Implementation of the Fifth Link of the Chain of Survival Concept for Out-of-Hospital Cardiac Arrest

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Background—The American Heart Association 2010 resuscitation guidelines recommended adding a fifth link (multidisciplinary postresuscitation care in a regional center) to the previous 4 in the chain of survival concept for out-of-hospital cardiac arrest. Our study aimed to determine the effectiveness of this fifth link.

Methods and Results—This multicenter prospective cohort study involved all eligible out-of-hospital cardiac arrest patients in the Aizu region (n = 1482, suburban/rural, Fukushima, Japan). Proportions of favorable neurological outcomes were evaluated before (January 2006–April 2008) and after (January 2009–December 2010) the implementation of the fifth link. After implementation, all patients were transported directly from the field to the tertiary-level hospital or secondarily from an outlying hospital to the tertiary-level hospital after restoration of circulation. The tertiary hospital provided intensive postresuscitation care, including appropriate hemodynamic and respiratory management, therapeutic hypothermia, and percutaneous coronary intervention. One-month survival with a favorable neurological outcome among all patients treated by emergency medical services providers improved significantly after implementation (4 of 770 [0.5%] versus 21 of 712 [3.0%]; P<0.001). The adjusted odds ratios of favorable neurological outcome were 0.9 (95% confidence interval, 0.7–1.1) for early access to emergency medical care, 3.1 (95% confidence interval, 1.2–14.4) for bystander resuscitation, 14.7 (95% confidence interval, 3.2–67.0) for early defibrillation, 1.0 (95% confidence interval, 1.0–1.1) for early advanced life support, and 7.8 (95% confidence interval, 1.6–39.0) for the fifth link.

Conclusion—The proportion of out-of-hospital cardiac arrest patients with a favorable neurological outcome improved significantly after the implementation of the fifth link, which may be an independent predictor of outcome.

Clinical Trial Registration—URL: http://wwwapps.who.int/trialsearch. Unique identifier: UMIN000001607.

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Key Words: cardiopulmonary resuscitation ■ heart arrest ■ hemodynamics ■ hypothermia ■ regional medical programs

Out-of-hospital cardiac arrest (OHCA) affects 235 000 to 325 000 people in the United States,1 275 000 in Europe,2 and 105 000 in Japan3 each year. However, the survival rate after OHCA, especially without neurological impairment, remains low,3–5 and the burden of the disease is high.6 To overcome this, in 2000 and 2005, the American Heart Association–International Liaison Committee on Resuscitation recommended a “chain of survival” concept consisting of the following 4 steps: early access to emergency medical care (first link), early cardiopulmonary resuscitation (CPR; second link), early defibrillation (third link), and early advanced cardiac life support (ACLS; fourth link).4–7 Connecting these links is crucial for increasing the survival rate after OHCA.8–10

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In addition to attempting resuscitation to promote return of spontaneous circulation (ROSC), it is important to perform...
postresuscitation care during the period of post–cardiac arrest syndrome, a pathophysiological state in OHCA patients after ROSC.11 This condition includes multiple life-threatening disorders caused by prolonged complete whole-body ischemia and reperfusion.11,12 Most post–cardiac arrest syndrome deaths occur as a result of hemodynamic failure during the first 24 hours after cardiac arrest.13,14 Therapeutic hypothermia improved neurological outcomes after cardiac arrest in 2 randomized clinical trials.15,16 Consequently, therapeutic hypothermia was incorporated into the guidelines for the treatment of post–cardiac arrest syndrome with a high level of evidence of recommendation.14 The feasibility and success of early coronary angiography and subsequent percutaneous coronary intervention after OHCA resulting from acute coronary syndrome have been described previously.14,17 However, it is difficult for a non–tertiary care hospital to deliver all these treatments as a bundle of postresuscitation care, so there are large interhospital variations in admission rate after successful resuscitation from OHCA and survival to hospital discharge.18–20 Implementation of a regional care system has improved outcomes for other conditions such as severe trauma and acute myocardial infarction.21–23 Therefore, resuscitation experts have recently recommended the development and implementation of regional resuscitation systems of care.24–26

Consequently, the 2010 AHA guidelines recommended adding another link to the chain of survival concept for postresuscitation care.14 The establishment of a postresuscitation care center and expansion to a 5-step chain of survival concept is a rational approach, but only limited evidence supports its implementation.27–30

This study (the Aizu Chain of Survival Concept Campaign) aimed to determine the effectiveness of a multidisciplinary and regional postresuscitation system of care for OHCA, the fifth link of the chain of survival concept.

Methods

Design

The Aizu Chain of Survival Concept Campaign was a multicenter prospective cohort study that included all eligible cardiac arrest patients in the region. The control (before) period data were collected during January 2006 to April 2008 (28 months). The concept of the campaign was established in May 2008, and multidisciplinary postresuscitation care was administered provisionally until the end of December 2008. The campaign was approved by the relevant institutional review boards, and all 12 emergency hospitals (1 tertiary care and 11 non–tertiary care hospitals) in the region that were eligible to treat OHCA agreed to participate in the study. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (http://wwwapps.who.int/trialsearch/trial.aspx?trialid=JPRN-UMIN00000016077; identifier, UMIN00000016077) and was initiated on January 1, 2009, ~2 years before the release of the 2010 AHA guidelines (Figure I in the online-only Data Supplement).14 Data for the intervention (after) period were collected during January 2009 to December 2010 (24 months). Verbal and written informed consent to participate was obtained from each patient’s next of kin before intervention in the tertiary-level hospital. Deferred informed consent was obtained from each patient as he or she recovered consciousness.

Setting

The Aizu region (Fukushima, Japan) comprises suburban/rural communities and covers 5420 km² with ~300 000 residents. The emergency medical services (EMS) providers in this region receive >12 000 emergency calls annually, including ~500 calls for suspected OHCA. EMS providers initiated CPR and ACLS according to the Japanese CPR guidelines, which were based on the 2005 AHA guidelines.4 After transfer of patients to the hospital, hospital healthcare providers performed ACLS according to the same guidelines (details are given in the online-only Data Supplement).

Definitions and Data Collection

Cardiac arrest was defined as the absence of mechanical cardiac activity determined by the absence of pulse and normal breathing. All OHCA patients in whom resuscitation was initiated by EMS providers were included. Individuals with obvious signs of death at the scene (eg, rigor mortis or lividity) were excluded because EMS did not initiate resuscitation under such circumstances. Other exclusion criteria were age <15 years, cardiac arrest secondary to trauma, and cardiac arrest associated with terminal cancer. The following Cerebral Performance Category scale was used to measure neurological outcome 1 month after successful resuscitation: 1=good cerebral performance, 2=moderate cerebral disability, 3=severe cerebral disability, 4=coma/vegetative state, and 5=death.31

Independently from this study, regional fire departments prospectively collected data in the standardized Utstein style3,32 and officially reported them to the Japan Fire and Disaster Management Agency, the national database.3,32 These national data include prehospital information, time of receipt of the emergency call by EMS, time of EMS arrival on the scene, time of the initial contact with the patient, time of CPR initiation, time of defibrillation by EMS personnel, time of arrival at the hospital, the sex and age of the patient, the initial cardiac rhythm, and the time course of resuscitation. Additional information included whether the arrest was witnessed by a bystander, whether a bystander initiated CPR, whether the patient was intubated, whether epinephrine was administered, and whether spontaneous circulation was restored before the patient arrived at the hospital.3,32 Regional fire departments provided the data after the study had been completed. We independently collected patient data from every institution and then compared them with the national data for verification. The institutional information also included whether and how much medication (including epinephrine) was administered, whether the patient returned to spontaneous circulation after arrival at the hospital, whether the patient was admitted to the hospital, descriptions of the in-hospital treatment process, duration of the hospital stay, and the final neurological outcome after the initial cardiac arrest.

Intervention (the Fifth Link of the Chain of Survival as a Bundle of Multidisciplinary Postresuscitation Care)

The prehospital and hospital treatment methods before ROSC did not change during the 2 study periods. In general, EMS transported the patient to the nearest hospital. If the nearest hospital was a tertiary care hospital and ROSC had been achieved, the patient received immediate postresuscitation care in the intensive care unit (ICU). Patients resuscitated in non–tertiary care hospitals were secondarily transported to a tertiary care hospital ICU. For those patients who achieved ROSC in a non–tertiary care hospital, the emergency physician in charge telephoned the tertiary care hospital ICU. The expert team from the ICU then used a physician-staffed ambulance containing medical devices capable of providing care similar to that at the tertiary-level hospital to transport the resuscitated patient from the outlying emergency department (Figure II in the online-only Data Supplement). Early prognostication was not performed because postarrest physical examination findings or diagnostic studies cannot yet predict the neurological outcome for comatose cardiac arrest survivors during the first 24 hours after ROSC.14

Hemodynamic and respiratory management was performed for all ROSC patients admitted to the ICU for postresuscitation care. Fluids, dopamine, dobutamine, noradrenaline, vasopressin, and milrinone were administered at the discretion of the intensivist in accordance with the hemodynamic and respiratory profiles of the PiCCO.
variables (Pulsion Medical Systems, Munich, Germany). In cases when hemodynamic and respiratory management failed to maintain the appropriate vital signs, extracorporeal membrane oxygenation and/or an intra-aortic balloon pumping system were added.

Therapeutic hypothermia was performed for all ROSC patients admitted to the ICU for postresuscitation care, regardless of the cause of cardiac arrest or the patient’s age, except for those in whom hemodynamic and respiratory status could not be maintained despite complete use of our protocol. In most patients, body temperature was maintained at a target of 33°C for 24 hours and then rewarmed by 1°C per day until normothermia (ie, 36°C–37°C) was attained. However, for patients who required extracorporeal membrane oxygenation owing to hemodynamic and/or respiratory failure, the target maintenance body temperature was 34°C. A bolus infusion of 2000 mL of chilled Ringer solution was administered as soon after ROSC as possible, either at the tertiary care hospital emergency department or in the ambulance during interfacility transport from the outlying hospital. After admission to the ICU at the tertiary care hospital, a transcutaneous cooling device (Arctic Sun 2000; Medivance, Inc, Louisville, CO) was used.

Immediate coronary angiography was performed in cases of ST-segment–elevation myocardial infarction or if a cardiologist suspected a cardiogenic origin. Percutaneous coronary intervention was performed if a recent coronary arterial occlusion was found.

**Outcome Measures**

The primary outcome analyzed in this study was patient survival at 1 month with minimal neurological impairment (favorable neurological outcome), which was defined as a Cerebral Performance Category scale of 1 or 2. The secondary outcome was survival to hospital discharge, which was defined as the patient’s leaving the hospital alive. All OHCA patients in the study region, including those from nontertiary hospitals who were not transferred to tertiary hospitals for whatever reason, were analyzed.

**Statistical Analysis**

The mean (SD) or median (interquartile range) was calculated for continuous variables and analyzed appropriately by use of the t test or Mann-Whitney U test. Outcomes before and after the campaign were compared by use of the χ² test or Fisher exact test. When applicable, the odds ratio (OR) and 95% confidence interval (CI) were determined. Logistic regression analysis was performed to control for the following previously recognized possible confounding variables: witness to the 9–1-1 call to access emergency medical care (first link), initiation of CPR by a bystander (second link), prehospital use of an automated external defibrillator (third link), time until the beginning of ACLS (fourth link), age, sex, time from receipt of call to arrival of EMS at the scene, time from collapse to ROSC, and prehospital ROSC. A segmented regression analysis of interrupted time-series data was used to analyze the effect of the intervention before and after the intervention. The percentages of favorable neurological outcome and ROSC level were evaluated for every 4 months of the study period by assessing the change(s) in the level and/or trend (slope) of the outcome before and after the intervention. A change in the outcome level, specifically a statistically significant increase or decrease in the outcome after the intervention, was defined as an intervention effect. A change in slope was defined as an increase or decrease in the slope of the segment after the intervention compared with the segment preceding the intervention and represents a long-term intervention effect. All data were analyzed with SPSS 17.0 (SPSS, Inc, Chicago, IL). A value of P<0.05 was considered significant.

**Results**

Of the 2558 cardiac arrests that occurred during the before and after periods, 1482 (770 before the campaign and 712 after) met the inclusion criteria and were evaluated further (Figure 1). There were no significant differences in bystander witness status (first link), bystander CPR performance (second link), prehospital use of automated external defibrillator (third link), time to the beginning of ACLS (fourth link), age, sex, presence of initial shockable rhythm, or prehospital ROSC between the before and after campaign groups (Tables 1 and 2). However, EMS-dispatch-to-scene time increased significantly in the after period. Although the number of patients who did not transfer from the field to the hospital tended to increase in the after period (373 [29%] versus 405 [32%]), this change was not statistically significant (P=0.22). The percentage of patients with asystole as the initial rhythm decreased in the after period. The percentage of ROSC events attained before arrival at the hospital did not differ between the 2 periods (14.5% for the before versus 16.5% for the after period; P=0.62). During the after period, 70 patients received intervention for postresuscitation care at a single tertiary hospital ICU (Table 2). Of the 122 ROSC patients resuscitated at the non–tertiary care hospitals in the after period, 62 rearrested in the emergency room immediately after ROSC. Thirty-three patients (family members) refused further intensive care, and 7 stopped treatments by the doctors in charge at the non–tertiary care hospitals. Twenty patients underwent interfacility transport to the tertiary hospital in the physician-staffed ambulance without rearrest (versus 0 patients in the before period), and 17 of these met the entry criteria and received postresuscitation care. No patient admitted to any

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**Figure 1.** Flow diagram of patient enrollment. The campaign refers to the Aizu Chain of Survival Concept Campaign. CPC indicates Cerebral Performance Category; HP, hospital; OHCAs, out-of-hospital cardiac arrests; ROSCs, returns of spontaneous circulation; and 5th link, multidisciplinary postresuscitation care.
hospital without the intervention during the after period achieved a favorable neurological outcome.

The rate of favorable neurological outcome improved significantly on initiation of the campaign (before, 4 of 770 [0.5%]; after, 21 of 712 [3.0%]; difference, 2.4%; 95% CI, 1.1–3.7; unadjusted OR, 5.8; 95% CI, 2.0–17.0; \( P < 0.001 \); adjusted OR, 7.8; 95% CI, 1.6–39.0; \( P = 0.01 \)). Figure 2 shows the logistic regression analysis of possible confounding variables, including the effect of each link of chain of survival for favorable neurological outcome. The age, prehospital achievement of ROSC, third link, and fifth link were independent predictors of favorable neurological outcome.

The proportion of patients with favorable neurological outcome among survivors at 1 month increased significantly (before, 4 of 21 [19%]; after, 21 of 41 [51%]; difference, 32.1%; 95% CI, 6.4–58.0; unadjusted OR, 4.5; 95% CI, 1.3–14.8; \( P = 0.01 \); adjusted OR, 10.3; 95% CI, 1.6–68.4; \( P = 0.02 \)). Among the 70 patients who received intervention for postresuscitation care in the after period, there was no difference in primary outcome between those who were transported from an outlying hospital (4 of 17, 24%) and those who were transported directly to a tertiary-level hospital (17 of 53, 32%; \( P = 0.50 \)).

Survival to discharge also improved significantly (before, 18 of 770 [2.3%]; after, 30 of 712 [4.2%]; difference, 1.9%; 95% CI, 0.1–3.8; OR, 1.8; 95% CI, 1.0–3.3; \( P = 0.04 \)). The rate of favorable neurological outcome also improved significantly among patients with witnessed ventricular fibrillation (before, 3 of 38 [7.9%]; after, 11 of 42 [26.2%]; difference, 18.3%; 95% CI, 1.6–35.0; OR, 4.1; 95% CI, 1.1–16.2; \( P = 0.03 \)).

Table 3 shows the results of the segmented regression analysis. The implementation of the campaign was associated with a significant sudden increase in the proportion of patients with a favorable neurological outcome (\( P = 0.04 \)). The initial slope (\( P = 0.99 \)) and the change in slope of the favorable neurological outcome rate after the campaign (\( P = 0.47 \)) were not significant. The proportion of patients who achieved ROSC did not change on implementation of the campaign (\( P = 0.17 \)). Neither the initial slope (\( P = 0.42 \)) nor the change in slope after the campaign (\( P = 0.22 \)) of the ROSC rate changed significantly. Figure 3 shows the time series of the rates of favorable neurological outcome and ROSC among all OHCA patients.

**Discussion**

This multicenter before-and-after study provides evidence of significant and important improvements in favorable neurological outcome and survival associated with implementation of the fifth link in the chain of survival.

The goal of resuscitation of OHCA is to return the patient home without any physical or neurological disability.\(^{14}\) Our study suggests that the fifth link of the chain of survival increases the probability of a favorable neurological outcome.
after OHCA. The 2 study periods did not differ in their percentages of witnessed arrests (first link), bystander-initiated CPR (second link), prehospital automated external defibrillator use (third link), or EMS transport time and time for initiation of ACLS (fourth link). However, they did differ significantly in the in-hospital treatment after ROSC (fifth link). There was a significant increase in the number of patients secondarily transferred by physician-staffed ambulance from outlying hospitals to the tertiary care hospital and treated with accurate hemodynamic management with/out extracorporeal membrane oxygenation, therapeutic hypothermia, or percutaneous coronary intervention. The percent-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before the Campaign</th>
<th>After the Campaign</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>74.1 (13.2)</td>
<td>74.4 (14.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>90 (57.0)</td>
<td>104 (55.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>Witnessed, n (%)</td>
<td>101 (64.0)</td>
<td>135 (71.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>CPR performed by layperson, n (%)</td>
<td>72 (45.6)</td>
<td>89 (47.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>CPR after bystander witness</td>
<td>43 (27.2)</td>
<td>64 (34.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>CPR without bystander witness</td>
<td>29 (18.4)</td>
<td>25 (13.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Initial rhythm, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>VF</td>
<td>20 (12.7)</td>
<td>32 (17.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Pulseless electrical activity</td>
<td>45 (28.5)</td>
<td>64 (34.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Asystole</td>
<td>79 (50)</td>
<td>73 (38.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (8.9)</td>
<td>19 (10.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Witness to 9-1-1 call, median (IQR), min</td>
<td>1 (2.0)</td>
<td>1 (2.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>Collapse-to-ROSC time, median (IQR), min</td>
<td>36 (15.1)</td>
<td>34 (18.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Prehospital AED use, n (%)</td>
<td>20 (12.7)</td>
<td>28 (15.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Collapse-to-AED time, median (IQR), min</td>
<td>10 (3.3)</td>
<td>13 (6.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>EMS-dispatch-to-scene time, median (IQR), min</td>
<td>7 (2.0)</td>
<td>8 (2.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Scene-to-hospital-arrival time, median (IQR), min</td>
<td>21 (4.5)</td>
<td>20 (5.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>EMS-dispatch-to-ACLS time, median (IQR), min</td>
<td>27 (6)</td>
<td>27 (5.5)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hospital admission, n (%)</td>
<td>104 (65.8)</td>
<td>132 (70.2)</td>
<td>0.38</td>
</tr>
<tr>
<td>Admitted patients treated in ICU, n (%)</td>
<td>9 (8.7)</td>
<td>70 (53.0)</td>
<td>&lt;0.01</td>
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<tr>
<td>ICU patients treated in-hospital with</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Accurate hemodynamic management</td>
<td>0 (0)</td>
<td>70 (100.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Therapeutic hypothermia</td>
<td>1 (11.1)</td>
<td>53 (75.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Emergency cardiac catheterization</td>
<td>3 (33.3)</td>
<td>21 (30.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Use of extracorporeal membrane oxygenation</td>
<td>1 (11.1)</td>
<td>10 (14.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Poisonous neurological outcome after ROSC, n (%)</td>
<td>4 (2.5)</td>
<td>21 (11.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation/pulseless ventricular tachycardia; IQR, interquartile range; ROSC, return of spontaneous circulation; AED, automated external defibrillator; EMS, emergency medical services; ACLS indicates advanced cardiac life support, which is defined as initiation of epinephrine administration either before or after hospital arrival; and ICU, intensive care unit.

Figure 2. Adjusted odds ratios for favorable neurological outcome. Akaike information criterion (a measure of the relative goodness of fit of a statistical model) was 89.5. The area under the receiver-operating characteristic curve (the validity of the model) was 0.95. CI indicates confidence interval; EMS, emergency medical service; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; and ACLS, advanced cardiac life support.
The higher rate of treatment in the ICU appears to have been an after-campaign effect; the postcardiac care that we performed was more aggressive than that suggested by the AHA guidelines. Postresuscitation care was performed for all ROSC patients admitted to the ICU, regardless of the patient’s age or cause of cardiac arrest. Although there were concerns that the proportion of survivors with Cerebral Performance Category scale 3 or 4 would increase, this did not occur. Moreover, the proportion of survivors with a favorable neurological outcome increased significantly from 19% to 51% (adjusted OR, 10.3). These findings suggest that the fifth link is associated with the increase in survival rate and improved quality of life among survivors. Therefore, the fifth link is important for achieving the goal of resuscitation.

A concept similar to the chain of survival in the present study was recommended in the 2010 AHA guidelines, which were published 2 years after the initiation of our study. The coordinated and seamless actions of laypeople and healthcare providers, including EMS personnel, emergency medicine physicians, cardiologists, critical care physicians, nurses, medical engineers, and other key personnel, are required for managing OHCA. In fact, the present study indicates that prehospital use of automated external defibrillators and achievement of ROSC in the field were two of the most significant predictors of the outcome. The OHCA patients who achieved ROSC before hospital arrival as a result of early defibrillation by laypeople or EMS may have had better outcomes. Other studies performed during this study period have reported similar results and concluded that earlier defibrillation was the reason for the improved outcomes of OHCA. Therefore, simple and effective guidelines are required to treat this severe and time-sensitive condition. Simplified basic life support and ACLS algorithms have been introduced with the revised traditional algorithms. The initial links of the chain of survival have been simplified in every revision. For example, for the first link, the guidelines now focus more on recognition of cardiac arrest with an appropriate set of rescuer actions. For the second link, look, listen, and feel has been removed from the algorithms for laypeople CPR, with hands-only CPR without rescue breathing and with the compression-to-ventilation ratio changed from 5:1 to 30:2. For the third link, the defibrillation sequence has been reduced from 3 stacked shocks to a single shock. For the fourth link, the routine use of atropine is now avoided. However, the fifth and final link cannot be simplified for nonspecialists and necessitates an additional, different approach; counteracting post–cardiac arrest syndrome requires a multidisciplinary approach to intensive care that is difficult to implement in a nonspecialized hospital. This study indicates that the introduction of the regional resuscitation system of care, the fifth link, made it possible to treat all potential ROSC patients in the ICU of a specialized hospital.

Moreover, previous studies have reported different outcomes of OHCA after the introduction of the 2005 guidelines (4-step concept); some reported improvements and others reported little or no improvement. Although epi-

<table>
<thead>
<tr>
<th>Baseline Level</th>
<th>Initial Slope (95% CI)</th>
<th>P</th>
<th>Change in Level After the Campaign (95% CI)</th>
<th>P</th>
<th>Change in Slope After the Campaign (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable neurological outcome*</td>
<td>0.5</td>
<td>0.004 (–0.5 to 0.5)</td>
<td>0.99</td>
<td>3.4 (0.2 to 6.7)</td>
<td>0.04</td>
<td>–0.3 (–1.0 to 0.5)</td>
</tr>
<tr>
<td>Return of spontaneous circulation†</td>
<td>16.9</td>
<td>0.8 (–1.1 to 2.7)</td>
<td>0.42</td>
<td>8.8 (–2.6 to 20.2)</td>
<td>0.17</td>
<td>–2.0 (–5.1 to 1.0)</td>
</tr>
</tbody>
</table>

Model summary: *$R^2=0.60$, $P=0.03$; †$R^2=0.46$, $P=0.11$. 

Figure 3. Time series of the rate of survival with favorable neurological outcome and return of spontaneous circulation after out-of-hospital cardiac arrest. The dots indicate the actual rate of survival with favorable neurological outcome and return of spontaneous circulation in the Aizu region over every 4-month period from January 2006 to December 2010. The fitted trend lines show the predicted values from the segmented regression model. The introduction of the campaign was associated with a significant sudden increase in the rate of survival with favorable neurological outcome ($P=0.04$).
nepraphine, which is the main component of the fourth link, is strongly associated with ROSC, it has not been strongly associated with postdischarge neurological outcome.\textsuperscript{10,32,42,43} In our study, the time elapsed from the initial telephone call to the first administration of epinephrine was not associated with outcome. In contrast, recent improvements in postresuscitation care, especially the use of therapeutic hypothermia and percutaneous coronary intervention, seem to represent a promising treatment modality.\textsuperscript{11,14} Therefore, we believe that these 2 processes (ie, efforts to achieve ROSC versus multidisciplinary postresuscitation care) must not be considered parts of the same link. Figure 2 clearly shows the significant contrast between the effects of the fourth and the fifth links on outcome. Our data strongly support the 5-step concept of the current AHA guidelines.\textsuperscript{14}

Segmented regression analysis of interrupted time-series data allows assessment of how much an intervention changed an outcome of interest, both immediately and over time, and whether factors other than the intervention could explain the change.\textsuperscript{36,37} Time-series designs are said to be the strongest quasi-experimental designs for estimating intervention effects in nonrandomized settings.\textsuperscript{37} By using this method, we were able to control for trends (slope) in the primary outcome and the dynamics of its change in response to the implementation of the fifth link. Although the outcomes could have been mediated by multiple factors, the results of the segmented regression analysis in this study suggest that the favorable neurological outcome level increased significantly and immediately after the implementation of the fifth link. A change in outcome level indicates an intervention effect.\textsuperscript{37} The initial slope and the change in slope of the favorable neurological outcome rate after the campaign were not significant. Therefore, this improvement in outcome was associated with the implementation of the campaign itself rather than with time-series trends. On the other hand, neither the outcome level nor the slope level of the ROSC changed significantly after the implementation of the campaign. The reason could be that we did not change the therapeutic strategy for the first 4 links to achieve ROSC. These results suggest that the increase in the ROSC rate detected by the $\chi^2$ test (Table 1) was, at least, not associated with the implementation of the campaign.

Study Limitations
This study has several limitations. First, it was conducted in a suburban/rural area. The design was essentially a single-region before-and-after study. Both secular trends and local characteristics of the region may confound the results in unknown, residual ways. Therefore, the results might not be similarly applicable in urban areas with short response and transport time intervals, so additional studies should be conducted to confirm these findings in that setting. Second, the ROSC rate increased significantly without any change in the prehospital and hospital resuscitation guidelines. This phenomenon may have been due to a Hawthorne-like effect (ie, the improvement may have been the result of improved provider performance because of increased attention to resuscitation care).\textsuperscript{28} In addition, the quality of any of the first 4 links might have improved during the study period. Third, although there were tendencies, no significant changes were seen in the characteristics of patients who experience cardiac arrest from the before period to the after period that would bias the analysis in favor of the intervention such as increased witnessed cardiac arrest and an initial rhythm of ventricular fibrillation and decreased asystole. Fourth, the number of patients with an initial rhythm of asystole decreased, which might affect the outcome. Although the prehospital protocols for EMS did not change between the before and after periods, the number of patients who did not have resuscitation initiated by EMS and were not transferred to the hospital from the field tended to be higher. This may be one of the reasons for the lower number of patients with an asystole rhythm in the after period. Finally, the ORs presented for favorable neurological outcome may lack robust precision owing to small numbers of survivors.

Conclusions
The proportion of OHCA patients with favorable neurological outcomes improved significantly after implementation of the fifth link of the chain of survival for OHCA in this region-wide study. Although the outcome is mediated by multiple factors, the fifth link may be an independent predictor of outcome. Our data support the 5-step chain of survival concept in the current AHA guidelines. These findings may require confirmation in an urban setting and/or with randomized trials.

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Disclosures
None.

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\begin{enumerate}
\item Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C,


The 2010 resuscitation guidelines from the American Heart Association (AHA) recommended adding a fifth link (postresuscitation care in a regional center) to the chain of survival concept for out-of-hospital cardiac arrest (OHCA), which had consisted of early access to emergency medical care (first link), early cardiopulmonary resuscitation (second link), early defibrillation (third link), and early advanced cardiac life support (fourth link). However, only limited evidence supports the implementation of the fifth link. The Aizu Chain of Survival Concept Campaign was a multicenter prospective cohort study that included all eligible OHCA in the region. The campaign was initiated on January 1, 2009, 2 years before the release of 2010 American Heart Association guidelines. We implemented the fifth link as part of a multidisciplinary postresuscitation care bundle without changing the protocols of the previous 4 links. After resuscitation, all eligible patients who achieved the return of spontaneous circulation were concentrated at a single postresuscitation-skilled hospital where they received intensive care, including appropriate hemodynamic and respiratory management, therapeutic hypothermia, and percutaneous coronary intervention. The survival rate and the proportion of OHCA patients with a favorable neurological outcome improved significantly after implementation of the fifth link. In addition, multivariate analysis suggested that the fifth link was an independent predictor of outcome. This study provides evidence that implementation of the fifth link in the chain of survival is associated with significant and important improvements in survival and favorable neurological outcome. Our data therefore support the 5-step chain of survival concept outlined in the current AHA guidelines.
Implementation of the Fifth Link of the Chain of Survival Concept for Out-of-Hospital Cardiac Arrest

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SUPPLEMENTAL MATERIAL

Implementation of the Fifth Link of the “Chain of Survival” Concept

for Out-of-Hospital Cardiac Arrest

Contents:

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Expanded Methods

Emergency Medical System

The Emergency Medical System (EMS) in the Aizu region comprises approximately 470 basic life support firefighter responders (EMS providers) and includes 83 advanced cardiopulmonary life support (ACLS) personnel. ACLS personnel have undergone extensive training in the provision of emergency care in the field (i.e., before the patient arrives at the hospital). EMS providers are not permitted to terminate resuscitation in the field unless obvious signs of death (e.g., rigor mortis, lividity) are present. ACLS personnel are allowed to insert an intravenous line, insert an adjunct airway, and use automated external defibrillators to treat patients. Some specially trained ACLS personnel are also permitted to insert tracheal tubes and administer intravenous epinephrine. Ambulances have a crew of three EMS providers and at least one ACLS provider is present in 50% of all crews. In general, most patients are transported to the nearest hospital in the region.

There was only one ICU at one tertiary care hospital in the region that was capable of providing intensive care for post-cardiac arrest syndrome by full time intensivists. Before the campaign, there was no protocol-based treatment strategy for post-cardiac arrest syndrome or any regional resuscitation system of care.
Supplemental Figures

Supplemental Figure 1.

Aizu Chain of Survival Concept Campaign

New Regional System of Care for Out-of-Hospital Cardiac Arrest

Registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR ID: UMIN000001607) on January 1st, 2009
Supplemental Figure 2.
Supplemental Figure legends

Supplemental Figure 1. Framework of the Aizu Chain of Survival Concept

Campaign

The fifth link of the “Chain of Survival” was defined as a multidisciplinary approach of post-resuscitation care. *Akabeko*, a legendary cow of the Aizu region, which helps sick people and brings peace, is the logo of the fifth link.

Supplemental Figure 2. Sophisticated ambulance (Dr. Car)

The main devices in the Dr.Car include the following: mechanical ventilation, hemodynamic monitors, defibrillator, automatic chest compressor, rapid infuser, syringe drivers, cooling devices, blood gas analysis devices, and ultrasonography machine and bronchoscope. Emergency thoracotomy and laparotomy can be performed in the Dr. Car for severe trauma patients.