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# Effects of repeated epinephrine administration and administer timing on witnessed out-of-hospital cardiac arrest patients

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ABSTRACT

*Background:* Repeated administration of epinephrine is associated with unfavorable cerebral outcome after out-of-hospital cardiac arrests (OHCA), but the timing of epinephrine administration has not been considered.
*Aim:* The aim of the study was to analyze the effects of repeated epinephrine administration after OHCA on favorable cerebral function coded by cerebral performance categories (CPC 1–2).
*Methods:* A nationwide, retrospective, population-based observational study was conducted by using Utstein-style data between 2010 and 2012 in Japan. The total of 11,876 cardiogenic and witnessed OHCA were stratified into 3 categories by the number of times epinephrine was administered (single, double, and three or more). In addition, the time elapsed between the emergency call and the initial epinephrine administration was divided into 3 time intervals (5 to 20 min for the early administration group [EAG], 21 to 26 min for the intermediate administration group [IAG], and 27 to 60 min for the late administration group [LAG]). The primary endpoint was CPC 1–2 at 1 month after cardiac arrest. A multivariable logistic regression was used for analysis.
*Results:* Achievement of CPC 1–2 at 1 month was 4.8% for single, 2.4% for double, and 1.7% for three or more administered doses. For single and three or more administrations, CPC 1–2 was significantly higher in the IAG than in the LAG (adjusted odds ratio [AOR], 3.54, 3.02; 95% confidence interval [CI], 2.04–6.39, 1.16–9.43, for single and three or more administrations, respectively). The EAG showed significantly higher achievement of CPC 1–2 in all the epinephrine administration groups (AOR, 9.26, 7.57, 4.07; 95% CI, 5.44–16.59, 3.39–19.60, 1.59–12.69, for single, double, and three or more administrations, respectively).
*Conclusion:* Repeated epinephrine administration improved CPC 1–2 outcome when epinephrine was administrated within 20 min after an emergency call for witnessed cardiogenic OHCA.


## 1. Introduction

The administration of epinephrine, a potent vasoconstrictor with positive inotropic effect, is recommended every 3 to 5 min as the first choice of treatment for out-of-hospital cardiac arrest (OHCA), according to the 2015 international resuscitation guidelines [1,2]. Epinephrine is effective for the return of spontaneous circulation (ROSC), but epinephrine is not effective for long-term improvement of cerebral function as numerous reports have indicated [3-10].

In animal research, epinephrine increases the perfusion of the coronary arteries and the brain during resuscitation, and improves the rate of ROSC [11,12], but epinephrine also induces myocardial damage, and inhibits cerebral blood flow [13,14]. Coinciding with these basic research results, randomized clinical comparative studies using large population clinical observational studies in humans and systematic reviews have all reported that while the rate of ROSC is improved, long-term cerebral function is not improved [3-10].

According to epinephrine research, high dose and standard dose epinephrine present no significant difference based on dose [15,16] on the ROSC and cerebral function, and repeated administration of epinephrine has not improved cerebral function. With regard to recent studies, early epinephrine administration has been reported to improve long-term cerebral function [17-24]. Therefore, we need to examine the time of administration. However, in previous studies of repeated epinephrine administration timing was not considered the important factor [25,26,27]. Prolonging cardiac-arrest time induces deterioration in long-term cerebral function [28], and the cardiac-arrest time interval is prolonged at least 3 to 5 min when administering each dose of epinephrine. We think this is one of the reasons for poor outcome.

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The aim of the study was to analyze the effects of repeated epinephrine administration, considering the timing of the initial administration for OHCA on favorable cerebral function outcome.

## 2. Methods

### 2.1. Study design

This is a nationwide, retrospective, population-based observational study. The study design was approved by the institutional review board of Kokushikan University.

### 2.2. Data collection and setting

The population studied included 127.5 million inhabitants in 2012 who were covered by a nationwide, single-tier, fire-based emergency medical system (EMS) in Japan. The data of each OHCA was recorded by an emergency life-support technician (ELST) based on EMS records, which had used Utstein-style guidelines since 2005. All the Japan Utstein-style data were adopted from the Fire and Disaster Management Agency.

### 2.3. EMT field protocol

All EMT field basic life support (BLS) and ELST advanced life support (ALS) protocols followed the 2015 Japan Resuscitation Council (JRC) guidelines [29]. After the initial assessment and electrocardiogram (ECG) rhythm are obtained, defibrillation is applied if the patient presents ventricle fibrillation (VF) or pulseless ventricle tachycardia (VT). Advanced airway management, for example, laryngeal mask airway (LMA), Combi-tube, King Airway, esophageal gastric tube airway (EGTA) and endotracheal tube (ET), are applied if patients present with difficulty in ventilation. A continuous bag valve mask is selected when the initial ventilation is successful. If the patient does not achieve ROSC after the initial EMS defibrillation or has non-shockable rhythm, an ELST can select intravenous epinephrine administration. ELSTs could additionally choose between ALS or BLS resuscitation protocols from the scene to hospital. Epinephrine is given by using prefilled syringes (1 mg epinephrine to 1 ml distilled water; 0.1% epinephrine injection; Terumo, Tokyo, JAPAN) administered every 3 to 5 min until ROSC is achieved and/or hospital arrival. In Japan, EMS providers are not permitted to terminate resuscitation in the field.

### 2.4. Patient population

In the study, 378,040 consecutive OHCA patients were registered in the national database covering the total population of Japan from Jan 1, 2010 to Dec 31, 2012.

Data from patients were excluded from our research under the following conditions: age under 15 or over 90 years old, no witness or being witnessed by EMS, non-cardiogenic, ALS by physicians at the scene, inference of ROSC before the arrival of the emergency services, non-administration of epinephrine, missing values (public access defibrillation, airway management devices), negative values (response time, initial epinephrine administration time), and outlying values (response time, initial epinephrine administration time, hospital arrival time above the 99th percentile). All of the time factors were calculated from the time of the emergency call. A total of 11,876 patients were eligible for analysis (Fig. 1).

### 2.5. Patient categories

The total of 11,876 patients were stratified into 3 categories by the number of times of epinephrine administration (single, double, and three times or more). Patients were allocated to one of 3 time intervals (by tertile: dividing the data set into 3 equal groups) from emergency call to initial epinephrine administration (5 to 20 min for the early administration group [EAG], n = 4548; 21 to 26 min for the intermediate administration group [IAG], n = 3541; and 27 to 60 min for the late administration group [LAG], n = 3787). It is difficult to define what the clinical cut-off time point of epinephrine administration is; therefore we divided the time factor by tertile without arbitrariness.

### 2.6. Study endpoint

The primary endpoint was a favorable cerebral function at 1 month after cardiac arrest. The secondary endpoint was a survival at 1 month after cardiac arrest. Cerebral functional outcomes were defined as a cerebral performance category (CPC) score (1 = good performance, 2 = moderate disability, 3 = severe cerebral disability, 4 = vegetative state, 5 = death). A favorable cerebral function was defined as CPC 1–2, and a survival was defined as CPC 1–4.

### 2.7. Statistical analysis

Continuous variables represented the median and interquartile range (IQR), and category variables represented numbers and proportion. Differences were assessed using a Kruskal-Wallis test and Pearson's chi-square test for continuous and category variables respectively. For the 3 groups categorized by number of epinephrine administrations, taking the single administration group as the reference, the outcomes, odds ratio and 95% confidence interval were calculated for double administrations, and three or more administrations. The LAG was taken as the reference. The outcomes, odds ratio and 95% confidence interval were calculated for the IAG and the EAG depending on the number of times epinephrine was given. Multivariable logistic regression with simultaneously introduced groups of confounding variables in the model was performed. Confounding variables considered in the models were age, sex, bystander CPR (chest compression [yes/no], rescue breathing [yes/no]), public access defibrillation (yes/no), initial ECG rhythm (shockable, non-shockable), the number of defibrillations (0, 1, 2–3, ≥4), type of advanced airway management device (None, LMA, EGTA, ET), response time, and time elapsed before initial epinephrine administration. Both the time factors were calculated from the time of the emergency call. The multicollinearity of the continuous variables of the time factors was confirmed using variance inflation factor (VIF). Multicollinearity was defined as present when VIF ≥ 10. As the sample size was sufficiently large, no overfitting of covariates was seen. The linearity of continuous variables was confirmed by entering each variable into the model categorized into quartiles, and calculating the $R^2$ of the odds ratio for outcome. Variables with low linearity were categorized by quartile before entry into the model. Interaction terms for the number times of epinephrine administration and initial administration time were included in a multivariable model and evaluated. No interaction between the initial administration time and the number of times of epinephrine administration indicated the effectiveness of the administration time regardless of the number of times of administration. The relationship between initial epinephrine administration and outcomes on the respective number of administration was fitted by the logistic regression curve. All tests were carried out as two-tailed tests, and $p$ value < 0.05 was taken to be a significant difference. JMP version 11.2.0 (SAS Institute Inc., Cary, NC, USA) was used for analysis.

## 3. Results

### 3.1. Patient characteristics

The characteristics of OHCA patients divided by the number of times of epinephrine administration are shown in Table 1. The median age for all cases was 75 (64–82), and a significant difference was seen depending on the number of epinephrine administrations ($p$ < 0.001). Of all the

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