Neurological Benefit of Therapeutic Hypothermia Following Return of Spontaneous Circulation for Out-of-Hospital Non-Shockable Cardiac Arrest

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Background: Although therapeutic hypothermia is an effective therapy for comatose adults experiencing out-of-hospital shockable cardiac arrest, there is insufficient evidence that is also applicable for those with out-of-hospital non-shockable cardiac arrest.

Methods and Results: Of 452 comatose adults treated with therapeutic hypothermia after return of spontaneous circulation (ROSC) subsequent to an out-of-hospital cardiac arrest of cardiac etiology, 372 who had a bystander-witnessed cardiac arrest, target core temperature of 32–34°C and cooling duration of 12–72 h were eligible for this study (75 cases of non-shockable cardiac arrest, 297 cases of shockable cardiac arrest). The median collapse-to-ROSC interval was significantly longer in the non-shockable group than in the shockable group (30 min vs. 22 min, P=0.008), resulting in a significantly lower frequency of 30-day favorable neurological outcome in the non-shockable group compared with the shockable group (32% vs. 66%, P<0.001). However, an analysis of data in quartiles assigned to varying lengths of collapse-to-ROSC interval revealed a similar frequency of 30-day favorable neurological outcome among both groups when the collapse-to-ROSC interval was ≤16 min (90% non-shockable group vs. 92% shockable group; odds ratio 0.80, 95% confidence interval 0.09–7.24, P=0.84).

Conclusions: Post-ROSC cooling is an effective treatment for patients with non-shockable cardiac arrest when the time interval from collapse to ROSC is short. (Circ J 2012; 76: 2579–2585)

Key Words: Cardiac arrest; Non-shockable rhythm; Post cardiac arrest care; Resuscitation; Therapeutic hypothermia

Despite advances in cardiopulmonary resuscitation (CPR), the neurological intact survival rate for patients with out-of-hospital shockable cardiac arrest remains low worldwide.1–3 Prompt implementation of bystander CPR and early defibrillation have been shown to benefit neurological outcome.1–5 However, the effect of conventional advanced cardiac life support (ACLS), such as drugs, airway adjuncts, tracheal intubation, etc, on neurological outcome remains unclear.1–3,6–8 In 2002, the neurological benefit of post-ROSC cooling in comatose adult patients with return of spontaneous circulation (ROSC)
after an out-of-hospital cardiac arrest with an initial cardiac rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) was reported in 2 randomized clinical trials. The 2010 International Consensus on CPR and Emergency Cardiovascular Care Science With Treatment Recommendations, the 2010 American Heart Association (AHA) CPR guidelines and the 2010 Japan Resuscitation Council Guidelines recommended post-ROSC cooling, administered at a core temperature of 32–34°C for 12–24 h, for comatose adult patients with ROSC after out-of-hospital shockable cardiac arrest (VF or pulseless VT). Induced post-ROSC cooling also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest with any type of initial rhythm or after an out-of-hospital cardiac arrest with an initial rhythm of non-shockable cardiac arrest (pulseless electrical activity or asystole). Further clinical research on post-ROSC cooling after in-hospital cardiac arrest or after out-of-hospital non-shockable cardiac arrest is needed. Some studies comparing shockable and non-shockable cases of cardiac arrest treated with post-ROSC cooling have concluded that the likelihood of a favorable neurological outcome is lower in cases of non-shockable cardiac arrest.12–15

The purpose of this study was to evaluate the efficacy of post-ROSC cooling in comatose adult patients with ROSC after an out-of-hospital non-shockable cardiac arrest using data from the J-PULSE-Hypo registry. Post-cardiac arrest brain injury is caused by the general cessation of blood flow associated with global brain ischemia. Previous reports have shown that longer collapse-to-ROSC intervals are more likely to result in unfavorable neurological outcomes. Our hypothesis was that post-ROSC cooling would have neurological benefit in cases of out-of-hospital non-shockable cardiac arrest when the collapse-to-ROSC interval is short.

**Methods**

**Patients**

The present study was conducted using data from the J-PULSE HYPO study registry. In order to evaluate the clinical factors of post-ROSC cooling, such as optimal candidates, cooling techniques, target core temperatures, time window of induction, cooling duration, timing of rewarming etc, we organized the J-PULSE HYPO study registry, a multicenter registry in which 14 hospitals throughout Japan participated. Between January 2005 and December 2009, 452 consecutive comatose (Glasgow coma scale ≤6) adult (≥18 years) patients who were treated with post-ROSC cooling after an out-of-hospital cardiac arrest of cardiac etiology were enrolled in this registry (UMIN000001935, Clinical Trials.gov: NCT00901134). Cardiac arrest was defined as cessation of cardiac mechanical activity, manifesting as unresponsiveness, apnea (or gasping breathing), and absence of pulse. The initial cardiac arrest rhythm was assessed by emergency medical services (EMS) on arrival at the patient’s side. The definition of ROSC was palpable pulse in the carotid or radial artery and ROSC before hospital arrival was judged by the EMS. The cause of arrest was determined clinically by the physician and the cause, except for an obvious non-cardiac etiology, was defined as cardiac arrest with presumed cardiac etiology. The J-PULSE HYPO study was conducted in accordance with the ethical guidelines for epidemiological studies and was approved by the ethics committee of each of the 14 participating facilities.

In this study, we selected patients who met the following inclusion criteria: bystander-witnessed cardiac arrest, target core temperature of 32–34°C, and cooling duration of 12–72 h.

**Treatment**

Patients were treated with standard CPR and post-cardiac arrest care according to the 2005 AHA guidelines. If hemodynamic instability (systolic blood pressure <100 mmHg and signs of shock) after ROSC persisted despite adequate fluid resuscitation and intravenous infusion of norepinephrine, epinephrine and/or dopamine, intra-aortic balloon pumping (IABP) and/or cardiopulmonary bypass (CPB) were performed as appropriate. Either non-invasive cooling with surface cooling (Blanketrol 2, CSZ Medical, Cincinnati, OH, USA; Arctic Sun, Medivance, Louisville, KY, USA) or invasive cooling with blood cooling (KTEK-3, Kawasumi, Tokyo, Japan; Cool Grad 3000, Alsius, Irvine, CA, USA) was used to maintain core temperature. Core temperature was immediately monitored by bladder temperature or rectum temperature after arrival at the hospital, and monitored by bladder temperature and/or blood
temperature using a balloon flotation right-heart catheter during the post-ROSC cooling period. A target core temperature of 32–34°C was maintained for 12–72 h, followed by gradual rewarming for 24–72 h. Sedation was administered during the post-ROSC cooling period. Emergency coronary angiography was performed if acute coronary syndrome (ACS) was suspected, and coronary reperfusion therapy with percutaneous coronary intervention (PCI) was performed when necessary.

**Data Collection**

Data were collected following Utstein-style guidelines using software designed exclusively for the J-PULSE HYPO study registry. The software was distributed to each of the 14 participating facilities. Data were accumulated and registered by each facility. The database contains information abstracted from medical records concerning cases of cardiac arrest treated with post-ROSC cooling. A unique code was assigned to each patient, and data relevant to patient identity were not collected in the database repository. Data were submitted either by diskette or by encrypted transmission over secure internet.

**Study Endpoints**

The primary endpoint was favorable neurological outcome at 30 days after cardiac arrest (Glasgow-Pittsburgh cerebral performance category of 1 or 2). The secondary endpoints were survival at 30 days after cardiac arrest (Glasgow-Pittsburgh cerebral performance category of 1, 2, 3, or 4) and complications occurring in the first 7 days after cardiac arrest in the following categories: arrhythmia, blood transfusion, infection, and other. Arrhythmia was defined as VF/VT, paroxysmal supraventricular tachycardia, atrial fibrillation/atrial flutter, sick sinus syndrome, or atrioventricular block. Infection was defined as pneumonia, urinary infection, or sepsis.

**Statistical Analysis**

Study patients were divided into 2 groups based on the initial cardiac arrest rhythm (non-shockable group and shockable group). Baseline characteristics were compared using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate. The chi-square test was used to compare the shockable and non-shockable groups.
with regard to study endpoints, and to compare cases in the quartiles of collapse-to-ROSC interval with regard to the primary endpoint. Among the non-shockable group, univariate analysis for the primary endpoint was performed in the quartiles of collapse-to-ROSC interval, and multiple logistic regression analysis for the primary endpoint was performed to adjust for possible confounders (age, sex, presence or absence of bystander CPR, cause of cardiac arrest [ACS or other cardiac etiology], and quartiles of collapse-to-ROSC interval). Statistical analyses were performed using SPSS, version 16.0 J (Chicago, IL, USA).

### Results

Of the 452 comatose adult patients treated with post-ROSC cooling and enrolled in the J-PULSE HYPO study registry, 376 met the inclusion criteria for this study. Of these, 4 were not eligible because the collapse-to-ROSC interval could not be determined. The remaining 372 patients were divided into 2 groups based on the initial cardiac arrest rhythm (75 [20%] cases of non-shockable cardiac arrest, 297 [80%] cases of shockable cardiac arrest) (Figure 1). Generally, the 2 groups had similar baseline characteristics inclusive of post-ROSC cooling treatment. However, significant differences were exhibited between the 2 groups in age, collapse-to-ROSC interval, cardiac arrest because of ACS, emergency coronary angiography, and PCI (Table 1).

### Outcome

Significant differences were observed between the 2 groups in the frequency of 30-day favorable neurological outcome (32% [24/75] non-shockable group vs. 66% [195/297] shockable group; odds ratio [OR] 0.25; 95% confidence interval [CI] 0.14–0.42; P<0.001) and in the frequency of 30-day survival (59%
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[44/75] non-shockable group vs. 85% [252/297] shockable group; OR 0.25; 95% CI 0.15–0.44; P<0.001). No significant differences between the 2 groups were found in the occurrence of complications during the first 7 days after cardiac arrest (Table 2).

Study patients were divided by time interval between collapse and ROSC at 5-min intervals from 0 to 60 min. The percentage of non-shockable cases at each time interval was between 10% and 30% (Figure 2).

The collapse-to-ROSC interval of all study patients ranged from 5 to 138 min, with a median of 24 min, and 25th and 75th percentile values of 16 min and 36 min, respectively. In the quartiles of collapse-to-ROSC interval and 30-day favorable neurological outcome, both non-shockable and shockable groups exhibited high frequencies of 30-day favorable neurological outcome in quartile 1, in which the collapse-to-ROSC interval was ≤16 min (90% non-shockable group vs. 92% shockable group, OR 0.80; 95% CI 0.09–7.24, P=0.84). However, the percentage of cases resulting in 30-day favorable neurological outcome was significantly lower in the non-shockable group.

**Figure 3.** Association between the quartiles of the collapse-to-ROSC interval and the frequencies of 30-day favorable neurological outcome in patients who were divided into 2 groups based on the initial cardiac arrest rhythm. The non-shockable group includes pulseless electrical activity or asystole, and the shockable group includes ventricular fibrillation or pulseless ventricular tachycardia. ROSC, return of spontaneous circulation.

**Table 3.** Unadjusted and Adjusted OR for 30-Day Favorable Neurological Outcome Associated With Selected Factors in the Non-Shockable Out-of-Hospital Cardiac Arrest Group

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collapse-to-ROSC interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.08</td>
<td>0.008–0.76</td>
<td>0.03</td>
</tr>
<tr>
<td>Quartiles 3 and 4</td>
<td>0.02</td>
<td>0.002–0.20</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple logistic regression analysis</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>0.59</td>
<td>0.17–2.04</td>
<td>0.41</td>
</tr>
<tr>
<td>Male</td>
<td>0.7</td>
<td>0.16–3.16</td>
<td>0.64</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>1.37</td>
<td>0.36–5.30</td>
<td>0.64</td>
</tr>
<tr>
<td>ACS</td>
<td>1.89</td>
<td>0.55–6.51</td>
<td>0.31</td>
</tr>
<tr>
<td>Collapse-to-ROSC interval</td>
<td></td>
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<td></td>
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<tr>
<td>Quartile 1 (reference)</td>
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<tr>
<td>Quartile 2</td>
<td>0.05</td>
<td>0.004–0.55</td>
<td>0.01</td>
</tr>
<tr>
<td>Quartile 3 and 4</td>
<td>0.02</td>
<td>0.001–0.15</td>
<td>&lt;0.001</td>
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</tbody>
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Abbreviations as in Tables 1, 2.
when compared with the shockable group in each of the remaining quartiles of longer collapse-to-ROSC intervals. A significant decrease in 30-day favorable neurological outcome was found in the non-shockable group as the quartile value of collapse-to-ROSC interval increased (P<0.001). This significant decrease was also seen in the shockable group (P<0.001) (Figure 3).

Both univariate and multiple logistic regression analyses showed that the longer time intervals of collapse-to-ROSC in quartiles 2, 3 and 4 were independent predictors of unfavorable neurological outcome in cases of non-shockable cardiac arrest. Because it contained only 1 case of non-shockable cardiac arrest, quartile 4 was combined with quartile 3 in both analyses (Table 3).

Discussion

This study presents a comparative analysis of cases of shockable and non-shockable out-of-hospital cardiac arrest in order to evaluate the efficacy of post-ROSC cooling. In comatose adult patients treated with post-ROSC cooling (32–34°C for 12–72h), the collapse-to-ROSC interval was found to be significantly longer, resulting in a significantly lower frequency of 30-day favorable neurological outcome, in the non-shockable group when compared with the shockable group (Tables 1,2). An analysis of study data in quartiles assigned to varying lengths of collapse-to-ROSC interval reveals a similar frequency of favorable neurological outcome among both groups when the collapse-to-ROSC interval was ≤16min (quartile 1). We believe that in such cases, post-ROSC cooling can be an effective treatment for out-of-hospital non-shockable cardiac arrest.

Previous reports have shown that the collapse-to-ROSC interval is longer in cases of non-shockable cardiac arrest when compared with shockable cases.12,14 A study by Oddo et al reported a collapse-to-ROSC interval of 34.6±11.9min (mean±SD) in non-shockable cases, and 23.1±9.0min (mean±SD) in shockable cases.12 In their later study, only 29% of cases of a non-shockable cardiac arrest achieved ROSC within 25min of collapse compared with 78% of the cases with a shockable cardiac arrest.14 Laurent et al identified a longer time interval as a risk factor of hemodynamic instability after ROSC.21 In the present study, the median collapse-to-ROSC interval among non-shockable cases was significantly longer than that for shockable cases (30 [20–40] vs. 22 [16–35] min). Previous studies have also shown that a longer collapse-to-ROSC interval is more likely to result in an unfavorable neurological outcome.13,15 According to Bernard et al, the probability of favorable neurological outcome drops by 14% at every 1.5min of collapse-to-ROSC interval in cases of shockable cardiac arrest.10 However, there are still not enough data to establish a conclusive relationship between collapse-to-ROSC interval and favorable neurological outcome in cases of non-shockable cardiac arrest. A detailed analysis of the time interval by quartile between the 2 groups in our study revealed that both the non-shockable and shockable group displayed the same high frequency of 30-day favorable neurological outcome when the collapse-to-ROSC interval was ≤16min. However, the frequency of 30-day favorable neurological outcome dropped rapidly in the non-shockable group as the time interval increased, and was significantly lower in the non-shockable group when compared with the shockable group in each of the quartiles of longer collapse-to-ROSC intervals (Figure 3). These findings suggest that in comatose adult patients with out-of-hospital cardiac arrest treated by post-ROSC cooling, the difference in collapse-to-ROSC intervals between non-shockable cases and shockable cases results in different frequencies of a favorable neurological outcome.

Previous reports comparing cases of shockable and non-shockable cardiac arrest treated with post-ROSC cooling have concluded that the likelihood of a favorable neurological outcome is lower in cases of non-shockable cardiac arrest.12,15 The present results confirm this (32% non-shockable group vs. 66% shockable group; Table 2). However, the frequency of favorable neurological outcome in cases of non-shockable cardiac arrest treated with post-ROSC cooling in this study (32%) was higher than reported in previous studies (8–22%).12,14,15,24–27 Several factors may account for this. First, in contrast to previous studies, which included cases of cardiac arrest with both cardiac and non-cardiac etiologies, this study included only cases of cardiac etiology. In a study by Dumas et al, 15% (38/261) of cases of non-shockable cardiac arrest treated with post-ROSC cooling resulted in favorable neurological outcome. However, the majority of those cases were non-cardiac etiology.26 It is possible that a favorable neurological outcome is more likely to be attained if the arrest is of cardiac etiology. Second, the 2010 CPR guidelines on post-ROSC cooling indicated a cooling duration of 12–24h.1,3 However, more than 75% of the cases in the present study underwent post-ROSC cooling for more than 24h. A longer period of cooling may improve the likelihood of a favorable neurological outcome. In addition, the majority of studies of post-ROSC cooling indicated a target core temperature ≤34°C.9,10,12,14,22 However, more than 90% of the cases in our study were maintained at a target core temperature of 34°C. A slightly higher target core temperature may preserve cardiac function after ROSC, and have a beneficial effect on neurological outcome. It is clear that further research is needed on factors such as optimal cooling duration and optimal target core temperature. Third, in some previous studies post-ROSC cooling was not implemented if postresuscitation shock persisted after ROSC.9,10,13 However, Oddo et al showed that post-ROSC cooling was effective even in patients with postresuscitation shock.12 Nielsen et al reported that 18% of the 986 patients in their study had postresuscitation shock before induction of post-ROSC cooling, but neurological benefit did not differ between the patients with postresuscitation shock and those without shock.19 In our study, 39% of the patients with a non-shockable cardiac arrest and hemodynamic instability were stabilized by IABP and/or CPB following adequate fluid resuscitation and vasoparative drugs. Furthermore, in this study, emergency coronary angiography was performed in 81% (302/372) of all study patients, which was a higher percentage than reported in previous studies (26–49%).15,24 CPR guidelines emphasize the effect of ACS and the importance of coronary reperfusion therapy in post-cardiac care.1,3 Even though the proportion of non-shockable cases in which emergency coronary angiography was performed was found to be significantly lower than that of shockable cases (60% vs. 85%) in this study, the proportion of non-shockable cases was still high. Such aggressive circulation control, combined with PCI, may have a favorable effect on neurological outcome.

Study Limitations

First, this study was a multicenter trial of post-ROSC cooling, not a randomized control trial, so we evaluated only cases in which post-ROSC cooling was administered, without a control group of cases in which post-ROSC cooling was not administered. Second, although all treatment was administered according to the post-cardiac arrest care protocol outlined in the 2005 AHA guidelines,21 the cases in this study do not share a uni-
form protocol in post-ROSC cooling strategies such as target core temperature, time window, cooling method, cooling dura-
tion and rewarming duration. However, there were no signif-
cicnt differences between the 2 groups in these strategies. Third,
this study’s main focus was the relationship between collapse-
to-ROSC interval and neurological outcome. Therefore, only
cases in which the collapse-to-ROSC interval could be deter-
mained were included.

Conclusion
Post-ROSC cooling was an effective treatment for cases of
non-shockable cardiac arrest when the time interval from col-
lapse-to-ROSC was short.

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