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Research article

The Effects of Bystander Cardiopulmonary Resuscitation in Patients with Epinephrine Administration

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Abstract

Introduction: The purpose of this study is to determine whether bystander cardiopulmonary resuscitation (BCPR) is associated with neurologically intact survival in patients who received epinephrine administration compared to non-BCPR in out-of-hospital cardiac arrest (OHCA).

Methods: This is a population-based observational study using national Utstein-style data from 2011 to 2015 in Japan. This study includes 17,136 eligible cases. To clarify the phase of epinephrine administration time when BCPR is the most effective on favourable cerebral function, the epinephrine-administered group was classified into three time-indexed groups based on the time between an emergency call and first epinephrine administration (EPI-time) using decision tree analysis. The early epinephrine group (EEG) included cases with times of 0 to 15 minutes, the intermediate epinephrine group (IEG) 16 to 24 minutes and the late epinephrine group (LEG) 25 to 48 minutes. To assess the validity of these groups, sensitivity analysis was performed using another six datasets which were created for a period of one minute before and after in each group. This study used multivariate analysis and calculated adjusted odds ratio (AOR) with a 95% confidence interval (95% CI).

Results: BCPR is associated with favourable prognoses in the overall data (AOR is 1.26 [95% CI; 1.02 - 1.55]). In the time-indexed EEG, BCPR is not associated with favourable outcomes (1.09 [95% CI: 0.72 - 1.63]. The IEG and LEG are associated with favourable outcomes, the AORs of BCPR are 1.40 (95% CI: 1.40 - 1.90) and 1.64 (95% CI: 1.04 - 2.61) respectively.

Conclusion: The effect of BCPR in patients who received epinephrine administration favourably affects neurological outcomes in the time phases which stratified by EPI-time of 17 to 25, 24 to 48 minutes, as compared to the non-BCPR group.

Keywords: *Pre-Hospital Bystander Cardiopulmonary Resuscitation; Epinephrine; Out-Of-Hospital Cardiac Arrest; Advanced Life Support*

Abbreviations

BCPR: Bystander Cardiopulmonary Resuscitation; EPI-Time: The Time Between an Emergency Call and First Epinephrine Administration; EEG: Early Epinephrine Group; IEG: Intermediate Epinephrine Group; LEG: Late Epinephrine Group; AOR: Adjusted Odds Ratio; EMS:

Emergency Medical Services; OHCA: Out-Of-Hospital Cardiac Arrest; FDMA: Fire and Disaster Management Agency; AED: Automated External Defibrillator; ROSC: Return of Spontaneous Circulation; ALS: Advanced Life Support; ELST: Emergency Life-Saving Technician; CPC: Cerebral Performance Category; AUC: Area Under the Curve

Introduction

Over 120,000 witnessed cardiogenic out-of-hospital cardiac arrest (OHCA) cases have occurred, according to an annual report of the Fire and Disaster Management Agency (FDMA) in Japan, but the survival rate is still low despite increasing rates of bystander intervention such as cardiopulmonary resuscitation (CPR) and use of automated external defibrillators (AED) [1]. Although the number of cases in which advanced life support (ALS) is provided by emergency medical services (EMS) in the pre-hospital setting is also increasing, the effects of epinephrine (adrenaline) administration on patients with witnessed cardiogenic OHCA are still controversial [1,2].

Hagiwara., *et al*. [2] have noted the improvement in return of spontaneous circulation (ROSC) in those who received epinephrine compared to the non-epinephrine-administered group, but epinephrine administration has not been found to improve survival with favourable neurological outcomes [2-4]. Nevertheless, a study by Hayashi., *et al*. [5] has shown that early administration of epinephrine can improve survival with favourable cerebral function in initially shockable rhythm and several other studies have thereafter demonstrated the time-dependent effects of epinephrine [5-7].

Whereas, bystander cardiopulmonary resuscitation (BCPR) is more effective than ALS implemented by EMS in attaining positive outcomes [8] and other studies have also reported that BCPR and early defibrillation is associated with favourable outcomes [9-12]. In a recent meta-analysis by Song., *et al*. [13] has also proven that BCPR increases the chance of survival in OHCA patients with initially shockable rhythm. However, many of these results are not adjusted for a covariate of epinephrine administration despite the increase in ALS cases by EMS. In addition, because epinephrine has a time-dependent effect, it is crucial to determine the association of favourable cerebral function between the effects of BCPR and epinephrine administration time.

Based on these clinical questions, we hypothesise that BCPR would be associated with favourable neurological outcomes in patients who received epinephrine administration, regardless of the time between an emergency call and first epinephrine administration (EPI-time), as compared to the non-BCPR group.

The purpose of this study is to demonstrate this hypothesis using multivariable analysis and to determine the association between the effects of BCPR and epinephrine administration.

Materials and Methods

Study design

This study is a population-based observational study using national Utstein-style data from 2011 to 2015 in Japan. This research was approved by the Institutional Review Board at Kokushikan University.

Study setting and data collection

The EMS system across the nation was covered by 750 fire departments which are controlled by the Fire and Disaster Management Agency (FDMA). Most fire-based ambulance teams were composed of three people, including emergency life-saving technicians (ELSTs) eligible to implement advanced treatments. Emergency life-saving technicians are allowed to provide airway management with intubation, oesophageal obturator airways and laryngeal masks; intravenous lines and epinephrine administration; and defibrillation with a semi-automated defibrillator. Emergency life-saving technicians follow protocols established by each local medical control council and based on the JRC guidelines. The number 119 is used as a dispatch for the EMS system. Dispatcher-assisted CPR is implemented when

needed. The average time from a 119-emergency call to EMS arrival on scene (response time) was 8.6 minutes in 2015, according to the annual FDMA report [1].

Out-of-hospital cardiac arrest data is recorded by ELSTs based on the EMS run sheets in each local station. These records are managed by the FDMA and data collection is based on Utstein-style guidelines that were launched in 2005 in Japan. To use the data, one must submit an application and be granted access by the FDMA. The records include the following variables: prefecture, year, sex, age, bystander-witnessed status, type of bystander(s), BCPR (conventional CPR with rescue breathing or chest compression-only CPR), use of an automated external defibrillator, first monitored rhythm, dispatcher's assist, use of advanced airway, use of epinephrine, time course of resuscitation, cause of cardiac arrest, ROSC in the pre-hospital setting, one-month survival and cerebral performance category (CPC). The Glasgow-Pittsburgh CPC scoring method was used and survival at one month, combined with a CPC score of 1 to 2, was defined as a favourable neurological outcome [14], while survival at one month with a CPC score of 3 to 4 was defined as an unfavourable neurological outcome. A CPC score of 1 to 4 was defined as a survival.

Emergency medical services protocol for epinephrine use

Emergency life-saving technicians follow the 2010 JRC guidelines [15]. After obtaining the initial electrocardiogram (ECG) rhythm, EMS defibrillation is performed if the ECG indicates ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT). If patients do not show any shockable rhythms, ELSTs prepare for epinephrine administration. The conditions for the use of epinephrine require the patient to be more than eight years old, with VF/pVT, pulseless electrical activity and witnessed asystole. Prefilled syringes are used for single administrations of epinephrine. Online permission from a medical control physician is required when ELSTs use advanced airway protocol or attempt epinephrine administration. Emergency life-saving technicians implement CPR and use of drugs on-scene and/or en route to the emergency department. In Japan, ELSTs frequently begin transportation without achieving ROSC on-scene.

Study population

The subjects of this study include 370,578 cases of cardiogenic OHCA patients from 2011 to 2015. In accordance with the purpose of this study, the following types of case were excluded: (1) under 15 years old and/or over 90 years old (ELSTs are allowed to perform endotracheal intubation for patients who are over 15 years old in Japan, so we excluded cases below this age; moreover, as there is very low survival rate in patients who are over 90 years old, we excluded them from the dataset); (2) ELSTs not on board the ambulance; (3) unwitnessed by laypeople and witnessed by EMS personnel; (4) physician on board and ALS performed in ambulance; (5) epinephrine not administered; (6) resuscitation not attempted by EMS; (7) unknown status of BCPR; (8) only rescue breathing CPR performed; (9) initial waveform unknown; (10) automated external defibrillator (AED) used by laypeople; (11) unknown status of epinephrine administration; (12) unknown status of EMS defibrillation; (13) unknown status of implementation of advanced airway; and (14) some ROSC cases, such as ROSC before EMS arrival, ROSC before epinephrine administration and EMS first defibrillation shock to ROSC < 3 minutes. Other details are shown in figure 1.

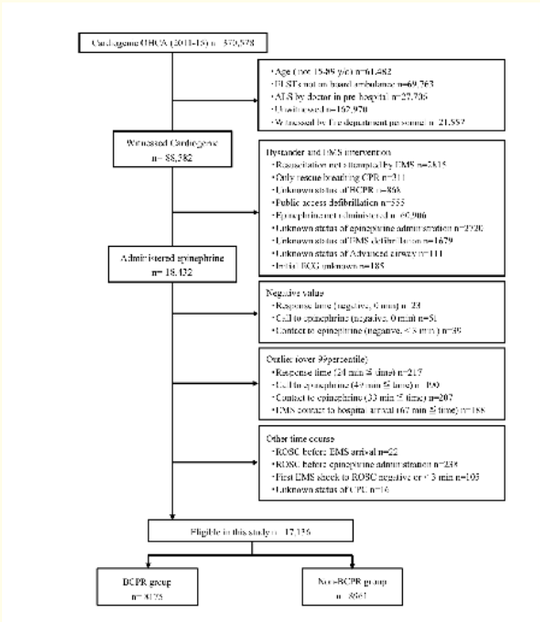

Figure 1: *Study enrolment.*
OHCA: Out-of-Hospital Cardiac Arrest; ELSTs: Emergency Life-Saving Technicians; ALS: Advanced Life Support; BCPR: Bystander Cardiopulmonary Resuscitation; EMS: Emergency Medical Service; ROSC: Return of Spontaneous Circulation; CPC: Cerebral Performance Category.

There were 17,136 eligible cases for this study. The epinephrine-administered group was classified into three time-indexed groups to clarify whether the implementation of BCPR was associated with favourable outcomes regardless of EPI-time, as compared to non-BCPR circumstances. A decision tree was used to divide these groups in order to provide objective results. The early epinephrine group (EEG) included times of 0 to 15 minutes from the 119 call to epinephrine administration, the intermediate epinephrine group (IEG) 16 to 24 minutes and the late epinephrine group (LEG) 25 to 48 minutes. The cases of EPI-time > 48 minutes were excluded from the dataset as they were outliers (99th percentile).

Study outcome

In this study, the primary outcome was a CPC score of 1 to 2 at one month after the event.

Statistical analysis

The univariate analysis was performed to create the logistic regression curve association of favourable cerebral function between the effects of BCPR and EPI-time. In addition, multivariable analysis was also implemented to calculate adjusted odds ratio of BCPR to survival with a CPC score of 1 to 2 in the overall group (BCPR vs. non-BCPR) and in each time-indexed group (EEG, IEG, LEG). Multivariable logistic regression with simultaneous forced entry method was adjusted for age, gender, type of bystander (other/family), implementation of BCPR (yes/no), dispatcher-assisted CPR (yes/no), response time, defibrillation by EMS, advanced airway management (0: bag mask, 1: intubation, 2: other airway devices), EPI-time, number of epinephrine uses (1, 2, ≥3) and time from EMS contact to hospital arrival. The adjusted odds ratio (AOR) and unadjusted odds ratio were calculated with a 95% confidence interval (95% CI). In addition, to evaluate the adequacy of each time period divided by decision tree, sensitivity analysis was performed. Based on the time periods divided by decision tree, another six datasets were created for a period of one minute before and after in each group. Adjusted odds ratios with 95% CI were also calculated to assess the effective time range of BCPR. Each continuous variable was categorized and introduced as a quantitative variable by quartile and each was input again as a continuous variable only if linearity was confirmed with R2 of odds ratio for outcomes. Multicollinearity was defined as a variance inflation factor > 10 and not observed in any continuous variables. Model fit was measured by area under the curve (AUC) with 95% CI. Goodness of fit was equated to AUC > 0.7. For statistical analysis in this study, R (version 3.3.2) was used with $p < 0.05$ as statistically significant [16]. Furthermore, to create three time-indexed groups based on EPI-time, decision tree analysis was performed using JMP version 11.2.0 (SAS Institute Inc., Cary, NC, USA).

Results and Discussion

Patient backgrounds

The backgrounds of patients in the BCPR group and the non-BCPR group are shown in table 1. The ROSC ratio of the BCPR group was the same as that of the non-BCPR group. Rates of both survival at one month and survival with a CPC score of 1 to 2 at one month were higher in the BCPR group. Backgrounds of patients in the three time-indexed groups classified by epinephrine administration time-EEG, IEG and LEG-are shown in table 2. The proportion of CPC scores of 1 to 2 in the IEG and LEG groups was higher in the BCPR group than in the non-BCPR group.

Effect of BCPR on favourable prognosis

The logistic regression curve association between the effect of BCPR and EPI-time was shown in figure 2. In the multivariate analysis, the odds of survival with a CPC score of 1 to 2 were higher in the BCPR group than in the non-BCPR group and the AOR of the BCPR group was 1.26 (95% CI: 1.02 - 1.55, non-BCPR was reference). In each time-indexed EEG, IEG and LEG, there was no difference in all datasets divided by decision tree. (AOR: 1.09 [95% CI: 0.72 - 1.63], AOR: 1.29 [95% CI: 0.97 - 1.73], AOR: 1.40 [0.87 - 2.36], respectively). Further details of COR are shown in table 3.

	All	BCPR	Non-BCPR
	17136	**8175**	**8961**
Age median (IQR)	75 (65, 83)	76 (65, 83)	75 (65, 82)
Sex male no. (%)	12087 (70.5)	5648 (69.1)	6439 (71.9)
Types of bystander			
Family no. (%)	11912 (69.5)	5224 (63.9)	6688 (74.6)
Others no. (%)	5224 (30.5)	2951 (36.1)	2273 (25.4)
Dispatcher-assist no. (%)	9052 (52.8)	6266 (76.6)	2786 (31.1)
EMS interventions			
Initial rhythm shockable no. (%)	4984 (29.1)	2551 (31.2)	2433 (27.2)
EMS defibrillation no. (%)	6700 (39.1)	3243 (39.7)	3457 (38.6)
Epinephrine administration no. (%)			
1	6028 (35.2)	2871 (35.1)	3157 (35.2)
2	4910 (28.7)	2358 (28.8)	2552 (28.5)
≥ 3	6198 (36.2)	2946 (36.0)	3252 (36.3)
Intubation no. (%)	2065 (12.1)	962 (11.8)	1103 (12.3)
Time intervals			
Response interval median (IQR)	9 (7, 11)	9 (7, 11)	8 (7, 10)
Call to epinephrine median (IQR)	22 (18, 28)	22 (18, 28)	23 (18, 28)
Contact to hospital arrival median (IQR)	26 (21, 33)	26 (21, 32)	27 (22, 33)
Outcome			
ROSC no. (%)	3252 (19.0)	1591 (19.5)	1661 (18.5)
One-month survival no. (%)	1389 (8.1)	711 (8.7)	678 (7.6)
CPC 1 - 2 at one-month no. (%)	551 (3.2)	309 (3.8)	242 (2.7)
CPC 3 - 4 at one-month no. (%)	757 (4.4)	368 (4.5)	389 (4.3)

Table 1: *Characteristics of adrenaline administration with/without BCPR.*

BCPR: Bystander Cardiopulmonary Resuscitation; IQR: Interquartile Range (25%, 75%); EMS: Emergency Medical Services; ROSC: Return of Spontaneous Circulation; CPC: Cerebral Performance Category.

	Time from 119 call to first epinephrine dose.					
	EEG		IEG		LEG	
	n = 2139		n = 8221		n = 6776	
	(5-15 min)		(16-24 min)		(25-48 min)	
	BCPR	Non-BCPR	BCPR	Non-BCPR	BCPR	Non-BCPR
	n= 1129	n= 1010	n= 3902	n= 4319	n=3144	n=3632
Age median (IQR)	76 (65, 83)	75 (65, 82)	75 (64, 83)	74 (64, 82)	77 (65, 84)	75 (65, 82)
Sex male no. (%)	782 (69.3)	729 (72.2)	2716 (69.6)	3136 (72.6)	2150 (68.4)	2574 (70.9)
Types of bystander						
Family no. (%)	685 (60.7)	683 (67.6)	2440 (62.5)	3130 (72.5)	2099 (66.8)	2875 (79.2)
Others no. (%)	444 (39.3)	327 (32.4)	1462 (37.5)	1189 (27.5)	1045 (33.2)	757 (20.8)
Dispatcher-assist no. (%)	904 (80.1)	416 (41.2)	2983 (76.4)	1343 (31.1)	2379 (75.7)	1027 (28.3)
EMS intervention						
Initial rhythm shockable no. (%)	400 (35.4)	321 (31.8)	1244 (31.9)	1347 (31.2)	907 (28.8)	765 (21.1)
EMS defibrillation no. (%)	488 (43.2)	405 (40.1)	1596 (40.9)	1853 (42.9)	1159 (36.9)	1199 (33.0)
Epinephrine administration no. (%)						
1	277 (24.5)	268 (26.5)	1247 (32.0)	1319 (30.5)	1347 (42.8)	1570 (43.2)
2	343 (30.4)	302 (29.9)	1084 (27.8)	1184 (27.4)	931 (29.6)	1066 (29.4)
≥ 3	509 (45.1)	440 (43.6)	1571 (40.3)	1816 (42.0)	866 (27.5)	996 (27.4)
Intubation no. (%)	107 (9.5)	134 (13.3)	427 (10.9)	477 (11.0)	428 (13.6)	492 (13.5)
Response interval median (IQR)	7 (6, 8)	6 (5, 8)	8(7, 10)	8 (7, 10)	10 (8, 13)	10 (8, 12)
Call to epinephrine median (IQR)	14 (13, 15)	14 (13, 15)	20 (18, 22)	20 (18, 22)	30 (27, 33)	29 (27, 33)
Contact to hospital arrival median (IQR)	22 (18, 26)	22 (19, 28)	25 (20, 30)	25 (21, 32)	29 (24, 35)	30 (25, 36)
Outcome						
ROSC no. (%)	355 (31.4)	289 (28.6)	824 (21.1)	909 (21.0)	412 (13.1)	463 (12.7)
One-month survival no. (%)	176 (15.6)	154 (15.2)	374 (9.6)	339 (7.8)	127 (4.0)	138 (3.8)
CPC 1 - 2 at one-month no. (%)	99 (8.8)	73 (7.2)	158 (4.0)	134 (3.1)	52 (1.7)	35 (1.0)
CPC 3 - 4 at one-month no. (%)	77 (6.8)	81 (8.0)	216 (5.5)	205 (4.7)	75 (2.4)	103 (2.8)

Table 2: *Characteristics of adrenaline administration with/without BCPR in time indexed phases.*

BCPR: Bystander Cardiopulmonary Resuscitation; EEG: Early Epinephrine Group (First Epinephrine Dose < 16 minutes from 119 call); IEG: Intermediate Epinephrine Group (First Epinephrine Dose 16-24 minutes from 119 call); LEG: Late Epinephrine Group (First Epinephrine Dose > 24 minutes from 119 call); IQR: Interquartile Range (25%, 75%); EMS: Emergency Medical Services; ROSC: Return of Spontaneous Circulation; CPC: Cerebral Performance Category.

One-month survival with CPC 1 - 2	Overall	EEG (n = 2139)5 - 15 min	IEG (n = 8221)16 - 24 min	LEG (n = 6776) 25 - 48 min
No. (%)	551 (3.2)	172 (8.0)	292 (3.6)	87 (1.3)
Odds ratio (95% CI)				
BCPR (Unadjusted)	1.42 (1.19 - 1.68)	1.23 (0.90 -1.69)	1.32 (1.04 - 1.67)	1.73 (1.10 - 2.74)
BCPR (Adjusted†)	1.26 (1.02 - 1.55)	1.09 (0.72 - 1.63)	1.29 (0.97 - 1.73)	1.40 (0.87 - 2.36)

Table 3: *Odds ratio of survival of BCPR in each phase*.*

BCPR: bystander cardiopulmonary resuscitation; CPC: cerebral performance category; EEG: early epinephrine group; IEG: intermediate epinephrine group; LEG: Late Epinephrine Group.

** Non-BCPR was reference.*

† Adjusted for age, sex, types of bystander (family or others), bystander cardiopulmonary resuscitation, dispatcher-assisted CPR, response time, initial rhythm (non-shockable[PEA, asystole] , shockable [VF, pulseless VT]), EMS defibrillation, advanced airway (bag-mask, intubation, other airway devices), epinephrine administration (1,2, ≥ 3), time from EMS contact to hospital arrival.

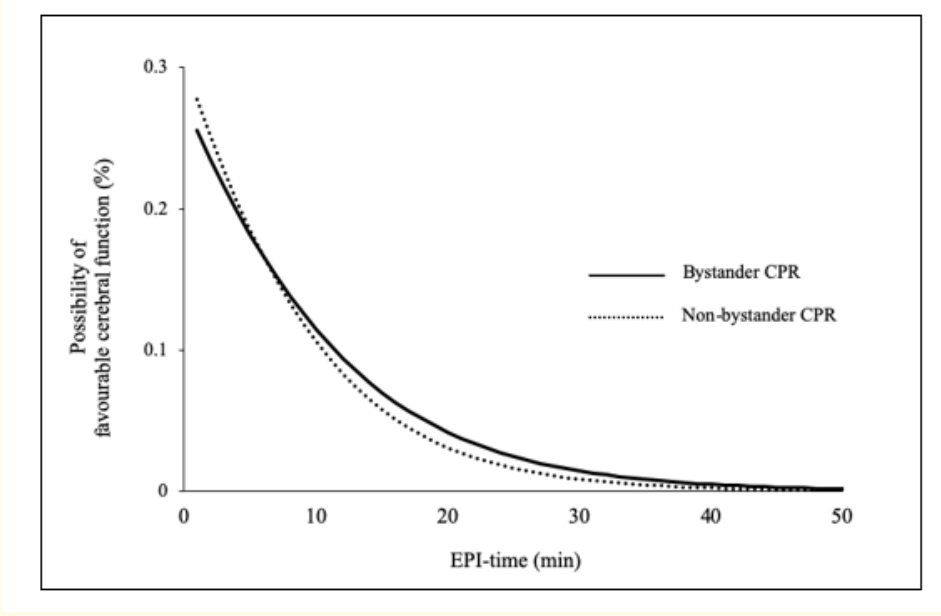

Figure 2: *Logistic regression curve of association between BCPR/Non-BCPR and EPI-time to favourable cerebral function. BCPR: Bystander Cardiopulmonary Resuscitation; NBCPR: Non-bystander Cardiopulmonary Resuscitation; EPI-Time: Emergency Call to First Epinephrine Administration Time.*

Effect of BCPR in other time-indexed groups (sensitivity analysis)

To evaluate the adequacy of each time period divided by decision tree, AOR was also calculated with 95% CI for other time-indexed datasets. Bystander cardiopulmonary resuscitation was significantly effective to CPC 1 to 2 in IEG (17 to 25 minutes) and LEG (24 to 48 minutes) and AOR was 1.40 [95% CI: 1.04 - 1.90] and 1.64 [95% CI: 1.04 - 2.61] respectively. Other details of sensitivity analysis are shown in table 4.

EEG	**5 - 14 min**	**5 - 15 min**	**5 - 16 min**
	n = 1443	**n = 2139**	**n = 2897**
CPC 1 - 2 No. (%)	119 (8.2)	172 (8.0)	223 (7.7)
Odds ratio (95%CI)			
BCPR (adjusted†)	1.20 (0.73 - 1.98)	1.09 (0.72 - 1.63)	1.09 (0.76 - 1.57)
IEG	**15 - 23 min**	**16 - 24 min**	**17 - 25 min**
	n = 8069	**n = 8221**	**n = 8245**
CPC 1 - 2 No. (%)	321 (4.0)	292 (3.6)	261 (3.2)
Odds ratio (95%CI)			
BCPR (adjusted†)	1.16 (0.88 - 1.54)	1.29 (0.97 - 1.73)	1.40 (1.04 - 1.90)
LEG	**24 - 48 min**	**25 - 48 min**	**26 - 48 min**
	n = 7624	**n = 6776**	**n = 5994**
CPC 1 - 2 No. (%)	111 (1.5)	87 (1.3)	67 (1.1)
Odds ratio (95%CI)			
BCPR (adjusted†)	1.64 (1.04 - 2.61)	1.40 (0.85 - 2.36)	1.17 (0.65 - 2.09)

Table 4: *Odds of survival of BCPR in a few minutes before and after the decision tree*.*

BCPR: Bystander Cardiopulmonary Resuscitation; CPC: Cerebral Performance Category; EEG: Early Epinephrine Group,

IEG: Intermediate Epinephrine Group; LEG: Late Epinephrine Group; PEA: Pulseless Electrical Activity; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia.

Non-BCPR was reference.

† Adjusted for age, sex, types of bystander (family or others), bystander cardiopulmonary resuscitation, dispatcher-assisted CPR,

response time, initial rhythm (non-shockable [PEA, asystole], shockable [VF, pulseless VT]), EMS defibrillation, advanced airway (bag-mask, intubation, other airway devices), epinephrine administration (1, 2, ≥ 3), time from EMS contact to hospital arrival.

Discussion

This study examines the association of the favourable neurological outcome between the effect of BCPR and the epinephrine administration time. The results of this study indicate that the effect of BCPR in patients who received epinephrine administration is limited to neurologically intact survival at one month. However, the effect of BCPR favourably affects neurological outcomes when EPI-time is 17 to 25 minutes of IEG, 24 to 48 minutes of LEG. In another time-indexed group, the BCPR was not associated with favourable neurological outcome.

As reported by Ono., *et al*. [17], a response time of ≤ 6.5 minutes is indicated as the threshold for a favourable outcome in bystander witnessed OHCA patients. In our study, because the median response time in the EEG phase was relatively close to the 6.5 minutes of their threshold, the non-BCPR group in the EEG phase were more likely to be favourable outcomes, regardless of BCPR implementation in patients who received epinephrine administration.

The effect of BCPR on survival with favourable cerebral function is well-documented [9-13]. Since AEDs were approved for use by laypeople in 2004, the CPR training course has rapidly spread in Japan. Currently, 1.44 million people participated in training at fire departments (FDs) in 2015. The implementation rate of BCPR in Japan was 44.9% in 2015 and as the spread of dispatcher-assisted CPR and quality-improved BCPR has been shown to improve outcomes [18,19], further improvement in the incidence of dispatcher-assisted CPR is required. In the results of this study and previous studies, the implementation of BCPR is shown to be crucial to enhancing the possibility of favourable outcomes in OHCA patients.

However, as EMS provides advanced care in the pre-hospital setting such as epinephrine for OHCA patients after performed BCPR in many cases, the effect of BCPR should be considered with the influence of epinephrine administration. Previous epinephrine studies have shown that the epinephrine-administered group did not have a better outcome than the non-administered group [20]. Even in the latest large-scale randomised controlled trial, published by Perkins., *et al*. [21], there was no significant difference in neurologically intact survival at one month, although a significant difference was observed in both ROSC and one-month survival. Furthermore, Perkins., *et al.* and other researchers have also pointed out that epinephrine increases the proportion of cases with cerebral damage [2,3,21]. These negative effects need to be considered. Furthermore, because recent epinephrine studies have emphasised that the effects of epinephrine depend on the timing of administration [5-7,22-24], we focused not only on epinephrine administration but on EPI-time. In present study, the association of favourable cerebral function between the effects of BCPR and EPI-time was found, especially in the IEG and LEG phases.

As the effects of BCPR in the IEG and LEG phases were higher than in the non-BCPR group, it was determined that BCPR still affected the odds of a favourable outcome, even when epinephrine administration was delayed from the early phase according to the results of our multivariable logistic regression analysis. This result could prove crucial for regions in which epinephrine administration is delayed from the early phase because of various factors.

This study has several limitations: this was an observational study, which may introduce unknown biases that have not been removed. The influences of patients' backgrounds and in-hospital procedures thought to affect long-term prognosis, such as temperature management, were not considered in this study [25]. Because this study did not consider the quality of CPR by either bystanders or EMS, an evaluation of the quality of CPR using devices is a worthwhile direction for further research. It is unknown whether the EMS provided manual or mechanical CPR, because the Japanese Utstein-style database did not include these variables. Due to the quality of data, this study did not consider the time from patient collapse to BCPR or the duration of BCPR, which may affect outcomes [26]. Cases including PAD implementation were removed from the dataset, because PAD is one of the most effective acts for witnessed OHCA patients. As this study included cases of witnessed cardiogenic OHCA in patients aged 15 to 90, its conclusions cannot be generalized to unwitnessed, non-cardiogenic, or pediatric OHCA.

Conclusion

This study finds that the association of the favourable neurological outcome between the effect of BCPR and the time of epinephrine administration in witnessed cardiogenic OHCA patients. The effect of BCPR in patients who received epinephrine administration favourably affects neurological outcomes in the time phases which stratified by EPI-time of 17 to 25, 24 to 48 minutes, as compared to the non-BCPR group.

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Conflict of Interest

All authors declare that they have no competing interests.

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