and analyze information on in-hospital cardiac arrest and resuscitation to understand the present status of in-hospital cardiac arrest in Japan.

Methods

Design and Setting

The J-RCPR is a prospective multisite observational study of in-hospital cardiac arrest and resuscitation in Japan. Because the primary purpose of the J-RCPR is quality improvement, participating hospitals are not required to obtain individual informed consent, as is the case for the NRCPR. This study was conducted in accordance with the ethical guidelines for epidemiological studies and was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center.

Data Collection

We designed the J-RCPR Data Collection software in a standardized format for the entering of information about each cardiac arrest and distributed the J-RCPR software to the 12 hospitals that participated in this study. Data were accumulated and registered between January 2008 and December 2009. The information was abstracted from hospital medical records. The database on in-hospital cardiac arrest and resuscitation was defined according to the international standard from the Utstein in-hospital guidelines.[9–11] Each patient was assigned a unique code, and no specific patient identifiers were transmitted to the central database repository. The data were submitted on diskette or sent by encrypted transmission over the secure Internet.

Case Inclusion and Exclusion Criteria for the J-RCPR

The eligibility criteria for enrollment of patients who experienced in-hospital cardiac arrest in the J-RCPR were: (1) all victims (adult, pediatric and neonatal) of in-hospital cardiac arrest that required chest compression or electrical defibrillation, or both, that elicited an emergency resuscitation response by facility personnel and resulted in a resuscitation record, (2) all in-hospital cardiac arrests that occurred not only in hospitalized patients, but also in outpatients, visitors, employees, and staff in a hospital, (3) out-of-hospital cardiac arrest patients transported to hospital, or an event that began outside the facility, spontaneous circulation was maintained for 20 min or more after hospital arrival, but cardiac arrest occurred again. Cardiac arrest was defined as cessation of cardiac mechanical activity, determined by the absence of a palpable central pulse, unresponsiveness, and abnormal respiration (apnea or gasping). Patients who had not had an attempt at resuscitation or who had defibrillation of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) only by an implantable cardioverter-defibrillator were excluded. In this article, cardiac arrests occurring in operating rooms or in children <18 years of age were excluded, because of the different pathologies involved in these cases.

Major Categories

Data in the J-RCPR were collected in 6 major categories of variables: facility data, patient demographic data, pre-event data, event data, outcome data, and quality improvement data.

(1) Facility data: number of total beds in the hospital and number of intensive care unit (ICU) beds.

(2) Patient demographic data: major reason for hospital admission was classified as cardiac, such as acute coronary syndromes (ACS), arrhythmia, congestive heart failure, cardiomyopathy, aortic disease (acute aortic dissection or aortic aneurysm), and noncardiac, such as respiratory disease, cerebrovascular disease, renal failure, and other. In the in-hospital Utstein style, summary categories were used, because full clinical details and diagnoses may not be immediately available to the event team.

(3) Pre-event data: information on the situation before the onset of in-hospital cardiac arrest (direct cause of the arrest and the recorded status at the last confirmation prior to the occurrence of the arrest) was registered. The immediate cause of in-hospital cardiac arrest (single or multiple choice), present within 1 h before arrest, was classified as arrhythmia, acute respiratory insufficiency, hypotension (systolic blood pressure <90 mmHg or mean blood pressure <60 mmHg, irrespective of the use of vasopressors and intra-aortic balloon pumping), ACS, metabolic and electrolyte abnormalities, and other causes (acute pulmonary edema, acute pulmonary thromboembolism, airway obstruction and toxicological problem etc). The heart rate during arrhythmia was not requested, following the in-hospital Utstein style. The interval from the time of the last confirmation of absence of signs of cardiac arrest in the patient prior to the occurrence of the in-hospital arrest was collected from medical record.

(4) Event data: location of onset (general ward, ICU, emergency room, clinical laboratory (including catheterization laboratories), and other), discovery status at the time of the in-hospital cardiac arrest (presence/absence of a witness, presence/absence of ECG monitoring, time at which cardiac arrest was confirmed, initial ECG rhythm at the time of the sudden change). First documented pulseless rhythm was defined as the first ECG rhythm documented at the time the patient became pulseless or, for those patients with an unwitnessed/unmonitored arrest, it was the first rhythm documented at the time a monitor arrived and was applied. Index events were defined as the patient's first cardiac arrest event during this hospitalization. In this study, the categories of acute respiratory compromise leading to cardiopulmonary arrest (CPA) and CPA were combined into 1 category 'cardiac arrest'.

(5) Outcome data: the primary endpoint was a favorable neurological outcome at 1 month after cardiac arrest defined according to the Glasgow-Pittsburgh cerebral-performance category (CPC) of 1 (good performance) or 2 (moderate disability) on a 5-category scale (the other categories are 3 (severe disability), 4 (vegetative state), and 5 (death)),[10,12] and the secondary outcome was return of spontaneous circulation (ROSC), the 24-h outcome and mortality at 30 days.

(6) Quality improvement data: information on the first responder, the status of the cardiopulmonary resuscitation (CPR) activities (time at which CPR was started, time at which a defibrillator was placed, time at which electrical defibrillation was performed, presence/absence of automated external defibrillator [AED] use). Resuscitation attempts were documented according to the in-hospial Utstein style guidelines.

Definition of the End of an Event

The end of an event was defined as ROSC, including with the support of a pace maker or cardiopulmonary bypass, lasting >20 min or the termination of the resuscitation event with the patient declared dead due to being unresponsive to resuscitative efforts, a medical futility advance directive, or restrictions imposed by family members. The typical descriptor 'spontaneous' was included in the definition because this is the standard accepted terminology, same as in the NRPCR.[7]

Statistical Analysis

Participant baseline characteristics and outcomes are reported

through means and standard deviation, and frequency and percentage for comparison between groups. Chi-square test or Fisher's exact test was used for binary or categorical comparisons, and unpaired t-test was used to compare continuous data. Odds ratio and 95% confidence intervals in the logistic regression model were used to compare the incidences in primary and secondary outcomes between groups in the study. All statistical analyses were performed using a commercially available statistical package (JMP software version 8.0J and Statistical Applications Software 8, SAS Institute, Cary, NC, USA).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Facility Data

In the J-RCPR study, participating hospital had a median of 490 total hospital beds (from 129 to 780) and a median of 14 ICU beds (from 0 to 74). **Figure 1** shows the distribution of the 12 participating hospitals across Japan.

Patient Demographic Data

During the 2-year study period, data for 491 adult patients with an in-hospital cardiac arrest in the 12 participating facilities were analyzed in the J-RCPR. The average number of events per year per facility was 20.5±22.1; however, the average number of index events, defined as the cardiac arrest event overall per bed per year was 0.053±0.046 events/bed annually. Patient demographic data are shown in **Table 1**. The mean age of the patients was 71.0±14.9 years and 63.3% of all the patients (n=311) were male. As for the reasons for hospital admission, cardiac disease comprised 55.1% (n=269) and noncardiac disease 44.9% (n=219). A witness to the cardiac arrest was present in 77.2% of cases, and 78.0% of the patients were under ECG monitoring at the time of the cardiac arrest. **Figure 2** shows the distribution of the patients stratified by age at 5-year intervals. The number of events increased with age and the incidence was the highest in

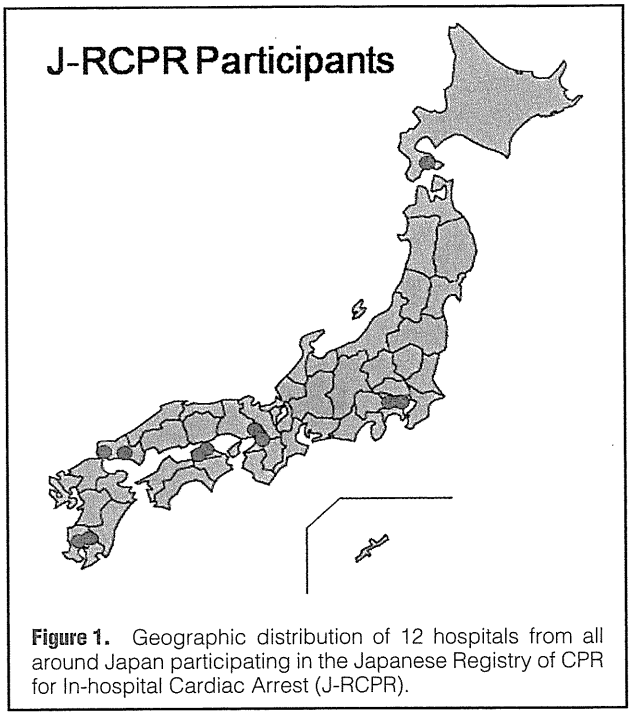

Figure 1. Geographic distribution of 12 hospitals from all around Japan participating in the Japanese Registry of CPR for In-hospital Cardiac Arrest (J-RCPR).

Table 1. Patient Demographic Data

No. of cases	491
Age (years); mean±SD	71.0±14.9
Sex (M/F)	311 (63.3%)/ 180 (37.7%)
Reason for hospital admission n (%)	
Cardiac disease	269 (55.1%)
Noncardiac disease	219 (44.9%)
Presence of witness to cardiac arrest n (%)*	377 (77.2%)
Presence of ECG monitoring n (%)*	383 (78.0%)

*At the time of the occurrence of the cardiac arrest.

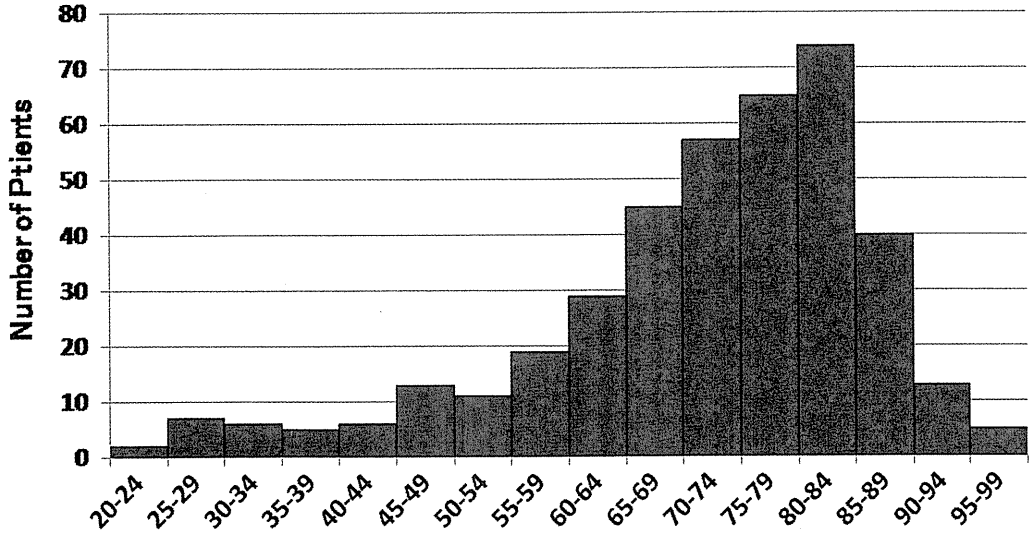

Figure 2. Distribution of the patients stratified by age at 5-year intervals. The number of events increased with age and the incidence was the highest in the group between 80 and 84 years of age.

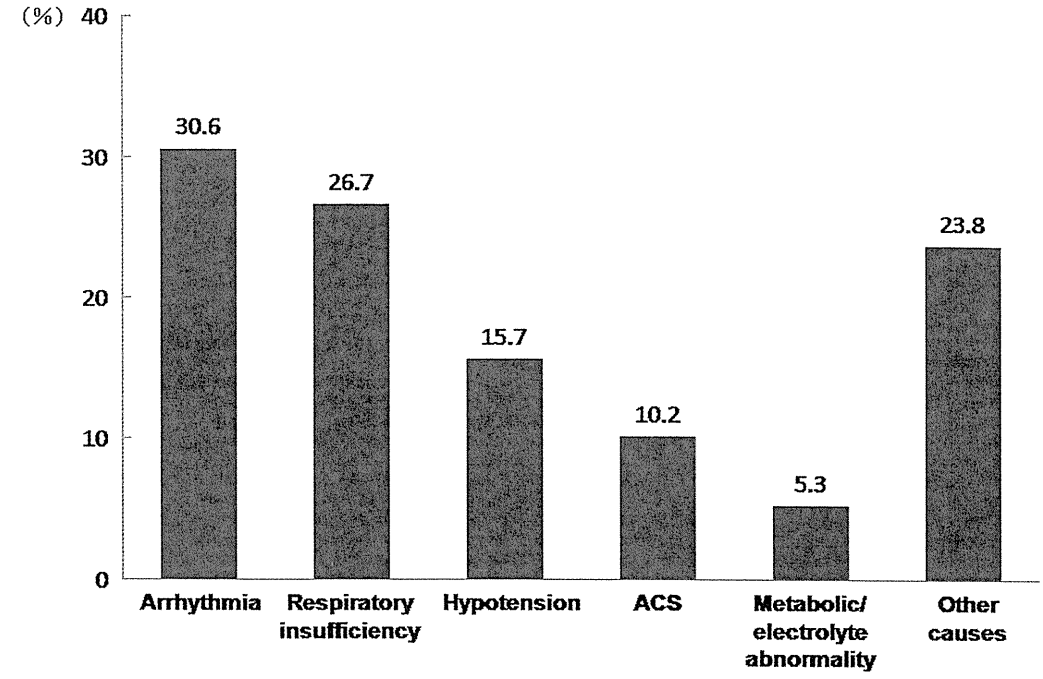

Figure 3. Immediate cause of in-hospital cardiac arrest. Arrhythmia was the most common cause, accounting for 30.6% of all cases (n=150), followed by respiratory insufficiency 26.7% (n=131), hypotension 15.7% (n=77), acute coronary syndrome (ACS) 10.2% (n=50), metabolic and electrolyte abnormality 5.3% (n=26), and others 23.8% (n=117). Because the selection was single or multiple choice, sum total proportion exceeds 100%.

Table 2. Pre-Event and Event Data

First documented pulseless rhythm	
Ventricular fibrillation/pulseless VT	138 (28.1%)
Pulseless electrical activity	202 (41.1%)
Asystole	145 (29.5%)
Unidentified	6 (1.2%)
Electrical defibrillation (includes use of AED)	141 (28.7%)
AED use	26 (5.4%)
Last confirmation prior to occurrence of cardiac arrest	
≤10 min	328 (78.1%)
≥10–≤20 min	34 (5.7%)
≥20–≤30 min	39 (4.8%)
>60 min	45 (9.2%)
Unknown	25 (5.1%)

First documented pulseless rhythm defined as the first ECG rhythm documented at the time the patient became pulseless and for those patients with an unwitnessed/unmonitored arrest, it represents the first rhythm documented at the time a monitor arrived and was applied.
AED, automated external defibrillator.

the group between 80 and 84 years of age.

Pre-Event Data

The immediate causes of the in-hospital cardiac arrest (single or multiple choice) are presented in **Figure 3**. Arrhythmia was the most common cause and accounted for 30.6% of all the cases (n=150), followed by acute respiratory insufficiency 26.7% (n=131), hypotension 15.7% (n=77), ACS 10.2% (n=50), metabolic and electrolyte abnormality 5.3% (n=26), and others 23.8% (n=117). As shown in **Table 2**, regarding the interval from the time of the last confirmation of absence of signs of cardiac arrest in the patient prior to the occurrence of the cardiac arrest, 66.9% (n=328) developed cardiac arrest within 10 min of the last checking time, 73.7% (n=362) within 20 min, 81.7% (n=401) within 30 min, and 9.2% (n=45) over 1 h after, and the time of the last check was unknown in 5.1% (n=25).

Event Data

As for the initial ECG rhythm at the time of occurrence of the in-hospital cardiac arrest, 28.1% (n=138) had shockable rhythm (pulseless VT/VF), 41.1% (n=202) had pulseless electrical activity, 29.5% (n=145) had asystole, and 1.2% (n=6) had a pacemaker rhythm. In regard to the location of onset of the in-hospital cardiac arrest, it occurred in the general ward in 54.0% of cases (n=265), in the intensive care unit in 25.4% (n=125), in the emergency room in 8.0% (n=39), in clinical laboratories in 5.8% (n=28), and in other locations in 6.8% (n=33) (**Figure 4**).

Outcome Data

Figure 5 shows the outcomes and acute prognosis in reference to assessment of neurological function in patients resuscitated from an in-hospital cardiac arrest. The proportion of ROSC was 64.7%, the proportion of 24-h survival was 49.8%, the proportion of 30-day survival was 27.8%, and the proportion of 30-day favorable neurological outcome with a CPC score of 1 or 2 was 21.4%.

Patients were classified according to the initial ECG rhythm at the time of the occurrence of the cardiac arrest, and the outcomes were compared, as shown in **Figure 6**. The propor-

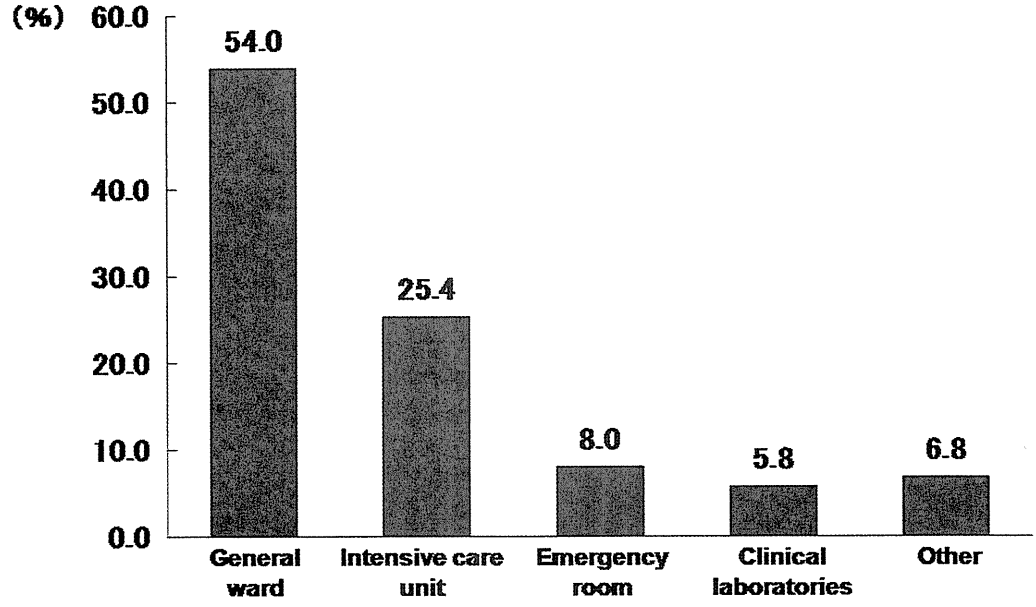

Figure 4. Location of the in-hospital cardiac arrest: in the general ward (n=265), in the intensive care unit (n=125), in the emergency room (n=39), in clinical laboratories including catheterization laboratories (n=28), and in other locations (n=33).

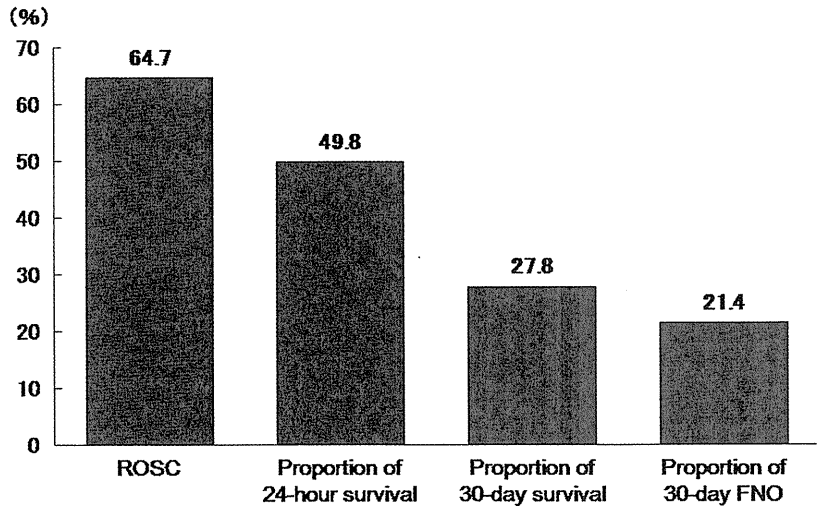

Figure 5. Outcomes of in-hospital cardiac arrest. The proportion of return of spontaneous circulation (ROSC) was 64.7%, the proportion of 24-h survival after cardiac arrest was 49.8%, the proportion of 30-day survival after cardiac arrest was 27.8%, and the proportion of 30-day favorable neurological outcome (FNO) with a Glasgow-Pittsburgh cerebral-performance category score of 1 or 2 was 21.4%.

tion of ROSC, the proportion of 30-day survival, and the proportion of favorable 30-day neurological outcome with a CPC score of 1 or 2 was 79.3%, 46.0% and 40.1%, respectively, in patients with pulseless VT/VF; 65.5%, 23.7%, and 17.3%, respectively, in patients with pulseless electrical activity; and 49.7%, 17.2%, and 9.0%, respectively, in patients with asystole.

Quality Improvement Data

CPR was performed by 96.3% of the first responders to the cardiac arrest. The median interval from cardiac arrest to the initiation of CPR was 0 min. Electrical defibrillation was performed during the resuscitation in 136 cases, and in 26 cases an AED was used.

Discussion

The J-RCPR is the first multicenter registry of in-hospital cardiac arrests and resuscitation in Japan. During the 2-year study period, data for 491 adult patients with in-hospital cardiac arrest in the 12 participating facilities were analyzed in the J-RCPR. Results of large-scale registry studies have also been reported from the UK[4,5] and Australia.[6] The British hospital Resuscitation study (BRESUS),[4] reported in 1992, registered 3,765 patients in 12 hospitals across the United Kingdom. However, nearly one-quarter of the patients in that registry had cardiac arrest in the prehospital setting. The Brain Resuscitation Clinical Trials (BRCT), a series of 3 international, multicenter, prospective, randomized, controlled cere-

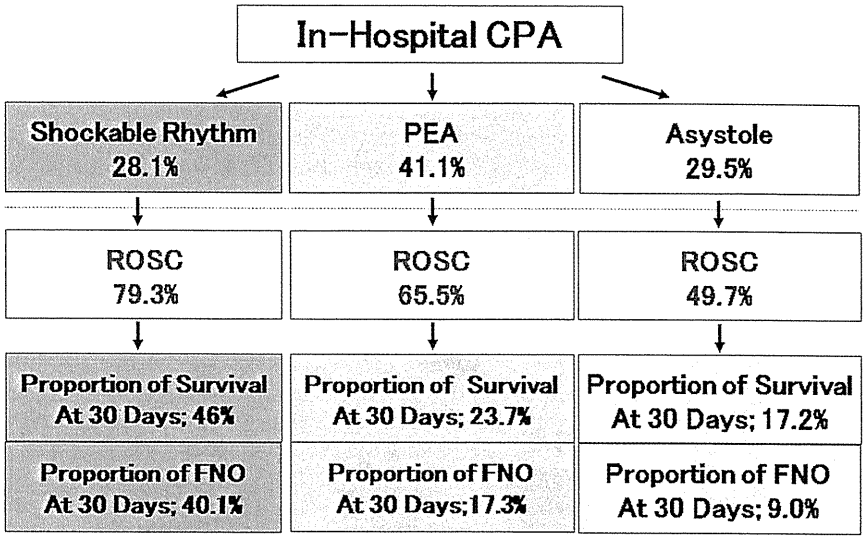

Figure 6. Classification of patients at the time of the cardiac arrest. Second row shows the initial ECG rhythm. Third row shows the proportion of return of spontaneous circulation (ROSC). Fourth row shows the proportion of survival at 30-day, and the bottom row shows the proportion of favorable neurological outcome at 30-days with a cerebral performance category score of 1 or 2. CPA, cardiopulmonary arrest; ROSC, return of spontaneous circulation; FNO, favorable neurological outcome; PEA, pulseless electrical activity.

bral resuscitation studies, were conducted from 1979 through 1992, but only 13–36% of events occurred in hospitals. A large-scale registry study, the NRCPR, was started in 2000 to collect data on in-hospital cardiac arrests in the United States, and the results of more than 110,000 enrolled cases from 550 US acute care hospitals were reported in 2008–2010.[8,13,14]

Facility Data

The circumstances and management methods of in-hospital cardiac arrest are greatly affected by the medical and healthcare systems in each country. In the J-RCPR, the 12 participating hospitals had a median of 14 ICU beds and a median of 490 total hospital beds. Participating hospitals in the NRCPR had a median of 20 ICU beds.[7] This result was consistent with a previous study that reported that Japanese hospitals have a mean 8 ICU beds and US hospitals have 22 ICU beds per hospital.[15] These differences in the medical and healthcare systems also may affect the average number of index events. The incidence of in-hospital cardiac arrest can be calculated either as the number of events per hospital bed per year or as the number of events per number of patient admissions. In the J-RPCR, we reported an incidence of 0.053 events/bed annually over a total of 491 arrests. The NRCPR reported in the same way an incidence of 0.174 events/bed/year over a total of 14,720 arrests. Other studies have used the second method and report an incidence of 1–5 arrests per 1,000 patient admissions.[16–18]

Patient Demographic Data

Several studies report that the older the patient, the lower the proportion of survival to hospital discharge after in-hospital cardiac arrest.[13,19,20] In the J-RCPR, the mean age of the patients was 71.0±14.9 years. The number of occurrences increased with age and the incidence was the highest in the group between 80 and 84 years of age.

Pre-Event Data

The direct causes of in-hospital cardiac arrest in the J-RCPR were arrhythmia (30.6%), acute respiratory insufficiency (26.7%) and hypotension (15.7%). These causes were reported from the NRCPR,[14] in which arrhythmia was 65%, acute respiratory insufficiency was 41% and hypotension was 44%. Thus according to both reports, the 3 most common reasons for in-hospital cardiac arrest are cardiac arrhythmia, acute respiratory insufficiency, and hypotension.

Event Data

As the initial ECG rhythm at the time of occurrence of the in-hospital cardiac arrest, the frequency of pulseless VT/VF was 28.1% in the J-RPCR. In the published literature, pulseless VT/VF on initial ECG in patients with in-hospital cardiac arrest has been reported to be detected at the rate of 20–35%.[5,7,17,20,21] Because VF is present in the majority of out-of-hospital cardiac arrests that occur with a continuous cardiac monitor in place,[22] it is surprising that the data showed an infrequent presence of pulseless VT/VF as the initial ECG rhythm at the time of occurrence of the in-hospital cardiac arrest. It may be that the low incidence of pulseless VT/VF and the predominance of asystole and pulseless electrical activity is because in-hospital cardiac arrest differs from out-of-hospital cardiac arrest in terms of mechanism and pathophysiology. As a reason for the lower frequency of pulseless VT/VF in in-hospital cardiac arrests than in out-of-hospital cardiac arrests, it has been suggested that cardiac arrest caused by hypoxemia and hypotension is more likely in the case of in-hospital cardiac arrest.[6,7] In addition, the shorter the interval between the onset and detection of cardiac arrest, the higher the frequency of VF and the lower the frequency of asystole.

In the comparison of the location of onset of the in-hospital cardiac arrests between the J-RCPR and the NRCPR,[14] the incidence in general wards was 55% and 35%, respectively, and that in ICU was 24% and 45%, respectively. The incidence in general wards was higher according to the J-RCPR and that in the ICU was higher according to the NRCPR, which might be a result of differences in the healthcare systems, reflected as less ICU beds in the J-RCPR than in the NRCPR.

Outcome Data

With regard to the outcomes of adult patients with in-hospital cardiac arrest, the proportion of ROSC was 64.7%, the proportion of 24-h survival after cardiac arrest was 49.5% and the proportion of 30-day survival was 27.8% in the

J-RCPR. The proportion of survival discharge is most widely used as an outcome measure for in-hospital cardiac arrests, and has been reported to be approximately 20%.[4,5,7,23–25] However, it can not be concluded from the present result that the resuscitation rate for in-hospital cardiac arrest is better in Japan than in the United States, because the circumstances and management methods of in-hospital cardiac arrests might be greatly affected by the medical and healthcare systems of each country. Use of the term 'overall survival' to describe outcome may be misleading. Because the proportion of survival is very different for pulseless VT/VF, asystole and pulseless electrical activity as the initial ECG rhythm at the time of occurrence of the in-hospital cardiac arrest, descriptions of outcome should be based on each of the initial arrest rhythms, not the overall survival from all arrest rhythms combined. In this study, the patients were stratified into 3 groups according to the initial ECG rhythm at the time of occurrence of the cardiac arrest, to investigate the proportion of ROSC. The proportion of ROSC for pulseless VT/VF was 79.3% and for pulseless electrical activity it was 65.5% in the J-RCPR. In contrast, the proportion of ROSC was 67% for pulseless VT/VF, 45% for pulseless electrical activity, and 52% for asystole in the NRCPR.[8] Also careful attention should be paid if the proportion of 24-h survival is selected to describe outcome. In the NRCPR, it has been reported that a large number of patients with ROSC after an in-hospital cardiac arrest are declared DNAR (do not attempt resuscitation) and nearly half of those have life support withdrawn, whereas only less than 10% are declared clinically brain dead. The aggressiveness with which an individual hospital withdraws care and withholds future resuscitation attempts has a significant bearing on both individual and aggregate survival data and can have a tremendous impact on a clinical trial with survival to hospital discharge as a primary endpoint. Further investigation is needed to evaluated the clinical factors and practice patterns that have an impact on these data. Also, if spontaneous circulation is successfully restored after a sudden in-hospital cardiac arrest, the original disease condition progresses to directly cause death in many patients. Therefore, it is necessary to investigate the causal relationships between the in-hospital cardiac arrest, the underlying disease and death when the proportion of survival is assessed as the primary outcome. As an outcome prediction model, the incidence of respiratory failure, shockable rhythm, chronic renal insufficiency, body mass index, and the interval from hospitalization to the occurrence of in-hospital CPA have been reported in the literature.[26] In addition, a relationship between the onset time and the outcome has also been reported.[8,27] In order to construct an outcome prediction model for patients with in-hospital CPA, more detailed investigation is required in the future.

Quality Improvement Data

In the J-RCPR, 96.3% of the first responders to the cardiac arrest performed CPR and the median interval from the occurrence of cardiac arrest to the initiation of resuscitation was 0 min. In regard to the interval from the occurrence of cardiac arrest to defibrillation for shockable cardiac arrest rhythm and its effect, although the median interval from cardiac arrest to defibrillation was only 1 min, a delay in administration of defibrillation by 3 min or more was found in 30.1% of the cases, and in the NRCPR the proportion of survival to hospital discharge was reduced in cases with such a delay.[28] However, the J-RCPR had not enough number of cases to analysis the time relation between onset of cardiac arrest and effect of defibrillation.

In the J-RPCR, electrical defibrillation was performed during CPR in 27.7% of cases (n=136), and in 5.3% of these cases (n=26) an AED was used. It was recently reported by the NRCPR that an AED was used in 38.6% of the 11,695 patients with in-hospital cardiac arrests, including 9,616 patients (82.2%) with non-shockable rhythms, and that although no differences were found in the proportion of survival to hospital discharge between patients with a shockable rhythm in whom an AED had been used and those in whom it had not been used, the proportion of survival was significantly reduced by the use of an AED in patients with a non-shockable rhythm.[14] In the J-RCPR, 53.8% of the patients in whom an AED had been used had a CPC score of 1 or 2 at 30 days, which was better than the proportion of 30.9% found in patients who had received manual electrical defibrillation without the use of an AED. The influence of the use of an AED was not investigated in this study. The aforementioned difference was caused by patients in the J-RCPR actually receiving electrical defibrillation, and more detailed investigation is necessary in the future to determine the circumstances surrounding the use of AED in hospitals. The J-RCPR did not provide a quality-improvement tool for hospitals that allows them to compare their performance against other institutions nationally and regionally, such as the NRCPR provides.

Study Limitations

The limitations of the J-RCPR include (1) not being a randomized controlled trial, although it is difficult to conduct a randomized controlled trial to investigate the effects of treatment for patients with in-of hospital cardiac arrest; (2) the participating J-RCPR hospitals not representing a random sample of Japanese hospitals, so a further, large sample size investigation is needed to collect representative data in Japan; (3) lack of on-site validation of data collection and processes for data checking; although data cleaning was performed, these limitations are similar to those of other contemporary in-hospital registries; (4) not using the in-hospital Utstein style template for prognosis; because this is the first report in Japan of in-hospital cardiac arrest, not only the prognosis of pulseless VT/VF but also that of pulseless electrical activity and asystole is important; (5) not collecting data for the heart rate of arrhythmia cases, even bradycardia/tachycardia, as the cause for hospital admission, the immediate cause of in-hospital cardiac arrest and initial ECG rhythm at the time of occurrence of the cardiac arrest. The heart rate may play an important role in-hospital cardiac arrest, but as it was not indicated as collected data in the in-hospital Utstein style nor as a parameter of the NRCPR, we did not collect the heart rate in this study protocol; (6) not analyzing the reason for hospital admission, which may also play an important role in the in-hospital cardiac arrest; however, full clinical details and diagnoses may not be immediately available to the event team, so we did not analyze these data in this study.

Conclusion

The status and management methods of in-hospital cardiac arrests are greatly affected by the medical and healthcare systems of a country. In this study, a multicenter prospective registry study of in-hospital cardiac arrests (the J-RCPR) was conducted for the first time in Japan. Measures to improve the proportion of survival of in-hospital cardiac arrests in Japan must be devised by conducting further detailed analysis of the assessment items related to in-hospital cardiac arrests.

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Disclosures

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References

1. Hanada H, Okumura K. From 4-links to 5-links of "chain of survival". Post-resuscitation care is critical for good neurological recovery. *Circ J* 2009; **73:** 1797–1808.
2. Iwami T, Nichol G, Hiraide A, Hayashi Y, Nishiuchi T, Kajino K, et al. Continuous improvements in "chain of survival" increased survival after out-of-hospital cardiac arrests: A large-scale population-based study. *Circulation* 2009; **119:** 728–734.
3. Sandroni C, Nolan J, Cavallaro F, Antonelli M. In-hospital cardiac arrest: Incidence, prognosis and possible measures to improve survival. *Intensive Care Med* 2007; **33:** 237–245.
4. Tunstall-Pedoe H, Bailey L, Chamberlain DA, Marsden AK, Ward ME, Zideman DA. Survey of 3765 cardiopulmonary resuscitations in British hospitals (the BRESUS Study): Methods and overall results. *BMJ* 1992; **304:** 1347–1351.
5. Gwinnutt CL, Columb M, Harris R. Outcome after cardiac arrest in adults in UK hospitals: Effect of the 1997 guidelines. *Resuscitation* 2000; **47:** 125–135.
6. Kause J, Smith G, Prytherch D, Parr M, Flabouris A, Hillman K. A comparison of antecedents to cardiac arrests, deaths and emergency intensive care admissions in Australia and New Zealand, and the United Kingdom--the ACADEMIA study. *Resuscitation* 2004; **62:** 275–282.
7. Peberdy MA, Kaye W, Ornato JP, Larkin GL, Nadkarni V, Mancini ME, et al. Cardiopulmonary resuscitation of adults in the hospital: A report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation* 2003; **58:** 297–308.
8. Peberdy MA, Ornato JP, Larkin GL, Braithwaite RS, Kashner TM, Carey SM, et al; National Registry of Cardiopulmonary Resuscitation Investigators. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA* 2008; **299:** 785–792.
9. Cummins RO, Chamberlain D, Hazinski MF, Nadkarni V, Kloeck W, Kramer E, et al. Recommended guidelines for reviewing, reporting, and conducting research on in-hospital resuscitation: The in-hospital 'Utstein style'. *Circulation* 1997; **95:** 2213–2239.
10. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update and simplification of the Utstein templates for resuscitation registries: A statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation* 2004; **110:** 3385–3397.
11. Peberdy MA, Cretikos M, Abella BS, DeVita M, Goldhill D, Kloeck W, et al. Recommended guidelines for monitoring, reporting, and conducting research on medical emergency team, outreach, and rapid response systems: An Utstein-style scientific statement: A scientific statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian Resuscitation Council, European Resuscitation Council, Heart and Stroke Foundation of Canada, Inter American Heart Foundation, Resuscitation Council of Southern Africa, and the New Zealand Resuscitation Council); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiopulmonary, Perioperative, and Critical Care; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *Circulation* 2007; **116:** 2481–2500.
12. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004; **291:** 870–879.
13. Nadkarni VM, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, et al; National Registry of Cardiopulmonary Resuscitation Investigators. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006; **295:** 50–57.
14. Chan PS, Krumholz HM, Spertus JA, Jones PG, Cram P, Berg RA, et al. Automated external defibrillators and survival after in-hospital cardiac arrest. *JAMA* 2010; **304:** 2129–2136.
15. Sirio CA, Tajimi K, Taenaka N, Ujike Y, Okamoto K, Katsuya H. A cross-cultural comparison of critical care delivery: Japan and the United States. *Chest* 2002; **121:** 539–548.
16. Skogvoll E, Isern E, Sangolt GK, Gisvold SE. In-hospital cardiopulmonary resuscitation: 5 years' incidence and survival according to the Utstein template. *Acta Anaesthesiol Scand* 1999; **43:** 177–184.
17. Sandroni C, Ferro G, Santangelo S, Tortora F, Mistura L, Cavallaro F, et al. In-hospital cardiac arrest: Survival depends mainly on the effectiveness of the emergency response. *Resuscitation* 2004; **62:** 291–297.
18. Hodgetts TJ, Kenward G, Vlackonikolis I, Payne S, Castle N, Crouch R, et al. Incidence, location and reasons for avoidable in-hospital cardiac arrest in a district general hospital. *Resuscitation* 2002; **54:** 115–123.
19. Cooper S, Janghorbani M, Cooper G. A decade of in-hospital resuscitation: Outcomes and prediction of survival? *Resuscitation* 2006; **68:** 231–237.
20. Skrifvars MB, Rosenberg PH, Finne P, Halonen S, Hautamäki R, Kuosa R, et al. Evaluation of the in-hospital Utstein template in cardiopulmonary resuscitation in secondary hospitals. *Resuscitation* 2003; **56:** 275–282.
21. Myrianthefs P, Kalafati M, Lemonidou C, Minasidou E, Evagelopoulou P, Karatzas S, et al. Efficacy of CPR in a general, adult ICU. *Resuscitation* 2003; **57:** 43–48.
22. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; **117:** 151–159.
23. Cooper S, Cade J. Predicting survival, in-hospital cardiac arrests: Resuscitation survival variables and training effectiveness. *Resuscitation* 1997; **35:** 17–22.
24. de Vos R, de Haes HC, Koster RW, de Haan RJ. Quality of survival after cardiopulmonary resuscitation. *Arch Intern Med* 1999; **159:** 249–254.
25. Aoyama N, Imai H, Kono K, Kato S, Fukuda N, Kurosawa T, et al. Patient selection and therapeutic strategy for emergency percutaneous cardiopulmonary system in cardiopulmonary arrest patients. *Circ J* 2009; **73:** 1416–1422.
26. Danciu SC, Klein L, Hosseini MM, Ibrahim L, Coyle BW, Kehoe RF. A predictive model for survival after in-hospital cardiopulmonary arrest. *Resuscitation* 2004; **62:** 35–42.
27. Brindley PG, Markland DM, Mayers I, Kutsogiannis DJ. Predictors of survival following in-hospital adult cardiopulmonary resuscitation. *Can Med Assoc J* 2002; **167:** 343–348.
28. Chan PS, Krumholz HM, Nichol G, Nallamothu BK. Delayed time to defibrillation after in-hospital cardiac arrest. *N Engl J Med* 2008; **358:** 9–17.

Appendix

Participating hospitals were: Division of Cardiac Care Unit, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka; Division of Cardiology, Hakodate National Hospital, Hokkaido; Division of Cardiology, Tokyo Medical Center, Tokyo; Division of Pediatric, Tokyo Metropolitan Children's Medical Centre, Tokyo; Department of Emergency Medicine, Osaka Medical College Hospital, Osaka; Division of Cardiology, Takamatsu Medical Center National Hospital, Kagawa; Division of Cardiology, Sakaide City Hospital, Kagawa; Advanced Medical Emergency and Critical Care Center, Yamaguchi University Hospital, Yamaguchi; Division of Cardiology, Kanmon Medical Center, Yamaguchi; Division of Cardiology, Iwakuni Clinical Center, Yamaguchi; Division of Cardiology, Kokubu Seikyo Hospital, Kagoshima; Division of Cardiology, Kagoshima Medical Center, Kagoshima.

Impact of Therapeutic Hypothermia in the Treatment of Patients With Out-of-Hospital Cardiac Arrest From the J-PULSE-HYPO Study Registry

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Background: Mild hypothermia is an effective therapy for patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest. However, evidence of the effectiveness of therapeutic hypothermia (TH) remains unclear.

Methods and Results: A multicenter registry in Japan (J-PULSE-HYPO study registry) was conducted to investigate the effectiveness of TH for post-resuscitation neurological dysfunction developing after out-of-hospital cardiac arrest from 14 institutions, between January 2005 and December 2009. The committee entrusted each hospital with the timing of cooling, cooling methods, target temperature, duration, and rewarming. There were 452 patients (375 men) enrolled into the registry. The mean age was 58.6±13.5 years. Initial electrocardiogram rhythm at the time of occurrence of the cardiac arrest showed 68.9% had ventricular fibrillation or pulseless ventricular tachycardia, 13.7% had pulseless electrical activity, and 9.1% had asystole. The median interval from the occurrence of cardiac arrest to ROSC was 26 min. The target core temperature during TH was 33.9±0.4°C and the mean duration of cooling was 31.5±13.9 h. Intra-aortic balloon pumping was used in 40.1% and percutaneous cardiopulmonary support in 22.6% of patients. At 30 days after cardiac arrest, the proportion of survival was 80.1% and the proportion of patients with favorable neurological functions, with a cerebral performance category score of 1 or 2, was 55.3%.

Conclusions: The J-PULSE-HYPO study registry showed a clinical aspect of TH. (*Circ J* 2011; **75:** 1063–1070)

Key Words: Multicenter registry; Out-of-hospital cardiac arrest; Therapeutic hypothermia

The proportion of survival of out-of-hospital cardiac arrest is improving with increased implementation of prompt bystander cardiopulmonary resuscitation (CPR) and early defibrillation; however, the neurologically intact survival for patients of out-of-hospital cardiac arrest still remains low worldwide. Furthermore, development of support measures such as pharmacological circulatory support for patients with post-resuscitation neurological dysfunction in whom circulation was restored by successful resuscitation but brain function did not show full recovery for the patient to return to society, is an urgent issue to be resolved.[1] In recent years, close attention has been paid to the effects of therapeutic hypothermia (TH) instituted in the metabolic phase even after 15 min of the onset of cardiac

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Facilities participating in the J-PULSE-HYPO study are listed in the Appendix.
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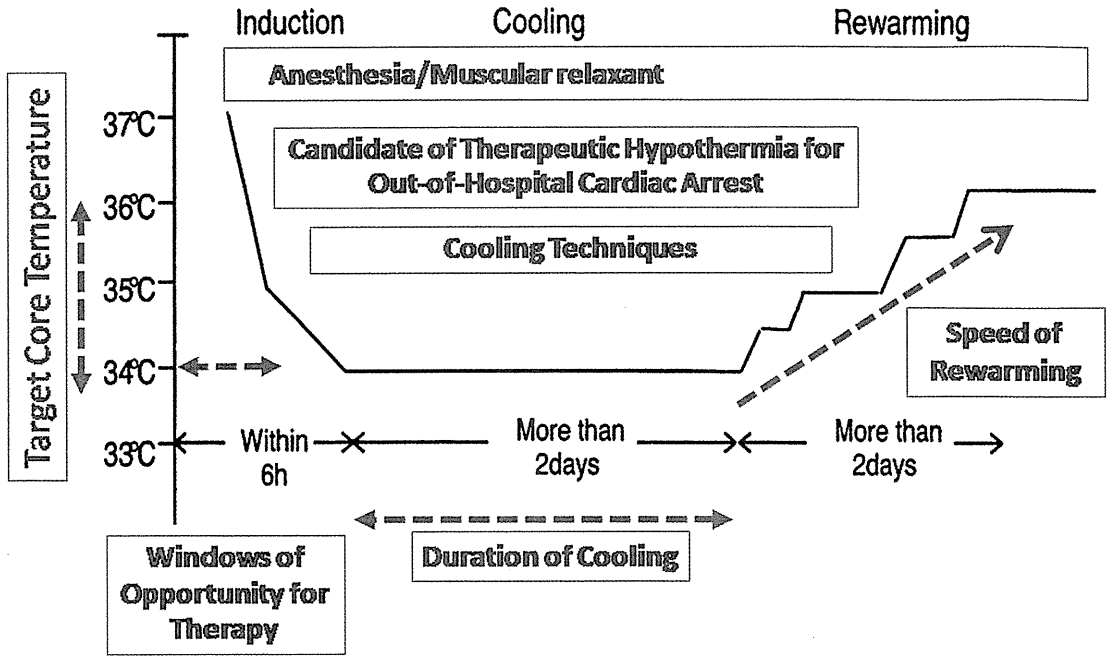

Figure 1. Clinical questions related to therapeutic hypothermia for out-of-hospital cardiac arrest. There are clinical questions related to therapeutic hypothermia for out-of-hospital cardiac arrest that remain to be resolved, such as the optimal candidate of therapeutic hypothermia for out-of-hospital cardiac arrest, optimal cooling techniques for therapeutic hypothermia, optimal target core temperature during hypothermia, optimal induction timing as the time windows of opportunity for therapeutic hypothermia, optimal duration of cooling, and optimal timing of rewarming.

arrest, and this therapy is expected to be effective for maintaining and improving brain function after resuscitation.[2–6] Mild TH had been proposed by Peter Safar in the 1960s as therapy following successful resuscitation after cardiac arrest,[7] and its effectiveness was confirmed by 2 randomized clinical trials (RCT) in 2002.[8,9] The 2005 CPR guidelines[10] state "unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest should be cooled to 32–34°C for 12–24 h when the initial rhythm was ventricular fibrillation (VF)" as a class IIa recommendation. Furthermore, in the 2010 CPR guidelines published in 2010,[3] TH for adults who do not regain consciousness after ROSC following out-of-hospital cardiac arrest due to ventricular fibrillation was upgraded to a class I recommendation. However, clinical trials on TH have not yet sufficiently addressed all the relevant issues, and a number of problems remain to be resolved, such as the optimal candidate of TH for out-of hospital cardiac arrest, optimal cooling techniques for TH, optimal target core temperature during hypothermia, optimal induction timing as the time windows of opportunity for TH, optimal duration of cooling, and optimal timing of rewarming (**Figure 1**).

The purpose of the present study is, through a large-scale multicenter registry, to investigate the effectiveness of TH for post-resuscitation neurological dysfunction developing after out-of-hospital cardiac arrest due to cardiac causes, aiming at improvement of the outcome of out-of-hospital cardiac arrest patients and reduction of the number of patients with post-resuscitation neurological dysfunction who need long-term hospitalization and management.

Methods

Design and Setting

To investigate the effects of TH on patients who have suffered from out-of-hospital cardiac arrest, we conducted a multicenter registry (retrospective and prospective cohort study) in Japan (J-PULSE-HYPO study registry; Japanese Population-based Utstein-style study with defibrillation and basic/advanced Life Support Education and implementation-Hypothermia). An overview of the study was registered in the UMIN as a clinical trial (UMIN000001935, available at: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000002348&language=J), and ClinicalTrials.gov (Identifier: NCT00901134; available at: http://clinicaltrials.gov/), both accessed 30 January 2011. Because the primary purpose of the J-PULSE-HYPO study registry is quality improvement, participating hospitals are not required to obtain individual informed consent. The present study was conducted in accordance with the ethical guidelines for epidemiological studies and was approved by the ethics committee of the National Cerebral and Cardiovascular Center. Also, the relevant review boards in all 14 participating centers approved the study protocol.

Data Collection

We designed the J-PULSE-HYPO study data collection software in a standardized format to enter information about each case of TH, and distributed this software to 14 hospitals that participated in this study; the data were accumulated and registered. The information is abstracted from hospital medical records. The database contains information about TH

after ROSC. Each patient was assigned a unique code, and no specific patient identifiers were transmitted to the central database repository. The data might be submitted on diskette or by encrypted transmission over secure internet.

Study Patients

Patients transported to the emergency room after out-of-hospital cardiac arrest were enrolled in the present study when they met the following criteria: (1) all patients who received TH at any of the 14 participating facilities during the 5-year period from January 2005 and December 2009, with successful ROSC after out-of-hospital cardiac arrest; (2) 18 years or older; (3) having stable hemodynamics after the return of circulation (including stabilization by drugs or assisted circulation, such as intra-aortic balloon pumping (IABP) or percutaneous cardiopulmonary support (PCPS); (4) persistent coma (Japan Coma Scale score of 200 or 300) after ROSC; and (5) presumed cardiac etiology of cardiac arrest according to the Utstein style guidelines.[11] All event times were measured by the dispatch center clock, and times of collapse and first bystander resuscitation attempts were obtained from the bystanders. Cardiac arrest was defined as the cessation of cardiac mechanical activity, manifesting as unresponsiveness, apnea (or gasping breathing), and absence of pulse. The arrest was presumed to be from a cardiac cause, unless it was known to have been caused by a non-cardiac cause including trauma, drowning, and asphyxia. Resuscitation attempts were documented by both paramedics and the attending physicians according to Utstein style reporting guidelines.[11] Data for individual patients were entered into a database by J-PULSE-HYPO study members at each hospital and were independently cross-checked twice by different investigators. The exclusion criteria were: (1) pregnancy; (2) aortic dissection; (3) pulmonary embolism; (4) drug addiction; and (5) poor daily activity before onset. Each patient was assigned a unique code, and no specific patient identifiers were transmitted to the central database repository. The data might be submitted on diskette or by encrypted transmission over secure internet.

First documented pulseless rhythm was defined as the first electrocardiogram rhythm documented at the time the patient became pulseless and, for those patients with unwitnessed/unmonitored arrests, it represents the first rhythm documented at the time a monitor arrives and is applied. Index events are defined as the patient's first cardiac arrest event during this hospitalization. In this study, the categories of acute respiratory compromise leading to cardiopulmonary arrest and cardiopulmonary arrest are combined into one category that comprises 'cardiac arrest'.

The timing of cooling induction, the cooling method, the target body temperature, the duration of cooling, the speed of rewarming, management of adverse events and use of sedatives and muscle relaxants in TH were according to the standards used during routine clinical practice at the participating facilities.

As hypothermia protocol, after sedation with analgesia and in some cases, ice cold intravenous fluid was administered over 30–60 min to initiate hypothermia. The methods of initiation or maintenance of hypothermia was attempted by one of the following 4 devices of 2 methods: (1) surface cooling: (a) Cooling Blanket (Blanketrol II, CSZ Medical, Cincinnati, OH, USA), and (b) cooling device with self-adhesive, hydrogel-coated pads (Arctic Sun, Medivance, Louisville, KY, USA); and (2) blood cooling: (c) extracorporeal direct blood cooling (KTEK-III, Kawasumi, Tokyo, Japan); and (d) endovascular cooling device (CoolGard 3000, Alsius, Irvine, CA, USA). Mild hypothermia (32–34°C) was maintained for 24–72 h. Rewarming was conducted slowly and gradually, and took at least 24–72 h. Protocol of hypothermia was determined in each institutional protocol.

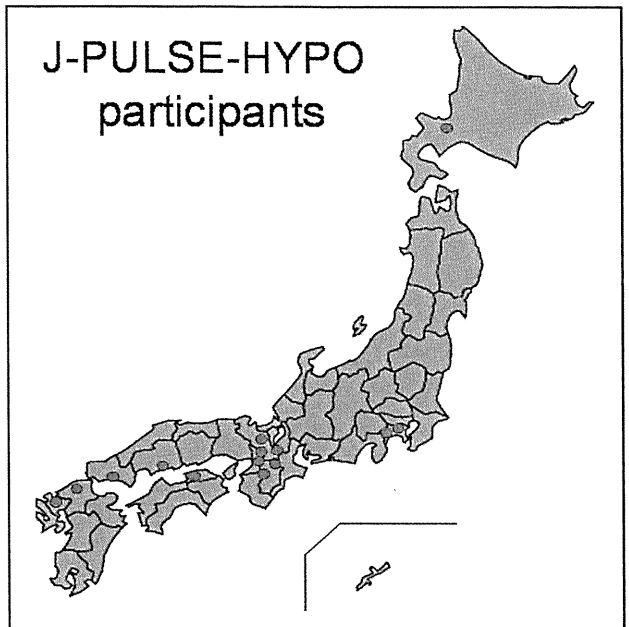

Figure 2. Geographic distribution of the 14 participating hospitals across Japan.

Study Endpoints

The primary endpoint was a favorable neurological outcome at 30 days after cardiac arrest defined according to the Glasgow–Pittsburgh cerebral performance category (CPC) of 1 (good performance) or 2 (moderate disability) on a 5-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).[11] The secondary outcomes were the outcomes at 24 h, 7 days, and discharge.

Statistical Analysis

The expected sample size was 500 patients. This sample size had statistical power over 0.80 and a 2-sided alpha value of 0.05 based on risk ratio 1.2 and 45.0% event in control. Participant baseline characteristics and outcomes are reported through means and standard deviation, median and quartile, and frequency and percentage for comparison between groups. All authors had full access to the study data and take full responsibility for their integrity. All authors have read and agreed to the manuscript as written.

Results

A total of 452 consecutive adult patients who did not regain consciousness after ROSC following cardiac arrest and received TH in any of the 14 participating facilities during the 5-year period were enrolled in the J-PULSE-HYPO study registry. **Figure 2** details the geographic distribution of the participating 14 hospitals across Japan. Clinical characteristics of patients are shown in **Table 1**. The mean age was 58.6±13.5 (min–max, 18–86 years). Of the enrolled patients, 82.5% were male, 51.1% had received bystander CPR, and 13.7% had received public-access defibrillation. In the analysis of the initial electrocardiogram (ECG) rhythm at the time

Table 1. Clinical Characteristics of Patients From the J-PULSE-HYPO Registry

Number of cases	n=452
Age (mean±SD)	58.6±13.5
Male (%)	373 (82.5)
Initial cardiac rhythm	
VF/pulseless VT (%)	314 (68.9)
Pulseless electrical activity (%)	62 (13.7)
Asystole (%)	41 (9.1)
Unidentified (%)	35 (7.7)
Witnessed cardiac arrest (%)	392 (86.7)
AED used (%)	61 (13.7)
Bystander CPR (%)	231 (51.1)
ROSC before admission (%)	289 (64.2)
Median interval from collapse to ROSC (min)	26 (17–42)
Median interval from collapse to hospital arrival (min)	32 (25–42)

Initial electrocardiogram rhythm at the time of occurrence of cardiac arrest.
Data are presented as mean±SD or the number (%) of patients. mean±SD, median (interquartile range).
VF, ventricular fibrillation; VT, ventricular tachycardia; AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

Table 2. Subjects and Methods of TH

Median interval from collapse to induction of TH (min)	82.5 (49–167)
Median interval from ROSC to induction of TH (min)	57.5 (21–138)
Median interval from induction of TH to achieve target core temperature (h)	3.0 (1.3–5.8)
Target core temperature (mean±SD) (°C)	33.9±0.4
Infusion of 4°C ice-cold fluid (%)	255 (56.4)
Cooling methods	
Surface cooling (%)	228 (50.4)
Extracorporeal circulation (%)	218 (48.2)
Median duration of cooling (h)	25 (24–43)
Duration of rewarming	
<24 h (%)	127 (28.0)
72 h< (%)	147 (32.6)
At the time of induction	
Systolic blood pressure (mean±SD) (mmHg)	130.3±36.5
Heart rate (mean±SD) (beats/min)	101.0±27.8

Mean±SD, median (interquartile range).
TH, therapeutic hypothermia; ROSC, return of spontaneous circulation.

of occurrence of the cardiac arrest, 68.9% had VF or pulseless ventricular tachycardia (VT), 13.7% had pulseless electrical activity, 9.1% had asystole, and 7.7% had an uninterpretable ECG rhythm due to pacemaker rhythm or other reasons. Circulation was restored before hospitalization in 64.2% of cases. The median interval (quartile) from the occurrence of cardiac arrest to ROSC was 26 (17–42) min, and the median interval from the occurrence of cardiac arrest to hospital arrival was 32 (25–42) min.

Subjects and methods of TH are shown in **Table 2**. The median interval (quartile) from the occurrence of out-of-hospital cardiac arrest to induction of TH was 82.5 (49–167) min and the median interval from ROSC to the induction of TH was 57.5 (21–138) min. The median interval (quartile)

Table 3. Frequencies of CAG and PCI, and Use of IABP/PCPS

Emergency coronary angiography (%)	363 (80.3)
Emergency PCI (%)	202 (44.7)
IABP usage (%)	185 (40.1)
PCPS usage (%)	102 (22.6)

CAG, coronary angiography; IABP, intra-aortic balloon pumping; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support.

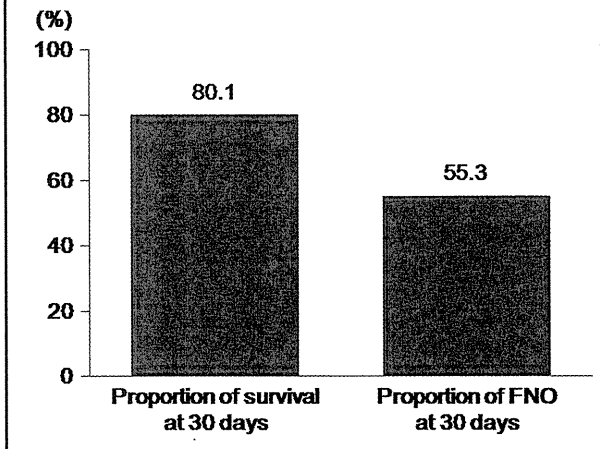

Figure 3. The proportion of survival and proportion of patients with favorable neurological functions (FNO), with a cerebral performance category score of 1 or 2 at 30 days after the cardiac arrest.

from the induction of TH to achievement of the target core temperature was 3.0 (1.3–5.8) h and the target core temperature during TH was 33.9±0.4°C. Ice-cold fluid at 4°C was infused for the induction of TH in 56.4% (n=255) of cases. As the method for the induction of TH, surface cooling and extracorporeal circulation were used in 50.4% (n=228) and 48.2% (n=218) of cases, respectively, and the median duration of cooling was 25 (24–43) h. The duration of rewarming was 24 h or less in 28.0% (n=127) of cases and 72 h or more in 32.6% (n=147) of cases. The mean systolic blood pressure and the mean heart rate at the time of induction of TH were 130.3±36.5 mmHg and 101.0±27.8 beats/min, respectively.

The frequencies of coronary angiography and percutaneous coronary intervention, usage of IABP and PCPS are shown in **Table 3**. Among the 452 patients who received TH did not regain consciousness after cardiac arrest, 80.3% (n=363) underwent emergency acute coronary angiography and 44.7% (n=202) underwent emergency percutaneous coronary intervention. IABP was used in 40.1% (n=185) of cases and PCPS in 22.6% (n=102). The proportion of patients with a favorable neurological outcome at 30 days after cardiac arrest was 58.4% (n=212) of patients who underwent emergency coronary angiography, 53.0% (n=107) of patients who underwent emergency percutaneous coronary intervention, 47.0% (n=87) of patients who underwent IABP, and 34.3% (n=35) of patients who underwent PCPS.

Side-effects of the TH, such as blood transfusion, disseminated intravascular coagulation, arrhythmias, infection or other, were shown in 138 patients (30.8%). The frequency of the side-effects of the TH was not different between the patients with and without ice-cold fluid infusion for the induc-

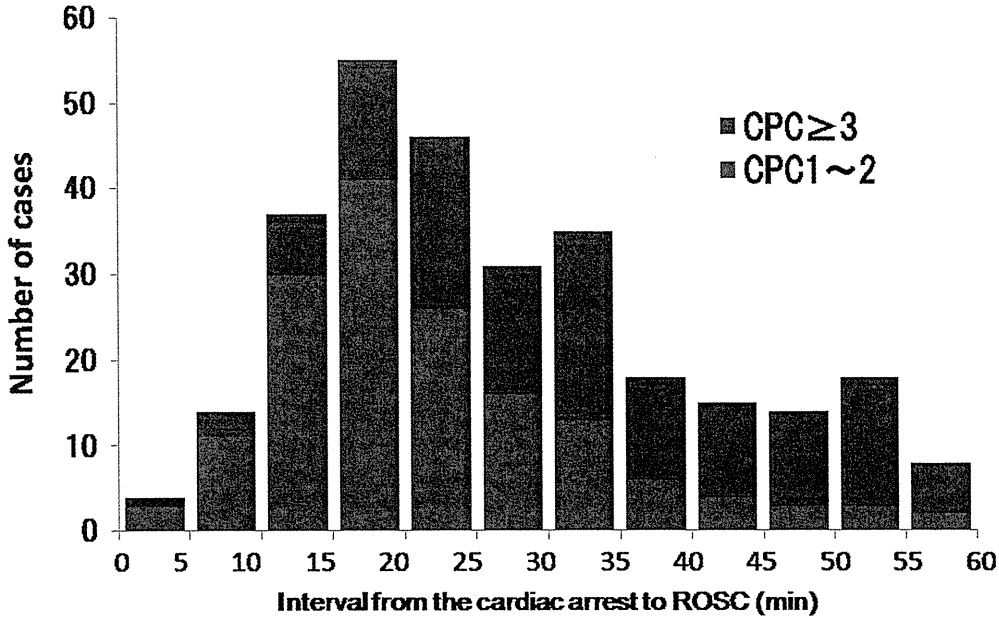

Figure 4. Relationship between the interval from cardiac arrest to return of spontaneous circulation (ROSC) and neurological outcome at 30 days are shown. Patients were grouped according to the interval from cardiac arrest to ROSC (in 5 min intervals), and the proportions of patients with favorable (in red) and poor (in blue) neurological outcomes at 30 days are shown.

Table 4. Clinical Characteristics of Patients With Favorable Neurological Outcome (CPC 1/2) and Poor Neurological Outcome (CPC ≥3) at 30 days

	CPC 1/2 at 30 days (n=250)	CPC ≥3 at 30 days (n=202)	P value
Age	55.6±14.0	62.3±11.7	<0.001
Male (%)	205 (82.0)	168 (83.2)	NS
Witnessed cardiac arrest (%)	228 (91.2)	164 (81.2)	<0.01
Bystander CPR (%)	137 (54.8)	94 (46.5)	NS
Median interval from collapse to ROSC (median; min)	19 (14–28)	38 (27–53)	<0.0001
Median interval from collapse to hospital arrival (median; min)	30 (23–40)	34 (27–44)	<0.01
Interval from collapse to induction of TH (median; min)	80 (45–165)	90 (51–173)	NS
Interval from ROSC to induction of TH (median; min)	55.5 (24–141)	59.5 (16–135)	NS
Interval from induction of TH to achieving target core temperature (median; h)	3.3 (1.7–6.0)	2.3 (1.0–4.9)	<0.01
Target core temperature (°C)	33.9±0.5	33.9±0.4	NS
Infusion of 4°C ice-cold fluid (%)	147 (55.8)	108 (53.4)	NS
Cooling method: surface cooling (%)	136 (55.0)	92 (46.0)	NS
Duration of cooling (median; h)	25 (24–42)	26 (24–44.5)	NS

Mean±SD, median (interquartile range).
CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; TH, therapeutic hypothermia.

tion of TH, 34.5% vs. 26.0%.

Outcome Data

Figure 3 shows the proportion of survival and the proportion of patients with favorable neurological outcome, with a CPC score of 1 or 2, at 30 days after the cardiac arrest. As for the 30-day outcome of the 452 patients who received TH, the proportion of survival was 80.1% (n=362) and the proportion of patients with a favorable neurological outcome was 55.3% (n=250). In 314 patients with the initial ECG rhythm of pulseless VT/VF, the proportion of 30-day survival was 85.4% and the proportion of patients with a favorable neurological outcome was 62.4%.

The relationship between the interval from the collapse to ROSC and the neurological outcome at 30 days are shown in **Figure 4**. Patients who received TH, because they did not regain consciousness after ROSC, were divided according to the interval from cardiac arrest to ROSC (in 5 min intervals), and the proportions of patients with a favorable neurological outcome and those with a poor neurological outcome (CPC ≥3) at 30 days are shown in **Figure 4**. In cases where the interval from the occurrence of cardiac arrest to ROSC was 30 min

or less, the proportion of patients with a favorable neurological outcome was 50% or more. As the interval from the cardiac arrest to ROSC increased, the proportion of patients with a favorable neurological outcome at 30 days decreased.

Table 4 shows the comparison between patients with a favorable neurological outcome (CPC 1 or 2; n=250) and patients with a poor neurological outcome (CPC≥3; n=202) at 30 days after cardiac arrest. In the patients with a favorable neurological outcome, the mean age was significantly younger (55.6±14.0 vs. 62.3±11.7; P<0.001), and the presence of a witness at the collapse was significantly more frequent (91.2% vs. 81.2%; P<0.01) than the patients with a poor neurological outcome. The median interval from cardiac arrest to ROSC (19 vs. 38 min), and the median interval from cardiac arrest to hospital arrival (30 vs. 34 min) were significantly shorter in patients with a favorable neurological outcome than in patients with a poor neurological outcome. However, the median intervals from cardiac arrest to induction of TH and the median intervals from ROSC to induction of TH were not significantly different between both groups; the median interval from induction of TH to achieve target core temperature was significantly longer in patients with a favorable neurological outcome (3.3 vs. 2.3 h). Also, there was no significant difference between both groups in the target core temperature, frequency of infusion of ice-cold fluid, surface cooling as the cooling method and duration of cooling (**Table 4**).

Discussion

A total of 452 consecutive adult patients who received TH because they did not regain consciousness after ROSC following cardiac arrest were enrolled in the J-PULSE-HYPO study registry during the 5-year study period. With regard to the 30-day outcomes after cardiac arrest among all the enrolled patients, the proportion of survival was 80.1% and the proportion of patients with a favorable neurological outcome with a CPC score of 1 or 2 was 55.3%. There have been 2 multicenter RCT on TH: the HACA study[8] and a report from Australia by Bernard et al.[9] In the HACA study, the subjects were limited to patients with initial ECG rhythm of VF or pulseless VT, in whom circulation was restored before hospitalization and who were 75 years or younger. Surface cooling was used with a target body temperature of 32–34°C, cooling duration of 24 h, and rewarming duration of 12 h. In the study by Bernard et al, the subjects were limited to patients with an initial ECG rhythm of VF, in whom circulation was restored before hospitalization, and male patients aged 19 years or older and female patients aged 51 years or older. Patients with shock and a systolic blood pressure of <90 mmHg at hospitalization were excluded. TH was initiated within 2 h of ROSC by surface cooling, with a target body temperature of 33°C, cooling duration of 12 h, and rewarming duration of 6 h. The proportion of patients with a favorable neurological outcome was 55% in the HACA study and 49% in the report by Bernard et al. The results of these reports were similar to the 55.3% of patients with a favorable neurological outcome in the J-PULSE-HYPO study registry. However, in our study, circulation was not restored at the time of hospital arrival in 35.8% of the enrolled patients and PCPS was used due to the very unstable hemodynamics after ROSC in 22.6% of patients. Therefore, the subjects in the present study included more severe patients than those in the 2 aforementioned RCT. In the present study, when 314 cardiac arrest patients with an initial ECG rhythm of pulseless VT/VF were extracted, 62.4% of patients had a favorable neurological outcome at 30 days, indicating the possibility that the outcome of patients who received TH was better in the J-PULSE-HYPO study registry than in the HACA study and the study by Bernard et al.

The optimal timing of induction of TH for patients with out-of-hospital cardiac arrest is unknown. In the HACA study,[8] the median interval from the occurrence of cardiac arrest to ROSC was 21 min. Bernard et al[9] reported that the mean interval from cardiac arrest to ROSC was 26.5±12.9 min and that the proportion of patients with a favorable neurological outcome was reduced by 14% for every 1.5 min increase in the interval from cardiac arrest to ROSC. In the J-PULSE-HYPO study registry, the median interval from the occurrence of cardiac arrest to ROSC was 26 min and the mean interval was 34.7±34.1 min. In cases where the interval from the occurrence of cardiac arrest to ROSC was 30 min or less, the proportion of patients with a favorable neurological outcome was 50% or more in this study (**Figure 4**). These findings suggest that in the J-PULSE-HYPO study registry there was a wider therapeutic time window for TH. Also, the median intervals from cardiac arrest to ROSC and to hospital arrival were significantly shorter in patients with a favorable neurological outcome than patients with a poor neurological outcome (**Table 4**). Therefore, the shorter duration of interval from cardiac arrest to ROSC and to hospital arrival, the better the neurological outcome.

With regard to the induction speed of TH for patients with out-of-hospital cardiac arrest, the 2005 American Heart Association/European Resuscitation Council guidelines[10] recommend that cooling be started as soon as possible. The interval from ROSC to the initiation of hypothermia was 2–6 h in the HACA study and the report by Bernard et al.[8,9] The median interval from collapse to induction of TH was 82.5 (quartile 49–197) min, and there was no significant difference in that interval between the patients with favorable and poor neurological outcomes in this study (**Table 4**). However, the range of the interval from collapse to induction of TH was wide in the present study, therefore more detailed investigation is required for further clarification.

It has been reported that when the cooling method in which 2L of 4°C cold saline or Ringer's solution is infused for 30 min is used, the core temperature is lowered by 1.2–1.8°C and the target core temperature is achieved more rapidly.[12,13] The median interval from the induction of TH to achievement of the target core temperature was 3.0 (1.3–5.8) h in the J-PULSE-HYPO study registry and rapid infusion of 4°C ice-cold fluid was used in 56.0% of cases. No significant correlation was found between the interval from induction of TH to achievement of the target body temperature and neurological outcomes in an observational study;[14] however, a significant difference was seen in this interval between patients with favorable and poor neurological outcomes in the J-PULSE-HYPO study registry (**Table 4**). However, in the present study, the cooling method varied at the participating facilities, therefore further investigation is necessary for more precise elucidation. Although there might be concern about rapid infusion of a large amount of 4°C cold water causing circulatory deterioration, deterioration of the heart rate or oxygenation and pulmonary congestion have not actually been reported. In the present study, there was no difference in the side-effects of TH in the patients using or not using 4°C ice-cold fluid infusions for the induction of TH.

At this time, there is no definite conclusion as to the optimal duration of cooling in TH for patients with out-of-hospital cardiac arrest. The cooling duration was 24 h in the HACA

study and 12h in the study by Bernard et al. According to a review by Lyon,[15] the cooling duration was 4–48h in 14 studies, including 5 randomized trials, with the most common cooling duration of 12–24h in 9 studies, but the relationship between the cooling duration and the outcome-improving effects of hypothermia has not yet been elucidated. The 2010 CPR guidelines[3] state that cooling therapy should be continued for 12 to 24h as TH for adults who do not regain consciousness after ROSC following out-of-hospital cardiac arrest due to ventricular fibrillation (class I). The median cooling duration in the J-PULSE-HYPO study registry was 25.0 (24–43) h, which is longer than that reported in Europe and the United States; however, there was no significant difference in the duration of cooling as TH between the patients with favorable or poor neurological outcome in this study, therefore more detailed investigation is required for further clarification.

There is also no definite conclusion as to the optimal cooling temperature for TH for patients with out-of-hospital cardiac arrest. It is said that the cooling temperature of 34–35.5°C causes shivering and that a temperature of less than 31°C is likely to cause arrhythmia.[16] The target body temperature of TH in the J-PULSE-HYPO study registry was 33.9±0.4°C, which was somewhat higher than the target core temperature of 33°C in the HACA study and the study by Bernard et al, and no difference in core temperature was observed between the patients with favorable or poor neurological outcomes in the present study (**Table 4**). Previously, a target core temperature of 32–34°C has been recommended in TH, considering the balance between the clinical organ-protective effects and cardiovascular toxicity.[16] Because this is a crucial matter for TH, more detailed investigation for precise determination of the target core temperature is required in the future.

In this study, surface cooling was used in 50.4% of cases and extracorporeal circulation was used in 48.2% of cases as the continuous cooling methods for TH in patients with out-of-hospital cardiac arrest. It has been reported that endovascular cooling enables more rapid and more stable management of hypothermia than surface cooling.[17] Because the cooling methods varied at the participating facilities in this study, more detailed investigation on the appropriate cooling method is necessary in the future.

Cases enrolled in the J-PULSE-HYPO study registry were characterized by a high frequency of acute emergency coronary angiography and a larger number of serious patients with unstable hemodynamics compared with those in the HACA study and the report by Bernard et al.[8,9] Acute emergency coronary angiography was performed in 80.3% of cases and emergency percutaneous coronary intervention was performed in 44.7%. IABP was used in 40.1% of cases and PCPS in 22.6% of cases. In the HACA study and the study by Bernard et al, the cases that needed PCPS due to collapsed hemodynamics were excluded from the study population and there were no data on such cases. Although the number of cases was small, in a study that investigated the effects of TH in patients with shock after cardiac arrest[18] it was reported that 5 out of 17 (29%) patients in the TH group had a favorable neurological outcome, whereas none of the 14 patients in the non-TH group had a favorable neurological outcome. It was reported in one study that when an endovascular cooling device was used in conscious patients with acute myocardial infarction and 34°C hypothermia was instituted during reperfusion therapy, the hemodynamic did not deteriorate due to hypothermia.[19] However, no significant differences were found in a study that investigated the effects of TH on the outcomes of patients with cardiac arrest due to acute ST-elevation myocardial infarction.[20] In this study, more than 80% of the resuscitated patients underwent cardiac catheterization, even though it was not required in the study protocol. However, recording of 12-lead ECG at hospital arrival or during cardiac catheterization were not required in the study protocol, therefore it was difficult to evaluate how many patients represented ST elevation at the first recording of 12-lead ECG. Because only 56% of patients who went to the cardiac catheterization were treated with emergency percutaneous coronary intervention, it is possible that patients without ST elevation at the first recording of the 12-lead ECG went to the cardiac catheterization, and further investigations on a larger number of cases are necessary.[6]

Study Limitations

Limitations of the J-PULSE-HYPO registry include: (1) this study was not a RCT but an observational study, therefore it might be possible that the criteria of induction for TH in the participating facilities had variations and the hospital did not attempt induction of TH on the patients who nearly died, such as those with very high age or delayed arrival at the hospital. Although it is difficult to conduct a RCT to investigate the effects of TH for patients with out-of hospital cardiac arrest, we considered multicenter registry data would answer the clinical questions associated with the effectiveness of TH for patients with out-of-hospital cardiac arrest; (2) hospitals participating in the J-PULUS-HYPO study registry do not represent a random sample of Japanese hospitals, and therefore a further large sample size investigation is needed to collect representative data in Japan; and (3) there is no on-site validation of data collection and processes for data checking, although data cleaning was performed. These limitations are similar to those of other contemporary in-hospital registries.

Conclusion

To investigate the effects of TH following resuscitation in patients with cardiac arrest, we conducted a multicenter registry, J-PULSE-HYPO study registry, for the first time in Japan, with 452 patients enrolled during the study period between 2005 and 2009. By analyzing the data of subjects in the J-PULSE-HYPO study registry, the optimal indications, optimal temperature, optimal induction timing, optimal rewarming timing, etc, in TH are expected to become possible.

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Disclosures

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References

1. Iwami T, Nichol G, Hiraide A, Hayashi Y, Nishiuchi T, Kajino K, et al. Continuous improvements in "chain of survival" increased survival after out-of-hospital cardiac arrests: A large-scale population-based study. *Circulation* 2009; **119:** 728–734.

2. Hanada H, Okumura K. From 4-links to 5-links of "chain of survival". Post-resuscitation care is critical for good neurological recovery. *Circ J* 2009; **73:** 1797–1798.
3. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: Post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; **122:** S768–S786.
4. Nagao K, Hayashi N, Kanmatsuse K, Arima K, Ohtsuki J, Kikushima K, et al. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. *J Am Coll Cardiol* 2000; **36:** 776–783.
5. Takeuchi I, Takehana H, Satoh D, Fukaya H, Tamura Y, Nishi M, et al. Effect of hypothermia therapy after outpatient cardiac arrest due to ventricular fibrillation. *Circ J* 2009; **73:** 1877–1880.
6. Nagao K, Kikushima K, Watanabe K, Tachibana E, Tominaga Y, Tada K, et al. Early induction of hypothermia during cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. *Circ J* 2010; **74:** 77–85.
7. Ravitch MM, Lane R, Safar P, Steichen FM, Knowles P. Lightning stroke: Report of a case with recovery after cardiac massage and prolonged artificial respiration. *N Engl J Med* 1961; **264:** 36–38.
8. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; **346:** 549–556.
9. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346:** 557–563.
10. ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005; **112:** IV1–IV203.
11. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: The Utstein Style: A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991; **84:** 960–975.
12. Kim F, Olsufka M, Longstreth WT Jr, Maynard C, Carlbom D, Deem S, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation* 2007; **115:** 3064–3070.
13. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: A randomized controlled trial. *Acta Anaesthesiol Scand* 2009; **53:** 900–907.
14. Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand* 2009; **53:** 926–934.
15. Lyon RM, Robertson CE, Clegg GR. Therapeutic hypothermia in the emergency department following out-of-hospital cardiac arrest. *Emerg Med J* 2010; **27:** 418–423.
16. Bernard S. Therapeutic hypothermia after cardiac arrest. *Neurol Clin* 2006; **24:** 61–71.
17. Kliegel A, Losert H, Sterz F, Kliegel M, Holzer M, Uray T, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest--a feasibility study. *Resuscitation* 2005; **64:** 347–351.
18. Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med* 2006; **34:** 1865–1873.
19. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol* 2002; **40:** 1928–1934.
20. Wolfrum S, Pierau C, Radke PW, Schunkert H, Kurowski V. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med* 2008; **36:** 1780–1786.

Appendix

Facilities Participating in the J-PULSE-HYPO Study

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Clinical Paper

Are trained individuals more likely to perform bystander CPR? An observational study☆

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ABSTRACT

Background: This study aimed to evaluate the association of cardiopulmonary resuscitation (CPR) training with bystander resuscitation performance and patient outcomes after out-of-hospital cardiac arrest (OHCA).

Methods: This was a prospective, population-based cohort study of all persons aged 18 years or older with OHCA of presumed intrinsic origin and their rescuers from January through December 2008 in Takatsuki, Osaka prefecture, Japan. Data on resuscitation of OHCA patients were obtained by emergency medical service (EMS) personnel in charge based on the Utstein style. Rescuers' characteristics including experience of CPR training were obtained by EMS personnel interview on the scene. The primary outcome was the attempt of bystander CPR.

Results: Data were collected for 120 cases out of 170 OHCAs of intrinsic origin. Among the available cases, 60 (50.0%) had previous CPR training (trained rescuer group). The proportion of bystander CPR was significantly higher in the trained rescuer group than in the untrained rescuer group (75.0% and 43.3%; $p = 0.001$). Bystanders who had previous experience of CPR training were 3.40 times (95% confidence interval 1.31–8.85) more likely to perform CPR compared with those without previous CPR training. The number of patients with neurologically favorable one-month survival was too small to evaluate statistical difference between the groups (2 [3.3%] in the trained rescuer group versus 1 [1.7%] in the untrained rescuer group; $p = 0.500$).

Conclusions: People who had experienced CPR training had a greater tendency to perform bystander CPR than people without experience of CPR training. Further studies are needed to prove the effectiveness of CPR training on survival.

1. Introduction

Three-quarters of the deaths from coronary heart disease occur suddenly in the out-of-hospital setting,[1,2] and approximately 50,000 sudden cardiac arrests are documented every year in Japan.[3] The high mortality of out-of-hospital cardiac arrest (OHCA) cases is one of the most important clinical issues to be addressed. It is widely accepted that successful resuscitation after OHCA depends on early initiation of cardiopulmonary resuscitation (CPR) and defibrillation,[4,5] and that bystanders CPR could potentially double survival after OHCAs.[3,5] Despite the proven effectiveness of bystander CPR, actual bystander CPR remains infrequent.[3–7] Previous studies indicated that CPR training improved willingness to perform CPR and would increase the proportion of bystander CPR.[8–13]

To increase bystander CPR, substantial societal resources are focused on CPR training, and elaborate CPR training programs are provided for over 1,620,000 persons every year in Japan.[3] However, most studies on the effectiveness of CPR training have evaluated only the improvements in rescuers' CPR skills[14–16] or attitude towards CPR,[8–12] and little is known about the effectiveness of CPR training on the rescuer's performance in real emergency settings or OHCA patient outcomes.

The Utstein Osaka project was launched in 1998, and is an ongoing large, prospective, population-based cohort study of OHCA in Osaka, Japan, covering 8.8 million people.[5,7,17–19] In this study, we collected data on lay rescuer's characteristics including their experience of CPR training by interviewing the lay rescuers on the scene, and linked them to the data on resuscitation simultaneously obtained according to the Utstein style guidelines. The purpose of this study was to evaluate the association of people's CPR train-

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ing with their subsequent resuscitation performances and patient outcomes after OHCA.

2. Methods

2.1. Study design, population and setting

This was a prospective, population-based cohort study of OHCA carried out in Takatsuki, Osaka prefecture, from January 28, 2008 through December 31, 2008. All persons aged 18 years or older who suffered OHCA of intrinsic etiology and were treated by emergency medical service (EMS) personnel, and their rescuers were enrolled in this study. Cardiac arrests from trauma, drowning, drug overdose, asphyxia, exsanguinations or any other external causes were excluded and those without trauma nor any external causes was defined as OHCAs of intrinsic origin. Rescuers who called an ambulance or performed CPR were identified by the EMS personnel at the event scene. If there were two or more rescuers, one of them was selected as the main rescuer by the EMS personnel. The main rescuer was defined as person who played a main role in CPR or called an ambulance when bystander CPR was not performed.

2.2. Emergency medical service system in Takatsuki

Takatsuki has 358,973 residents in an area of 105 km^2. The municipal EMS system is basically the same as the standard of Osaka prefecture which was previously described.[17–19] The EMS system is operated by the Takatsuki Fire Department and activated by dialing 119 on the telephone. The population is covered by a single fire station with an emergency dispatch center. The most highly trained pre-hospital emergency care providers are the Emergency Life Saving Technicians (ELSTs). Each ambulance has 3 providers with at least one ELST. The ELSTs can deliver shocks without online medical direction, and specially trained ELSTs can insert tracheal tubes and use epinephrine. When an OHCA occurs in the city, an additional ambulance with a physician and two staff members follows the regular ambulance. At the scene, 6 EMS personnel in total perform basic and advanced life support.

CPR training programs for the general public were provided about 220 times by the fire department and a total of 6000 citizens attended the program in 2006.[20] Public access defibrillation (PAD) programs were started in July 2004 in Japan.[21] The cumulative number of public-access automated external defibrillators (AEDs) has been increasing year by year and contributes better outcomes after OHCA in Japan.[21,22] Although we could not know the whole number of AEDs because many AEDs were located in private areas, at least 124 AEDs were placed in the city in 2009.[23]

2.3. Data collection

Data on the rescuers' performance were obtained by EMS personnel interview with the main rescuer using a specific data form for this study. Data included bystander's sex, age, relationship to the patient, occupation, experience and the number of previous CPR training (once, twice, ≥three times, unknown), the time of the latest CPR training (within a year, between 1 and 3 years, over 3 years, unknown), knowledge of AEDs, and awareness of the neighborhood AED locations.

Patients' data were collected using a data form that included all core data recommended in the Utstein-style reporting guidelines for OHCA,[24,25] including sex, age, location, activities of daily living before arrest, witness status, initial cardiac rhythm, time-course of resuscitation, type of bystander-initiated CPR, return of spontaneous circulation (ROSC), hospital admission, one-month survival, and neurological outcome one month after the event. All patients who survived the cardiac arrest were followed for up to 1 month after the event by the EMS personnel in charge. One-month neurological outcome was determined by 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.[24,25] Neurologically favorable survival was defined as a CPC score of 1 or 2. The data form was filled out by the EMS personnel in cooperation with the physicians caring for the patient, transferred to the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned, and the data sheet was completed.

2.4. Statistical analyses

The primary outcome measure was the attempt of bystander CPR. Secondary outcomes included rescuers' performance including bystander CPR with telephone-guidance, knowledge of AEDs, awareness of the neighborhood AED locations, use of an AED, resuscitation time course, ventricular fibrillation (VF) as the initial rhythm, pre-hospital ROSC, one-month survival, and neurologically favorable one-month survival.

The sample size was calculated based on the proportion of bystander CPR in Takatsuki during the last 3 years and previous studies, assumed to be 30% in the untrained rescuer group and 50% in the trained rescuer group. Under the conditions of an alpha error of 5% and a power of 70%, 47 subjects in the trained rescuer group and 154 subjects in the untrained rescuer group were needed. Because approximately 200 people had suffered OHCA in the city in the recent years, we considered one year of data as sufficient to achieve our study aim.

The data were compared between groups using the *chi*-square test or Fisher's exact test for categorical variables, and Student's *t*-test or Mann–Whitney *U* test for numerical variables depending on whether the data were normally distributed or not. Multivariable-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to assess the relationship between the bystanders' previous CPR training and the bystander CPR performance. We adjusted for bystanders' sex and age (<40, 40–64, or ≥65 years), patients' sex and age (<75 or ≥75 years), and factors which was reported to affect CPR performance in previous studies: bystander's occupation[9] (health professionals including physician, nurse, EMS personnel, and care worker or not) and witness status.[13] All analyses were performed using SPSS ver.16.0 (SPSS, Inc., Chicago, IL). A two-tailed value of $p < 0.05$ was considered to be statistically significant.

2.5. Ethical considerations

All procedures were conducted according to the Declaration of Helsinki. This study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine and the Takatsuki Fire Department. Oral informed consent was obtained from all participants (rescuers) by EMS personnel before the interview. The requirement of informed consent for the review of patients' outcomes was waived by the Personal Information Protection Law and the national research ethics guidelines of Japan.

3. Results

3.1. Study flow and baseline characteristics of bystanders and patients

During this study period, 273 adult OHCA patients were documented, and resuscitation was attempted in 258 cases by EMS

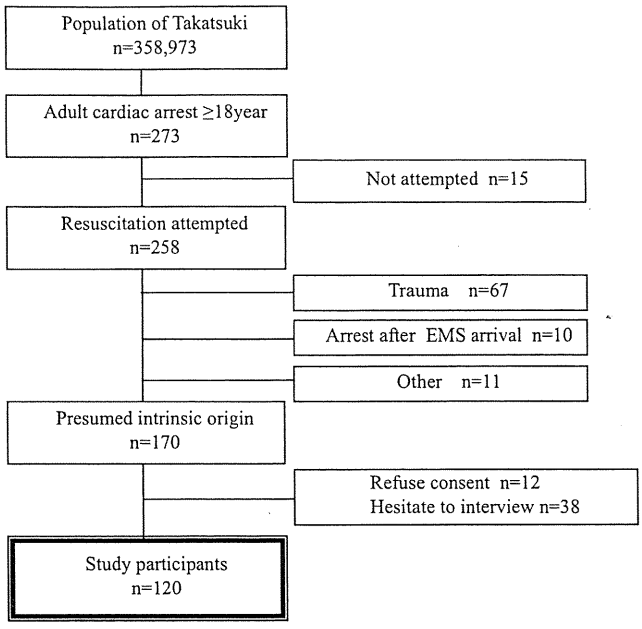

Fig. 1. Participant flow.

personnel. Among them, 170 subjects met the inclusion criteria and interviews were completed for 120 cases (Fig. 1). Rescuer and patient characteristics are shown in Table 1. Just half of the rescuers had experienced CPR training (trained rescuer group) and the remainder did not (untrained rescuer group). In the trained rescuer group, rescuers were younger (52.5 ± 16.1 versus 61.1 ± 15.6 years; $p = 0.018$), less likely to be family members (51.7% versus 83.3%; $p < 0.001$), and more likely to be health professionals (30.0% versus 5.0%; $p < 0.001$) than in the untrained rescuer group. In the trained rescuer group, 60.0% had received CPR training only once, 41.7% had received it more than three years ago, and 50.0% had attended the CPR training courses that included AED operation.

The patients' age was higher (80.3 ± 12.6 versus 75.7 ± 11.4 years; $p = 0.042$) and good activities of daily living before arrest were less frequent (46.7% versus 68.3%; $p = 0.026$) in the trained rescuer group than in the untrained rescuer group. Telephone CPR instruction (i.e., dispatcher assisted CPR via telephone) was frequently and equally provided (62.7% in the trained versus 61.7% in the untrained; $p = 1.000$). The time from call to the first shock was shorter in the trained rescuer group (9.0 min versus 12.0 min; $p = 0.013$).

3.2. Bystander resuscitation performance

Resuscitation performances of the rescuers according to their experience of CPR training are shown in Table 2. The proportion of bystander CPR was significantly greater in the trained rescuer group than in the untrained rescuer group (75.0% versus 43.3%; $p = 0.001$). In the trained rescuer group, the proportion of bystander CPR was greater in those with recent CPR training. One-fourth (13/45) in the trained rescuer group performed CPR without telephone instruction, while no one did in the untrained rescuer group ($p = 0.002$). In the telephone CPR instruction cases, 86.5% (32/37) in the trained rescuer group and 70.3% (26/37) in the untrained rescuer group were ultimately provided CPR by bystanders. In the trained rescuer group, rescuers were more likely to perform CPR with other persons than in the untrained rescuer group (37.8% versus 11.5%; $p = 0.027$). The proportion of those who had knowledge of AEDs and the neighborhood AED location were significantly greater in the trained rescuer group than in the untrained rescuer group (88.3% versus 45.0%; $p < 0.001$, 38.6% versus 18.4%; $p = 0.043$, respectively). Among those who had knowledge of AEDs, 6 (11.3%) rescuers in the trained rescuer group actually used an AED, while none in the untrained rescuer group used it. The resuscitation time course was similar in both groups.

Fig. 2 shows multivariable adjusted ORs of the factors possibly associated with bystander CPR performance in attempted bystander CPR. Rescuers who had experienced previous CPR training were 3.4 times (95% CI 1.31–8.85) more likely to perform CPR compared with those without such experience. Middle-aged rescuers (40–64 years compared to under 40 years; adjusted OR, 0.21;

Table 1
Rescuer and patient characteristics according to rescuer's CPR training experience.

	Trained ($n = 60$)	Untrained ($n = 60$)	p-Value
Rescuer characteristics			
Age, year, SD	52.5 ± 16.1	61.1 ± 15.6	0.018
Male, n (%)	22 (36.7)	25 (41.7)	0.354
Family member, n (%)	31 (51.7)	50 (83.3)	<0.001
Health professional, n (%)	18 (30.0)	3 (5.0)	<0.001
Patient characteristics			
Age, year, SD	80.3 ± 12.6	75.7 ± 11.4	0.042
Male, n (%)	32 (53.3)	30 (50.0)	0.428
ADL before arrest, good, n (%)	28 (46.7)	41 (68.3)	0.026
Witnessed, n (%)	18 (30.0)	29 (48.3)	0.030
Location of arrest, n (%)			<0.001
Home	35 (58.3)	52 (86.7)	
Healthcare facility	17 (28.3)	1 (1.7)	
Other	8 (13.3)	7 (11.7)	
Cardiac origin, n (%)	52 (86.7)	50 (83.3)	0.799
Rescue situation			
Telephone CPR instruction, n (%)[a]	37 (62.7)	37 (61.7)	1.000
Resuscitation time course by EMS, min, median (IQR)			
Call to CPR[b]	6.0 (1.0–66.0)	7.0 (1.0–13.0)	0.341
Call to shock[c]	9.0 (4.0–26.0)	12.0 (9.0–27.0)	0.013
Call to hospital arrival[d]	31.0 (18.0–99.0)	32.5 (19.0–91.0)	0.241

CPR denotes cardiopulmonary resuscitation; SD, standard deviation; ADL, activities of daily living; EMS, emergency medical service; IQR, interquartile range.
[a] Data on one participant in trained group were missing ($n = 59$ in trained group, $n = 60$ in untrained group).
[b] Data available for patients with CPR by EMS ($n = 15$ in trained group, $n = 34$ in untrained group).
[c] Data available for patients with EMS shock ($n = 12$ in trained group, $n = 13$ in untrained group).
[d] Data available for patients arriving at hospital ($n = 34$ in trained group, $n = 48$ in untrained group).

Table 2
Resuscitation performances according to rescuer's CPR training experience.

	Trained (n=60)	Untrained (n=60)	p-Value
Bystander CPR, n (%)	45/60 (75.0)	26/60 (43.3)	0.001
Previous CPR training, n (%)			
Within a year	17/21 (81.0)	-	-
Between 1 and 3 years	9/12 (75.0)	-	-
Over 3 years	17/25 (68.0)	-	-
Bystander CPR with telephone CPR instruction, n (%)	32/37 (86.5)	26/37 (70.3)	0.157
Number of rescuers, >2, n (%)	44/60 (73.3)	28/60 (46.7)	<0.001
Number of CPR performers, >2, n (%)	17/45 (37.8)	3/26 (11.5)	0.027
Knowledge of AEDs, n (%)	53/60 (88.3)	27/60 (45.0)	<0.001
Knowledge of the neighborhood AED location, n (%)	22/60 (38.6)	7/60 (18.4)	0.043
Using of AED, n (%)	6/15 (40.0)	0/0 (0.0)	-
Resuscitation time course, min, median (IQR)			
Collapse to call[a]	2.5 (−2.0–17.0)	3.0 (−3.0–30.0)	0.918
Collapse to bystander CPR[b]	2.0 (0.0–17.0)	2.0 (1.0–6.0)	0.765
Call to guided CPR via telephone[c]	0.0 (0.0–2.0)	0.5 (0.0–2.0)	0.959

CPR denotes cardiopulmonary resuscitation; AED, automated external defibrillator; IQR, interquartile range.
[a] Data available for witnessed patients (n=18 in trained group, n=29 in untrained group).
[b] Data available for witnessed patients with CPR (n=12 in trained group, n=6 in untrained group).
[c] Data available for patients with bystander CPR and who received telephone-guided CPR (n=23 in trained group, n=22 in untrained group).

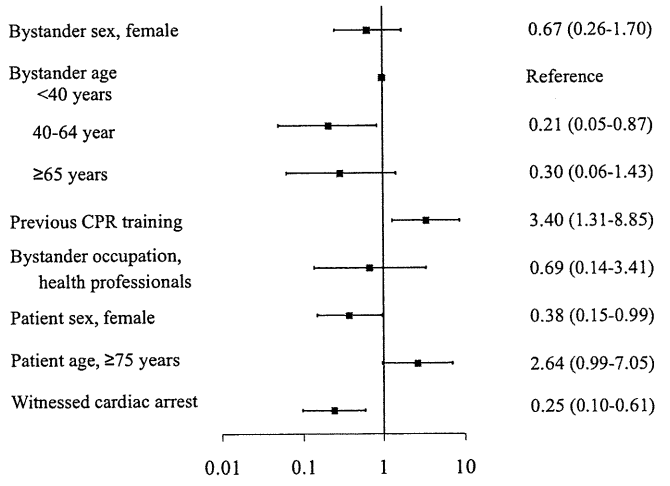

Fig. 2. Multivariable adjusted odds ratios (95% confidence intervals) of the factors possibly associated with bystander CPR performances.

95% CI 0.05–0.87) and female patients (adjusted OR, 0.38; 95% CI 0.15–0.99) were associated with lower proportion of bystander CPR. Surprisingly, patients with witnessed arrest were less likely to receive bystander CPR compared to those without it (adjusted OR, 0.25; 95% CI 0.10–0.61).

3.3. Patient outcomes

Patient outcomes according to the rescuers' experience of CPR training are shown in Table 3. One-month survival was 13.3% in the trained rescuer group, while 8.3% in the untrained rescuer group (p=0.279). Neurologically favorable one-month survival was 3.3% in the trained rescuer group, against 1.7% in the untrained rescuer group (p=0.500). However the number of survivors was too small to evaluate the difference between the groups.

4. Discussion

This study clearly demonstrated that people who experienced CPR training were more likely to perform CPR at the cardiac arrest scene than those without such experience. Because CPR by bystanders is strongly linked to improved patient survival, increase in CPR attempts should improve patient outcomes. Our study evaluated not only the associations between the rescuers' previous CPR training and their CPR performance, but also that between rescuers' previous CPR training and patient survival after OHCA. In this study, unlike a similar study,[13] which conducted a telephone interview two weeks after the event to obtain data on the rescuers, the EMS personnel interviewed the actual rescuers at the scene which assured the quality of data and minimized recall biases.

There was a trend to improved neurologically favorable survival in the trained rescuer group compared with those in the untrained rescuer group. But unfortunately, the number of survivors was too small to evaluate this intergroup difference. Many reports show bystander CPR increases survival after OHCA.[5,19,26,27] The experience of CPR training could improve rescuers willingness to perform CPR and could result in better patient outcomes after OHCA.

When telephone CPR instruction was provided, CPR was more often provided to OHCA cases treated by the rescuers with previous CPR training. Previous studies reported that CPR instruction by dispatchers could encourage lay rescuers to perform CPR[28,29] and improve the quality of CPR performed by bystanders with previous CPR training.[29] Bystanders with previous CPR training might have a better understanding of the dispatcher's directions for CPR and more likely to perform CPR. In addition, our finding suggested that rescuers with previous CPR training were sometimes confident enough to start CPR without telephone instruction. Both CPR training and telephone CPR instruction could increase bystander CPR.

This study showed that CPR training increased the knowledge of not only an AED itself but also the neighborhood AED locations, which suggested that CPR training engaged their attention to AEDs because there was no uniform location of public access AEDs and no established education about AED location in the training. These improvements in attitudes towards CPR and AEDs would result in increase in willingness to perform CPR or use an AED. However, the actual use of an AED was rare even if the lay rescuers had experienced CPR training. In Japan, nationwide dissemination of public access AEDs produced an increase in public access defibrillation with an AED and survival after out-of-hospital VF.[22] A previous study pointed out difficulties in the actual use of an AED for the general public even if they were trained in CPR and AED use.[30] We need to consider ways to increase the number of people who can use an AED in actual emergency settings.

Our finding is consistent with previous studies showing the importance of CPR training with practice.[14–16,31–33] Some of them suggested the needs of brief re-assessment or refresher course to improve CPR skills and its retention.[14,31] CPR training with practice, therefore, should be widespread. However, the length of conven-