Early Defibrillation and Circulatory Support Can Provide Better Long-Term Outcomes Through Favorable Neurological Recovery in Patients With Out-of-Hospital Cardiac Arrest of Cardiac Origin

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Background Early defibrillation and cardiopulmonary bypass have been postulated to be a promising intervention against out-of-hospital cardiac arrest (OHCA); however, little is known about the long-term prognosis. The effects of early recovery of circulation (ROC) on neurological recovery and the long-term outcome in patients with OHCA were examined.

Methods and Results Functional recovery and long-term (22.0±15.3 months) outcome were examined in 100 patients with definite diagnosis of OHCA. Spontaneous circulation recovered in 79% of the patients (using on-site counter shock in 20% of the patients). Cardiopulmonary bypass was performed in 38 of the OHCA patients. The total survival and favorable neurological recovery rates were 40% and 25%, respectively. The patients with favorable recovery obtained early ROC (28.2±16.0 min). Receiver-operating characteristic analysis showed that a period of less than 35 min for ROC was the optimal period for achieving a favorable recovery, with sensitivity of 68% and specificity of 73%. The patients with a prior history of heart failure or reduced left ventricular ejection fraction exhibited more frequent, exacerbated heart failure and ventricular arrhythmias.

Conclusions Early ROC using on-site counter shock or cardiopulmonary bypass might result in better long-term outcome in patients with OHCA of cardiac origin. (Circ J 2005; 69: 1302–1307)

Key Words: Cardiopulmonary bypass; Implantable cardioverter defibrillator; Mild hypothermia; Out-of-hospital cardiac arrest

The reduction of the mortality rate for patients with out-of-hospital cardiac arrest (OHCA) is an important clinical issue to be resolved when considering primary and secondary prevention of sudden cardiac arrest in patients with cardiovascular disease, because acute survival rate and long-term outcomes are not satisfactory. Favorable neurological recovery from OHCA with minimal neurological deficit is still limited to exceptional individuals. Detailed information about community-based out-of-hospital basic life-support and automated external defibrillator programs has been provided to improve the acute-phase prognosis of OHCA patients. Though the early recovery of circulation (ROC) has been postulated as an important determinant factor for favorable neurological recovery from cardiac arrest, the rate of successful out-of-hospital defibrillation in patients with OHCA remains low.

Cardiopulmonary bypass, percutaneous coronary intervention and mild hypothermia have been thought to be promising therapeutic options for OHCA in order to improve in-hospital prognosis. The use of an implantable cardioverter defibrillator has also been recommended for preventing sudden cardiac arrest in high-risk patients with or without a history of organic heart disease, such as lethal arrhythmias and left ventricular dysfunction. However, there is little information on the long-term prognosis of OHCA.

The aim of the present study was to determine whether the early ROC using on-site counter shock or mechanical support such as a cardiopulmonary bypass results in survival with minimal neurological deficits and better long-term outcomes in patients with OHCA of cardiac origin.

Methods

Medical Area and Organization of an Emergency System

Our referable medical area is a metropolitan region in Japan located at 43°N with a residential population of 1,847,496 in 2001 and an area of 1,121.12 km² (distances in both the north–south and in west–east directions being about 40 km). Most OHCA patients are transferred to the nearest emergency medical centers, including a university hospital. The number of endogenous OHCA cases in this area is about 1,100/year (including about 400 non-transferred cases). Each emergency medical unit consists of 3 ambulance staff, including at least 1 emergency life-saving
technician. Emergency life-saving technicians must pass a state examination for qualification and they are permitted to insert an intravenous line and use a semi-automated external defibrillator provided that they have on-line confirmation by a medical doctor. However, they are not allowed to do tracheal intubation or to use any cardiovascular drugs without permission from a doctor.

Patients
From April 1999 to July 2003, we examined 313 consecutive adult patients with presumed cardiac-origin OHCA (212 males and 101 females, aged 66.6±16.4 years), who were diagnosed according to the recommendation of the Utstein consensus conference.\(^{17}\) Of those 313 patients, 100 cardiac-origin OHCA patients with definite diagnosis (78 males and 22 females; mean age, 58.3±14.3 years; age: 16–82 years) were selected for the present prognosis study. Patients without definite diagnosis (n=213) were not included.

Diagnosis of cardiovascular disease was determined by direct interviews with the patients and their families and by retrospective examination of patients' prior medical records after receiving written informed consent. Standard laboratory examinations, chest X-ray, computed tomography, electrocardiography and/or cardiac catheterization (including myocardial biopsy in cases of suspected cardiomyopathy) were performed. Ventricular fibrillation without organic heart disease was defined as idiopathic.

Methods
Essential information about OHCA, such as cardiac rhythm on initial electrocardiographic monitor recordings (ventricular fibrillation, asystole, pulseless electrical activity) and out-of-hospital circumstances (witness in cardiac arrest, bystander or emergency life-saving technician cardiopulmonary resuscitation, on-site counter shock), was analyzed. The time interval from collapse (time to emergency call, time to arrival of an emergency life-saving technician, time to transportation to an emergency room, time to return of spontaneous circulation (ROSC)) was analyzed with the patient with a witness to the cardiac arrest. Cardiopulmonary bypass was performed in the OHCA patients with the following indication criteria: 1) presumed cardiac-origin OHCA with a witness; and 2) hemodynamically unstable OHCA with incessant ventricular fibrillation or ventricular tachycardia that was not terminated by advanced cardiac life support. Mild hypothermia was performed in the unconscious patients after OHCA whose blood pressure was over 90 mmHg using spontaneous cardiac rhythm or mechanical support. The standard protocol of mild hypothermia was rapid cooling to 34°C for 3 days followed by step-wise rewarming for 2 days. ROC was defined as obtaining blood pressure over 90 mmHg for more than 5 min using spontaneous cardiac rhythm or mechanical support such as cardiopulmonary bypass and/or intra-aortic balloon pumping. The functional recovery state (mainly of neurological deficit) was evaluated on the 30th day after onset using the Glasgow outcome scale by several medical staff as follows: good recovery, moderate disability, severe disability, vegetative state, and death. Survivors with good recovery or moderate disability were defined as patients having favorable recovery with minimal neurological deficit (favorable recovery group) and survivors with severe disability or in a vegetative state were defined as patients having unfavorable recovery with severe neurological deficit (unfavorable recovery group). Incidence of cardiac events, defined as cardiac death, recurrent lethal arrhythmia, implantable cardioverter defibrillator discharge, recurrent acute coronary syndrome and hospitalized congestive heart failure, was analyzed in the entire cohort and subcohort divided by diagnostic criteria.
failure, were examined. All of the variables on clinical data and future outcomes were compared in the death, favorable recovery and unfavorable recovery groups.

**Statistical Analysis**

All numeric data are expressed as means ± SD. The differences between 2 independent variables or incidences in 2 groups were compared using the Student’s unpaired t-test or by the chi-square test. Comparison of data between more than 3 groups was first done using a one-way analysis of variance and then, if significant, Bonferroni analysis was performed. Kaplan–Meier life table analysis was used for determining group differences in cardiac events during the follow-up period. A p<0.05 was considered to be statistically significant.

**Results**

**Survival Rate of Patients With OHCA (Fig 1)**

In the presumed cardiac-origin OHCA patients (n=313), the rates of ROSC, survival at 1 month and favorable neurological recovery were 31%, 13% and 8%, respectively. In witnessed OHCA patients with ventricular fibrillation on initial electrocardiographic monitoring, the favorable neurological recovery rate was 24%. Seventy-five of the 100 cardiac-origin OHCA patients in the present study had a witness to their collapse (including 13 patients for whom OHCA was witnessed by an emergency life-saving technician and 29 patients in whom bystander cardiopulmonary resuscitation was performed). Initial electrocardiographic monitoring revealed ventricular fibrillation in 64%, asystole in 20% and pulseless electrical activity in 16% of the OHCA patients, and 79% of the OHCA patients exhibited ROSC. The rate of ROSC achieved using on-site counter shock was 31%. In the OHCA patients with ROSC, the rate of survival at 1 month and favorable neurological recovery were 80% and 55%, respectively. Cardiopulmonary bypass was performed in 38 (38%) of the OHCA patients. Twenty-eight patients exhibited ROSC after cardiopulmonary bypass support. Intra-aortic balloon pumping was performed in 37 (37%) of the OHCA patients. Percutaneous coronary intervention combined with coronary stenting was performed in 31 patients among 54 acute coronary syndrome patients, in accordance with the ACC/AHA (American College of Cardiology/American Heart Association) guidelines for the treatment of acute myocardial infarction. Percutaneous coronary intervention was successfully performed for 37 vessels (mean of 1.2 vessels/person) without complications. The rate of ROSC after admission was 54%. Mild hypothermia was performed in 39 (39%) of the unconscious patients after OHCA. The total survival rate and favorable neurological recovery rate in cardiac-origin OHCA patients with definite diagnosis were 40% (n=40) and 25% (n=25), respectively.

Differences in clinical backgrounds, circumstances at onset of OHCA, time intervals and therapies among the functional recovery groups are shown in Table 1. No sig-
significant differences were found in gender, age, underlying heart disease and prior history of heart failure. The incidences of ventricular fibrillation in the favorable recovery group (88%) and unfavorable recovery group (87%) were higher than the incidence in the death group (48%). No group differences were found in the rates of witnessed OHCA and bystander cardiopulmonary resuscitation. The time intervals (min) from onset to emergency call, to arrival of an emergency life-saving technician and to arrival at an emergency room were also the same. However, the time intervals from onset to ROSC and from onset to ROC in the favorable recovery group (38.5±25.6 and 28.2±16.0, respectively) were significantly shorter than those in the death group (76.5±62.9 and 53.3±24.9, respectively).

The total numbers of patients according to the time interval from onset to ROC are shown in Fig 2 (Left panel). Patients with ROC within 15 min after onset (n=5) generally showed a favorable recovery. The favorable recovery rate of patients with ROC within 35 min after onset (n=31) was 55%. Receiver-operating characteristic analysis showed a period of less than 35 min for ROC was the optimal period for achieving a favorable recovery. The sensitivity and specificity at this point (ROC within 35 min) were 68% and 73%, respectively. Total numbers of patients who obtained ROC by cardiopulmonary bypass according to the time interval from onset to ROC are shown in Fig 2 (Right panel). Receiver-operating characteristic analysis showed a period of less than 45 min for ROC was the optimal period for achieving a favorable recovery, with sensitivity of 63% and specificity of 73%.

Long-Term Outcome of OHCA Patients

Following further medical examination, implantable cardioverter defibrillators were implanted in accordance with the ACC/AHA guideline in 9 patients with favorable neurological recovery. Coronary artery bypass grafting was performed in 3 OHCA patients with residual ischemia. Patients with unfavorable recovery did not undergo bypass surgery or the implantation of implantable cardioverter defibrillator. Both patients with favorable recovery and unfavorable recovery were followed every month for 22.0±15.3 months (range of follow-up periods, 1–53 months). The total cumulative survival rates of patients in the favora-

![Fig 2.](image)

Fig 2. (Left) Total number of patients according to the time interval from onset to recovery of circulation (ROC). Receiver-operating characteristic analysis showed a period of less than 35 min for ROC was the optimal period for achieving a favorable recovery with sensitivity of 68% and specificity of 73%. (Right) Total number of patients who obtained ROC using cardiopulmonary bypass according to the time interval from onset to ROC.

Fig 3. Kaplan–Meier analysis of long-term outcome in patients with favorable recovery and those with unfavorable recovery showed statistically significant differences between the 2 groups. The 1-year survival rate of patients with unfavorable recovery was only 50%, because of multiple organ failure.

![Fig 3.](image)

Fig 3. Kaplan–Meier analysis of long-term outcome in patients with favorable recovery and those with unfavorable recovery showed statistically significant differences between the 2 groups. The 1-year survival rate of patients with unfavorable recovery was only 50%, because of multiple organ failure.

ble and unfavorable recovery groups are shown in Fig 3. During an observation period (follow-up rate: 100%), only 1 of the patients with favorable recovery died from a non-cardiac cause (due to purulent mediastinitis); however, half of the patients with an unfavorable recovery died during the first year. The cause of death in most cases with unfavorable recovery was multiple organ failure. In sub-analysis of the favorable recovery group (n=25) for 27.2±14.8 months (Fig 4), patients with previous history of heart failure (n=9) or reduced left ventricular function (left ventricular ejection fraction <35% (n=4)) in the chronic phase had greater exacerbation of heart failure. Two of the 4 patients with heart failure suffered a recurrence of ventricular fibrillation with implantable cardioverter defibrillator discharge.

**Discussion**

In the era of community-based life support for cardiac arrest, it is of interest that early ROC can improve the prognosis of OHCA patients. The aim of the present study was to determine whether early ROC using on-site counter shock or cardiopulmonary bypass can result in an improved survival rate and better long-term outcome in OHCA.
patients (n=100). The main results of the present study were as follows: (1) 79% of the OHCA patients achieved ROSC, 20% achieving ROSC through an on-site counter shock; (2) early ROC (within 35 min), even using cardiopulmonary bypass, resulted in favorable functional recovery with minimal neurological deficit; and (3) the long-term outcome in OHCA patients was closely related to acute-phase neurological recovery, prior history of heart failure and chronic-phase left ventricular ejection fraction. Therefore, early ROC using on-site counter shock or cardiopulmonary bypass might be beneficial for achieving a good long-term outcome through favorable neurological recovery in cardiac-origin OHCA patients.

Survival Rate of OHCA Patients

The rates of ROSC (79%), survival at 1 month (40%) and favorable neurological recovery (25%) in the patients in the present study were better than those previously reported. However, the survival rate of OHCA patients without definite diagnosis was very low (2/212, 1%). Therefore, the overall mortality rate of cardiac-origin OHCA patients is still unsatisfactory.

As described in previous reports, OHCA patients with ROSC achieved using on-site counter shock had a high survival rate (16/20, 80%) and highly favorable neurological recovery rate (11/20, 55%); however the rate of ROSC achieved by on-site counter shock was low (20/64, 31%). Possible reasons for the low success rate of on-site counter shock are: (1) the bystander was not permitted to use an automated external defibrillator; (2) the emergency lifesaving technician was permitted to use an automated external defibrillator only with on-line confirmation by a medical doctor; and (3) the emergency life-saving technician was not allowed to use any cardiovascular drugs. The rate of ROSC after admission was high, 54% (after cardiopulmonary bypass support in 28 patients). In the patients in the present study, cardiopulmonary bypass was performed immediately after admission in cases of witnessed OHCA with incessant ventricular fibrillation that was not responsive to advanced cardiac life support, and early ROC (within 45 min) resulted in favorable neurological recovery.

Our previous study in which autopsy examinations were conducted on non-survivors of OHCA showed that coronary artery disease, especially acute myocardial infarction, is the main cause of cardiac-origin OHCA (causing OHCA in 56.3% of cases). Therefore, coronary angiographic evaluation and percutaneous coronary intervention with stabilized circulation using cardiopulmonary bypass might be beneficial for improving the survival of OHCA patients. However, the present study was not intended to determine the efficacy of percutaneous coronary intervention for acute coronary syndrome with OHCA, so we could not determine the efficacy of percutaneous coronary intervention in the improving acute-period recovery.

Improvement in Long-Term Prognosis of OHCA Patients

Our data on long-term outcomes clearly showed that favorable neurological recovery was an important factor for determining long-term prognosis. Early recovery of circulation using on-site counter shock or cardiopulmonary bypass will be beneficial for better long-term outcomes through favorable neurological recovery in cardiac-origin OHCA patients. During the long-term follow-up in patients with favorable neurological recovery, prevention of recurrent lethal arrhythmia is very important. It seems that additional treatment such as coronary artery bypass grafting or the implantation of an implantable cardioverter defibrillator performed for patients in the chronic stage is associated with a good prognosis. Several recent multi-center trials have revealed that implantation of implantable cardioverter defibrillator for OHCA patients could reduce the risk of cardiac death, especially for patients complicated with heart failure. The recently published ACC/AHA guidelines merely indicates that a survivor of cardiac arrest caused by ventricular fibrillation should be treated with an implantable cardioverter defibrillator. However, there have been very few detailed reports on the incidences of the recurrence of lethal arrhythmias and the efficacy of use of an implantable cardioverter defibrillator for preventing sudden cardiac arrest in OHCA patients during a long-term follow-up. Ruppel et al reported that among 40 patients who had survived an episode of ventricular fibrillation and subsequently received an implantable cardioverter defibrillator, 41 episodes of ventricular arrhythmias were documented in 13 patients (33%). In the present study, we also found implantable cardioverter defibrillator discharge in 2
(22%) of the 9 survivors. Moreover, cases with reduced left ventricular function (left ventricular ejection fraction <35%) had a higher incidence of the exacerbation of heart failure (3/4, 75%) as reported by Rea et al.33

Complete revascularization was obtained in 8 of the 10 percutaneous coronary intervention cases of favorable recovery, including 3 cases in which a coronary artery bypass grafting was performed, and no case exhibited a recurrence of acute coronary syndrome. It has been reported that a coronary artery bypass grafting reduces the mortality rate of patients at high risk of ventricular arrhythmia.24,25 The need for the implantation of an implantable cardioverter defibrillator for patients with OHCA caused by acute myocardial infarction with reduced left ventricular function (left ventricular ejection fraction <35%) was reported by Moss et al.34 However, in the present study, all the survivors of OHCA caused by acute coronary syndrome had relatively good left ventricular function (left ventricular ejection fraction ≥35%), and there was no cardiac death. We therefore conclude that the implantation of implantable cardioverter defibrillator should be performed to prevent lethal arrhythmia recurrence in survivors of OHCA with favorable neurological recovery who have a previous history of heart failure or reduced left ventricular function.

Study Limitations

This is a study from a single cardiovascular center with a small number of patients and is not a double-blind randomized trial. However, considering the ethical aspects of OHCA therapy, it would be difficult to carry out a double-blind study.

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References