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Clinical paper

Current termination of resuscitation (TOR) guidelines predict neurologically favorable outcome in Japan☆

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ABSTRACT

Background: It is unclear whether the basic life support (BLS) and advanced life support (ALS) pre-hospital termination of resuscitation (TOR) rules developed in North America can be applied successfully to patients with out-of-hospital cardiac arrest (OHCA) in other countries.
Objectives: To assess the performance of the BLS and ALS TOR in Japan.
Methods: Retrospective nationwide, population-based, observational cohort study of consecutive OHCA patients with emergency responder resuscitation attempts from 1 January 2005 to 31 December 2009 in Japan. The BLS TOR rule has 3 criteria whereas the ALS TOR rule includes 2 additional criteria. We extracted OHCA patients meeting all criteria for each TOR rule, and calculated the specificity and positive predictive value (PPV) of each TOR rule for identifying OHCA patients who did not have neurologically favorable one-month survival.
Results: During the study-period, 151,152 cases were available to evaluate the BLS TOR rule, and 137,986 cases to evaluate the ALS TOR rule. Of 113,140 patients that satisfied all three criteria for the BLS TOR rule, 193 (0.2%) had a neurologically favorable one-month survival. The specificity of BLS TOR rule was 0.968 (95% CI: 0.963–0.972), and the PPV was 0.998 (95% CI: 0.998–0.999) for predicting lack of neurologically favorable one-month survival. Of 41,030 patients that satisfied all five criteria for the ALS TOR rule, just 37 (0.1%) had a neurologically favorable one-month survival. The specificity of ALS TOR rule was 0.981 (95% CI: 0.973–0.986), and the PPV was 0.999 (95% CI: 0.998–0.999) for predicting lack of neurologically favorable one-month survival.
Conclusions: The prehospital BLS and ALS TOR rules performed well in Japan with high specificity and PPV for predicting lack of neurologically favorable one-month survival in Japan. However, the specificity and PPV were not 1000 and we have to develop more specific TOR rules.

1. Introduction

Sudden cardiac arrest remains a major public health problem in the industrialized world.[1] Despite improvements in resuscitation practices including the chain of survival, outcomes from out-of-hospital cardiac arrest (OHCA) remain poor.[2–4] In many industrialized countries, pre-hospital termination of resuscitation (TOR) for OHCA have been implemented to allow for better utilization of hospital health care resources.[5–8]

Both the American Heart Association (AHA) and European Resuscitation Council (ERC) 2010 cardiopulmonary resuscitation (CPR) guidelines recommend that emergency medical services (EMS) personnel consider TOR for OHCA patients that have failed to respond to basic life support (BLS) and/or advanced life support (ALS) treatment efforts. TOR is preferred instead of transporting these patients to the hospitals for ongoing resuscitation because of their poor survival and heavy economic burdens.[9,10]

Recently, several studies have independently validated the BLS and ALS TOR rules which were originally developed in North America. These studies have shown that these rules have a high specificity and positive predictive value (PPV) and performed well in identifying patients with OHCA who had little or no chance of survival.[5,6,8,11] However, we thought that it was important to evaluate whether this 'North American TOR rules' was acceptable in

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not only the different EMS systems but also areas where different races lived. In Japan, EMS personnel are not legally permitted to terminate resuscitation for OHCA patients in the pre-hospital setting. Therefore, EMS personnel in Japan are required to transport almost all OHCA patients to a hospital regardless of the success or failure of their resuscitation efforts.[12] In this study, we aimed to investigate whether BLS and ALS TOR rules can predict neurologically favorable one-month survival for OHCA patients in Japan using a large population based registry covering the whole of Japan.

2. Methods

2.1. Study design and settings

The All-Japan Registry of the Fire and Disaster Management Agency (FDMA) is a nationwide, population-based registry of OHCAs that is based on the standardized Utstein style.[2] This study enrolled all patients aged ≥ 18 years who had an OHCA of presumed cardiac origin, were treated by EMS personnel, and were transported to medical institutions from January 1, 2005 to December 31, 2009. The ethics committee at Kyoto University Graduate School of Medicine approved the study. The requirement of written informed consent was waived. Cardiac arrest was defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.[13,14] The arrest was presumed to be of cardiac origin unless it was caused by cerebrovascular disease, respiratory disease, malignant tumor, external causes including trauma, hanging, drowning, drug overdose, and asphyxia, or any other non-cardiac cause. These diagnoses of presumed cardiac or non-cardiac origin were determined clinically by the physician in charge in collaboration with the EMS personnel.

Do-not-resuscitate orders or living wills are generally not used in Japan,[12] and EMS providers are not legally permitted to terminate resuscitation in the field. Therefore, most patients with OHCA treated by EMS personnel were transported to hospital and registered in this cohort. The cohort excluded cases with obvious signs of death on EMS arrival such as decapitation, incineration, decomposition, rigor mortis, or dependent lividity.

2.2. The EMS system in Japan

Japan has an area of approximately 378,000 km^2 and with a population of approximately 127 million in 2005.[2] EMS is provided by municipal governments through a fire department model. There were 804 fire departments with dispatch centers in 2009. Usually, a fire department ambulance has a crew of three emergency providers, including at least one emergency lifesaving technician (ELST). ELSTs are trained to insert an intravenous line, place adjunct airways and to use semi-automated external defibrillators. ALS measures in Japan are limited to advanced airway management and epinephrine. Under the online medical control, specially trained ELSTs can also insert endotracheal tubes (since July 2004), and administer intravenous epinephrine (since April 2006). All EMS providers perform CPR according to the Japanese CPR guidelines which are based on the AHA and the International Liaison Committee on Resuscitation (ILCOR) recommendations. AHA Guidelines 2000 were in effect until September 2006 and the AHA 2005 Guidelines were followed thereafter.[12] In Japan, approximately 1.6 million citizens participate each year in community CPR programs which includes training in chest compressions, mouth-to-mouth ventilation, and the use of an automated external defibrillator (AED).[2]

2.3. Data collection and quality control

Data were collected with the use of a form based on the Utstein-style guidelines for reporting OHCA,[11,12] and included details on sex, age, witness status, initial cardiac rhythm, time course of resuscitation, bystander-initiated CPR, advanced airway management, intravenous epinephrine, as well as pre-hospital return of spontaneous circulation (ROSC), one-month survival, and neurological status one month after the event. The time course of resuscitation included details on the time the call was received, vehicle arrival at the scene, contact with patient, initiation of CPR, defibrillation by EMS, and hospital arrival. All survivors were evaluated at one month after the event for their neurological function by the EMS personnel in charge.

The data form was filled out by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the FDMA database server. They were logically checked by the computer system and were confirmed by the implementation working group. If a data form was incomplete, the FDMA would return it to the respective fire station for completion and follow up on the missing data.

2.4. Main outcome measurement

Neurological outcome was clinically determined by the physician caring for the patients one month after 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. The primary outcome measure was neurologically favorable one-month survival, defined as CPC category 1 or 2.[13,14] The secondary outcome measure was one-month survival.

2.5. Patient eligibility

OHCA patients aged ≥ 18 years of presumed cardiac etiology who had resuscitation attempted by EMS personnel were included in these analyses. We classified that level from EMS personnel's activity on the scene. The cases who received only BLS were classified into the BLS group (eligible OHCA patients for the BLS TOR rule) and the cases who received BLS plus ALS were classified into the ALS group (eligible OHCA patients for the ALS TOR rule).[6] The BLS TOR rule has 3 criteria (not witnessed by EMS, no public-access AED use or shock by EMS, and no pre-hospital ROSC) while the ALS rule added 2 additional criteria (not witnessed by bystanders and no bystander-initiated CPR).

2.6. Statistical analysis

We extracted OHCA patients meeting the criteria for each TOR rule and calculated the sensitivity, specificity, PPV, and negative predictive value (NPV) and their respective 95% confidence intervals (CI) for identifying OHCA patients without one-month survival and neurologically favorable one-month survival. Statistical analyses were performed using the SPSS statistical package version 15.0J (SPSS, Inc, Chicago, IL). A p-value < 0.05 was considered statistically significant.

3. Results

From Jan 2005 to December 2009, 537,519 adult OHCAs in Japan were documented (Fig. 1). Out of 530,084 patients with resuscitation attempts, 294,193 were presumed to be of cardiac origin. Of these, 151,659 received only BLS care by EMS personnel, while

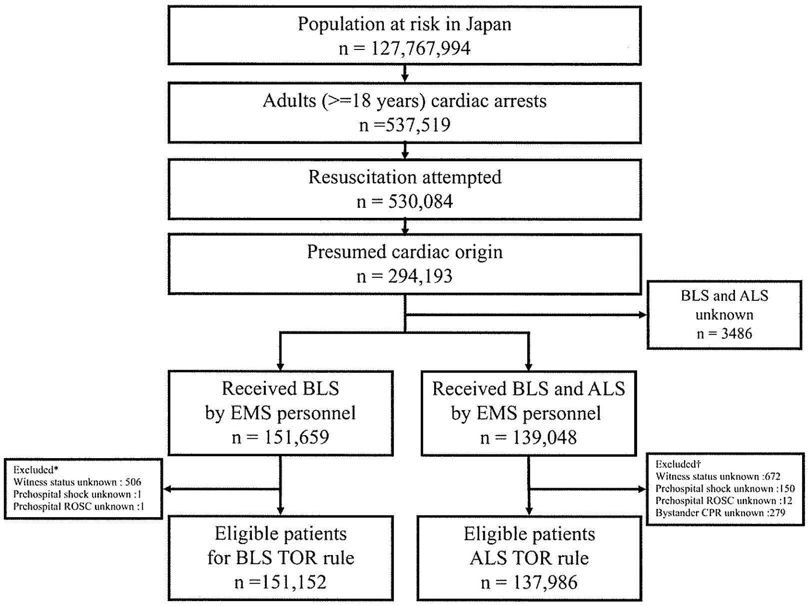

Fig. 1. Flow chart of patients. EMS, emergency medical service; BLS, basic life support; ALS, advanced life support; TOR, termination of resuscitation; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation. *One case was unknown in multiple subjects. †Fifty-one cases were unknown in multiple subjects.

139,048 received both BLS and ALS care by EMS personnel. Excluding cases without complete data, 151,152 were eligible to evaluate the BLS TOR rule, and 137,986 to evaluate the ALS TOR rule.

3.1. *The BLS TOR rule*

Table 1A shows clinical characteristics and outcomes among OHCA patients eligible for the BLS TOR rule. Mean age was 75.5 years old, and 56.8% were male. The percentage of arrests witnessed by bystanders, receiving bystander CPR, or having VF as an initial rhythm were 29.8%, 36.3%, and 11.1%, respectively. The mean time interval from call to ambulance arrival on the scene and from call to hospital arrival was 7.1 min and 29.9 min, respectively. The proportion of patients with pre-hospital ROSC, one-month survival, and one-month survival with favorable neurological outcome was 7.2%, 6.6%, and 4.0%, respectively.

Among 151,152 eligible patients, 113,140 (74.9%) satisfied all three criteria for the BLS TOR rule (Fig. 2A). Neurologically

Table 1A
Characteristics and outcomes among eligible OHCA patients for BLS TOR rule.

	Eligible OHCA patients for BLS TOR rule (n = 151,152)
Age (years), mean (SD)	75.5 (14.4)
Male, n (%)	85,791 (56.8)
Witness status, n (%)	
Arrest not witnessed	90,256 (59.7)
Arrest witnessed by bystanders	45,017 (29.8)
Arrest witnessed by EMS	15,879 (10.5)
Bystander-initiated CPR, n (%)	54,970 (36.3)
VF as an initial rhythm, n (%)	16,859 (11.1)
EMS care interval (min), mean (SD)	
Call to ambulance arrival on the scene	7.1 (3.7)
Call to hospital arrival	29.9 (11.8)
Clinical outcomes, n (%)	
Prehospital ROSC	10,933 (7.2)
One-month survival	9516 (6.3)
One-month survival with neurologically favorable outcome	6001 (4.0)

OHCA, out-of-hospital cardiac arrest; BLS, basic life support; TOR, termination of resuscitation; EMS, emergency medical service; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; ROSC, return of spontaneous circulation.

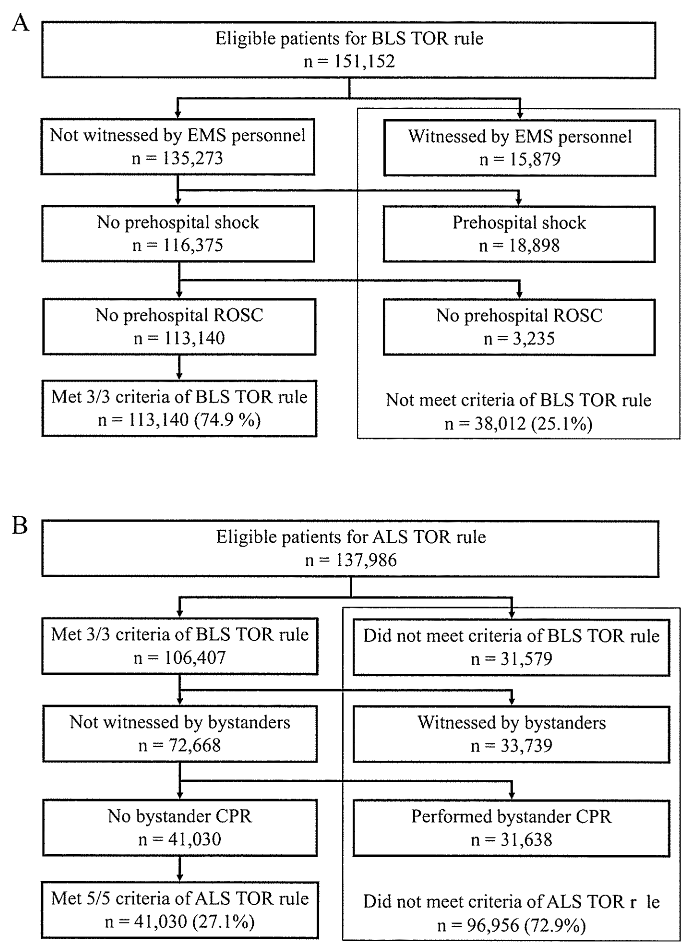

Fig. 2. Sampling OHCA patients meeting criteria for (A) the BLS TOR rule and (B) the ALS TOR rule. EMS denotes emergency medical service; BLS, basic life support; ALS, advanced life support; TOR, termination of resuscitation; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation.

Table 1B
Characteristics and outcomes among eligible OHCA patients for ALS TOR rule.

	Eligible OHCA patients for ALS TOR rule (n = 137,986)
Age (years), mean (SD)	74.4 (14.1)
Male, n (%)	82,696 (59.9)
Witness status, n (%)	
Arrest not witnessed	81,992 (59.4)
Arrest witnessed by bystanders	49,640 (36.0)
Arrest witnessed by EMS	6354 (4.6)
Bystander-initiated CPR, n (%)	57,704 (41.9)
VF as an initial rhythm, n (%)	16,562 (12.0)
EMS care interval (min), mean (SD)	
Call to ambulance arrival on the scene	7.3 (3.7)
Call to hospital arrival	33.5 (11.5)
Outcomes, n (%)	
Prehospital ROSC	7076 (5.1)
One-month survival	5455 (4.0)
One-month survival with neurologically favorable outcome	1902 (1.4)

OHCA, out-of-hospital cardiac arrest; ALS, advanced life support; TOR, termination of resuscitation; EMS, emergency medical service; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; ROSC, return of spontaneous circulation.

favorable outcome among OHCA patients meeting criteria for the BLS TOR rule are summarized in Table 2A. Of 113,140 patients who satisfied all three criteria, 193 (0.2%) had one-month survival with neurologically favorable survival. The specificity of BLS TOR rule was 0.968 (95% CI: 0.963–0.972), and the PPV was 0.998 (95% CI: 0.998–0.999) for predicting lack of neurologically favorable one-month survival. For one-month survival, the specificity of BLS TOR rule was 0.878 (95% CI: 0.872–0.884), and the PPV was 0.990 (95% CI: 0.989–0.990) (Table 2C).

3.2. The ALS TOR rule

Table 1B shows characteristics and outcomes among eligible OHCA patients for the ALS TOR rule. Mean age was 74.4 years old and 59.9% were male. The proportion of arrests witnessed by bystanders, receiving bystander CPR, and having VF as an initial rhythm were 36.0%, 41.9%, and 12.0%, respectively. The mean time interval from call to ambulance arrival on the scene and from call to hospital arrival was 7.3 min and 33.5 min, respectively. The proportion of patients with pre-hospital ROSC, one-month survival, and one-month survival with favorable neurological outcome was 5.1%, 4.0%, and 1.4%, respectively.

Among 137,986 eligible patients, 41,030 (27.1%) satisfied all five criteria for the ALS TOR rule (Fig. 2B). Neurologically favorable outcome among OHCA patients meeting criteria for the ALS TOR rule are noted in Table 2B. Of 41,030 patients satisfying all five criteria, only 37 (0.1%) had one-month survival with neurologically favorable survival. The specificity of ALS TOR rule was 0.981 (95% CI: 0.973–0.986), and the PPV was 0.999 (95% CI: 0.998–0.999) for predicting lack of neurologically favorable one-month survival. For one-month survival, the specificity of ALS TOR rule was 0.923 (95% CI: 0.916–0.930), and the PPV was 0.990 (95% CI: 0.989–0.991) (Table 2D).

4. Discussion

Using a nationwide population-based Utstein registry of OHCA in Japan, we investigated whether BLS and ALS TOR rules can predict neurologically favorable one-month survival for OHCA patients in Japan, and demonstrated that both rules had high specificity and PPV in this population.

The prior studies on the validation of TOR rules were conducted in limited geographic areas of North American, Europe and Singapore,[5–7,10,15] and it is not clear whether latest BLS and ALS TOR rules can predict neurologically favorable one-month survival for OHCA patients in Japan.[5,6] This clearly demonstrates the effectiveness of BLS and ALS TOR rules for predicting neurologically favorable outcome in over 300,000 OHCAs in Japan. This suggests that these TOR rules would be of considerable helpful to detect refractory OHCA patients.

In this study, we note that the specificity and PPV of both BLS and ALS TOR rules for predicting non-survival in this population was high. Our results were consistent with those of previous studies.[5,6] The PPV (0.998) of the BLS TOR rule in this study was very similar to that in Ontario (0.995)[5] and in the CARES study (0.998),[6] and the PPV of the ALS TOR rule was also similar to previous studies. Therefore, these findings suggest that BLS and ALS TOR rule are valid beyond North American could possibly be introduced to the pre-hospital settings of the industrialized world. An important difference between this study and prior validation studies is that there was no termination of resuscitation protocols in place since EMS personnel in Japan are not legally permitted to do this. In the other preceding studies, 17.2% in the CARES study received the declaration of TOR on the scene.[6] In addition, the prevalence of OHCA patients satisfying the ALS TOR rule was higher than that in the CARES study (27% vs 22%),[6] and it might suggest differences in ALS procedures between Japan and North America. Of note, the proportion of patients satisfying the ALS TOR rule was higher in this study then in the validation study using the CARES registry. The reasons for this difference are not clear but may be related to differences in ALS capabilities between Japan and North America. For example, ALS measures in Japan are limited to advanced airway management and epinephrine whereas more interventions are performed in North America. These differences require further study.

Currently, both AHA and ERC recommend permitting the termination of resuscitation efforts that have failed for selected OHCA patients in the pre-hospital setting. However, one report showed that the adherence to these recommendations is variable in that guidelines were used in only 44% for eligible patients,[16] and as much as 40% of EMS personnel felt that resuscitation efforts should be continued even if the chances of survival were poor.[17] In addition, some experts suggest that rapid transportation of OHCA patients who have little or no chance of survival simply adds additional costs to the system while also increasing the risk of ambulance/motor vehicle crashes, vehicle-pedestrian collision, and occupational exposure to blood contamination and body secretions.[18,19] However, most people in North America still desire to be transported to a hospital when they collapse in pre-hospital settings, and implementation of the TOR rule is still under vigorous debates.[20] The increasing number of transportation of

Table 2A
Neurologically favorable outcome among out-of-hospital cardiac arrest patients meeting criteria for the BLS TOR rule.

	CPC ≥ 3	CPC 1 or 2	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
BLS TOR rule						
Met 3/3 criteria	112,947	193	0.778	0.968	0.998	0.153
Did not meet criteria	32,204	5808	(0.776–0.780)	(0.963–0.972)	(0.998–0.999)	(0.149–0.156)

BLS, basic life support; TOR, termination of resuscitation; CPC, cerebral performance category; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 2B
Neurologically favorable outcome among out-of-hospital cardiac arrest patients meeting criteria for the ALS TOR rule.

	CPC ≥ 3	CPC 1 or 2	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
ALS TOR rule						
Met 5/5 criteria	40,993	37	0.301	0.981	0.999	0.019
Did not meet criteria	95,091	1865	(0.299–0.304)	(0.973–0.986)	(0.998–0.999)	(0.018–0.020)

ALS, advanced life support; TOR, termination of resuscitation; CPC, cerebral performance category; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 2C
One-month survival among out-of-hospital cardiac arrest patients meeting criteria for the BLS TOR rule.

One-month survival	Died	Survived	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
BLS TOR rule						
Met 3/3 criteria	111,980	1160	0.791	0.878	0.990	0.220
Did not meet criteria	29,656	8356	(0.790–0.791)	(0.872–0.884)	(0.989–0.990)	(0.218–0.221)

BLS, basic life support; TOR, termination of resuscitation; CPC, cerebral performance category; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 2D
One-month survival among out-of-hospital cardiac arrest patients meeting criteria for the ALS TOR.

One-month survival	Died	Survived	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
ALS TOR rule						
Met 5/5 criteria	40,612	418	0.306	0.923	0.990	0.052
Did not meet criteria	91,919	5037	(0.306–0.307)	(0.916–0.930)	(0.989–0.991)	(0.052–0.052)

ALS, advanced life support; TOR, termination of resuscitation; CPC, cerebral performance category; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

out-of-hospital patients by ambulances is a serious social and medical issue in Japan.[4,21] We should, therefore, consider the introduction of the TOR rule in the pre-hospital settings in Japan to concentrate limited resources for people who have more chance of survival. The verification and implementation of the TOR rule for OHCA patients in Japan would be an important topic in any revisions of the Japanese CPR guidelines in near future.

In this study, both the BLS and ALS TOR rules could detect refractory OHCA patients but the specificity and PPV were not 1.000. Although the North American TOR rules had the specificity and PPV of 1.000 in United States and Canada,[5,6] these studies were conducted in limited areas and populations. Therefore, our findings were also important because these TOR rules could not show the specificity and PPV of 1.000 for predicting lack of neurologically favorable outcome and one-month survival among the whole Japanese population. These results suggest that we have to consider whether these TOR rules should be used and to develop more specific TOR rules that could be applied successfully in each area.

These data also suggest that TOR rules cannot be always correct (i.e., TOR rules might be going to terminate potential survivors in the fields), and we need to develop a strong argument for the cost-effectiveness. To improve survival from OHCA, we must consider limited medical resources and the cost-effectiveness of treatment for OHCA patients. National organizations such as the AHA and the National Association of EMS Physicians have promoted guidelines that allow for termination of futile cardiac resuscitation efforts in the out-of hospital setting. Both organizations recognize that rapid transport of patients who have little or no chance of survival poses risks and generates needless costs.[6] The time has come for discussion of the TOR rule including the cost-effectiveness with all citizens. In addition, we must consider that the citizens might have different religious and ethical views regarding the implementation of the TOR rule. Therefore, consultation on the introduction of the TOR rule to our pre-hospital settings should be done with the public, administrative bodies, and the police and fire authorities.

5. Limitations

As with any study, there are several limitations that deserve mention. First, this study used neurologically favorable survival at one-month as the primary outcome for the TOR rules, unlike survival to discharge from hospital that was used in the prior validation studies. This makes direct comparison to other validation studies more challenging but we feel that neurologically favorable survival is a more important survival outcome. Second, these study subjects were classified by BLS or ALS depending on the level of EMS personnel's activity on the scene. Although it might influence our results, All-Japan Utstein registry did not obtain information on the EMS rescuer level. Third, our data does not address potential variability in in-hospital post-arrest care (hemodynamic support, induced hypothermia, and coronary interventional therapies).[22] Fourth, as with all epidemiological observational studies, data integrity, validity, and ascertainment bias are potential limitations. The use of uniform data collection based on Utstein-style guidelines for reporting cardiac arrest, large sample size, and a nationwide population-based design to cover all known adult OHCA in Japan were intended to minimize these potential sources of biases.

6. Conclusion

The BLS and ALS TOR rules had high specificity and PPV for predicting lack of neurologically favorable one-month survival and both rules could be used to identify cases of OHCA unlikely to benefit from transport to the hospital for further attempts at resuscitation in Japan. However, the specificity and PPV were not 1.000 and we have to develop more specific TOR rules. The implementation of TOR rules in Japan merits further discussion.

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Conflict of interest statement

There are no conflicts of interest to declare.

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Clinical Paper

Prodromal symptoms of out-of-hospital cardiac arrests: A report from a large-scale population-based cohort study☆

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ABSTRACT

Objective: Little is known about which symptoms are manifested before out-of-hospital cardiac arrest (OHCA). The objective of this study is to describe the prodromal symptoms of OHCA focusing on the onset of the symptom in relation of etiology of cardiac arrests, and to analyze the association between those symptoms and their outcomes after OHCA.
Methods: This prospective, population-based cohort study enrolled all persons aged 18 years or older who had experienced OHCA of presumed cardiac and non-cardiac origin that were witnessed by bystanders or emergency medical system (EMS) personnel in Osaka from 2003 through 2004.
Results: There were 1042 were presumed to be of cardiac origin and 424 of non-cardiac. Patients with non-cardiac origin were more likely to have prodromal symptoms than those with cardiac etiology (70.0% vs. 61.8%, $p = 0.003$). Over 40% of OHCA regardless of etiology had displayed symptoms at least several minutes before their arrest (40.2% [259/644] in those of cardiac origin and 45.5% [135/297] in those of non-cardiac origin). As to cardiac origin, the most frequent prodromal symptom was dyspnea (27.6%), followed by chest pain (20.7%) and syncope (12.7%). For non-cardiac origin, the most frequent symptom was also dyspnea (40.7%), but chest pain was rarely presented (3.4%). Although, prodromal symptoms themselves were not associated with better neurological outcomes (adjusted odds ratio [AOR], 2.03; 95% confidence interval [CI], 1.00–4.13), earlier contact to a patient yielded better neurological outcomes (AOR per every one-minute increase, 0.90; 95% CI, 0.82–0.99).
Conclusions: Many of OHCA regardless of etiology have prodromal symptoms before arrest. Prodromal symptoms induced early activation of the EMS system, and may thus improve outcomes after OHCA.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a common public health problem accounting for more than 60% of deaths from cardiovascular diseases.[1–3] Although fatalities from acute myocardial infarction (AMI) have been decreasing mainly due to recent substantial advances in in-hospital treatments, many AMI patients die before arriving at a hospital.[4] In Japan, approximately 60,000 OHCAs of cardiac origin occur every year, and the number has been steadily increasing.[5,6] Despite continuous improvements in the "chain of survival", survival after OHCA remains low.[1,2,6,7]

Cardiac arrest is the first manifestation in about one third of AMI cases.[8] It is well known that most OHCAs occur in persons who have neither past history nor major risk factors of heart disease, which makes it quite difficult to predict the occurrence of OHCAs.[8] On the other hand, one study indicated that some OHCA patients had manifested prodromal symptoms before their arrests.[9] If we knew specific symptoms suggesting the threat of a cardiac arrest, we could develop preventive measures against OHCA.

The Utstein Osaka Project, launched in 1998, is a large, ongoing, prospective, population-based cohort study of OHCA in Osaka, Japan that covers 8.8 million people.[6,10,11] Approximately 5000 OHCA patients were newly registered in this project every year. For

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this study, we collected data on prodromal symptoms in addition to the Utstein-style data. The objective of this study is to describe the prodromal symptoms of OHCA focusing on the onset of the symptom in relation of etiology of cardiac arrests, and to analyze the association between those symptoms and their outcomes after OHCA.

2. Methods

2.1. Study design, population, and setting

The present study was carried out within the Utstein Osaka Project, which is a prospective, population-based cohort study of all persons with OHCA who are treated by emergency medical service (EMS) personnel in the city of Osaka, Japan. This study included all OHCA patients aged 18 years or older who were presumed to be of cardiac and non-cardiac origin and who were witnessed by bystanders or EMS personnel from January 1, 2003 through December 31, 2004. Osaka is the third largest city in Japan with a population of 2,626,635 residents (2004) in an area of 221.96 km^2.

Cardiac arrest has been defined as the cessation of cardiac mechanical activities as confirmed by the absence of signs of circulation.[12] An arrest was presumed to be of cardiac etiology unless it was caused by trauma, drowning, drug overdose, asphyxia, exsanguination, or by any other non-cardiac causes determined by a physician in charge, working in collaboration with the EMS.

2.2. The emergency medical service system in Osaka

There is one fire station in Osaka with an emergency dispatch center. Emergency life support is provided 24 h a day. The most highly-trained pre-hospital emergency care providers are the Emergency Life-Saving Technicians (ELSTs). Each ambulance has three providers, including at least one ELST. ELSTs can use semi-automated external defibrillators for OHCA without online medical direction, and specially trained ELSTs are qualified to insert tracheal tubes since July 2004. Public access defibrillation (PAD) programs were also started in 2004.[13]

2.3. Data collection

Data on prodromal symptoms and all core data recommended by the Utstein-style reporting guidelines for cardiac arrests were prospectively collected using a form,[12] which included sex, age, location of arrest, activities of daily living before their arrest, witness status, initial cardiac rhythm, time-course of resuscitation, type of bystander-initiated cardiopulmonary resuscitation (CPR), return of spontaneous circulation (ROSC), hospital admission, one-month survival, and neurological outcomes one-month after the event. Patients' prodromal symptoms and their time of onset, and other data on patients' characteristics were obtained by EMS personnel's interview to the bystanders or patient him/herself (in case of EMS witnessed cardiac arrests) on the scene. Prodromal symptoms were categorized into 8 groups: chest pain, dyspnea, syncope, cold sweats, back pain, abdominal pain, palpitation, and other miscellaneous symptoms, and reported multiply if each symptom was observed. Chest pain, dyspnea, syncope, and cold sweats were defined as heart-attack-specific symptoms. Time intervals from the onset of a prodromal symptom to cardiac arrest were categorized into 4 groups; within 2–3 min, within 1 h, within 24 h, and over 24 h. Data on outcomes and etiology was gathered by EMS personnel in cooperation with the physicians in charge. The data form was filled out by EMS personnel, transferred to the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If a data sheet was incomplete, the relevant EMS personnel were contacted and questioned, and the data sheet was completed.

All survivors were followed for up to one month after the events by the EMS personnel in charge. Neurological outcomes one month after the events were determined by the physician responsible for the care of the patient, 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.[12] Neurologically favorable survival was defined as a CPC category 1 or 2.

2.4. Statistical analysis

Patients' characteristics and outcomes were compared by etiology of cardiac arrests (cardiac or non-cardiac). Then, frequency of prodromal symptoms and timing of their symptoms were described. The primary outcome measure was a one-month survival with favorable neurological outcomes. Secondary outcomes included ROSC, admission to a hospital, and a one-month survival.

The data were compared using chi-square test or Fisher's exact test for categorical variables. Age was compared using Student's *t*-test, and resuscitation time interval variables were compared with Mann–Whitney *U* test. Multivariable-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to assess the factors associated with a one-month survival with favorable neurological outcomes. Potential confounding factors that were biologically essential and considered to be associated with outcomes were included in the multivariable analysis. Those factors included sex, age (<75 or ≥75), location (at home or not), past history of cardiac diseases (yes or no), activities of daily living (good or not), prodromal symptom (yes or no/unknown), arrest after EMS arrival (yes or no), bystander CPR (yes or no), initial rhythms (VF or others), cardiac arrest (cardiac or non-cardiac), and time intervals from collapse to first contact (every one-minute increase). Analyses were performed using the SPSS Ver.15J (SPSS, Inc., Chicago, IL). A two-tailed value of $p < 0.05$ was considered statistically significant.

2.5. Ethical approval

This study was approved by the Ethics Committees of the Kyoto University Graduate School of Medicine. The requirement of giving individual informed consent for the reviews of patients' outcomes was waived by the Personal Information Protection Law and the national research ethics guidelines of Japan.

3. Results

3.1. Patients' characteristics and resuscitation situations

A total of 3093 OHCA cases of age 18 years or older were documented during the study period. Among them, resuscitation was attempted in 2999, and 1183 were witnessed by bystanders and 283 were witnessed by EMS (Fig. 1). Of those who were witnessed, 1042 were presumed to be of cardiac origin and 424 of non-cardiac origin.

Table 1 shows patients' and resuscitation characteristics according to etiology of cardiac arrests. Patients with presumed cardiac origin were more likely to have past history of cardiac diseases and VF as their initial rhythm compared to those with non-cardiac origin. Patients with non-cardiac origin were more likely to have prodromal symptoms than those with cardiac etiology (70.0% [297/424] vs. 61.8% [644/1042], $p = 0.003$).

Table 1
Characteristics of the 1466 study patients.

	Cardiac origin n = 1042	Non-cardiac origin n = 424	p
Age, year (SD)	69.9 (14.6)	71.0 (14.7)	0.180
Sex, male, n (%)	670 (64.3)	262 (61.8)	0.370
Past history of cardiac diseases, n (%)	163 (15.6)	5 (1.2)	<0.001
ADL, Good, n (%)	711 (68.2)	232 (54.7)	<0.001
Location, home, n (%)	546 (52.4)	261 (61.6)	0.001
Prodromal symptoms, n (%)	644 (61.8)	297 (70.0)	0.003
Initial rhythm, VF, n (%)	230 (22.1)	13 (3.1)	<0.001
Bystander CPR, n (%)	299 (28.7)	106 (25.0)	0.157
Arrest after EMS arrival, n (%)	181 (17.4)	102 (24.1)	0.004
Type of etiology			
Cerebrovascular disorder	–	67 (15.8)	
Respiratory diseases	–	92 (21.7)	
Aortic disease	–	44 (10.4)	
Malignancy	–	93 (21.9)	
Others	–	128 (30.2)	
Time from collapse to call, min, mean (SD)	3.1 (7.0)	3.0 (7.2)	0.960
Time from collapse to bystander CPR, min, mean (SD)	3.2 (5.6)	2.9 (4.9)	0.693
Time from collapse to EMS's CPR, min, mean (SD)	9.2 (7.3)	8.9 (8.2)	0.254

SD, standard deviation; ADL, activity of daily living; VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; EMS, emergency medical system; IQR, interquartile range.

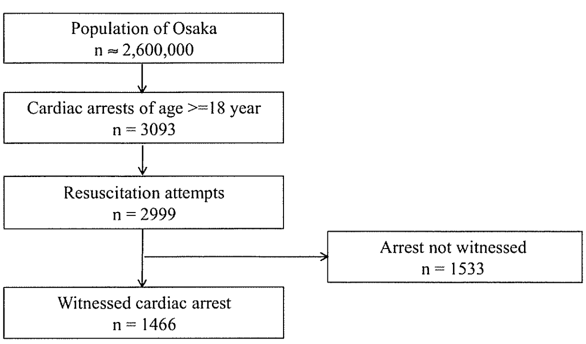

Fig. 1. Patients flow.

3.2. *Outcomes of study patients by etiology of cardiac arrest*

As shown in Table 2, both one-month survival and one-month survival with favorable neurological outcome was more frequent in OHCA with presumed cardiac origin than those with non-cardiac origin.

3.3. *Frequency of prodromal symptoms according to time to cardiac arrest*

Table 3a indicates the frequency of prodromal symptoms among witnessed cardiac arrests of presumed cardiac origin according to the time from its onset to cardiac arrest. Among 644 patients with prodromes, 133 (20.7%) patients experienced chest pain, 178 (27.6%) dyspnea, 82 (12.7%) syncope, 23 (3.6%) cold sweats, 17 (2.6%) back pain, 13 (2.0%) abdominal pain, and 8 (1.2%) palpitations. As for the elapsed time from the onset of prodromes to cardiac arrest, 259 (40.2%) in total displayed some kind of prodromal symptoms at least several minutes before the arrest.

Among OHCAs with non-cardiac origin (Table 3b), dyspnea (40.7%) was the most frequent prodromal symptoms followed by syncope (14.5%). Different from OHCAs of cardiac origin, only 3.4% of OHCAs with non-cardiac origin exhibited chest pain. Even then, 45.5% (135/297) had prodromal symptoms at least several minutes before their arrest.

Prodromal symptoms were 'unknown or not observed' in 525 cases.

3.4. *Resuscitation time course and outcomes according to prodromal symptom*

Among OHCA cases with prodromal symptoms, the median time intervals from collapse to first contact, initiation of CPR by EMS personnel, and hospital arrival were shorter compared to OHCA without prodromes {8 (interquartile range [IQR], 4–12) min vs. 9 (IQR, 2–11) min, $p < 0.001$, 8 (IQR, 3–12) min vs. 10 (IQR 6–13) min, $p < 0.001$, and 25 (IQR 18–31) min vs. 26 (IQR 20–31) min, $p < 0.008$, respectively}. Importantly, a cardiac arrest after an EMS arrival was more frequent in OHCA with prodromes than without them (23.2% vs. 12.1%; $p < 0.001$). OHCA with prodromes had higher one-month survival rates and one-month survival with favorable neurological outcomes compared to OHCA without them, although there were no statistically significant (10.0% vs. 7.0%; $p = 0.069$, 4.4% vs. 2.5%; $p = 0.082$, respectively).

3.5. *Factors associated with better neurological outcomes*

Fig. 2 illustrated the factors associated with a one-month survival with better neurological outcomes. Every one-minute

Table 2
Outcomes of study patients by etiology of cardiac arrests.

	Cardiac origin		Non-cardiac origin		p
	n = 1042		n = 424		
ROSC, n (%)	426	(40.9)	208	(49.1)	0.004
Hospital admission, n (%)	330	(31.7)	164	(38.7)	0.011
One-month suvival, n (%)	107	(10.3)	24	(5.7)	0.005
Neurologically favorable one-month survival, n (%)	47	(4.5)	7	(1.7)	0.009

ROSC, return of spontaneous circulation.

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Table 3a
Frequency of prodromal symptoms for witnessed cardiac arrests of presumed cardiac origin according to time to cardiac arrest.

Prodromal symptoms, *n* (%)[a]	Time from prodromes to cardiac arrest				
	≤2–3 min *n* = 385	≤1 h *n* = 162	≤24 h *n* = 73	>24 h *n* = 24	Total *n* = 644
Heart-attack-specific symptoms, *n* (%)					
Chest pain	78 (12.1)	33 (5.1)	18 (2.8)	4 (0.6)	133 (20.7)
Dyspnea	112 (17.4)	53 (8.2)	11 (1.7)	2 (0.3)	178 (27.6)
Syncope	72 (11.1)	9 (1.4)	1 (0.2)	0	82 (12.7)
Cold sweat	11 (1.7)	11 (1.7)	1 (0.2)	0	23 (3.6)
Non-specific symptoms, *n* (%)					
Back pain	7 (1.1)	2 (0.3)	7 (1.1)	1 (0.2)	17 (2.6)
Abdominal pain	2 (0.3)	6 (0.9)	4 (0.6)	1 (0.2)	13 (2.0)
Palpitation	3 (0.5)	3 (0.5)	2 (0.3)	0	8 (1.2)
Others	124 (19.3)	59 (9.2)	34 (5.3)	12 (1.9)	229 (35.6)

[a] Two or more symptoms can be present in a patient.

Table 3b
Frequency of prodromal symptoms for witnessed cardiac arrests of non-cardiac origin according to time to cardiac arrest.

Prodromal symptoms, *n* (%)[a]	Time from prodromes to cardiac arrest				
	≤2–3 min *n* = 162	≤1 h *n* = 89	≤24 h *n* = 31	>24 h *n* = 15	Total *n* = 297
Heart-attack-specific symptoms, *n* (%)					
Chest pain	7 (2.3)	1 (0.3)	2 (0.8)	0	10 (3.4)
Dyspnea	63 (21.2)	49 (16.5)	5 (1.7)	4 (1.3)	121 (40.7)
Syncope	38 (12.8)	5 (1.7)	0	0	43 (14.5)
Cold sweat	5 (1.7)	0	0	0	5 (1.7)
Non-specific symptoms, *n* (%)					
Back pain	6 (2.0)	1 (0.3)	2 (0.7)	0	9 (3.0)
Abdominal pain	2 (0.7)	2 (0.7)	0	0	4 (1.3)
Palpitation	0	1 (0.3)	0	0	1 (0.3)
Others	46 (15.5)	31 (10.4)	20 (6.7)	10 (3.4)	108 (36.0)

[a] Two or more symptoms can be present in a patient.

increase in time interval of contacting to a patient was associated with decreased survival with better neurological outcomes (adjusted odds ratio [AOR], 0.90; 95% CI 0.82–0.99). Younger age (AOR, 0.40; 95% CI 0.18–0.86), good ADL (AOR, 2.62; 95% CI 1.06–6.44), and VF as the initial rhythm (AOR, 4.38; 95% CI 2.23–8.61) were also associated with better outcomes.

4. Discussion

This study clearly demonstrated that many OHCA patients regardless of type of etiology manifested prodromal symptoms

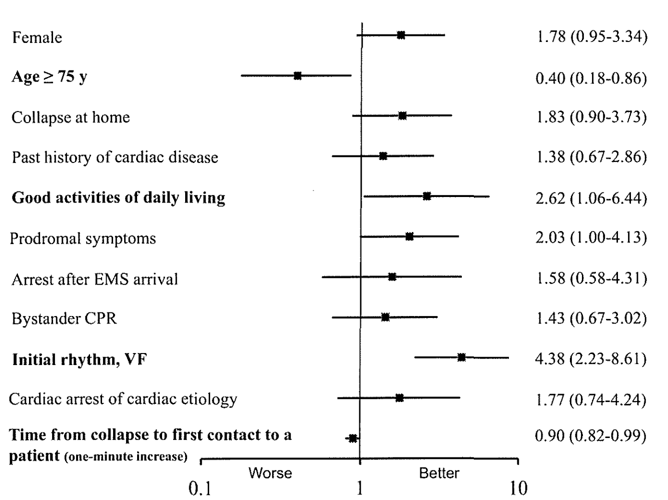

Fig. 2. Factors associated with better neurological outcomes.

prior to their arrests. Although there are some articles on prodromal symptoms in cardiac arrests, most studies focused on specific situations such as younger generation,[14] athletes,[15] cardiac disease patients,[16] or people with family history of cardiac disease,[17] and there were few studies like ours. A small study from Germany reported that 50% of OHCA occurred after typical long-lasting warning symptoms,[9] but the actual frequency of prodromal symptoms has not been sufficiently described. A large sample size covering entire population of a metropolis and prospective data collection enabled us to investigate this important and difficult information.

In addition to the description of the frequency and timing of prodromal symptoms of OHCA, this study suggested the importance of early activation of EMS system when prodromal symptoms were observed to improve survival after OHCA. Among OHCA cases with prodromal symptoms, resuscitation time course were likely to be shorter and outcomes tended to be better. Though the results of multivariable regression analysis indicated that the presence of prodromal symptoms itself was not associated with a favorable outcome, there was a significant association between earlier contact by the EMS personnel and better outcome. A previous study analyzing acute coronary syndrome patients showed that those with prodromes had sought more medical attention before their fatal event and assured greater intact survival than patients without prodromes.[18] Our data suggest that prodrome-induced earlier activation of EMS may result in better outcomes.

In this study, over 40% of OHCA patients had experienced some kind of symptoms at least several minutes before their cardiac arrest. This finding was in line with that of Müller et al.[9] In cases with sufficient incubation time, it might be possible to avoid cardiac arrest by immediately calling EMS. However, in the present study, EMS activation before cardiac arrest was not frequent. Given the fact that it is difficult to survive from cardiac arrest,[5–7] preventive approach to OHCAs should be reinforced. Importance of early recognition of not only cardiac arrest but also the prior signs of subsequent cardiac arrest, and early activation of the EMS system should be more emphasized as the new CPR guidelines recommend.[1,19,20] Knowledge of prodromal symptoms should be propagated to the general public as well as to heart disease patients, persons with coronary risk factors, and their family members.[9,21] Proper education of EMS personnel regarding prodromal symptoms of OHCA is also crucial.[22]

One-fifth of OHCA cases of cardiac origin with the prodromal symptoms had chest pain, which is the hallmark of ischemic heart disease. Previous study indicated that the most common complains was chest pain and 25% of arrest patients had it.[9] However, another previous study pointed out that the symptoms before cardiac arrest were not specific enough to summon an ambulance.[21] By combining chest pain with other heart-attack-specific symptoms, including dyspnea, syncope, and cold sweat and/or ECG, sensitivity and specificity for sudden cardiac arrest might increase.[1] Details in prodromal symptoms including chest pain should be further examined to distinguish signs of a subsequent cardiac arrest.

In our study, dyspnea (27.6%) is the most common prodromal symptom of cardiac arrests followed by chest pain (20.7%). In Japan, the mortality of heart failure (HF) is larger than IHD.[23] This result might reflect that there are many cardiac arrest patients with HF. As well as cardiac origin, dyspnea was most common symptom among non-cardiac origin of OHCA (40.7%). These results suggest that the general public should be informed that dyspnea could also be a warning sign of OHCA. We encourage those who complained of dyspnea to call 911 prior to OHCA.

This study has some limitations. First, our data on prodromal symptoms were based on bystanders' interviews, while the data for OHCA cases without bystanders were not obtained. In addition, some recall biases might exist, although our interviews were conducted at the arrest scenes. Second, patients with some symptoms, who did not suffer cardiac arrest, were not included in this study. Therefore, we did not cover patients who were able to circumvent cardiac arrest by virtue of their prodromal symptoms. Further prospective study analyzing symptoms and subsequent cardiac arrests would be needed to assess the appropriate prodromal symptoms for the prevention of OHCA. Third, coronary risk factors such as hypertension, dyslipidemia, diabetes, smoking habits, and family history of ischemic heart disease might have contributed to the sudden cardiac arrest.[24–26] However, information on these medical conditions was not available.

5. Conclusions

This large population-based observational study indicated that over 60% of OHCA patients had prior symptoms to their cardiac arrests, and 40% of such symptoms had been manifested at least several minutes before their arrests regardless of etiology.

Early activation of the EMS system by recognizing these prodromal symptoms might improve outcomes after OHCA.

Conflicts of interest

There are no conflicts of interest to declare.

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Anterior Cerebral Artery and Heubner's Artery Territory Infarction

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Abstract

Anterior cerebral artery (ACA) territory strokes account for 0.5–3% of all ischemic strokes. The etiological mechanisms of ACA territory strokes vary by race; ACA dissection is a frequent cause in Japan. The most prevalent symptom of such strokes is contralateral hemiparesis or monoparesis, usually affecting the leg predominantly. Predominant leg weakness is attributed to damage in the paracentral lobule, and weakness of the arm and face is associated with involvement of Heubner's artery and the medial striate arteries. Hypobulia, typically 'akinetic mutism', is also common. Several behavioral disorders, including the grasp reflex and the alien hand sign, can present as callosal disconnection signs. Transcortical aphasia and urinary incontinence are other frequent symptoms. A non-throbbing headache is common at stroke onset in patients with ACA dissection.

Cerebral infarcts localized in the anterior cerebral artery (ACA) territory are relatively rare, accounting for 0.5–3% of all ischemic strokes [1–7]. Some investigators reported that embolism from the heart or carotid arteries is the leading mechanism [1, 2, 4], while others from Eastern Asia reported a high prevalence of intrinsic ACA atherosclerosis [3, 5]. Our recent study on consecutive Japanese patients with isolated ACA territory infarction showed that 18 of 42 patients (43%) had ACA dissection verified on digital subtraction angiography [6] (fig. 1). A nationwide survey in Japan showed that, among patients with cervicocephalic arterial dissection, there was a relatively high percentage of intracranial dissection, including that involving the ACA [7].

The ACA is divided into the proximal segment (A1), the ascending segment (A2, A3), and the horizontal segment (A4, A5). The anterior communicating artery (ACoA) arises at the end of A1 and connects the bilateral ACAs. Sometimes, the A1 segment is absent or hypoplastic, and the contralateral ICA supplies the ACA territory via the ACoA. The recurrent artery of Heubner and other medial striate arteries arise near the origin of the ACoA and supply the anteromedial portion of the caudate nucleus, the anterior limb of the internal capsule, and the anterior perforated substance. The distal ACA divides into the pericallosal and callosomarginal arteries and supplies the paramedian frontal lobe, including the corpus callosum, cingulate gyrus, frontal pole/gyrus rectus, medial aspect of the superior frontal gyrus, supplementary motor area, paracentral lobule, and precuneus [5].

According to magnetic resonance imaging studies, infarcts occur predominantly on the left side [4–6]. In these studies, bilateral ACA infarcts were identified in 0–9% of all patients with

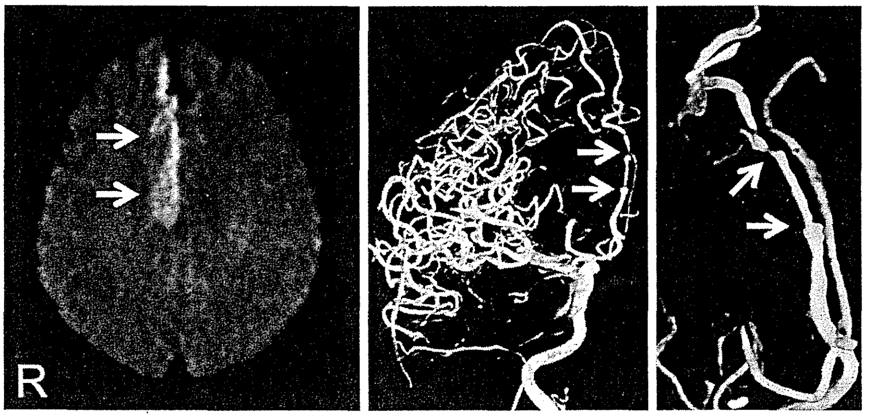

Fig. 1. Representative image of a fresh infarct in the right ACA territory (left panel, diffusion-weighted image) and three-dimensional rotational angiograms showing the right ACA dissection with the 'pearl-and-string' sign (aneurysmal dilatations followed by segmental stenosis) of the A2 segment (middle and right panels). Images of the patient described in Sato et al. [6].

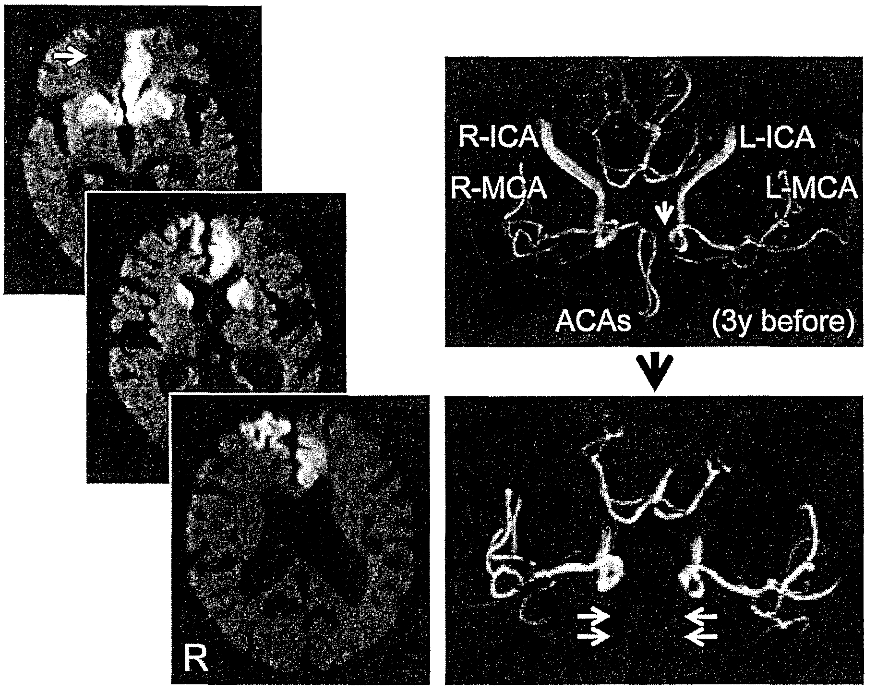

Fig. 2. Representative images of fresh cardioembolic infarcts in the bilateral ACA territories (left panel, diffusion-weighted images) with an old infarct in the terminal branches of the right ACA territory (arrow). This patient with atrial fibrillation was diagnosed as having intact ACAs except for absence of the left A1 segment (arrow) on magnetic resonance angiography (MRA) 3 years before (right top panel). This time, MRA does not reveal either side of ACA (arrows, right bottom panel).

ACA infarction [4–6] (fig. 2). The most prevalent symptom of ACA territory infarction is contralateral hemiparesis or monoparesis, usually affecting the leg predominantly. Of the 100 patients with isolated ACA infarction reported by Kang and Kim [5], 91 showed motor deficits: hemiparesis in 70, leg monoparesis in 18, and paraparesis in 3. Leg weakness was dominant in 58 of these 91 patients (64%). Of the 48 patients in the study by Kumral et al. [4], 46 (96%) showed motor deficits, and all but 1 of these had leg weakness. In our cohort involving 42 patients with isolated ACA infarction, the median 'motor leg' subscore of the admission National Institutes of Health Stroke Scale on the weaker side was 2.5, while the median 'motor arm' subscore on the weaker side was 1 [6]. Predominant leg weakness is attributed to damage in the paracentral lobule. In contrast, weakness of the arm and face contralaterally to the ACA infarction is associated with involvement of Heubner's artery and the medial striate arteries. Paraparesis is caused by bilateral ACA infarction, which is often associated with absence or hypoplasia of the A1 segment. A sensory deficit is usually associated with motor weakness and predominantly involves the leg.

The second most common symptom among the 100 patients reported by Kang and Kim [5] was hypobulia (abulia) in 43. Lesions of the corpus callosum and cingulate gyrus are the major culprits. When such lesions are bilateral, hypobulia can occur more frequently. A typical symptom is 'akinetic mutism': patients may open their eyes and seem alert, and brief movement, speech, or even agitation may follow powerful stimuli, but they are otherwise indifferent, detached, frozen, and apathetic [8].

Several behavioral disorders can present as callosal disconnection signs. The grasp reflex, clenching the fingers to tactile stimulation of the palm, is a well-known sign. Patients grasp objects used for stimulation more firmly when an examiner tries to remove them (instinctive grasp reaction, forced grasping). Some patients have difficulty with bimanual tasks. In particular, the 'alien hand sign' occurs when an upper limb performs complex motor activities outside of volitional control. 'Diagnostic dyspraxia' is defined as abnormal and conflicting motor behavior of the left hand activated by voluntary movements of the right hand [9]. Other behavioral disorders include compulsive manipulation of tools and gait apraxia.

Several patterns of speech dysfunction can occur. In particular, aphasia is often transcortical and transient [4–6]. A lesion involving the left supplementary motor area is the major culprit for aphasic patients with ACA infarction [8]. Urinary incontinence developed in around 30% of all patients with ACA infarction in the studies by both Kumral et al. [4] and Kang and Kim [5]. Although headache has not been regarded as a typical symptom of ACA infarction, 13 of 42 patients (31%) in our series felt headache at stroke onset; 11 of these had a non-throbbing headache. This high frequency seems to be partly due to the high prevalence of ACA dissection in our patients. At 3 months, all patients reported by Kumral et al. [4] had survived. Of the 34 patients in our series who were completely independent prior to stroke, corresponding to a modified Rankin scale score of 0–1, 18 (53%) had a score of 0–1 again, and 5 patients (15%) had a score of 2 (functionally independent) at discharge from the acute hospital [6].

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EDITORIAL

The cerebro-renal interaction in stroke neurology

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Chronic kidney disease (CKD), defined as a reduced glomerular filtration rate (GFR) or albuminuria, is a known, strong risk factor for stroke. Meta-analyses of cohort studies and trials indicate that proteinuria/albuminuria increases the risk of stroke by 71%–92%, and estimated GFR (eGFR) <60 mL/min/1.73 m^2 increases the risk by 43%.[1,2] CKD is also predictive of poor outcomes after stroke; reduced eGFR is independently associated with increased 1- and 10-year mortalities.[3,4] Since end-stage renal disease (ESRD) is another established predictor of stroke risk and poor stroke outcomes,[5] stroke neurologists should fully understand the interaction between stroke and CKD/ESRD.

In this issue of *Neurology*®, Kumai et al.[6] studied 3,778 patients admitted within 24 hours of onset of their first-ever ischemic stroke from a large-cohort multicenter stroke registry; of these, 1,320 (34.9%) had CKD defined as proteinuria or reduced eGFR on admission. They found that CKD patients had a 49% greater risk of neurologic deterioration, defined as a ≥2-point increase in the NIH Stroke Scale, during hospitalization; a 138% greater risk of in-hospital mortality; and a 25% greater risk of a modified Rankin Scale score (mRS) ≥2 at discharge than non-CKD patients after adjustment for potential confounding factors, including initial stroke severity. As a component of CKD, proteinuria showed a much stronger association with unfavorable outcomes than reduced eGFR; for example, patients with mild proteinuria, with an estimated amount of urine protein of 30–100 mg/mL, had a 69% greater risk of an mRS ≥2 than patients without proteinuria. In contrast, reduced eGFR was not associated with stroke outcomes in the study by Kumai et al.[6] Albuminuria and reduced eGFR may involve separate pathologic processes. Kumai et al. did not measure filtration function prior to stroke onset but only on admission, when it may have been affected by acute stroke damage. Measurement of eGFR and urine protein in the chronic stage of stroke might show different associations.

Other potential limitations include use of semiquantitative measurement of urine protein using dipstick testing, which may result in frequent false-positive and false-negative results. However, it is meaningful that such a handy and economical measurement can predict stroke outcomes. Also, outcomes were measured after only a short interval. Vital and functional outcomes were assessed at hospital discharge (median, 23 days after stroke onset). Because their registry has a plan to perform yearly follow-up for enrolled patients, this limitation will eventually be resolved.

Renal dysfunction is a bystander of stroke, since both conditions are associated with hypertension and several traditional vascular risk factors. Additionally, albuminuria is an indicator of cephalocervical and systemic vascular dysfunction via nontraditional vascular risk factors, including endothelial dysfunction, maladaptive carotid arterial remodeling, homocystinemia, coagulation disorders, impaired endothelial release of tissue plasminogen activator, extravascular coagulation, and higher levels of inflammatory cytokines and oxidative stress. An association between albuminuria and hemorrhagic transformation of infarcts has also been noted.[7] Such factors might cause both initial severity and unfavorable outcomes of stroke in patients with proteinuria.

These data underscore the fact that one can no longer manage and care for stroke patients while disregarding their renal condition. CKD/ESRD is not only predictive of unfavorable outcomes after general stroke, but also of stroke outcomes after specific therapies. In our multicenter observational studies (the SAMURAI rt-PA Registry), reduced eGFR was associated with early symptomatic hemorrhagic conversion, mortality, and an mRS ≥4 at 3 months after IV recombinant tissue plasminogen activator therapy.[8] Although thrombolysis is generally not considered safe for stroke patients undergoing hemodialysis, most experts who responded to an international survey favored its use.[9] Patients with stages 4 and 5 CKD (eGFR <30 mL/min/1.73 m^2) have a high 30-day mortality when

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undergoing carotid endarterectomy or carotid angioplasty and stenting.[10] Dabigatran, a new oral anticoagulant for stroke prevention, is mainly excreted by the kidneys, and should be used cautiously even in patients with moderate renal damage.

Another essential issue that must be resolved is whether active treatment to reduce albuminuria and improve filtration dysfunction can decrease stroke risk and improve stroke outcomes. CKD is also associated with subclinical brain abnormalities, including white matter changes, microbleeds, mild cognitive disorders, and intima-medial thickening of carotid arteries. The cerebro-renal interaction is an understudied and underused concept at present, but it has as great a clinical significance as the cardio-renal interaction and should be studied more extensively and in great detail.

Finally, the Fukuoka Stroke Registry that Kumai et al.[6] used as a study cohort merits specific comment. This multicenter registry for acute stroke patients in the Fukuoka metropolitan area, in western Japan, has several strengths, since the database includes extensive underlying patient information, image data principally from MRI/magnetic resonance angiography, long-term follow-up of vital and functional conditions for many years, and the results of serologic and genome genetic analyses for most participants. This systematic stroke registry will help resolve several problems in stroke neurology, in particular in relation to stroke in the Asian population, in whom the stroke burden is increasing.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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Run-up to participation in ATACH II in Japan

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Abstract

Intracerebral hemorrhage (ICH) is a major cause of morbidity and mortality in Japan. Seventeen Japanese institutions are participating in the Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH) II Trial (ClinicalTrials.gov no. NCT01176565; UMIN 000006526). This phase III trial is designed to determine the therapeutic benefit of early intensive systolic blood pressure (BP) lowering for acute hypertension in ICH patients. This report explains the long run-up to reach the start of patient registration in ATACH II in Japan, including our preliminary study, a nationwide survey on antihypertensive treatment for acute ICH patients, a multicenter study for hyperacute BP lowering (the SAMURAI-ICH study), revision of the official Japanese label for intravenous nicardipine, and construction of the infrastructure for the trial.

Keywords

acute stroke; antihypertensive treatment; blood pressure; clinical trial; hypertension; intracerebral hemorrhage; nicardipine

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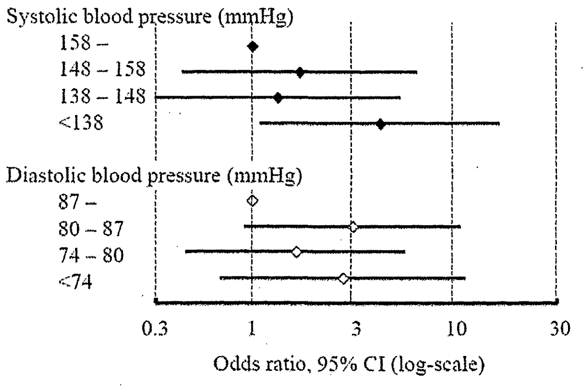

Figure 1. Average of blood pressure levels during the initial 24 h and an mRS of 1 or less at 3 weeks after intracerebral hemorrhage from a Japanese dual-center observational study.
Compared with patients with the average of systolic blood pressure at least 158 mmHg, patients with the level <138 mmHg more frequently had an mRS of 1 or less after multivariate adjustment (OR 4.36, 95% CI 1.10–17.22). The frequency did not differ among the patient quartiles based on diastolic blood pressure.
See Itabashi *et al* [3] for more information.

Introduction

Asian ethnic origin is an important risk factor for intracerebral hemorrhage (ICH). A recent meta-analysis reported that the incidence of ICH per 100,000 person-years was 51.8% in Asian people as compared to 24.2% in Caucasians [1]. The high prevalence of small-artery cerebrovascular lesions in Asians may be responsible for the high prevalence of ICH. In Japan, acute ICH patients account for 17–30% of overall acute stroke patients [2]. Undoubtedly, ICH is a burden for the Japanese population that needs to be overcome, though the meta-analysis also provided some good news: the median case fatality at 1 month after ICH was lower in Japan than anywhere else in the world (16.7 vs. 42.3%) [1].

A problem in acute ICH management is the lack of a therapeutic strategy that brings dramatic symptomatic improvement like that seen with thrombolysis for ischemic stroke. Blood pressure (BP) lowering during the hyperacute stage may prevent hematoma expansion and improve outcomes after ICH. We reported an observational study involving 244 patients who were admitted to the National Cerebral and Cardiovascular Center, Osaka, or the National Hospital Organization Kyushu Medical Center, Fukuoka, within 24 h after ICH onset [3]. Lowering the systolic BP (SBP) to less than 138 mmHg during the initial 24 h immediately after identification of ICH on emergency computed tomography was predictive of independent activity corresponding to a modified Rankin Scale (mRS) score of 1 or less at 3 weeks (Figure 1). Although this result is promising, a prospective interventional trial is required to ascertain the clinical significance of the cutoff level (138 mmHg or roughly 140 mmHg) as an emergent antihypertensive goal.

Palesch and Qureshi offered us the chance to be involved in such a trial by inviting us to join the NIH-funded trial, the Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH) II [4], and they visited Tokyo for our first domestic meeting on this trial in October, 2008. However, to facilitate trial participation in Japan, some problems needed to be resolved, including reassessment of the official label for nicardipine, a trial drug. This is a report of the long run-up to reach the start of patient registration in ATACH II in Japan.

Nationwide survey of acute BP control in Japan

As the first step, it was necessary to ascertain the current status of antihypertensive treatment for acute ICH patients in Japan. Thus, a nationwide survey was conducted in 2008 [5]. Web questionnaires regarding acute ICH management and antihypertensive treatment strategies were sent to 1,424 hospitals, and 600 (42%) responded. Most respondents answered that the goal of lowering SBP was to reach a maximum of 140, 150, or 160 mmHg (82%). The results indicated that aggressive BP lowering was common in Japan as compared to the recommendations of domestic and Western guidelines.