Timing of inducing therapeutic hypothermia in patients successfully resuscitated after out-of-hospital cardiac arrest

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Abstract

Background: Therapeutic hypothermia can improve neurological status in cardiac arrest survivors. Objectives: We investigated the association between the timing of inducing therapeutic hypothermia and neurological outcomes in patients who experienced out-of-hospital cardiac arrest. Methods: We evaluated data from 116 patients who were comatose after return of spontaneous circulation and those who received therapeutic hypothermia between January 2013 and April 2017. The primary endpoint was good neurological outcomes during index hospitalization, defined as a cerebral performance category score of 1 or 2. Therapeutic hypothermia timing was defined as the duration from the return of spontaneous circulation to hypothermia initiation. We analyzed the effect of early hypothermia induction on neurological results. Results: In total, 112 patients were enrolled. The median duration to hypothermia initiation was 284 min (25th–75th percentile, 171–418 min). Eighty-two (69.5%) patients underwent hypothermia within 6 h, and 30 (25.4%) had good neurological outcomes. The rates of good neurological outcomes by hypothermia initiation time quartile (shortest to longest) were 28.3%, 34.5%, 14.8%, and 28.6% (p = 0.401). The good neurologic outcomes did not differ between hypothermia patients within 6 h or after (26.5% vs 26.7%, p = 0.986). Short low-flow time and bystander resuscitation were associated with good neurological outcomes (p = 0.044, confidence interval: 0.027–0.955), but the timing of hypothermia initiation was not (p = 0.602, confidence interval: 0.622–1.317). Conclusion: A shorter low-flow time was associated with good neurological outcomes in out-of-hospital cardiac arrest patients who experienced hypothermia. However, inducing hypothermia sooner, even within 6 h, did not improve the neurological outcomes. Thus, as current guidelines recommend, initiating hypothermia within 6 h of recovery of spontaneous circulation is reasonable.

Introduction

Neurological impairment is an important and critical complication to consider for patients who are successfully resuscitated after cardiac arrest. Therapeutic hypothermia (TH) has been proposed in previous studies as a method for improving neurological status in cardiac arrest survivors, and several studies have shown that TH can reduce neurological complications in unconscious patients who experienced...
out-of-hospital cardiac arrest (OHCA).\textsuperscript{4,5} The Hypothermia after Cardiac Arrest Study Group\textsuperscript{6} analyzed patients who recovered after cardiac arrest due to ventricular fibrillation and concluded that TH can improve their neurological outcomes and reduce mortality.

On the basis of prior studies, TH has been included as a treatment option for cardiac arrest in the American Heart Association’s guidelines.\textsuperscript{7} Regardless of initial rhythm (i.e. shockable or not) and the location where cardiac arrest occurred (i.e. in hospital or out of hospital), well-controlled TH (32°C–34°C for at least 24h) is strongly recommended in comatose patients following successful resuscitation.\textsuperscript{8}

Recently, a randomized clinical trial\textsuperscript{9} reported promising efficacy for TH in cardiac arrest. However, several factors in daily clinical practice, including the time interval between the occurrence of cardiac arrest and the initiation of TH, can affect the efficacy of TH. Unlike in controlled trials, the time interval in practice could vary according to the hospital’s emergency triage protocol, resuscitative techniques, and the specific device used to initiate cooling.

Several studies have revealed that a longer “down time” (i.e. the no-flow time plus the low-flow time) is related to worse neurological outcomes and lower survival rates for OHCA patients, which is presumably due to the longer duration of cerebral ischemia.\textsuperscript{10} A study using registry data showed that a down time lasting longer than 30 min was associated with very low survival at 1 month.\textsuperscript{11} Another study showed that a shorter period between cardiac arrest and achievement of mild hypothermia and the coldest temperature was associated with good neurological outcomes.\textsuperscript{12} However, it is unclear whether the time interval between the occurrence of cardiac arrest and the initiation of TH is associated with neurologic outcomes.

Thus, this study aimed to investigate the association between the time to TH initiation and neurological outcomes in patients who experienced OHCA and return of spontaneous circulation (ROSC). We hypothesized that early initiation of TH, which would decrease the time interval between cardiac arrest and the coldest temperature, would be associated with better neurological outcomes.

**Methods**

**Study design and participants**

We retrospectively evaluated data from a group of consecutive OHCA patients treated at a single tertiary educational center between January 2013 and April 2017. The hospital has an extensive regional emergency medical and trauma center with 1300 inpatient beds. The study protocol was approved by an institutional review board and ethics committee waived informed consent due to the study’s retrospective nature. The study was performed in accordance with the Helsinki Declaration. Patients or the public were not involved in the design or planning of our research. The study population consisted of all patients older than 19 years admitted for OHCA who were comatose after successful ROSC and those who underwent TH. Comatose patients with neurological problems, such as cerebral hemorrhage and extensive stroke, were excluded, as hypothermia is contraindicated in these patients.

In total, 480 patients with OHCA were treated at the emergency department during the study period. Of those, 357 were successfully resuscitated and experienced ROSC, and 116 patients who were comatose after successful ROSC underwent TH. After excluding four of these patients because of an unknown hypothermia initiation time, 112 patients were ultimately included in the study. Patients were divided into quartile groups according to the time to TH initiation (Figure 1).

**Definitions and endpoints**

The timing of TH was calculated as the time interval between ROSC and TH initiation. No-flow time was defined as the interval from the detection of cardiac arrest to the beginning of resuscitation. Low-flow time was defined as the time interval from resuscitation (by bystander or emergency medical services) to ROSC. Sustained ROSC was defined as the restoration of a palpable pulse for at least 20 min. Down time was defined as the time span between lack of pulse and ROSC, thus comprising no-flow time and low-flow time. The primary endpoint was good neurological outcomes during the index hospitalization. The neurological condition of patients who survived until discharge was evaluated using the cerebral performance category (CPC) and Glasgow Coma Scale (GCS) scores, as measured by a neurologist during consultation and recorded in the discharge summary. The CPC scores were as follows: 1 (no significant impairment), 2 (moderate impairment but able to complete activities of daily living), 3 (severe impairment but conscious), 4 (vegetative state or coma), and 5 (death). A good neurological outcome was defined as a CPC score of 1 or 2. Mild impairments were generally defined as those associated with GCS scores of 13–15; moderate impairments with GCS scores of 9–12; and severe impairments with GCS scores of 8 or less.

**TH**

The ARCTIC SUN® Temperature Management System (Medivance Inc., Louisville, CO, USA), designed to monitor and control a patient’s temperature within a range of 32°C–38.5°C, was used in this study. The apparatus consists of an electronic module and disposable ARCTICGEL™ pads used to achieve the target TH set according to our protocol. In our TH protocol, body temperature (BT) was lowered to 34°C over 4 h and maintained for 20 h. Rewarming was initiated after 24 h, during which BT was increased slowly for 12 h and then continued at normothermia (37°C) for up to 12 h, for a total TH duration of 48 h.
Statistical analysis

Data are expressed as mean values ± standard deviations or medians and interquartile ranges (25th–75th percentile) for continuous variables and as numbers and percentages for categorical variables. Between-group comparisons were performed using a one-way analysis of variance or Kruskal–Wallis, chi-square, or Fisher’s exact tests, as appropriate. Logistic regression analysis was used to identify predictors of good neurological outcomes. The variables were as follows: age, sex, prior coronary artery disease, comorbidity, transfer from another hospital, location of cardiac arrest, witnessed or not, bystander cardiopulmonary resuscitation, pulse rate, first type of rhythm, and low-flow time and timing of therapeutic HT. A multiple logistic regression model was constructed using a stepwise method for all analyses; complete data sets were used, and the level of statistical significance was set at p < 0.05. All analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The median duration to initiating TH was 284 min (range: 171–418 min). In total, TH was initiated in 82 patients (73.2%) within 6 h of ROSC. There were 30 patients (26.8%) who showed good neurological outcomes (CPC scores of 1 or 2).

Baseline characteristics according to the timing of TH initiation

The patients were divided into quartile groups according to the TH initiation time, as shown in Table 1. There were no significant differences in age, sex, hypertension status, the presence or absence of diabetes, or the presence of other comorbidities between groups. The rates of witnessed cardiac arrest (i.e. OHCA but in the presence of another person), cardiopulmonary resuscitation (CPR) performed by a bystander, initial shockable or non-shockable rhythm, low-flow time, and duration of hypothermia did not differ between groups. The target temperature for hypothermia and the time to reach target temperature were also not different between groups. Patients transferred from other hospitals had longer intervals to TH initiation. Initial vital signs were slightly different between groups, but the difference between the highest and lowest mean arterial blood pressure was only 2 mmHg. The initial BT was higher in patients with delayed initiation of TH (36.6°C) and lower in patients with early initiation of TH (35.8°C). Laboratory test results revealed higher lactic acid concentrations and a lower pH in patients with early initiation of TH, while all other values were not significantly different.

Neurological outcomes according to the time to TH initiation

We evaluated the rate of good neurological outcomes based on the time to TH initiation (Table 2). The overall rates of good neurological outcomes for quartiles 1 through 4 were 28.3%, 34.5%, 14.8%, and 28.6%, respectively, (Figure 2). Early TH initiation was not associated with a tendency toward either increased or decreased neurological outcomes. The rate of good neurological outcomes was higher in patients with an initial shockable rhythm than in those with an initial non-shockable rhythm (39% vs 19%). The rate of good neurological outcomes based on the time to TH initiation did not differ between patients with initial shockable and non-shockable
rhythms. The neurologic outcomes related to TH within 6 h are presented in Supplementary Table s1, which shows that the neurologic outcomes did not differ between patients that received TH within or after 6 h (CPC 1–2: 26.8% vs 26.7%, p = 0.757 in overall patients with any type of rhythm; 40% vs 36.4%, p = 0.833 in patients with shockable rhythm; 20% vs 23.5%, p = 0.757 in patients with non-shockable rhythm).

**Independent predictors of good neurological outcomes**

The logistic regression analysis showed that the performance of bystander CPR (odds ratio (OR) = 3.451, 95% confidence interval (CI) = 1.16–10.67, p = 0.032) and a shorter low-flow time (OR = 0.162, 95% CI = 0.027–0.955, p = 0.044) were statistically significant predictors of good neurological outcomes. However, early TH within 6 h (OR = 0.905, 95% CI = 0.622–1.317, p = 0.602) or continuous variable (OR = 1.000, 95% CI = 0.998–1.001, p = 0.635) was not a statistically significant predictor (Figure 3). In addition, TH as a quartile group was not an independent predictor, as shown in the Supplementary file (Table s2).

**Discussion**

In our study, we divided the length of time from ROSC to the initiation of TH into four quartiles to investigate the association between early TH induction and neurological

| Table 1. Baseline characteristics according to timing of therapeutic hypothermia initiation. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|-----------------------------|
| **Patients variables**          | **Quartile group divided by timing of therapeutic hypothermia initiation** | **p-value**                     |
|                                 | Q1, <171 min                   | Q2, 171–283 min                 | Q3, 284–417 min                 | Q4, >418 min                   |
|                                 | (n = 28)                       | (n = 29)                        | (n = 27)                        | (n = 28)                       |
| **Age, years**                  | 52.5 ± 16.4                    | 51.9 ± 17.3                    | 55.4 ± 16.1                    | 57.1 ± 14.0                    | 0.578                       |
| **Sex, male**                   | 21 (75.0%)                     | 24 (82.8%)                     | 20 (74.1%)                     | 23 (82.1%)                     | 0.769                       |
| **Hypertension**                | 8 (28.6%)                      | 10 (34.5%)                     | 10 (37.0%)                     | 10 (35.7%)                     | 0.915                       |
| **Diabetes**                    | 6 (21.4%)                      | 3 (10.3%)                      | 7 (25.9%)                      | 5 (17.9%)                      | 0.493                       |
| **Prior coronary artery disease** | 4 (14.3%)                     | 7 (24.1%)                      | 7 (25.9%)                      | 4 (14.3%)                      | 0.559                       |
| **Comorbidities**               | 18 (64.3%)                     | 15 (51.7%)                     | 18 (66.7%)                     | 21 (75.0%)                     | 0.326                       |
| **Transfer from other hospital** | 7 (25.0%)                      | 13 (44.8%)                     | 12 (44.4%)                     | 18 (64.3%)                     | 0.033                       |
| **Location of cardiac arrest**  |                                |                                |                                |                                | 0.677                       |
| **Private**                     | 12 (42.9%)                     | 12 (41.4%)                     | 11 (40.7%)                     | 9 (32.1%)                      | 0.789                       |
| **Public**                      | 15 (53.6%)                     | 17 (58.6%)                     | 16 (59.3%)                     | 19 (67.9%)                     | 0.591                       |
| **Unknown**                     | 1 (3.6%)                       | 0 (0.0%)                       | 0 (0.0%)                       | 0 (0.0%)                       | 0.001                       |
| **Witnessed**                   | 18 (64.3%)                     | 24 (82.8%)                     | 18 (66.7%)                     | 22 (78.6%)                     | 0.323                       |
| **Bystander CPR**               | 11 (39.3%)                     | 11 (37.9%)                     | 7 (25.9%)                      | 10 (35.7%)                     | 0.724                       |
| **First rhythm**                |                                |                                |                                |                                | 0.455                       |
| **Shockable**                   | 8 (28.6%)                      | 14 (48.3%)                     | 9 (33.3%)                      | 10 (35.7%)                     | 0.578                       |
| **Non-shockable**               | 20 (71.4%)                     | 15 (51.7%)                     | 18 (66.7%)                     | 18 (64.3%)                     | 0.578                       |
| **Low-flow time, min**          | 18.6 ± 13.2                    | 20.8 ± 15.4                    | 22.5 ± 21.4                    | 17.7 ± 12.4                    | 0.687                       |
| **Duration of hypothermia, min** | 1781 ± 918                    | 2023 ± 590                    | 2057 ± 518                    | 2231 ± 532                    | 0.093                       |
| **Time to reach TT, min**       | 254 ± 36                      | 234 ± 23                      | 246 ± 63                      | 235 ± 69                      | 0.459                       |
| **Initial vital signs**         |                                |                                |                                |                                | 0.003                       |
| **Systolic BP, mm Hg**          | 105 ± 35.7                     | 136 ± 35.7                     | 109 ± 32.6                     | 110 ± 31.4                     | 0.003                       |
| **Diastolic BP, mm Hg**         | 64 ± 20.3                      | 82 ± 19.2                     | 64 ± 22.4                     | 65 ± 18.5                     | 0.002                       |
| **Heart rate, /min**            | 108 ± 26.3                     | 109 ± 28.5                     | 103 ± 34.6                     | 108 ± 23.9                     | 0.882                       |
| **MAP, mm Hg**                  | 78 ± 25.1                      | 100 ± 24.2                     | 79 ± 25.2                     | 80 ± 22.3                     | 0.002                       |
| **Respiration rate, /min**      | 18 ± 5.4                       | 19 ± 5.8                       | 18 ± 5.6                       | 20 ± 7.7                       | 0.607                       |
| **Body temperature, °C**        | 35.8 ± 0.7                     | 35.8 ± 1.2                     | 36.0 ± 1.0                     | 36.6 ± 0.8                     | 0.010                       |
| **Laboratory findings**         |                                |                                |                                |                                | 0.003                       |
| **Lactate, mmol/L**             | 11.2 ± 5.5                     | 9.1 ± 4.1                      | 9.6 ± 5.5                      | 7.1 ± 4.2                      | 0.023                       |
| **Glucose, mg/dL**              | 263 ± 120.7                    | 246 ± 73.5                     | 267 ± 111.7                    | 205 ± 132.9                    | 0.153                       |
| **PaO₂, mmHg**                  | 105 ± 82.6                     | 102 ± 65.1                     | 108 ± 86.3                     | 112 ± 106.4                    | 0.979                       |
| **pH**                          | 7.07 ± 0.22                    | 7.20 ± 0.18                    | 7.11 ± 0.20                    | 7.21 ± 0.15                    | 0.017                       |
| **Na, mmol/L**                  | 140 ± 4.4                      | 139 ± 6.2                      | 140 ± 0.2                      | 139 ± 4.4                      | 0.790                       |
| **K, mmol/L**                   | 4.9 ± 2.0                      | 4.2 ± 1.1                      | 4.4 ± 1.1                      | 4.1 ± 1.0                      | 0.183                       |
| **Creatinine, mg/dL**           | 1.1 ± 0.3                      | 1.7 ± 1.9                      | 1.6 ± 1.7                      | 1.2 ± 0.7                      | 0.261                       |
| **Hematocrit, %**               | 41 ± 5.7                       | 41 ± 6.3                       | 37 ± 7.6                       | 40 ± 6.7                       | 0.215                       |
| **White blood cell, /μL**       | 12,552 ± 5632                  | 15,039 ± 5902                  | 15,027 ± 6932                  | 15,285 ± 5377                  | 0.279                       |

BP: blood pressure; CPR: cardiopulmonary resuscitation; MAP: mean arterial pressure; Q: quartile; TT: target temperature (34°C). Data are expressed as n (%) or mean value ± standard deviation.
Table 2. Neurologic outcomes according to timing of therapeutic hypothermia initiation and initial rhythm.

| Neurologic outcome                  | Quartile group divided by timing of therapeutic hypothermia initiation | p-value |
|-------------------------------------|-----------------------------------------------------------------------|---------|
| Overall patients with any type of rhythm | Q1, <171 min (n = 28)  | Q2, 171–283 min (n = 29) | Q3, 284–417 min (n = 27) | Q4, >418 min (n = 28) | 0.515 |
| CPC score                           | 1  | 6 (21.4%) | 9 (31.0%) | 4 (14.8%) | 5 (17.9%) |
|                                     | 2  | 2 (7.1%)  | 1 (3.4%)  | 0 (0.0%)  | 3 (10.7%) |
|                                     | 3  | 6 (21.4%) | 7 (24.1%) | 7 (25.9%) | 11 (39.3%) |
|                                     | 4  | 6 (21.4%) | 4 (13.8%) | 5 (18.5%) | 5 (17.9%) |
|                                     | 5  | 8 (28.6%) | 8 (27.6%) | 11 (40.7%)| 4 (14.3%) |
| CPC score                           | 1–2 | 8 (28.6%) | 10 (34.5%)| 4 (14.8%) | 8 (28.6%) |
|                                     | 3–5 | 20 (71.4%)| 19 (65.5%)| 23 (85.2%)| 20 (71.4%) |
| Subgroup 1: patients with shockable rhythm | Q1, <171 min (n = 8) | Q2, 171–283 min (n = 14) | Q3, 284–417 min (n = 9) | Q4, >418 min (n = 10) | 0.700 |
| CPC                                | 1  | 2 (25.0%) | 7 (50.0%) | 2 (22.2%) | 3 (30.0%) |
|                                     | 2  | 1 (12.5%) | 0 (0.0%)  | 0 (0.0%)  | 1 (10.0%) |
|                                     | 3  | 2 (25.0%) | 2 (14.3%) | 4 (44.4%) | 3 (30.0%) |
|                                     | 4  | 1 (12.5%) | 2 (14.3%) | 0 (0.0%)  | 2 (20.0%) |
|                                     | 5  | 2 (25.0%) | 3 (21.4%) | 3 (33.3%) | 1 (10.0%) |
| CPC                                | 1–2 | 3 (37.5%) | 7 (50.0%) | 2 (22.2%) | 4 (40.0%) |
|                                     | 3–5 | 5 (62.5%) | 7 (50.0%) | 7 (77.8%) | 6 (60.0%) |
| Subgroup 2: patients with non-shockable rhythm | Q1, <171 min (n = 20) | Q2, 171–283 min (n = 15) | Q3, 284–417 min (n = 18) | Q4, >418 min (n = 18) | 0.678 |
| CPC                                | 1  | 4 (20.0%) | 2 (13.3%) | 2 (11.1%) | 2 (11.1%) |
|                                     | 2  | 1 (5.0%)  | 1 (6.7%)  | 0 (0.0%)  | 2 (11.1%) |
|                                     | 3  | 4 (20.0%) | 5 (33.3%) | 3 (16.7%) | 8 (44.4%) |
|                                     | 4  | 5 (25.0%) | 2 (13.3%) | 5 (27.8%) | 3 (16.7%) |
|                                     | 5  | 6 (30.0%) | 5 (33.3%) | 8 (44.4%) | 3 (16.7%) |
| CPC                                | 1–2 | 5 (25.0%) | 3 (20.0%) | 2 (11.1%) | 4 (22.2%) |
|                                     | 3–5 | 15 (75.0%) | 12 (80.0%) | 16 (88.9%) | 14 (77.8%) |

CPC: cerebral performance category; Q: quartile.
Data are expressed as n (%). Three patients could not determine the initial rhythm.

Figure 2. Neurological outcomes according to the timing of therapeutic hypothermia initiation.
CPC: cerebral performance category score; Q: quartile.
outcomes. We did not observe any statistically significant associations between the time to TH initiation and good neurological outcomes. There were also no significant associations between good neurological outcomes and initial cardiac rhythms. Logistic regression analysis revealed that CPR performed by a bystander and shorter low-flow times were independent predictors of good neurological outcomes, but early TH was not.

In an animal study, early hypothermia initiation had a positive effect on neurological status. Colbourne et al. demonstrated a neuroprotective effect of hypothermia initiated 6 hours after brain ischemia in rats. Two prospective randomized studies also showed the effectiveness of early hypothermia within 6 hours after brain ischemia in rats. Two previous studies using data from SCAR and cardiac arrest cases witnessed by Emergency Medical Services in Sweden showed that ventricular fibrillation was an independent predictor of a good survival rate. Early cerebral blood perfusion can be achieved via defibrillation in patients with a shockable rhythm; therefore, neurological impairment can be reduced. We did not find this result in our study, possibly because down time was not significantly different between patients with shockable and non-shockable rhythms.

Two previous studies using data from SCAR showed that ventricular fibrillation was an independent predictor of a good survival rate.
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Author contributions
J.S.P. researched and conceived the study. D.Y.K. and J.S.P. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Informed consent
Informed consent was not sought for this study because of the study’s retrospective nature.

Ethical approval
Ethical approval for this study was obtained from the Institutional Review Board of Pusan National University.

Human rights
This study was performed according to the Helsinki Declaration.

Trial registration
It is not applicable, as this study was not a clinical trial.

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Supplemental material
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