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# Interaction of defibrillation waveform with the time to defibrillation or the number of defibrillation attempts on survival from out-of-hospital cardiac arrest

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ABSTRACT

*Aim:* Early biphasic defibrillation is effective in out-of-hospital cardiac arrest (OHCA) cases. In the resuscitation of patients with OHCA, it is not clear how the defibrillation waveform interacts with the time to defibrillation to influence patient survival. The second, and any subsequent, shocks need to be administered by an on-line physician in Japan. Thus, we investigated the interaction between the defibrillation waveform and time to or the number of defibrillation on resuscitation outcomes.
*Methods:* This prospective observational study used data for all OHCAs that occurred between 2005 and 2014 in Japan. To investigate the interaction effect between the defibrillation waveform and the time to defibrillation or the number of defibrillations on the return to spontaneous circulation (ROSC), 1-month survival, and cerebral performance category (CPC) (1, 2), we assessed the modifying effects of the defibrillation waveform and the time to or the number of defibrillation on additive scale (*i.e.,* the relative excessive risk due to interaction, RERI) and multiplicative scale (*i.e.,* ratio of odds ratios (ORs)).
*Results:* In total, 71,566 cases met the inclusion criteria. For the measure of interaction between the defibrillation waveform and the time to defibrillation, ratio of ORs for ROSC was 0.84 (0.75–0.94), implying that the effect of time to first defibrillation on ROSC was negatively modified by defibrillation waveform. For the interaction between the defibrillation waveform and the number of defibrillations, RERI and ratio of ORs for CPC (1, 2) was −0.25 (−0.47 to −0.06) and 0.79 (0.67–0.93), respectively. It is implied that the effect of number of defibrillation on CPC (1, 2) was negatively modified by defibrillation waveform.
*Conclusions:* An increased number of defibrillations was associated with a decreased ROSC in the case of biphasic and monophasic defibrillation, while an increased number of defibrillations was related to an increased 1-month survival rate and CPC (1, 2) only in the case of biphasic defibrillation. When two or more defibrillations were performed, a biphasic waveform was more effective in terms of long-term survival than a monophasic waveform.



## Introduction

There are two types of defibrillators which have monophasic or biphasic waveform. According to the 2010 American Heart Association (AHA)/International Liaison Committee on Resuscitation (ILCOR) guidelines, biphasic waveforms are suggested to be more effective for defibrillation than monophasic ones [1]. Commercial biphasic defibrillators are equipped with different waveforms, and different amount and duration of defibrillation energy [2–4]. In the recent years, monophasic defibrillators have been rapidly replaced by biphasic defibrillators [5,6].

Early defibrillation is critical for the survival of out-of-hospital cardiac arrest (OHCA) cases [7,8]. A three-phase time-sensitive model shows that there is a distinct optimal therapeutic approach depending upon the time from collapse of a patient with OHCA [9]. Although defibrillation when the collapse time is <4 min (*i.e.,* the electrical phase) or chest compression when the collapse time is between 4 and 10 min (*i.e.,* the circulatory phase) is most appropriate as life-saving intervention, the effectiveness of defibrillation and chest compression decreases rapidly and survival rates

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become poor when the collapse time is >10 min (*i.e.,* the metabolic phase). In reality, ventricular fibrillation (VF) may persist longer in some OHCA victims because of underlying conditions, the effect of bystander CPR, etc. Previous studies in OHCA patients have shown that the median time to first defibrillation was 11 min in 11 regional centers in the United States and Canada between 2005 and 2007 [10] and in Japan in 2012 [11].

There are several findings implying that monophasic defibrillation with higher energy could more effectively remove VF than biphasic fibrillation with lower energy in patients with OHCA who had been in VF for very long time [12,13]. It is not known how the defibrillation waveform interacts with the time to defibrillation to influence survival in OHCA patients. Therefore, using national data from the entire sample of OHCAs that occurred between 2005 and 2014 in Japan, we investigated the interaction between the defibrillation waveform and the time to defibrillation on resuscitation outcomes. When two or more defibrillation shocks are necessary because of recurrence of VF after the first fibrillation [14–16], the second, and any subsequent, shocks must be administered under the guidance of an on-line physician in Japan [17,18]. Thus, as a secondary aim, we investigated the interaction between the defibrillation waveform and the number of defibrillations on resuscitation outcomes.

## Methods

This prospective observational study was conducted using national registry data. The study was approved by the ethics committee of Kyushu University Graduate School of Medicine. The requirement for written informed consent was waived.

### *Data collection*

The emergency medical services (EMS) system in Japan has been described elsewhere [19]. Briefly, EMS is provided by municipal governments through about 800 fire stations with dispatch centers. Since the Japanese guidelines do not allow EMS providers to terminate resuscitation in the field, all patients with OHCA who are treated by EMS personnel are transported to hospitals [20]. The Fire and Disaster Management Agency (FDMA) has maintained a prospective, nationwide, population-based registry of all OHCA cases in Japan using a standardized Utstein-style template. EMS personnel, in cooperation with the physicians in charge of patients with OHCA, summarize each OHCA case in the standardized Utstein style [20,21]. Data from the 800 fire stations with dispatch centers in the 47 prefectures of Japan are then integrated into the national registry system on the FDMA database server. The data are checked electronically by the FDMA, and returned to the respective fire stations for error correction when problems are detected.

### *Subjects*

The patients were aged 18–110 years and had OHCAs of presumed-cardiac origin before the arrival of EMS personnel between 1 January 2005 and 31 December 2014 in Japan (Fig. 1). Intervals from calls to first defibrillation by EMS and to arrival at the hospital were ≤60 min and ≤120 min, respectively. OHCA were analysed if they were witnessed, non-traumatic, did not have bystander automated external defibrillation, EMS personnel performed defibrillation, and defibrillation waveform was known. All patients were transported to medical institutions thereafter.

### *Study variables*

EMS performed defibrillation to all patients with OHCA by using monophasic or biphasic defibrillators. Table 1 shows the variables used in the study by the type of defibrillation waveform. Different types of biphasic waveforms were combined as a general biphasic form. When patients survived cardiac arrest, they were followed for up to 1 month after the event, and information on survival and neurological function at 1 month after the event or at hospital discharge, whichever was earlier, was collected. Neurological outcomes 1 month after successful resuscitation were evaluated using the Cerebral Performance Category (CPC) scale (1: good cerebral performance, 2: moderate cerebral disability, 3: severe cerebral disability, 4: coma or vegetative state, 5: death) [20–22].

### *Endpoints*

Endpoints were return of spontaneous circulation (ROSC) before hospital arrival, survival at 1 month after the event, and survival with minimal neurological impairment, defined as CPC category 1 or 2 (Table 1), 1 month after the event [20–22].

### *Statistical analysis*

In Japan, the second, and any subsequent, shocks are under the control of an on-line physician [17,18] and the median time to the first defibrillation was 12 min in the study. Using this information, two $2 \times 2$ tables of defibrillation waveform (biphasic or monophasic) and the time to first defibrillation ($\leq 12$ min or $> 12$ min) or the number of defibrillations (1 or $\geq 2$) were made. To investigate the interaction effect between defibrillation waveform and the time to defibrillation or the number of defibrillation on ROSC, 1-month survival, and CPC (1, 2), we assessed effect modification of defibrillation waveform and the time to defibrillation or the number of defibrillation on additive and multiplicative scales. Relative excessive risk due to interaction (RERI) on an additive scale was calculated as $OR_{2,2} - OR_{1,2} - OR_{2,1} + 1$ in the $2 \times 2$ table where OR is odds ratio and $OR_{1,1}$ is reference (=1). The measure of interaction on a multiplicative scale is the ratio of ORs in the strata of defibrillation waveform [23,24]. Ninety five percent confidence intervals (CIs) of RERI were derived using the delta method [24]. The significance level for all tests was $P < 0.05$ (two-sided). All statistical analyses were conducted using SAS software (ver. 9.3; SAS Institute Inc., Cary, NC, USA). $P$-values < 0.05 (two-sided) were deemed to indicate statistical significance.

## Results

### *Patient characteristics*

Of the 1,176,351 patients with OHCA who were registered between 1 January, 2005 and 31 December, 2014, in Japan, 71,566 patients with OHCA met the inclusion criteria and were used for analysis (Fig. 1). Since the Japanese guidelines do not allow EMS providers to terminate resuscitation in the field, all patients with OHCA who are treated by EMS personnel are transported to hospitals, excluding those with decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis [18]. Thus, in order to show the characteristics of study subjects, we also evaluated the proportions of VF/VT patients among subgroups categorized by age, witness status and the origin of OHCA (Supplementary data, Fig. S1). Among patients who were 18–110 years of age, witnessed, and with cardiac origin, the proportion of VF/VT was 19.5%. Among 71,566 patients with OHCA who met the inclusion criteria, the proportion of VF/VT was 71.9%. Table 1 shows characteristics of patients with OHCA by defibrillation waveform. Notably, during the study period, majority of patients (84.43%) were administered biphasic defibrillation, and the yearly number of biphasic defibrillation cases has increased while that of monophasic defibrillation cases has decreased ($p < 0.001$). Significant differences between the