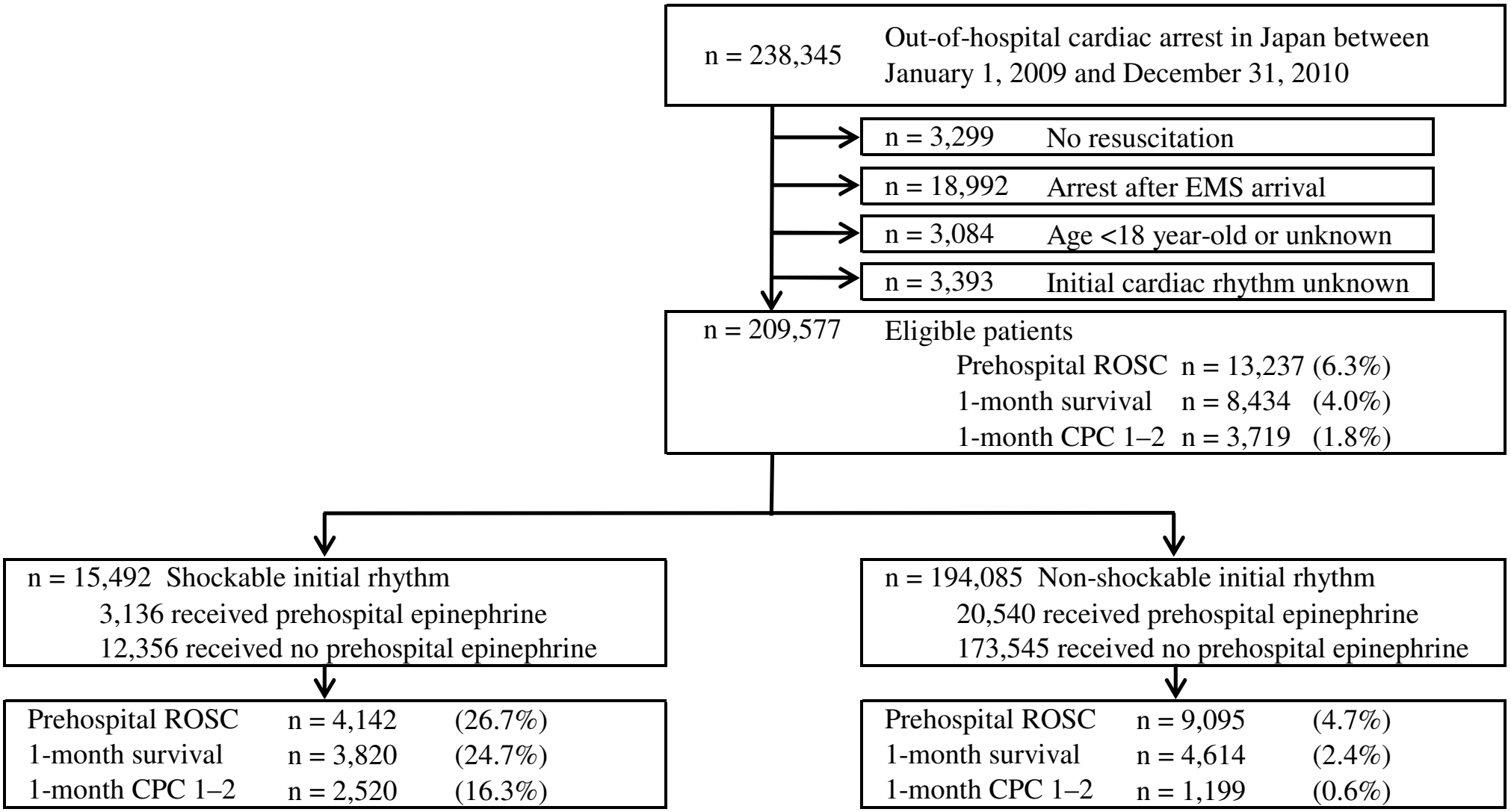
n = 238,345
Out-of-hospital cardiac arrest in Japan between January 1, 2009 and December 31, 2010
n = 3,299 No resuscitation
n = 18,992 Arrest after EMS arrival
n = 3,084 Age <18 year-old or unknown
n = 3,393 Initial cardiac rhythm unknown
n = 209,577 Eligible patients
Prehospital ROSC n = 13,237 (6.3%)
1-month survival n = 8,434 (4.0%)
1-month CPC 1–2 n = 3,719 (1.8%)
n = 15,492 Shockable initial rhythm
3,136 received prehospital epinephrine
12,356 received no prehospital epinephrine
Prehospital ROSC n = 4,142 (26.7%)
1-month survival n = 3,820 (24.7%)
1-month CPC 1–2 n = 2,520 (16.3%)
n = 194,085 Non-shockable initial rhythm
20,540 received prehospital epinephrine
173,545 received no prehospital epinephrine
Prehospital ROSC n = 9,095 (4.7%)
1-month survival n = 4,614 (2.4%)
1-month CPC 1–2 n = 1,199 (0.6%)

Figure 1