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Supplementary Files

Supplementary File 1

Table S1. Patient and EMS Pediatric OHCA Characteristics by Region in Japan and Age Group

Table S2. Pediatric OHCA Outcome by Region in Japan and Age Group

Please find supplementary file(s);
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RESEARCH ARTICLE Open Access

An association between systolic blood pressure and stroke among patients with impaired consciousness in out-of-hospital emergency settings

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Abstract

Background: Stroke is difficult to diagnose when consciousness is disturbed. However few reports have discussed the clinical predictors of stroke in out-of-hospital emergency settings. This study aims to evaluate the association between initial systolic blood pressure (SBP) value measured by emergency medical service (EMS) and diagnosis of stroke among impaired consciousness patients.

Methods: We included all patients aged 18 years or older who were treated and transported by EMS, and had impaired consciousness (Japan Coma Scale ≧ 1) in Osaka City (2.7 million), Japan from January 1, 1998 through December 31, 2007. Data were prospectively collected by EMS personnel using a study-specific case report form. Multiple logistic regressions assessed the relationship between initial SBP and stroke and its subtypes adjusted for possible confounding factors.

Results: During these 10 years, a total of 1,840,784 emergency patients who were treated and transported by EMS were documented during the study period in Osaka City. Out of 128,678 with impaired consciousness, 106,706 who had prehospital SBP measurements in the field were eligible for our analyses. The proportion of patients with severe impaired consciousness significantly increased from 14.5% in the <100 mmHg SBP group to 27.6% in the > =200 mmHg SBP group (*P* for trend <0.001). The occurrence of stroke significantly increased with increasing SBP (adjusted odd ratio [AOR] 1.34, 95% confidence interval [CI] 1.33 to 1.35), and the AOR of the SBP > =200 mmHg group versus the SBP 101-120 mmHg group was 5.26 (95% CI 4.93 to 5.60). The AOR of the SBP > =200 mmHg group versus the SBP 101-120 mmHg group was 9.76 in subarachnoid hemorrhage (SAH), 16.16 in intracranial hemorrhage (ICH), and 1.52 in ischemic stroke (IS), and the AOR of SAH and ICH was greater than that of IS.

Conclusions: Elevated SBP among emergency patients with impaired consciousness in the field was associated with increased diagnosis of stroke.

Keywords: Systolic blood pressure, Prehospital, Impaired consciousness

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Background

Stroke is an important public health problem in the industrialized world [1] and there are 300,000 estimated strokes encounter in the prehospital settings annually Japan [2]. To improve neurologic outcomes after stroke, earlier identification and treatment is most important, but it takes longer time for EMS personnel to transport emergency stroke patients to the stroke centers if EMS personnel could not appropriately recognize these patients [3]. If EMS personnel can discriminate patients with stroke in prehospital settings, these patients can be transported fast to appropriate hospitals that offer advanced treatments such as thrombolytic therapy and interventional radiology.

Importantly, it is difficult to assess neurological findings such as paralysis of stroke in patients with impaired consciousness, and an alternative way to select these patients would, therefore, be needed. Although a lot of studies have showed the positive association between systolic blood pressure (SBP) and the risk of stroke occurrence [4], little is known about the relationship between SBP measured by EMS personnel and the risk of stroke occurrence among patients with impaired consciousness.

Osaka City is a largest urban community in western Japan with approximately 2.7 million population, and approximately 200,000 ambulance runs documented annually since January 1998. The purpose of this study was to evaluate the relationship between SBP measured by EMS in prehospital settings and stroke occurrence among emergency patients with impaired consciousness.

Table 1 Japan Coma Scale for grading impaired consciousness

Mild disturbance:
The patient is awake without any stimuli, and is
1. Almost completely conscious,
2. Unable to recognize time, place and person,
3. Unable to recall name and date of birth.
Moderate disturbance:
The patient can be aroused
10. Easily by being spoken to,
*(responsive with purposeful movements, phrases, or word)
20. With loud voice or shaking the shoulders,
*(almost steadily responsive with very simple words-yes or no, or movements)
30. Only by repeated mechanical stimuli.
Then, the patient falls into the previous state by cessation of stimulation.
Severe disturbance:
The patient cannot be aroused by any forceful mechanical noise stimuli, and
100. Responds with movements to avoid the stimulus,
200. Responds with slight movements including decerebrate and decorticate postures,
300. Does not respond at all except for change in respiratory rhythm.

*Used in patients who cannot open their eyes for any reason.
This table was revised from Reference [5].

Methods

Study design, population, and setting

This is a retrospective, population-based observational study based on the ambulance records of Osaka Municipal Fire Department. The study period was from January 1, 1998 to December 31, 2007. This study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine.

All adult patients aged > =18 years who suffered impaired consciousness, and were transported to medical institutions by EMS in Osaka City were enrolled in this study. Diagnoses of stroke and its subtypes such as subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), and ischemic stroke (IS) were clinically determined by the physicians caring for the patients in collaboration with the EMS personnel.

Japan Coma Scale

Table 1 shows Japan Coma Scale (JCS) for grading impaired consciousness [5]. The level of consciousness among emergency patients was recorded by EMS personnel according to JCS. The JCS is a simple way for evaluating neurological disturbance focused on patient's awareness. EMS personnel have generally been using it in prehospital settings. The JCS was roughly divided into the three categories (e.g., mild disturbance, moderate disturbance, and severe disturbance).

Emergency medical service systems and hospitals in Osaka City

Osaka City, which is a largest urban community in western Japan, has an area of 222 km^2, and its population was approximately 2.7 million in 2000 (population density, approximately 12,000 persons/km^2). The municipal EMS system has been previously described [6]. Briefly, the EMS system is operated by the Osaka Municipal Fire Department and activated by dialing 119 on the telephone. There were 25 fire stations and a dispatch center in 2007 in Osaka City [7]. Life support is provided 24 hours every day. Usually, each ambulance has a crew of three emergency providers including at least one Emergency Life-Saving Technician (ELST), a highly-trained prehospital emergency care provider. Osaka City included 194 hospitals (34,209 beds) in 2007. Of them, 90 hospitals including 5 critical care centers can accept patients transported by ambulance [8].

Data collection and quality control

Data were uniformly collected using the specific forms that included sex, age, location, vital signs such as first documented systolic and diastolic blood pressure measured manually with sphygmomanometer, heart rate, respiratory rate, and oxygen saturation. The diagnosis was determined by the physician responsible for the care of the patient before admission in the emergency department. The data form was filled out by the EMS personnel in cooperation with the physicians caring for the patient, transferred to the EMS Information Center of Osaka Municipal Fire Department, and then checked by the investigators. If the data sheet was incomplete, the investigators returned it to the relevant EMS personnel for data completion.

Statistical analysis

The association between the occurrence risk of stroke and SBP (every 20 mmHg) was *"a priori"* analyzed considering its subtype (SAH, ICH, or IS). Patient characteristics with and without SBP measurements were evaluated with the use of the *t*-test for numeric variables and the chi-square test for categorical variables. Trends in categorical values and numerical values were tested with logistic regression models and linear tests for trend, respectively. Multiple logistic regression analysis was used to assess the occurrence risk of stroke and its subtype among emergency patients with impaired consciousness by 20 mmHg stratum; Adjusted Odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated. Potential confounding factors were sex, age, and level of consciousness. In addition, the relationship between prehospital SBP and stroke occurrence by impaired consciousness level was evaluated. Statistical analyses were performed with SPSS statistical package version 17.0 J (SPSS, INC., Chicago, IL). *P* value of <0.05 was considered statistically significant.

Results

During these 10 years, a total of 1,840,784 emergency patients were documented during the study period in Osaka City (Figure 1). Among 1,463,890 adult patients, 643,141 had medical causes excluding obstetrical and trauma causes, 128,678 yielded an impaired consciousness, and 106,706 with prehospital SBP data were eligible for our analyses.

Table 2 shows the characteristics between 106,706 patients with SBP value and 21,972 patients without SBP value. In patients with SBP, mean men age was 63.1 years, and 54.2% were male. The proportion of mild impaired consciousness was 70.7%, moderate impaired consciousness 15.9%, and severe impaired consciousness 13.4%, respectively. Forty-nine percent of patients with impaired consciousness were assessed in a private residence. Mean initial SBP was 139.5 mmHg. Time interval from call to hospital arrival was 25.1 minutes. Although there were statistically significant differences because of the very large number, the characteristics between the groups were almost similar.

Table 3 shows the characteristics of eligible patients with impaired consciousness by prehospital SBP. As a whole, the proportion of patients with severe impaired consciousness significantly increased from 14.5% in the <100 mmHg SBP group to 27.6% in the > =200 mmHg SBP group (*P* for trend <0.001). Because there was an increase on the proportion of severe disturbance from 10.6% in the 101–120 mmHg group to 14.5% in the = <100 mmHg suggesting that low BP might be a factor in the altered mentation, the group with 101–120 mmHg SBP was defined as a

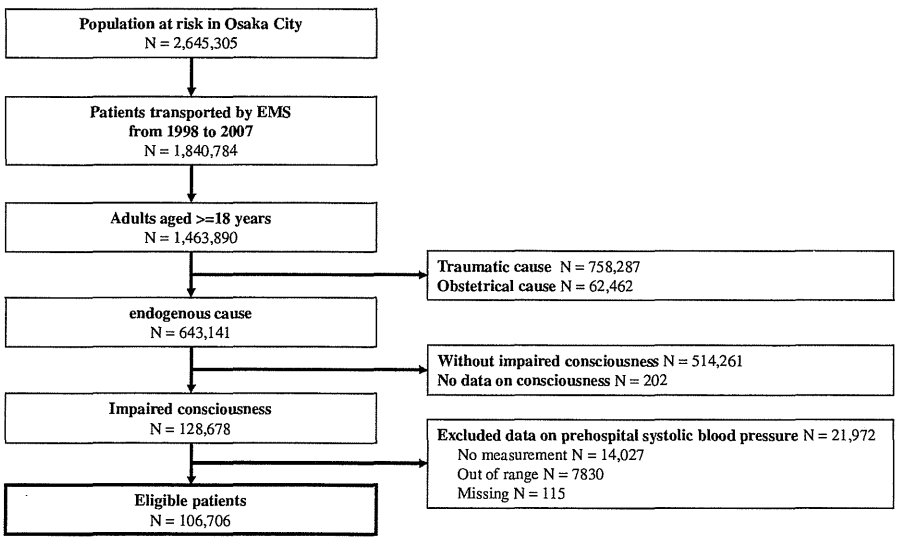

Figure 1 Study flow of emergency patients from January 1, 1998 to December 31, 2007. EMS: emergency medical service.

Table 2 Characteristics of eligible and non-eligible patients

	Eligible (N = 106,706)	No eligible (N = 21,972)	P value
Men, n (%)	57,879 (54.2)	13,341 (60.7)	<0.001
Age, year, mean (SD)	63.1 (20.7)	62.3 (20.4)	<0.001
> = 75 years, n (%)	37,793 (35.4)	7167 (32.6)	<0.001
Consciousness, n (%)			<0.001
Mild disturbance	75,437 (70.7)	12,573 (57.2)	
Moderate disturbance	16,979 (15.9)	2121 (9.7)	
Severe disturbance	14,290 (13.4)	7278 (33.1)	
Home, n (%)	52,936 (49.6)	10,164 (46.3)	<0.001
SBP, mmHg, mean (SD)	139.5 (36.1)	—	
DBP, mmHg, mean (SD)	77.8 (21.1)	—	
HR, counts per a minute, mean (SD)	89.0 (22.3)	70.7 (39.9)	<0.001
SpO_2, %, median (IQR)	96 (94–98)	95 (88–98)	<0.001
Call to arrival at the scene, minute, mean (SD)	6.3 (2.5)	6.1 (2.5)	<0.001
Call to contact with patients, minute, mean (SD)	7.5 (2.7)	7.2 (2.8)	<0.001
Call to hospital arrival, minute, mean (SD)	25.1 (8.6)	22.3 (8.7)	<0.001

SBP denotes systolic blood pressure, DBP diastolic blood pressure, HR heart rate; SD standard deviation, IQR inter-quartile range.

reference group to show the relationship between prehospital SBP and stroke occurrence among patients with impaired consciousness.

The proportions of patients with or without stroke according to the SBP were noted in Table 4. Among patients with impaired consciousness, 31.0% had the proportion of stroke (SAH 1.5%, ICH 6.3%, and IS 23.2%, respectively). This significantly increased from 17.1% to 63.7% (*P* for trend <0.001). The trends by the subtype of stroke were qualitatively similar.

Figure 2 shows the relationship between SBP measured by EMS in prehospital settings and stroke occurrence among patients with impaired consciousness. The occurrence of stroke significantly increased with increasing SBP (AOR 1.34, 95% CI 1.33 to 1.35), and the AOR of the SBP > =200 mmHg group versus the SBP 101-120 mmHg group was 5.26 (95% CI 4.93 to 5.60). In the subgroup analyses in the Figure 3, the AOR for 20 mmHg-increment of SBP was 1.48 (95% CI 1.43 to 1.52) in SAH, 1.69 (95% CI 1.66 to 1.72) in ICH, and 1.14 (95% CI 1.13 to 1.15) in IS, and the AOR of SAH and ICH was greater than that of IS. The AOR of the SBP > =200 mmHg group versus the SBP 101-120 mmHg group was 9.76 (95% CI 7.86 to 12.12) in SAH, 16.16 (95% CI 14.43 to 18.10) in ICH, and 1.52 (1.42 to 1.62) in IS, and the AOR of SAH and ICH was greater than that of IS.

Table 5 shows the relationship between prehospital SBP and stroke occurrence by impaired consciousness level. The AOR of the SBP > =200 mmHg group versus the SBP 101-120 mmHg group was 16.84 (95% CI 11.71 to 24.21) in mild disturbance and 11.55 (95% CI 6.70 to 19.90) in moderate disturbance among SAH patients,

Table 3 Characteristics of patients with impaired consciousness according to prehospital systolic blood pressure

	SBP (mmHg)						
	= < 100 (N = 14,410)	101-120 (N = 22,352)	121-140 (N = 23,776)	141-160 (N = 19,465)	161-180 (N = 12,970)	181-200 (N = 7791)	> = 201 (N = 5942)
Age, year, mean (SD)	64.0 (21.0)	57.2 (22.4)	59.5 (22.3)	65.2 (19.1)	68.7 (15.9)	70.1 (14.1)	69.9 (13.2)
> = 75 years, n (%)	5485 (38.1)	6743 (30.2)	7639 (32.1)	7294 (37.5)	5243 (40.4)	3212 (41.2)	2177 (36.6)
Men, n (%)	7434 (51.6)	11,221 (50.2)	12,962 (54.5)	11,227 (57.7)	7357 (56.7)	4312 (55.3)	3366 (56.6)
Consciousness, n (%)							
Mild disturbance	9915 (68.8)	16,547 (74.0)	17,705 (74.5)	14,081 (72.3)	8948 (69.0)	4977 (63.9)	3264 (54.9)
Moderate disturbance	2408 (16.7)	3425 (15.3)	3608 (15.2)	3014 (15.5)	2092 (16.1)	1392 (17.9)	1040 (17.5)
Severe disturbance	2087 (14.5)	2380 (10.6)	2463 (10.4)	2370 (12.2)	1930 (14.9)	1422 (18.3)	1638 (27.6)

SBP denotes systolic blood pressure, SD standard deviation.

Table 4 Proportion of stroke patients with impaired consciousness according to prehospital systolic blood pressure

		SBP (mmHg)						
	All	=< 100	101-120	121-140	141-160	161-180	181-200	> = 201
	(N = 106,706)	(N =14,410)	(N =22,352)	(N =23,776)	(N =19,465)	(N =12,970)	(N =7791)	(N =5942)
Stroke, n (%)	33,084 (31.0)	2467 (17.1)	4515 (20.2)	6050 (25.4)	6752 (34.7)	5506 (42.5)	4008 (51.4)	3786 (63.7)
SAH, n (%)	1631 (1.5)	81 (0.6)	124 (0.6)	243 (1.0)	285 (1.5)	270 (2.1)	286 (3.7)	342 (5.8)
ICH, n (%)	6699 (6.3)	228 (1.6)	434 (1.9)	709 (3.0)	1100 (5.7)	1260 (9.7)	1274 (16.4)	1694 (28.5)
IS, n (%)	24,754 (23.2)	2158 (15.0)	3957 (17.7)	5098 (21.4)	5367 (27.6)	3976 (30.7)	2448 (31.4)	1750 (29.5)
No stroke, n (%)	73,622 (69.0)	11,943 (82.9)	17,837 (79.8)	17,726 (74.6)	12,713 (65.3)	7464 (57.5)	3783 (48.6)	2156 (36.3)

SBP denotes systolic blood pressure, SAH subarachnoid hemorrhage, ICH intracranial hemorrhage, IS ischemic stroke.

and 21.19 (95% CI 17.86 to 25.13) in mild disturbance, 13.58 (95% CI 10.71 to 17.22) in moderate disturbance, and 12.61 (95% CI 10.35 to 15.35) in severe disturbance among ICH patients.

Discussion

From this large registry of ambulance records, we demonstrated a significant positive relationship between prehospital SBP and the risk of stroke occurrence among emergency patients with impaired consciousness. Although little attention has been paid to SBP measured by EMS in prehospital settings in terms of diagnostic information for stroke, this large population-based registry enabled us to evaluate the relationship between prehospital SBP and stroke occurrence among these patients, and would add new insights on the importance of prehospital SBP measurement. Our results also suggest that prehospital SBP measurements in the patient with impaired conscious level might be a helpful guide as to where to transport a patient especially in communities that have both comprehensive stroke centers and primary ischemic stroke centers.

This study showed that the risk of stroke occurrence among emergency patients with impaired consciousness increased with increasing prehospital SBP. A previous study showed that initial SBP at emergency department arrival was of help for diagnosing intracranial lesion of patients with impaired consciousness [9]. However, diagnosis after hospital arrival is too late to transport the stroke patient to appropriate institution and start treatments against stroke in the effective time window [10]. Guidelines for the Early Management of Adults With Ischemic Stroke by American Heart Association recommend quicker transportation of suspected stroke patients to stroke care units to improve better neurological outcome [11]. Importantly, paralysis of stroke patients is frequently difficult to evaluate when their consciousness is disturbed. Therefore, this study showing the association between prehospital SBP measurements and stroke occurrence among patients with impaired consciousness would contribute to earlier detection of stroke and subsequent rapid transport to appropriate hospitals that can conduct specific treatments for them.

In analyses by stroke subtype, increased SBP was more strongly associated with occurrence of stroke among patients with hemorrhagic brain lesions such as SAH and ICH. The mechanism of hypertensive response among stroke patients is unclear [12] although patients with

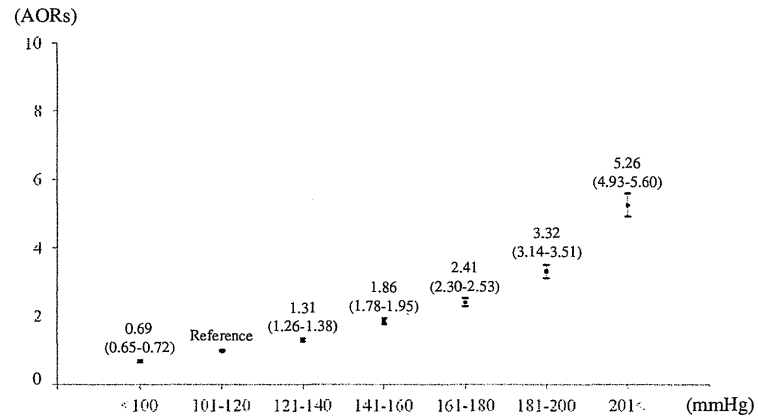

Figure 2 Relationship between SBP measured by EMS personnel in prehospital settings and the risk of stroke occurrence among patients with impaired consciousness. AORs: adjusted odds ratios.

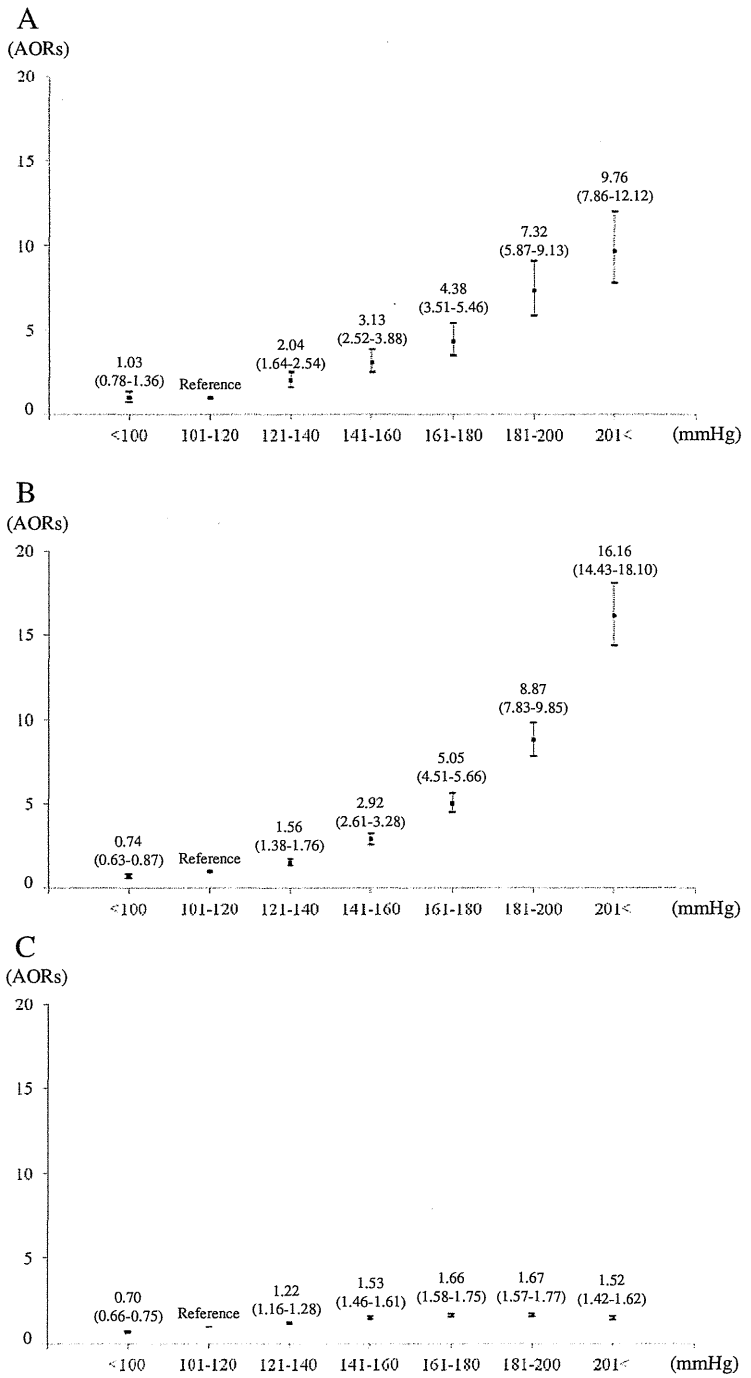

Figure 3 Relationships between SBP measured by EMS personnel in prehospital settings and the risk of stroke occurrence by its stroke subtype among patients with impaired consciousness. (A) SAH, **(B)** ICH, and **(C)** IS. AORs; adjusted odds ratios; SAH: subarachnoid hemorrhage; IS: ischemic stroke; ICH: intracranial hemorrhage.

acute stroke and those with increased intracranial pressure often have hypertension. It was reported that 84% of patients with stroke had increased blood pressure in the acute phase [13]. The arterial pressure elevation in response to cerebral ischemia is known as the central nervous system ischemic response [14]. In ischemic stroke, hypertension maybe adaptive response to improve perfusion to the ischemic penumbra protecting

Table 5 Relationship between prehospital SBP and stroke occurrence by impaired consciousness level

		SBP (mmHg)						
		= < 100	101-120	121-140	141-160	161-180	181-200	> = 201
Stroke	Mild disturbance	0.70 (0.65-0.75)	Reference	1.30 (1.23-1.38)	1.78 (1.68-1.88)	2.31 (2.17-2.45)	2.98 (2.78-3.20)	4.30 (3.96-4.66)
	Moderate disturbance	0.66 (0.58-0.75)	Reference	1.29 (1.16-1.44)	2.05 (1.84-2.29)	2.55 (2.26-2.87)	3.57 (3.12-4.08)	6.69 (5.72-7.82)
	Severe disturbance	0.70 (0.61-0.80)	Reference	1.39 (1.23-1.56)	2.03 (1.80-2.29)	2.75 (2.42-3.12)	4.80 (4.15-5.56)	8.21 (7.04-9.56)
SAH	Mild disturbance	0.99 (0.60-1.63)	Reference	2.35 (1.66-3.34)	3.75 (2.64-5.32)	5.91 (4.13-8.45)	8.91 (6.14-12.94)	16.84 (11.71-24.21)
	Moderate disturbance	1.01 (0.50-2.09)	Reference	2.34 (1.36-4.03)	3.59 (2.10-6.15)	5.08 (2.93-8.78)	9.92 (5.81-16.93)	11.55 (6.70-19.90)
	Severe disturbance	0.98 (0.66-1.46)	Reference	1.72 (1.23-2.39)	2.50 (1.81-3.45)	3.12 (2.25-4.32)	5.35 (3.89-7.37)	6.23 (4.58-8.48)
ICH	Mild disturbance	0.74 (0.57-0.96)	Reference	1.76 (1.47-2.10)	3.17 (2.67-3.76)	5.82 (4.91-6.90)	10.90 (9.17-12.94)	21.19 (17.86-25.13)
	Moderate disturbance	0.45 (0.31-0.67)	Reference	1.14 (0.88-1.48)	2.68 (2.11-3.39)	4.64 (3.67-5.87)	7.19 (5.66-9.14)	13.58 (10.71-17.22)
	Severe disturbance	0.88 (0.68-1.13)	Reference	1.62 (1.31-2.01)	2.80 (2.28-3.43)	4.35 (3.55-5.33)	7.34 (5.98-9.00)	12.61 (10.35-15.35)
IS	Mild disturbance	0.70 (0.65-0.75)	Reference	1.23 (1.16-1.30)	1.59 (1.47-1.65)	1.77 (1.67-1.89)	1.83 (1.70-1.97)	1.75 (1.60-1.90)
	Moderate disturbance	0.70 (0.61-0.81)	Reference	1.26 (1.12-1.41)	1.65 (1.47-1.86)	1.63 (1.44-1.85)	1.68 (1.46-1.93)	1.84 (1.58-2.15)
	Severe disturbance	0.67 (0.58-0.78)	Reference	1.15 (1.00-1.31)	1.27 (1.12-1.45)	1.26 (1.10-1.44)	1.16 (1.00-1.34)	0.91 (0.78-1.06)

SBP denotes systolic blood pressure, SAH subarachnoid hemorrhage, ICH, intracranial hemorrhage, IS ischemic stroke.
Odds ratio were adjusted for sex and age.

the brain from further ischemia. On the other hand, hypertension in hemorrhagic brain lesion like SAH or ICH may cause further damage by worsening cerebral edema, increasing intracranial pressure, or causing hematoma expansion [15,16]. Our result showing difference by the subtype of stroke might be partially explained by such pathophysiological differences between hemorrhagic and ischemic lesions.

From our results, emergency patients with impaired consciousness and high SBP should be considered to be transported to the comprehensive stroke centers with capabilities of either neurosurgery or tissue plasminogen activator (t-PA) administration because these patients might have stroke but prehospital EMS personnel could not distinguish brain hemorrhagic lesions from ischemic ones. In addition, this study showed the strong relationship between high prehospital SBP and the occurrence of SAH and ICH, and those patients should be treated as quick as possible in order to prevent re-rupture of aneurysms and recurrent bleeding [17,18]. Especially, the strength of association between SBP and stroke subtype by impaired conscious level was very powerful with ICH and to some extent with SAH (mild and moderate disturbances), which would suggest that prehospital SBP can be an important triage guide for selecting patients. Further studies identifying an accurate cutoff point in this regard for SBP in conjunction with level of consciousness would make the EMS triage decision more precise and reduces the risk of overwhelming comprehensive stroke centers with patients that do not need the advanced capabilities. On the other hand, the relationship between SBP in prehospital settings and the occurrence of IS was relatively small. Therefore, to improve positive predictive value for IS patients who are most treatable, development of additional clinical indicators should be found out to make it possible to transport patients with IS to the primary ischemic stroke centers where only t-PA administration could be performed.

There were some limitations to this study. First, in Japan, EMS personnel evaluated level of consciousness among prehospital emergency patients by using JCS rather than the commonly-used Glasgow Coma Scale (GCS). JCS is not preferable to GCS as a consciousness evaluation system in the acute phase of SAH [19]. However, traditionally in Japanese prehospital setting, EMS has been evaluating stroke patients with impaired consciousness by JCS. Although our study cannot compare with GCS directly, these results should, nevertheless, provide useful information on the relationship between SBP and stroke occurrence among patients with impaired consciousness. Second, this study did not obtain data on advanced treatments and neurological outcomes among stroke patients after hospital arrival. Third, data on patient's past history and medications that might affect the occurrence of stroke was lacking. Fourth, we did not obtain information on other diagnosis that could mimic stroke such as hypoglycemia, complicated migraine, prolonged seizures, and subdural hematomas. Finally, there might be unmeasured confounding factors and selection bias that might have influenced the relationship between prehospital SBP and stroke occurrence among emergency patients with impaired consciousness.

Conclusions

Elevated SBP among emergency patients with impaired consciousness in the field was associated with the increased risk of stroke. Additional research is necessary to determine if field diagnosis of stroke with measuring BP improves procession of care or outcome.

Abbreviations
SBP: Systemic blood pressure; EMS: Emergency medical service; AOR: Adjusted odds ratio; CI: Confidence interval; SAH: Subarachnoid hemorrhage; IS: Ischemic stroke; ICH: Intracranial hemorrhage; JCS: Japan come scale; ELST: Emergency life-saving technician; CIs: Confidence intervals; GCS: Glasgow Come Scale.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
TI, TI, TK, CN, TS, KT, SH, TN, TS, OT, TK, AH, and TS participated in the idea formation, study design, data analyses, interpretation of results and writing of the report. All the authors read and approved the final manuscript.

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ORIGINAL ARTICLE
Critical Care

Impact of Early Intravenous Epinephrine Administration on Outcomes Following Out-of-Hospital Cardiac Arrest

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Background: The effectiveness of epinephrine administration for cardiac arrests has been shown in animal models, but the clinical effect is still controversial.

Methods and Results: A prospective, population-based, observational study in Osaka involved consecutive out-of-hospital cardiac arrest (OHCA) patients from January 2007 through December 2009. We evaluated the outcomes among adult non-traumatic bystander-witnessed OHCA patients for whom the local protocol directed the emergency medical service personnel to administer epinephrine. After stratifying by first documented cardiac rhythm, outcomes were compared among the following groups: non-administration, ≤10, 11–20 and ≥21 min as the time from emergency call to epinephrine administration. A total of 3,161 patients were eligible for our analyses, among whom 1,013 (32.0%) actually received epinephrine. The epinephrine group had a significantly lower rate of neurologically intact 1-month survival than the non-epinephrine group (4.1% vs. 6.1%, P=0.028). In cases of ventricular fibrillation (VF) arrest, patients in the early epinephrine group who received epinephrine administration within 10 min had a significantly higher rate of neurologically intact 1-month survival compared with the non-epinephrine group (66.7% vs. 24.9%), though other epinephrine groups did not. In cases of non-VF arrest, the rate of neurologically intact 1-month survival was low, irrespective of epinephrine administration.

Conclusions: The effectiveness of epinephrine after OHCA depends on the time of administration. When epinephrine is administered in the early phase, there is an improvement in neurological outcome from OHCA with VF. (*Circ J* 2012; **76:** 1639–1645)

Key Words: Cardiac arrest; Cardiopulmonary resuscitation; Epidemiology; Epinephrine; Sudden death

Sudden cardiac arrest is one of the most important public health problems in developed countries,[1] and approximately 60,000 cases occur every year in Japan.[2] To improve survival from out-of-hospital cardiac arrest (OHCA), it is also important to improve the "chain of survival",[3] in which epinephrine administration is a major component of advanced life support (ALS) measures.[1]

Although epinephrine is one of the most widely used resuscitation drugs across the world, its benefits and risks remain controversial.[4–8] Recently, a major randomized controlled trial (RCT), which assessed survival from OHCA with and without drug administration including epinephrine in the prehospital setting, failed to show improved survival by drug administration, and concluded that it should not be recommended before hospital arrival.[9]

Interestingly, animal studies have indicated that epinephrine improves survival after cardiac arrests.[10–13] Differences in epinephrine's effects between human and animal studies might be explained by the time difference in epinephrine administration, because the mean time to administer epinephrine in animal studies has been 10 min, against 20 min in human studies.[14–16] Therefore, because the effectiveness of epinephrine might be time-dependent, early administration might improve survival in clinical settings, though no studies have been conducted to evaluate the time-dependent effectiveness of epinephrine for OHCA patients. In addition, some studies have

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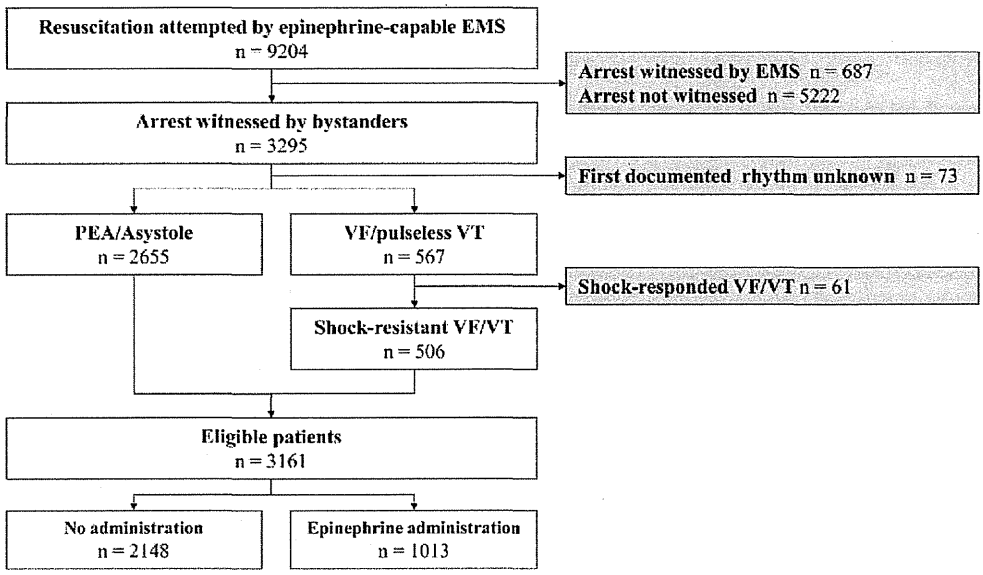

Figure 1. Overview of epinephrine-capable EMS-treated cardiac arrests with an abridged Utstein template from January 1, 2007 through December 31, 2009. EMS, emergency medical service; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.

suggested that survival after epinephrine administration would differ depending on the cardiac rhythm (ventricular fibrillation [VF] or non-VF rhythm).[4,9]

In Japan, since July 2006, intravenous epinephrine administration by specially trained emergency life saving technicians (ELSTs) under strict medical directions has been legally permitted. The Utstein Osaka Project is a large prospective population-based cohort study of OHCA in Osaka, Japan, covering approximately 8.8 million inhabitants.[17,18] Using this database, we collected over 3,000 cases of adult non-traumatic bystander-witnessed OHCA patients who were considered for treatment with epinephrine administration under medical direction (either shock-resistant VF or witnessed arrest with pulseless electrical activity [PEA]/asystole). We then examined the effects of epinephrine on neurological outcomes following OHCA, considering the time to epinephrine administration and the first documented cardiac rhythm. We hypothesized that early intravenous epinephrine administration within 10 min after OHCA occurrence would improve neurological outcomes compared with non-epinephrine administration, and that the effect would differ by the type of first documented cardiac rhythm.

Methods

Study Design and Setting

The Osaka Utstein registry is a large-scale, prospective, population-based registry of OHCA based on the standardized Utstein style.[19,20] In this observational study, we enrolled all patients aged ≥18 years who had experienced OHCA before the arrival of the emergency medical services (EMS), had been resuscitated by EMS personnel, and then transported to a medical institution in Osaka Prefecture between January 1, 2007 and December 31, 2009. The research protocol was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

Cardiac arrest was defined as the cessation of cardiac mechanical activity, as confirmed by the loss of signs of circulation.[19,20] An arrest was presumed to be of cardiac etiology unless it was caused by trauma, drowning, drug overdose, asphyxia, exsanguination, or any other noncardiac cause. These diagnoses were determined by the physician in charge in collaboration with the EMS rescuers.

EMS System in Osaka

Details of the EMS system in Osaka Prefecture have beendescribed previously.[17] Osaka Prefecture has approximately 8.8 million residents in urban and rural areas totaling 1,892 km^2. As of 2011, there were 35 fire stations with a dispatch center, and their EMS systems are essentially all the same. Each ambulance has 3 emergency providers, including at least 1 ELST, who is a highly trained prehospital emergency care provider. ELSTs are allowed to place an intravenous line, insert an adjunct airway, and use semi-automated external defibrillators for OHCA.[17] Public-access automated external defibrillators were introduced after July, 2004. All EMS providers performed cardiopulmonary resuscitation (CPR) according to the Japanese CPR guidelines based on other national CPR guidelines.[1,21–23] EMS providers were not permitted to terminate resuscitation in the field.

Study Patients

Among the non-traumatic bystander-witnessed OHCA patients aged ≥18 years who were resuscitated by epinephrine-capable EMS personnel, those who were eligible for treatment with epinephrine under medical direction (either shock-resistant VF or witnessed arrest with PEA/asystole) were included in these analyses.

Epinephrine Administration by EMS Personnel

In Japan since July 2006, specially trained ELSTs have been legally allowed to administer intravenous epinephrine in the

Table 1. Clinical and EMS Characteristics of Eligible Patients With and Without Epinephrine Administration

	Total	No administration	Epinephrine administration	P value
n	3,161	2,148	1,013	
Age, years, mean (SD)	73.3 (15.2)	73.9 (15.2)	72.1 (15.0)	0.002
Men, n (%)	1,903 (60.2)	1,243 (57.9)	660 (65.2)	<0.001
Public space, n (%)	410 (13.0)	254 (11.8)	156 (15.4)	0.005
Bystander-initiated CPR, n (%)	1,314 (41.6)	898 (41.8)	416 (41.1)	0.694
Cardiac etiology, n (%)	2,126 (67.3)	1,389 (64.7)	737 (72.8)	<0.001
VF, n (%)	506 (16.0)	301 (14.0)	205 (20.2)	<0.001
Endotracheal intubation, n (%)	1,163 (36.8)	854 (39.8)	309 (60.1)	<0.001
Call to EMS arrival, min, mean (SD)	6.3 (2.6)	6.2 (2.5)	6.4 (2.7)	0.177
Call to shock by EMS, min, mean (SD)*	9.1 (3.3)	9.1 (3.2)	9.2 (3.4)	0.541
Call to hospital arrival, min, mean (SD)	30.3 (8.8)	28.6 (8.6)	33.9 (8.4)	<0.001
Call to intravenous epinephrine administration, min, mean (SD)			21.3 (6.9)	

CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; EMS, emergency medical service.
*Calculated for cases with VF as initial cardiac rhythm.

field. They are not allowed, however, to administer intratracheal or intraosseous epinephrine nor other drugs such as vasopressin, atropine, and lidocaine.[24] The local medical protocol directs the ELSTs to administer epinephrine for either shock-resistant VF arrest or witnessed arrest with PEA/asystole under on-line medical direction from the corresponding physician. The protocol allows them to only attempt intravenous access twice, with each attempt lasting no longer than 90 s. The allowable dosage of epinephrine is 1 mg per attempt and they can administer it a total of 3 times every 4 min.

Data Collection and Quality Control

Data were collected prospectively with the use of a data form based on the Utstein-style international guideline of reporting OHCA.[19,20] First documented rhythm was recorded and diagnosed on the scene by EMS personnel with semi-automated defibrillators, then confirmed by the physician responsible for on-line medical direction. The times when an EMS call was received and a vehicle arrived at the scene were recorded automatically at the dispatch center. The initiation of bystander CPR was obtained by EMS personnel interviewing bystanders before leaving the scene. The defibrillation time was recorded by a semi-automated defibrillator, and the epinephrine administration time was recorded by the EMS personnel using their watches, which were synchronized with the clock at their dispatch center.

All OHCA survivors were followed for up to 1 month after the event by the EMS personnel and investigators with the cooperation of the Osaka Medical Association and medical institutions in the Osaka area. Neurological outcome was determined by the physician responsible for the care of the patient at 1 month after a successful resuscitation, 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.[25]

Statistical Analysis

A primary outcome was regarded as neurologically intact 1-month survival as defined by CPC categories 1 or 2.[25] Secondary outcome measures included return of spontaneous circulation (ROSC) before hospital arrival, ROSC (total), hospital admission, and 1-month survival. The outcomes were compared between with and without epinephrine administration, and further compared after stratifying by first documented cardiac rhythm (VF or non-VF). Next, in keeping with our hypothesis that early intravenous epinephrine administration within 10 min after OHCA occurrence should improve neurological outcome, we subdivided the cases of epinephrine administration into 3 groups: ≥10, 11–20 and ≥21 min from the time of the call until epinephrine administration, and compared the patients outcomes with those in the non-epinephrine group.

Statistical Analysis

Patients' and EMS characteristics and outcomes between groups were compared using a t-test for numerical variables and a chi-square test for categorical variables. Multiple logistic regression analysis assessed the association between the time to epinephrine administration and favorable neurological outcome, and the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were included in the multivariate analyses: sex, age, location of cardiac arrest, bystander CPR, etiology, first documented cardiac rhythm, endotracheal intubation, and the year of cardiac arrest (time trend). All statistical analyses were performed using SPSS statistical package version 16.0 J (SPSS, Inc, Chicago, IL, USA). All tests were 2-tailed, and a P value <0.05 was considered statistically significant.

Results

Overview of OHCA Patients in Osaka

Figure 1 is an overview of the study patients based on the Utstein template. A total of 9,204 patients resuscitated by epinephrine-capable EMS personnel were registered. Of them, 3,295 were witnessed by bystanders. Among the witnessed cases, 567 had VF including pulseless ventricular tachycardia, and 2,655 PEA/asystole. After excluding 61 shock-responding VF arrests, 3,161 cases were eligible for our analyses. Of these, 1,013 (32.0%) actually received epinephrine.

Table 2. Outcomes for OHCA With and Without Epinephrine Administration by Epinephrine-Capable EMS

	No administration	Epinephrine administration	P value
n	2,148	1,013	
ROSC before hospital arrival, n (%)	287 (13.4%)	297 (29.3%)	<0.001
ROSC (total), n (%)	1,015 (47.3%)	511 (50.4%)	0.094
Hospital admission, n (%)	881 (41.0%)	432 (42.6%)	0.385
1-month survival, n (%)	258 (12.0%)	137 (13.5%)	0.245
Neurologically intact 1-month survival, n (%)	130 (6.1%)	42 (4.1%)	0.028

OHCA, out-of-hospital cardiac arrest; EMS, emergency medical service; ROSC, return of spontaneous circulation.

Table 3. Outcomes for OHCA With and Without Epinephrine Administration by Epinephrine-Capable EMS According to the First Documented Cardiac Rhythm

	VF as initial cardiac rhythm (n=506)			Non-VF as initial cardiac rhythm (n=2,655)		
	No administration	Epinephrine administration	P value	No administration	Epinephrine administration	P value
n	301	205		1,847	808	
ROSC before hospital arrival, n (%)	96 (31.9%)	61 (29.8%)	0.610	191 (10.3%)	236 (29.2%)	<0.001
ROSC (total), n (%)	189 (62.8%)	108 (52.7%)	0.038	827 (44.8%)	402 (49.8%)	0.018
Admission, n (%)	177 (58.8%)	95 (46.3%)	0.010	705 (38.2%)	336 (41.6%)	0.097
1-month survival, n (%)	109 (36.2%)	61 (29.8%)	0.188	150 (8.1%)	75 (9.3%)	0.347
Neurologically intact 1-month survival, n (%)	76 (25.2%)	29 (14.1%)	0.006	55 (3.0%)	12 (1.5%)	0.027

Abbreviations as in Table 2.

Patients' and EMS Characteristics by Epinephrine Administration

Table 1 shows the characteristics of eligible patients according to epinephrine administration. Mean age was lower in the epinephrine administration group than in the non-administration group, but the male/female ratio was higher in the epinephrine administration group. OHCA among the patients in the epinephrine administration group was more likely to occur in public spaces, be cardiac in etiology and VF, and require endotracheal tube than those in the non-administration group. Although there was no difference between the groups in the time from call to both EMS arrival and defibrillation, the time from call to hospital arrival was significantly longer in the epinephrine administration group than in the non-administration group (33.9 vs. 28.6 min, P<0.001). The mean time from call to epinephrine administration was 21.3 min.

Outcomes by Epinephrine Administration

Table 2 shows the outcomes according to epinephrine administration. Although the rate of ROSC before hospital arrival was significantly higher in the epinephrine administration group than in the non-administration group (29.3% vs. 13.4%, P<0.001), the rate of neurologically intact 1-month survival was lower in them compared with that in the non-epinephrine group (4.1% vs. 6.1%, P=0.028). The outcomes of OHCA according to epinephrine administration and the type of first documented cardiac rhythm are listed in **Table 3**. Although the proportion of ROSC before hospital arrival was significantly higher in the epinephrine administration group than in the non-administration group (29.2% vs. 10.3%, P<0.001) for non-VF arrests, the epinephrine administration group had a significantly lower rate of neurologically intact 1-month survival than the non-administration group among both VF (14.1% vs. 25.2%, P=0.006) and non-VF arrests (1.5% vs. 3.0%, P=0.027).

Time of Epinephrine Administration and Favorable Neurological Outcome by the Type of First documented Cardiac Rhythm

The association between the time from call to epinephrine administration and neurologically intact survival is shown in **Figure 2**. In VF arrests (**Figure 2A**), the early group that received epinephrine within 10 min of the call had a significantly higher rate of neurologically intact 1-month survival compared with the non-epinephrine administration group (66.7% [6/9] vs. 24.9% [75/301]; adjusted OR 6.34, [95%CI 1.49–27.02]), whereas the prolonged epinephrine administration groups (time to epinephrine administration: 11–20 and ≥21 min) did not. In multivariate analysis, provision of bystander CPR was also associated with better neurological outcome (**Figure 3**). In non-VF arrests (**Figure 2B**), however, the proportion of neurologically intact 1-month survival was, however, very low irrespective of the time of epinephrine administration, and there was no significant difference between the groups.

Discussion

From this prospective registry of OHCA, we have demonstrated that early epinephrine administration within 10 min of a cardiac arrest increases 1-month survival with favorable neurological outcome after VF arrest, based on our hypothesis. In Japan, specially trained ELSTs are legally allowed to use only intravenous epinephrine on the scene, and the protocol of epinephrine administration is uniform and strict based on the Japan CPR guidelines.[23] Moreover, all patients enrolled in this study qualified to receive epinephrine. Therefore, we consider that in these situations the possibility of any intentional bias for epinephrine administration would be negligible. Under these uniform conditions, our large-scale population-based observational study covering 8.8 million inhabitants enabled us to evaluate the time-dependent effect of epinephrine on OHCA patients. This is, to our knowledge, the first major

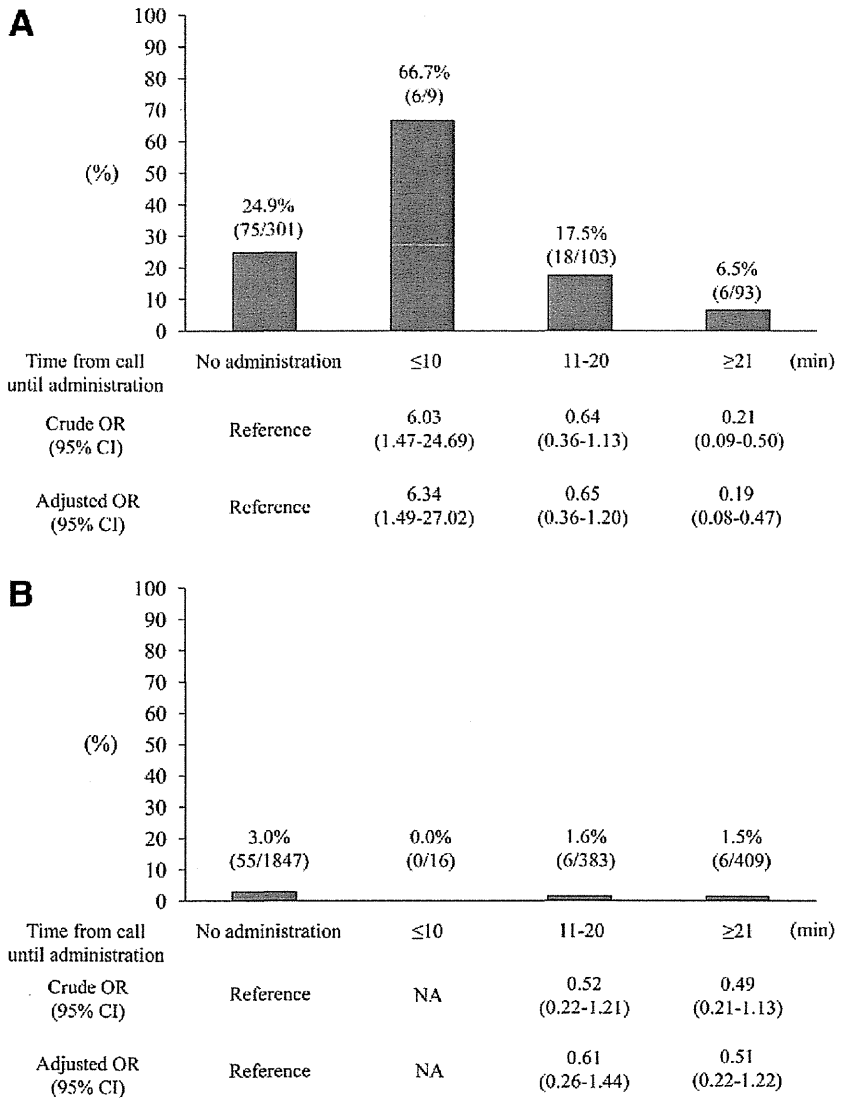

Figure 2. Proportion of neurologically intact 1-month survival by time from call to epinephrine administration among (**A**) VF and (**B**) non-VF arrests. OR, odds ratio; CI, confidence interval; NA, not analyzed; VF, ventricular fibrillation.

clinical study to show that epinephrine administration can improve survival from OHCA in some selected cases.

Although early epinephrine administration increased 1-month survival with favorable neurological outcome after VF arrest, it did not improve neurological outcomes in all cases. These results are consistent with those of some previous observational studies.[4-8] In Singapore, survival from OHCA showed no change between before and after the introduction of intravenous epinephrine administration to the EMS system.[4] The Ontario Prehospital Advanced Life Support (OPALS) study, a large "before-and-after" controlled study of the effects of prehospital care, demonstrated that ALS procedures did not produce improved survival from OHCA.[8] In addition, a large RCT recently failed to show improved survival after drug administration.[9] However, those studies did not sufficiently consider the time- and cardiac rhythm-dependent effectiveness of epinephrine. Our results showing the effectiveness of early epinephrine administration among VF arrests with no overall improvement suggest that the benefit of epinephrine is different by situation such as the timing of administration and the first cardiac rhythm of OHCA patients.

Our findings that epinephrine has an incremental benefit only when the time to administration was within 10 min of the cardiac arrest and lower overall survival in the epinephrine administration group were consistent with recent animal studies,[10-13] in which the time to epinephrine administration was usually within 10 min, compared with 20 min in human studies, as our data showed. The main pharmacological and physiological effects of epinephrine are to increase aortic diastolic pressure as a result of its alpha-adrenergic agonist properties. This can produce high coronary perfusion pressure, and subsequently, high rates of ROSC and survival.[10-13] However, epinephrine also increases myocardial oxygen consumption, and postresuscitation myocardial dysfunction.[26-28] Another animal study indicates that the cardiovascular response to epinephrine varies with the increasing duration of cardiac arrest, and myocardial depression subsequently develops.[29] These can be possible explanations for the positive results in those with early epinephrine administration and the negative result for overall survival of this study. Although this is the first study to suggest the benefit of early epinephrine administration for OHCA in humans, it is clinically very difficult to

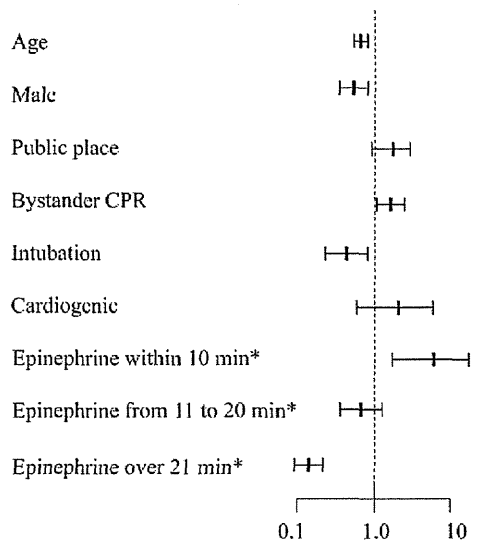

Figure 3. Multivariate-adjusted odds ratios for neurologically intact 1-month survival among ventricular fibrillation arrests. *Reference=no epinephrine. CPR, cardiopulmonary resuscitation.

administer epinephrine in this early period and the number of OHCA patients who received intravenous epinephrine within 10 min after OHCA occurrence was small. Further accumulation of patients who have received epinephrine in the early phase after collapse is needed for better ascertainment of the impact of early epinephrine administration on OHCA.

In this study, a time-dependent effectiveness of epinephrine administration was observed only among OHCA patients who had VF as their first documented rhythm. Some studies suggest that survival after epinephrine administration in OHCAs differs by cardiac rhythms.[4,9] In an RCT[9] and a study from Singapore,[4] the OR of survival in cases of VF arrest was higher compared with non-VF arrests, although the difference was insignificant. Importantly, outcomes were dismal regardless of epinephrine administration among cases of non-VF arrest.

Our data suggest a need to establish a new strategy for the use of epinephrine. Epinephrine use without discrimination should be discontinued, and more targeted use for cardiac arrest patients in the early phase after collapse and those with VF should be considered. In addition, the quality of CPR might have an impact on the effects of epinephrine in OHCA patients.[30] Early epinephrine administration for VF cardiac arrests following early defibrillation together with continuous high-quality chest compressions should contribute to improving survival. For non-VF cardiac arrests, further efforts including not only ALS procedures but also cause-specific therapy would be needed to increase survival.

Even if early epinephrine administration improved survival from OHCA with VF, it remains difficult to administer epinephrine from intravenous access within 10 min on the scene. In this study, patients who received intravenous epinephrine within 10 min after the call accounted for only 2.5% (25/1013) of the patients in the epinephrine administration group. Because ELSTs in Japan are only allowed to administer epinephrine via intravenous access, other routes, such as intraosseous access, for administering epinephrine more quickly should be considered.[31]

Study Limitations

First, as with all observational studies, data integrity, validity, and ascertainment bias are potential limitations. The use of uniform data collection based on the Utstein-style guidelines for reporting cardiac arrest, the large sample size, and a population-based design to cover all known adult cases of OHCA in Osaka were intended to minimize such potential sources of bias. Second, our data do not address potential variability in post-arrest care (hemodynamic support, induced hypothermia, and coronary interventional therapies).[32–35] Third, there could be unmeasured confounding factors that might have influenced the association between epinephrine administration and outcomes.

Further, large-scale observations or RCT are needed to confirm the results.

Conclusions

The effectiveness of epinephrine after OHCA depends on the time of administration. When epinephrine is administered in the early phase, it assists in improving the neurological outcome of OHCA with VF. A new strategy using epinephrine for targeted populations with VF cardiac arrests in the early phase after collapse should be considered.

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Disclosures

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Cerebrorenal Interaction and Stroke

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Abstract

Beyond the original meaning of chronic kidney disease (CKD) as high-risk state for future dialysis, CKD is now known as an established risk factor for cardiovascular diseases. Stroke is a major player of cardiovascular disease and has deep two-way relationships with CKD. CKD is an evident risk factor for stroke. Meta-analyses of cohort studies and trials indicate that proteinuria/albuminuria increases the risk of stroke by 71–92%, and reduced glomerular filtration rate increases the risk by 43%. In addition, CKD has a strong relationship with subclinical brain damage including white matter changes, microbleeds, cognitive impairment, and carotid atherosclerosis. CKD is prevalent in acute stroke patients; patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2 or proteinuria amounted to 46% of total ischemic stroke patients and 39% of total intracerebral hemorrhage patients in our institute. Acute and chronic management of stroke are influenced by CKD. Therapeutic effects of several antithrombotic and thrombolytic agents, including recently-developed novel oral anticoagulants, are affected by renal function. Moreover, reduced glomerular filtration rate is independently associated with increased 1- and 10-year mortalities in the end. Stroke also has deep relationships with end-stage kidney disease. Stroke occurs much more commonly in dialysis patients than general population or CKD patients without need for dialysis. The triggers of ischemic and hemorrhagic stroke in patients with end-stage kidney disease include special characteristics unique to dialysis, such as drastic hemodynamic change, dialysate and anticoagulants, and vascular calcification. As cohorts of dialysis patients become older, more hypertensive, and more diabetic than before, stroke become more prevalent and more serious events in dialysis clinics. Now, clinicians should have much interest in the association between CKD and cerebrovascular diseases, so-called the cerebro-renal interaction.

More than ten years have passed since the National Kidney Foundation in the United States first advocated the concept of chronic kidney disease (CKD) [1], and it is now seen as a major public health problem. According to the 2002 ver-

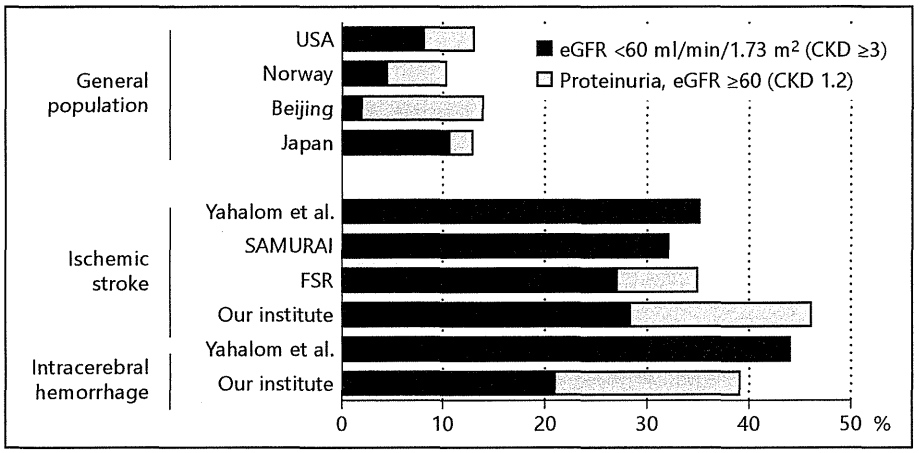

Fig. 1. The prevalence of eGFR <60 ml/min/1.73 m^2 or proteinuria in both the general population and stroke patients. Cited from refs. 2–5 and 12–14. Note that both eGFR and proteinuria in stroke patients were measured during the acute stage of stroke, and thereby might have been affected by stroke damage.

sion of the guideline, the prevalence estimates of CKD in the United States (1999–2004) were as follows [1]: 1.8% (95% CI 1.4–2.3%) for stage 1 (estimated glomerular filtration rate (eGFR) >90 ml/min/1.73 m^2 and albuminuria); 3.2% (95% CI 2.6–3.9%) for stage 2 (GFR 60–89 ml/min/1.73 m^2 and albuminuria); 7.7% (95% CI 7.0–8.4%) for stage 3 (GFR 30–59 ml/min/1.73 m^2), and 0.35% (0.25–0.45%) for stage 4 (GFR 15–29 ml/min/1.73 m^2) [2]. Estimates were 2.7 ± 0.3, 3.2 ± 0.4, 4.2 ± 0.1, and 0.2 ± 0.01%, respectively, in Norway (1995–1997) [3]; 7.4% (95% CI 6.9–7.8%), 4.7% (4.4–5.1%), 1.8% (1.5–2.0%), and none, respectively, in Beijing [4], and 0.6, 1.7, 10.4, and 0.2% (including CKD stage 5 without dialysis), respectively, in Japan (2005) [5] (fig. 1). Thus, more than one tenth of the general population worldwide is estimated to have CKD, and its prevalence increases dramatically with age.

Beyond the original meaning of CKD as a high-risk state for future dialysis, CKD is now known to be an established risk factor for cardiovascular diseases. This message was clarified by the Kaiser Permanente Renal Registry involving more than one million adults [6]. An independent, graded association was observed between a reduced eGFR and the risk of death and cardiovascular events including stroke. Since then, many studies have proven the positive association of CKD with risk and outcomes of cardiovascular disease. The reason for the positive association is partly the high prevalence of traditional cardiovascular risk factors in CKD patients. In addition, nontraditional risk factors, including endothelial dysfunction, maladaptive arterial remodeling,

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homocysteinemia, coagulation disorders, impaired endothelial release of tissue plasminogen activator (t-PA), extravascular coagulation, anemia, and higher levels of inflammatory cytokines and oxidative stress, seem to increase the risk of cardiovascular disease. In 2008, a consensus conference on cardiorenal syndromes was held to identify and classify dysfunction of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other organ [7]. Now, cardiologists cannot overlook CKD.

Stroke is a major player in cardiovascular disease and it has strong two-way relationships with CKD. Nevertheless, clinicians are often more indifferent to the association between CKD and cerebrovascular diseases, the so-called cerebrorenal interaction, than the cardiorenal interaction [8]. For example, cerebrovascular disease was rarely discussed in the lengthy *Contributions to Nephrology* series. This may be due to the fact that both renal and cerebral pathophysiologies are quite difficult for nonexperts to grasp and fully understand. Therefore, we have prepared this volume entitled 'Brain, stroke, and kidney'.

Now, let us think about the cerebrorenal interaction, particularly with respect to stroke. First, the glomerular afferent arterioles of the juxtamedullary nephrons and the cerebral perforating arteries share an anatomical feature. These small, short vessels directly arise from large high-pressure arteries, and are thus exposed to high pressure. They have to maintain a strong vascular tone in order to provide a large pressure gradient over a short distance [9]. Severe hypertensive vascular damage occurs first in such strain vessels. Since albuminuria reflects glomerular damage distal to the juxtamedullary afferent arterioles, albuminuria may also be an early sign of damage to the cerebral perforating arteries.

Second, CKD is an evident risk factor for stroke. Meta-analyses of both cohort studies and trials indicate that proteinuria/albuminuria increases the risk of stroke by 71–92% [10], and reduced eGFR (<60 ml/min/1.73 m^2) increases the risk by 43% [11]. In addition, CKD has a strong relationship with subclinical brain damage, including white matter changes, microbleeds, cognitive impairment, and carotid atherosclerosis. Of these, cognitive impairment and dementia are becoming as serious a burden as stroke worldwide.

Third, CKD is prevalent in acute stroke patients. Patients with eGFR <60 ml/min/1.73 m^2 based on the creatinine level during acute stroke accounted for 35% of total ischemic stroke patients and 44% of total intracerebral hemorrhage (ICH) patients in an Israeli hospital [12], and 32% of total patients receiving intravenous recombinant t-PA from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry in Japan

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[13]. Patients with eGFR <60 ml/min/1.73 m^2 or proteinuria accounted for 46% of total ischemic stroke patients and 39% of total ICH patients in our institute and 34.9% of total ischemic stroke patients in the Fukuoka Stroke Registry [14] (fig. 1).

Fourth, acute and chronic stroke management strategies are influenced by CKD. A good example of this is the recently developed novel oral anticoagulants. Atrial fibrillation is a major risk factor for initial and recurrent stroke. To judge the indications and dosage of dabigatran and factor Xa inhibitors for stroke patients having atrial fibrillation, many neurologists are now familiar with the Cockcroft-Gault equations. Therapeutic effects of other antithrombotic and thrombolytic agents also seem to be affected by renal function. For example, in our multicenter SAMURAI rt-PA Registry [13], reduced eGFR was associated with early symptomatic ICH, mortality, and a modified Rankin scale score ≥4 at 3 months after intravenous thrombolysis in ischemic stroke patients.

Fifth, reduced eGFR is independently associated with increased 1- and 10-year mortalities [12, 15]. Two groups reported that proteinuria, but not a reduced eGFR, was associated with a poor functional outcome after ischemic stroke [14, 16]. Thus, the kidneys cannot be ignored by stroke neurologists.

Stroke also has strong relationships with end-stage kidney disease (ESKD). Stroke and other cardiovascular diseases occur much more commonly in dialysis patients than in the general population or in CKD patients who do not require dialysis [17, 18]. The triggers for ischemic and hemorrhagic strokes in ESKD patients include traditional cardiovascular risk factors, CKD-related nontraditional risk factors, and special characteristics unique to dialysis, such as drastic hemodynamic change, dialysate, anticoagulants, and vascular calcification. As cohorts of dialysis patients become older, more hypertensive, and more diabetic than before, strokes become more prevalent and more serious events in dialysis clinics. Strokes in ESKD patients pose problems, such as the contraindication to some pharmacotherapy (like dabigatran) and the difficulty of continuing dialysis under good conditions when severe neurological deficits remain. Though thrombolysis is not contraindicated for ESKD patients, even thrombolysis experts often have had limited experience with this therapy for ESKD patients [19].

In this volume, clinical and epidemiological specialists on 'Brain, stroke and kidney' present superb reviews for clinicians. I hope that you, the reader, enjoy this collection and that it promotes both further understanding and multidisciplinary collaboration between nephrologists and neurologists.

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