Original Article

Association of Repeated Defibrillation with Outcomes for Out-of-Hospital Cardiac Arrest Associated with Ventricular Fibrillation

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ABSTRACT

Background: Ventricular fibrillation (VF) is a life-threatening arrhythmia, and the success rate for defibrillation decreases rapidly with increasing time since collapse. Chest compression must be interrupted during rhythm analysis and defibrillation, and this may adversely affect outcomes. This study investigated the effectiveness of repeated defibrillation for persons with cardiogenic out-of-hospital cardiac arrest (OHCA) associated with VF.

Methods: Using Utstein template data collected throughout Japan during the period from July 2006 through December 2010, we identified patients with VF on an initial electrocardiogram who underwent defibrillation within 10 minutes of collapse (N=9865). To determine the optimal frequency of defibrillation, we evaluated rates of return of spontaneous circulation (ROSC) and survival at 1 month with a good neurologic outcome (cerebral performance category [CPC] 1–2).

Results: ROSC was achieved in 38.2% of patients, and 28.5% had a CPC score of 1 or 2 at 1 month post-event. Receiver operating characteristic curve analysis showed that a defibrillation frequency cutoff value of 1.5 ($p<0.001$; 95% confidence interval, 0.61–0.63) was optimal for ROSC. The same cutoff was associated with a CPC of 1 to 2 ($p<0.001$; 95% confidence interval, 0.57–0.60). As the number of shocks increased, the rates of ROSC and good neurologic outcomes decreased. Among patients who achieved ROSC and a good neurologic outcome, half had received 1 defibrillation.

Conclusions: Repeated defibrillation may be associated with worse outcomes.

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KEYWORDS: defibrillation, ventricular fibrillation (VF), cardiac arrest, out-of-hospital

Improving the rate of survival after out-of-hospital cardiac arrest (OHCA) is an important issue in emergency medicine and intensive care. A number of randomized studies of rates of successful resuscitation have high-

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lighted the importance of early access to emergency medical services (EMS), cardiopulmonary resuscitation (CPR), and defibrillation, as well as the effectiveness of advanced cardiac life support and integrated treatment after return of spontaneous circulation (ROSC), in improving survival after OHCA. One-month survival and favorable neurologic outcomes after witnessed OHCAs increased from 5% and 2%, respectively, in 1998 to 12% and 6% in 2006, but these rates are nevertheless low.[1,2]

Most OHCAs involve adults, and cardiac arrest associated with ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) has the best resuscitation rates.[3] VF accounts for approximately 20% of all OHCAs, and the elapsed time between cardiac arrest and electrocardiogram (ECG) recording is less than 3 minutes in 50% to 60% of cases.[4] The outcomes for patients with VF or pulseless VT cardiac arrest are far better than those for patients with asystole or pulseless electrical activity cardiac arrest,[3,5,6] and the rates of 1-month survival and favorable neurologic outcomes in witnessed cardiogenic OHCAs for which the initial rhythm was VF increased from 9.8% in 2005 to 20.6% in 2009.[7]

Continuous chest compressions and early defibrillation are important considerations in VF. Shorter pre-shock pauses are also associated with successful defibrillation (odds ratio [OR], 1.86 per 5-second decrease).[8] Patients with VF who receive immediate CPR from bystanders can survive without neurologic sequelae, provided that defibrillation is performed within 5 to 10 minutes.[9,10] However, interrupting chest compressions during ECG interpretation or defibrillation may worsen outcomes.[11,12] VF is a life-threatening arrhythmia, and the rate of successful defibrillation decreases over time[12]; therefore, early defibrillation is important. In 2010, the mean elapsed time between contact with EMS and the arrival of emergency personnel to assist the patient was 8.1 minutes in Japan.[13] However, studies have not addressed the association between frequency of defibrillation and outcomes. This study investigated the association of number of EMS-delivered on-site defibrillations with 1-month survival and neurologic outcomes.

Methods

Study design and setting

A nationwide population-based registry of OHCAs throughout Japan is maintained by the Fire and Disaster Management Agency. Using this registry, we prospectively collected Utstein template data for the period from July 1, 2006 through December 31, 2010[14,15] The subjects of this observational study were persons with a witnessed OHCA who received CPR from EMS personnel. The sample was further limited to those patients with VF during their initial ECG who received a first defibrillation by EMS personnel within 10 minutes of their witnessed cardiogenic OHCA. This study was performed in accordance with Japanese CPR guidelines, which are based on the 2005 American Heart Association (AHA) guidelines, as a 1-shock protocol, that is to say when VF or pulseless VT rhythm was present, 1-shock was delivered and CPR was immediately resumed, beginning with chest compressions.[16]

Cardiac arrest was classified as cardiogenic if it was not endogenous (caused by a central nervous system disorder, circulatory disorder, malignant tumor, or other similar condition), exogenous (caused by, for example, trauma, strangulation, drowning, or drug overdose), or attributable to disorders believed to be noncardiogenic. Cardiogenic and noncardiogenic cardiac arrests were distinguished on the basis of the clinical judgment of the doctor who provided initial care after the patient arrived at the hospital.

The Resuscitation Science Group Subcommittee of the Japanese Circulation Society was provided with date form the governmental legal procedures. This study was reviewed and approved by the ethics committee of Toho University (approval number 25086).

EMS system

Data published by the Japanese Fire and Disaster Management Agency in 2010 showed that EMS were contacted approximately 5.46 million times; the mean interval between receiving a call and arriving at the patient's side was 8.1 minutes.[13] In Japan, an EMS team typically includes 3 emergency providers, including at least 1 emergency lifesaving technician. Emergency lifesaving technicians are permitted to insert intravenous lines and adjunct airways and to use semiautomatic defibrillators before OHCA patients arrive at a hospital.

Since July 2004, trained emergency medical technicians have been allowed to perform tracheal intubation and, in 2006, they were authorized to administer intravenous adrenaline. All emergency technicians can perform CPR according to the Japanese guidelines, which are based on the 2005 AHA guidelines. Emergency lifesaving technicians are not permitted to terminate CPR on-site, and most patients are transported to a hospital.[16]

Data collection

The OHCA data included information on age, sex, presence of a witness, whether and how CPR was performed by a bystander, ECG waveform classification, how the airway was secured, drugs administered, whether and how many times defibrillation was performed, whether ROSC was achieved, and when these actions were performed. In addition, the times at which EMS personnel were contacted, arrived at the patient's side, and arrived at the hospital with the patient were also recorded. To assess outcomes, 1-month survival and neurologic outcome, as determined by cerebral performance category (CPC),[17] were recorded. Patient CPC was determined by the attending physician. A good neurologic outcome was defined as a CPC score of 1 or 2 and a poor outcome as a CPC score of 3 to 5. Successful defibrillation was defined as achieving ROSC.

Statistical analysis

We compared patients who achieved ROSC with those who did not (ROSC and non-ROSC groups), and those with good and poor neurologic outcomes. Multivariate analysis using logistic regression models (forward selection) was used to examine factors associated with ROSC and a CPC score of 1 or 2; adjusted ORs and 95% confidence intervals (CIs) were calculated. The optimal number of defibrillations needed to achieve ROSC and a CPC score of 1 or 2 were determined using receiver operating characteristic (ROC) curves to calculate cutoff points, which were defined as the maximum point calculated using the equation sensitivity + specificity. The SPSS version 20 software package (International Business Machines [IBM] Corp., Armonk, NY, USA) was used to perform the analyses, and all values are expressed as mean ± SD or number and percentage. Intergroup comparisons were done by using the *t* test or χ^2 test. A p value of less than 0.05 was considered to indicate statistical significance.

Results

In total, 510727 OHCAs (281453 cardiogenic and 229274 noncardiogenic) were recorded between July 1, 2006 and December 31, 2010. Among the cardiogenic OHCAs, 114815 were witnessed; 9865 of these occurred in persons with an initial ECG waveform of VF who received initial defibrillation by EMS within 10 minutes of cardiogenic cardiac arrest (Fig. 1).

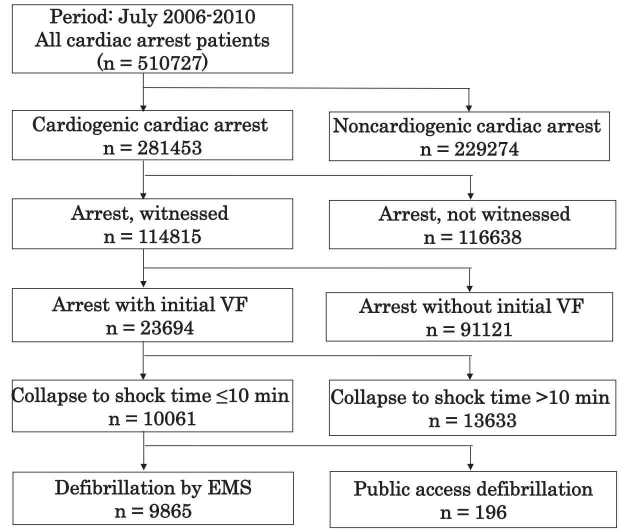

Fig. 1 Study flow for out of hospital cardiac arrest patients.
VF: ventricular fibrillation, EMS: emergency medical service

Baseline characteristics

Among the 9865 patients included in the study, 3812 had circulation restored and 6053 did not (Table 1). Among the 3812 patients with restored circulation, 2811 had a good neurologic outcome (CPC score, 1–2) and 7054 had a poor outcome (CPC score, 3–5) at 1 month. Younger patients were significantly more likely to have circulation restored and to have a good neurologic outcome. Similarly, early CPR, early defibrillation, chest compression and ventilation, and use of a biphasic waveform defibrillator were significantly associated with restoration of circulation and a good neurologic outcome. Use of an advanced airway device and use of adrenaline by EMS personnel were significantly more frequent in non-ROSC patients and those with a CPC score of 3 to 5. The time taken for EMS personnel to arrive at the patient's side was not associated with ROSC or a good neurologic outcome. The interval between collapse and hospital arrival was longer in the ROSC group and shorter in patients with a good neurologic outcome.

Multivariate analysis of ROSC

Multivariate analysis (Table 2) showed that ROSC was associated with chest compression (adjusted OR, 1.293; 95% CI, 1.167-1.433) and use of a biphasic waveform defibrillator by EMS personnel (adjusted OR, 1.208; 95% CI, 1.078-1.354). ROSC was associated with early defibrillation (adjusted OR per 1-minute increment between collapse and defibrillation time, 0.942; 95% CI, 0.928-0.956) and age (adjusted OR per 1-year increase in age, 0.989; 95% CI, 0.986-0.992). Use of an advanced airway device was in-

Table 1 Baseline characteristics of patients

	ROSC N = 3812 (38.2%)	Non-ROSC N = 6053 (61.8%)	P value	CPC 1-2 N = 2811 (28.5%)	CPC 3-5 N = 7054 (71.5%)	P value
Age, years	63.4 ± 15.2	65.2 ± 15.4	< 0.001	60.6 ± 15.0	66.0 ± 15.2	< 0.001
Men (%)	2985 (78.3)	4861 (80.3)	0.014	2272 (80.8)	55742 (79.0)	0.054
Bystander CPR						
Chest compression (%)	1534 (40.2)	2306 (38.0)	0.029	1182 (41.9)	2658 (37.7)	0.001
Ventilation (%)	530 (13.8)	746 (12.3)	0.039	410 (14.5)	866 (12.3)	0.003
Biphasic waveform defibrillation (%)	3207 (84.1)	4972 (82.1)	0.013	2422 (86.1)	5757 (81.6)	< 0.001
Number of defibrillations	1.9 ± 1.3	2.5 ± 1.7	< 0.001	1.9 ± 1.3	2.4 ± 1.6	< 0.001
Use of advanced airway device (%)	960 (25.1)	2800 (46.3)	< 0.001	568 (20.1)	3192 (45.3)	< 0.001
Use of adrenaline by EMS (%)	318 (8.2)	853 (14.1)	< 0.001	145 (5.1)	1026 (14.5)	< 0.001
Interval from collapse to EMS arrival at patient's side (min)	5.5 ± 2.5	5.6 ± 2.5	0.101	5.5 ± 2.5	5.6 ± 2.6	0.08
Interval from collapse to start of CPR (min)	4.5 ± 3.2	5.0 ± 3.1	< 0.001	4.4 ± 3.2	5.0 ± 3.1	< 0.001
Interval from collapse to defibrillation (min)	5.8 ± 3.3	6.6 ± 3.0	< 0.001	5.7 ± 3.3	6.5 ± 3.1	< 0.001
Interval from collapse to hospital arrival (min)	26.6 ± 14.1	25.9 ± 11.3	0.006	25.0 ± 14.4	26.6 ± 11.6	< 0.001

ROSC: return of spontaneous circulation, CPC: cerebral performance category, CPR: cardiopulmonary resuscitation, EMS: emergency medical services

Table 2 Logistic regression analysis of the associations of patient and treatment characteristics with return of spontaneous circulation

Variable	Adjusted odds ratio (95% CI)	P value
Age *1	0.989 (0.986-0.992)	< 0.001
Male, sex	0.860 (0.773-0.958)	0.006
Chest compression	1.293 (1.167-1.433)	< 0.001
Ventilation (%)	1.050 (0.913-1.209)	0.492
Biphasic waveform defibrillation	1.208 (1.078-1.354)	0.001
Number of defibrillations *2	0.753 (0.729-0.779)	0.001
Use of advanced airway device	0.446 (0.406-0.490)	< 0.001
Use of adrenaline by EMS	0.938 (0.810-1.087)	0.396
Interval from collapse to defibrillation *3	0.942 (0.928-0.956)	< 0.001

CI: confidence interval, CPR: cardiopulmonary resuscitation, EMS: emergency medical service
*1: per 1-year increment, *2: per additional defibrillation, *3: per 1-min increment

versely associated with ROSC (adjusted OR, 0.446; 95% CI, 0.406-0.490).

Multivariate analysis of good neurologic outcome

Multivariate analysis (Table 3) showed that a good neurologic outcome was associated with chest compression (adjusted OR, 1.494; 95% CI, 1.334-1.673) and use of a biphasic waveform defibrillator by EMS personnel (1.492; 1.311-1.698). ROSC was associated with early defibrillation (adjusted OR per 1-minute increment, 0.922; 95% CI, 0.907-0.936) and age (adjusted OR per 1-year increment, 0.974; 95% CI, 0.971-0.977). As was the case for factors contributing to ROSC, however, a good neurologic outcome was not associated with use of an advanced airway device (adjusted OR, 0.361; 95% CI, 0.324-0.402) or adrenaline (0.497; 0.410-0.602).

Number of shocks

As the number of shocks increased, the rates of ROSC and good neurologic outcomes decreased (Table 4). Among patients who achieved ROSC and a good neurologic outcome, half had received 1 defibrillation.

Table 3 Logistic regression analysis of the associations of patient and treatment characteristics with a good neurologic outcome

Variable	Adjusted odds ratio (95% CI)	P value
Age *1	0.974 (0.971-0.977)	<0.001
Male sex	0.986 (0.875-1.111)	0.816
Chest compression	1.494 (1.334-1.673)	<0.001
Ventilation (%)	1.041 (0.895-1.211)	0.603
Biphasic waveform defibrillation	1.492 (1.311-1.698)	<0.001
Number of defibrillations *2	0.829 (0.801-0.859)	<0.001
Use of advanced airway device	0.361 (0.324-0.402)	<0.001
Use of adrenaline by EMS	0.497 (0.410-0.602)	<0.001
Interval from collapse to defibrillation *3	0.922 (0.907-0.936)	<0.001

CI: confidence interval, CPR: cardiopulmonary resuscitation, EMS: emergency medical service
*1: per 1-year increment; *2: per additional defibrillation; *3: per 1-min increment

Table 4 ROSC and CPC in relation to the number of shocks administered

Number of shocks	ROSC (N = 3812)	Non-ROSC (N = 6053)	CPC 1-2 (N = 2811)	CPC 3-4 (N = 7054)
1 (%)	2044 (53.6)	2104 (32.4)	1455 (51.8)	2693 (38.2)
2 (%)	942 (24.7)	1567 (24.1)	691 (24.6)	1818 (25.8)
3 (%)	460 (12.1)	1085 (16.7)	369 (13.1)	1176 (16.7)
4 (%)	192 (5.0)	565 (8.7)	140 (5.0)	617 (8.7)
≧5 (%)	174 (4.6)	732 (12.1)	156 (5.5)	750 (10.6)

ROSC: return of spontaneous circulation, CPC: cerebral performance category

ROC curve analysis

The ROC curve analysis of ROSC and number of defibrillations showed that the cutoff value for the optimal number of shocks required to maximize successful ROSC was 1.5, with a sensitivity of 65%, a specificity of 54%, and an area under the curve (AUC) of 0.62 ($p<0.001$; 95% CI, 0.61-0.63) (Fig. 2A). A similar analysis showed that the optimal number of defibrillations required to maximize neurologic outcome (CPC score, 1–2) was also 1.5 (sensitivity, 62%; specificity, 52%; AUC, 0.59; $p<0.05$; 95% CI, 0.57-0.60) (Fig. 2B).

Time to hospital arrival

The mean time between collapse and hospital arrival was 24.9±12.6 minutes for patients receiving 1 or 2 shocks and 28.7±11.9 minutes for those receiving 3 or more shocks. The time between collapse and hospital arrival was significantly shorter for patients receiving 1 or 2 shocks than for those receiving 3 or more shocks ($p<0.001$).

Discussion

ROC curve analysis showed that the optimal number of pre-hospital shocks for OHCA patients (as determined by rates of ROSC and a CPC score of 1–2) was 1.5; thus, use of 2 shocks is appropriate in clinical practice. As the number of shocks increased, rates of ROSC and good neurologic outcomes decreased, and about half of patients were successfully treated with 1 shock. If frequent shocks are administered, EMS personnel must stop the ambulance and interrupt chest compressions for each cycle of ECG analysis and shock administration. Coronary perfusion pressure decreases if chest compressions are interrupted, causing a decline in coronary arteries. Even when chest compression is restarted, several consecutive compressions are required for coronary artery perfusion to return to its previous level.[18] Interrupting chest compressions during CPR was found to reduce ROSC rate, survival rate, and post-resuscitation cardiac function.[19] Minimizing the chest compression interruptions necessary to analyze cardiac rhythm, defibrillate, and administer advanced life support

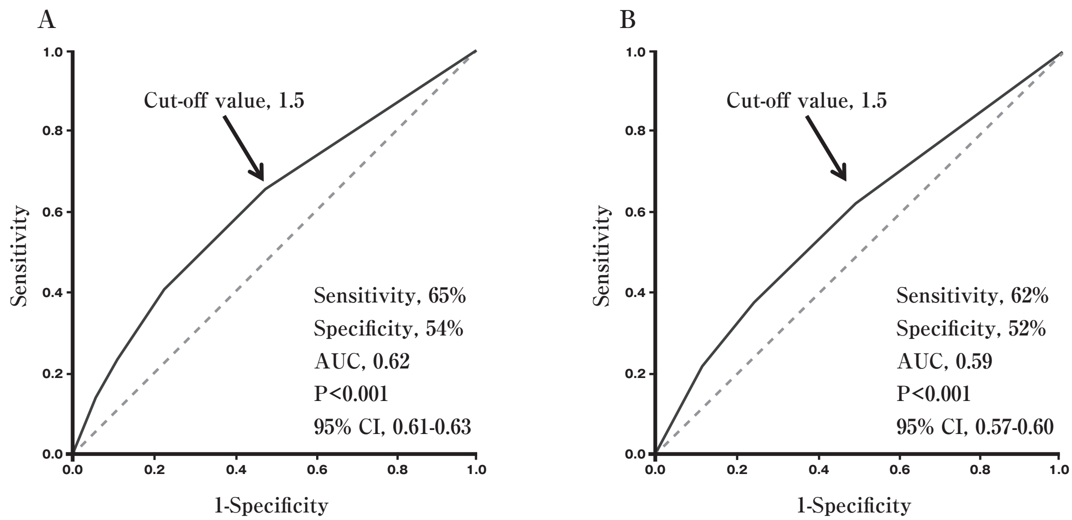

Fig. 2 Receiver operating curve (ROC) analysis of the number of defibrillations and return of spontaneous circulation **(A)** and a good neurologic outcome **(B)**. A cerebral performance category (CPC) score of 1 or 2 was defined as a good neurologic outcome.
AUC: area under the curve, CI: confidence interval

improves defibrillation outcomes.[20, 21]

VF is divided into 3 stages according to the interval from onset. The period within 4 to 5 minutes of VF onset is known as the electrical phase and is characterized by mild ischemia. ROSC can easily be obtained by rapid electrical defibrillation during this phase. The period 4 to 10 minutes after VF onset is referred to as the hemodynamic or circulatory phase. During this phase, myocardial adenosine triphosphate is depleted, which increases the difficulty of restarting a spontaneous rhythm, even if defibrillation is performed. Performing chest compressions during this phase maintains cerebral and coronary artery perfusion and reduces ischemia, which increases the possibility of achieving ROSC by defibrillation. The metabolic phase begins at 10 minutes after VF onset. During this phase, ROSC is difficult to achieve by regular CPR, including defibrillation; treatment of the underlying cause or adjunctive treatment is required.[22]

The outcomes for shock-resistant VF are disappointing: ROSC in 20.4% of cases and a CPC score of 1 or 2 in 5.6% of cases in 2006.[23] More time passes as additional unsuccessful defibrillations are performed, and the success rate decreases. The need for multiple defibrillation attempts increases interruptions to chest compression; thus, unsuccessful defibrillations result in myocardial damage and decreased survival.[24, 25]

The time taken for EMS personnel to arrive at the patient's side was not associated with ROSC or a good neurologic outcome; however, CPR and defibrillation should be performed as quickly as possible, and the patient should be hospitalized quickly. For persons with shock-resistant VF, early transportation for administration of anti-arrhythmic drugs, emergency cardiopulmonary bypass, and therapeutic hypothermia may be more important than repeated defibrillation.[26] To improve neurologic outcomes, the frequency of defibrillation — namely, limiting the number of shocks — should be considered by EMS personnel on the scene.

Bystander CPR, especially chest compression, was an important factor in achieving ROSC and good neurologic outcomes. Previous studies reported that a longer interval between cardiac arrest and defibrillation was associated with worse patient survival.[27] If CPR is withheld, the survival rate after witnessed VF cardiac arrest declines by an average of 7% to 10% for each minute between collapse and defibrillation.[12] If CPR is performed by bystanders, however, the survival rate declines by only 3% to 4% per minute.[12, 27–29] Performing CPR also reportedly doubles or triples the survival rate for a patient with a witnessed cardiac arrest, even if some time elapses before defibrillation.[12, 30, 31]

Our results suggest that adrenaline administration and use of advanced airway devices is disadvantageous to ROSC and worsens neurologic outcomes. However, adrenaline and use of advanced airway devices are not indicated for patients in whom ROSC was achieved by defibrillation and thus may only have been used for patients without ROSC in the present study. In other words, only patients in worse condition received an advanced airway device.

Use of a biphasic defibrillator was an important factor in achieving ROSC and a good neurologic outcome in the present patients. Biphasic defibrillators are reported to have a higher defibrillation rate than monophasic defibrillators.[32–34] The considerable energy needed for a successful shock causes myocardial damage. Biphasic defibrillators use lower energy than monophasic defibrillators and are less likely to cause post-shock VF.[35]

As compared with men, women had a higher rate of ROSC, but the proportions of men and women with a good neurologic outcome did not significantly differ. Some studies reported that the central nervous system and heart of women are protected by the effect of endogenous female hormones.[36] An animal study found that hormone administration improved cardiac arrest outcomes.[37] Studies clearly show that rates of survival and good neurologic outcomes decrease with advancing age.[38] In this study, the men were younger (mean age: 62.7 ± 14.5 years for men and 71.2 ± 16.6 years for women, $p < 0.005$). Thus, age appears to be strongly associated with neurologic outcome.

Study limitations

This study had some limitations. First, it was not a randomized controlled study. Second, we only analyzed prehospitalization data and thus have no information on treatments received in hospital, anti-arrhythmic drug use, coronary interventions, emergency cardiopulmonary bypass, or use of therapeutic hypothermia. Neurologic outcomes would likely be improved by a combination of emergency cardiopulmonary bypass, percutaneous coronary intervention, and early therapeutic hypothermia for OHCA patients unresponsive to conventional CPR for whom the period of circulatory arrest is comparatively short and the cause of cardiac arrest is known.[26] However, the evidence for this hypothesis is not conclusive.

Conclusions

Bystander CPR, biphasic waveform defibrillation, and temporal factors were important in achieving ROSC and good neurologic outcomes. Analysis of the data showed that, for an OHCA patient with VF, 2 shocks was the optimal number of defibrillations by EMS personnel on the scene. These data suggest that repeated defibrillation is associated with worse prognosis and that patients should be transported to a hospital as quickly as possible while chest compressions are maintained.

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Conflicts of interest: The authors have no conflicts of interest to disclose.

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