Do Lower Target Temperatures or Prolonged Cooling Provide Improved Outcomes for Comatose Survivors of Cardiac Arrest Treated With Hypothermia?

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Background—Optimal protocols for targeted temperature management are still unclear. This study investigated whether lower target temperatures and/or prolonged cooling could provide improved outcomes in comatose survivors of cardiac arrest.

Methods and Results—This observational study was conducted using the prospectively collected targeted temperature management database in Hiroshima, Japan. Between September 2003 and September 2014, 237 patients treated with TTM after cardiac arrest were enrolled in this study. The target temperatures and durations were assigned by the treating physicians regardless of the patients' conditions. Favorable outcomes were defined as a cerebral performance category scale of 1 or 2 at the 90-day follow-up time point. The rate of favorable outcomes were similar between the patients whose protocols of target temperature were <34°C and ≥34°C (40% versus 35%, *P*=0.41), cooling durations were <28 and ≥28 hours (33% versus 44%, *P*=0.11), and rewarming durations were <28 and ≥28 hours (35% versus 41%, *P*=0.39). However, in patients treated with extracorporeal cardiopulmonary resuscitation, target temperatures <34°C were associated with more favorable outcomes (29% versus 8%, *P*=0.01). The cooling and rewarming durations >28 hours and target temperatures <34°C were associated with more frequent lethal arrhythmia, pneumonia, and/or bleedings.

Conclusions—Prolonged durations of cooling and rewarming ≥28 hours may not improve outcomes and may increase complications. Further studies are necessary to assess the hypothesis that target temperatures <34°C provide improved outcomes in patients treated with extracorporeal cardiopulmonary resuscitation. (***J Am Heart Assoc***. 2015;4:e002123 doi: 10.1161/JAHA.115.002123)

Key Words: cardiopulmonary resuscitation • extracorporeal circulation • heart arrest • targeted temperature management • therapeutic hypothermia

Sudden cardiac arrest is a major cause of unexpected death in developed countries and is a major clinical issue. Despite cardiopulmonary resuscitation (CPR), only a few patients are able to return to their former lifestyle.[1,2] Among out-of-hospital cardiac arrest victims, 80% were comatose after the return of spontaneous circulation (ROSC), and 6% to

8% survived to hospital discharge.[3] Targeted temperature management (TTM), so-called therapeutic hypothermia, improves survival and neurological outcomes in comatose survivors of cardiac arrest.[4,5] The current resuscitation guidelines recommended that comatose adult patients with ROSC after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours as class l, according to the protocols in the randomized clinical trials.[4–6] However, there were many unsolved questions regarding TTM, such as the optimal target temperature (TT) and cooling and rewarming durations.[7,8] Adverse postreperfusion cascades result in delayed neuronal death, which occurs minutes to days after reperfusion; on the other hand, TTM was usually discontinued within 12 to 24 hours of cooling, which was not long enough to finish some of the above cascade.[6,9] In some animal models, longer cooling durations were associated with a more neuroprotective effect than shorter durations of cooling.[10,11] Meanwhile, regarding the rewarming duration, rapid rewarming was associated with

adverse outcomes in basic research.[12] In the context of TTs, cerebral metabolic rates decrease by 7% for every 1°C reduction in an animal model, and it was reported that lower TTs may provide more neuroprotection in animal studies.[13] We assessed the hypothesis that lower TTs and/or prolonged cooling was associated with improved neurological outcomes in comatose survivors of cardiac arrest.

Methods

Study Patients

This study is a retrospective analysis of the registry data. We collected data from TTM registries that consist of prospectively collected data from TTM patients at Hiroshima City Asa Hospital and Hiroshima City Hospital from September 2003 to September 2014 in Hiroshima, Japan. Additional data were obtained from previous reports on the same patients that did not include data focusing on the details of the TTs and durations of TTM.[14–17] Written informed consent for clinical studies was obtained from family members. This study was approved by the local institutional review board.

Hypothermia Protocol

Both hospitals have similar clinical practices and similar equipment, including the catheter laboratories and intensive/ coronary care units. In the study patients, the core temperatures were immediately monitored at the bladder and/or pulmonary artery and were used for the management of patients (Figure 1). Because pulmonary artery catheters were not placed in all of the study patients, the bladder temperatures were analyzed in this study. The TTs and the durations of cooling and rewarming were determined by the treating physicians regardless of the patients' illness and conditions. The hospital protocols of TTM encouraged the physicians to decrease the core temperature as early as possible to the TT.

Data Collection

Data pertaining to CPR and TTM were collected from the medical records. The primary goal was to examine the effect of TTs and cooling and rewarming durations on the outcomes. Favorable outcomes were defined as a cerebral performance category (CPC) of 1 or 2 on a 5-point scale 90 days after the index cardiac arrest.[18] The CPC scales include the following: CPC 1, good cerebral performance: conscious, alert, able to work, and might have mild neurologic or psychologic deficit; CPC 2, moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life, and able to work in sheltered environment; CPC 3, severe cerebral disability: conscious, dependent on others for daily support
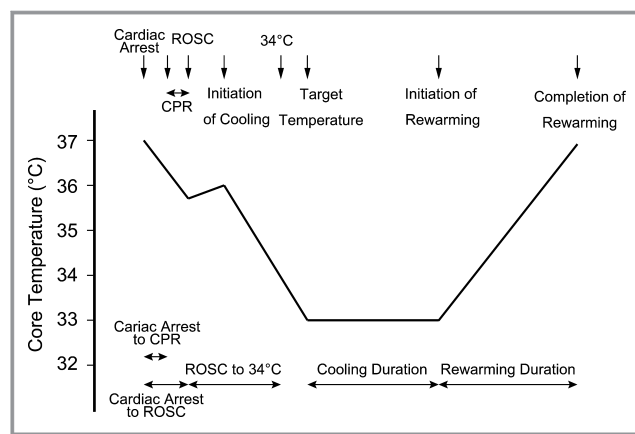

Figure 1. Shema of protocols for targeted temperature management. CPR indicates cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

because of impaired brain function, and ranges from ambulatory state to severe dementia or paralysis; CPC 4, coma or vegetative state: not conscious, unaware of surroundings, no cognition, and no verbal or psychological interactions with environment; and CPC 5, death: certified brain dead or dead by traditional criteria.

Safety end points were the rate of complications during the first 7 days after the index cardiac arrest. Data on complications, including lethal arrhythmia, pneumonia, and bleeding of any severity, were collected from the medical records. Lethal arrhythmia was defined as ventricular fibrillation, ventricular tachycardia, torsade de pointes, hemodynamic unstable supraventricular tachycardia, or atrioventricular block. Pneumonia was assessed by ≥2 physicians according to physical examinations, laboratory data, and/or imaging modalities. The sites of bleeding were the catheter or cannulation sites, mucous membranes, the nose, the urinary tract, the gastrointestinal tract, subcutaneous tissue, and skin, as well as intracerebral and intraabdominal sites.[4]

Statistical Analysis

All of the study patients were analyzed in an intention-to-treat fashion by using temperatures and durations that were decided at the time of TTM initiation. Continuous variables are presented as medians (with interquartile range), and categorical variables are presented as numbers (with percentages). To assess the TT and durations of cooling and rewarming, we divided the study patients into 2 groups according to the thresholds as follows: the TTs were divided by 34°C because most patients were treated at 33°C or 34°C. The durations of cooling and rewarming were divided by 28 hours because the majority of patients were treated for 24 or 48 hours to assess the prolonged durations of cooling and rewarming that were listed in the current guidelines.

To assess the changes in the protocols in this study period, the cohort was divided into 2 eras according to the date of cardiac arrest (2003 to 2008 [early period] or 2009 to 2014 [late period]), and the clinical characteristics, protocols, and outcomes were assessed. The Mann–Whitney U test for continuous variables and the χ^2 test or Fisher exact test for categorical variables were used as appropriate to identify the factors associated with favorable outcomes. As a subgroup analysis, the odds ratio (OR) for favorable outcomes of TT <34°C relative to ≥34°C was evaluated in subgroups that included patients with out-of-hospital cardiac arrest, in-hospital cardiac arrest, shockable initial recorded rhythms, unshockable initial recorded rhythms, acute coronary syndromes (ACS), non-ACS, conventional CPR, and ECPR (i.e., CPR with initiation of venoarterial extracorporeal membrane oxygenation [ECMO] during CPR) by using a univariable logistic-regression model. ACS was diagnosed by ≥2 on-site cardiologists according to previous symptoms of the index cardiac arrest, laboratory data, ECG, and/or coronary angiography. Tests for interaction between TTs <34°C and the subgroups for each outcome were conducted by using logistic regression. Multivariable logistic regression was used to assess the durations and TTs as predictors of a favorable outcome. To select variables, a univariable analysis was performed to identify potentially relevant covariates ($P<0.2$) to predict favorable outcomes, including age ≥55 years, shockable initial recorded rhythms, out-of-hospital cardiac arrest, ACS, cardiac arrest to CPR ≥5 minutes, cardiac arrest to ROSC ≥32 minutes, ROSC to 34°C ≥167 minutes, TT <34°C, duration of cooling ≥28 hours, duration of rewarming ≥28 hours, and the late period (after 2009). Safety end points were compared between the patients of different protocols by using the χ^2 test. Statistical analysis was performed with the JMP 8.0.2.2 statistical package (SAS Institute). A value of $P<0.05$ was considered statistically significant.

Results

Patients

A total of 237 patients were enrolled in the study. The clinical characteristics are shown in Table 1. The median age of the study patients was 62 years (interquartile range, 52 to

Table 1. Characteristics of the Study Patients According to the Different Protocols

	TT <34°C (n=90)	TT ≥34°C (n=147)	P Value	Cooling <28 h (n=162)	Cooling ≥28 h (n=75)	P Value	Rewarming <28 h (n=158)	Rewarming ≥28 h (n=79)	P Value
Age, y	58 (52 to 70)	63 (52 to 72)	0.116	64 (53 to 72)	58 (49 to 69)	0.042	64 (53 to 72)	56 (52 to 68)	0.013
Male	70 (78)	110 (75)	0.606	116 (72)	64 (85)	0.022	113 (72)	67 (85)	0.024
Out-of-hospital cardiac arrest	124 (84)	69 (77)	0.140	123 (76)	70 (93)	0.001	119 (75)	74 (94)	<0.001
Witnessed arrest	81 (90)	112 (76)	0.008	138 (85)	55 (73)	0.029	134 (85)	59 (75)	0.059
Bystander cardiopulmonary resuscitation	57 (63)	70 (48)	0.019	92 (57)	35 (47)	0.146	88 (56)	39 (49)	0.357
Initial shockable rhythm	52 (58)	74 (50)	0.265	82 (51)	44 (59)	0.248	81 (51)	45 (57)	0.407
Acute coronary syndrome	44 (49)	53 (36)	0.051	61 (38)	36 (48)	0.132	58 (37)	39 (49)	0.062
Immediate coronary angiography	76 (84)	68 (46)	<0.001	102 (63)	42 (56)	0.307	99 (63)	45 (57)	0.397
Subsequent percutaneous coronary intervention	40 (44)	36 (24)	0.001	52 (32)	24 (32)	0.988	49 (31)	27 (34)	0.623
Extracorporeal membrane oxygenation	48 (53)	39 (27)	<0.001	72 (44)	15 (20)	<0.001	68 (43)	19 (24)	0.004
Patients survived up to completion of rewarming	66 (73)	113 (77)	0.539	42 (26)	16 (21)	0.444	117 (74)	62 (78)	0.455

Data presented as number (%) of patients or median (interquartile range). TT indicates target temperature.

72 years), 180 patients (76%) were male, 193 patients (81%) experienced out-of-hospital cardiac arrest, and 126 patients (53%) showed an initial shockable rhythm. In this study, 144 patients (61%) underwent immediate coronary angiography, and 76 patients (32%) underwent subsequent percutaneous coronary revascularization. Among the study patients, cold saline was administered rapidly in 156 patients (66%), surface cooling with ethanol evaporation was performed in 4 (2%) patients, gastric lavage with cold saline was performed in 19 (8%) patients, water circulating mattress was used in 142 (60%) patients, Arctic Sun (Medivance Inc) was used in 38 (16%) patients, coil cooling device attached to a hemodiafiltration system was used in 22 (9%) patients, and heat exchanger with ECMO was used in 65 (28%) patients.

The distributions of the TTM protocols by the cooling and rewarming durations and TTs are shown in Figure 2A. In the TT protocols, 90% of the study patients were subjected to 33°C (32%) or 34°C (62%). In terms of the cooling duration TTM protocols, 94% of the patients were subjected to durations of cooling for 24 hours (62%) or 48 hours (31%). Regarding the rewarming duration TTM protocols, 97% of the patients were subjected to rewarming durations of 12 (28%), 24 (36%), 48 (23%), or 72 hours (10%). Among 237 patients, 58 patients died before the completion of rewarming. The distributions of the durations and TTs in the patients who

survived through the completion of rewarming (n=179) are also shown in Figure 2B.

The clinical characteristics, protocols of TTM, and outcomes according to the study period are shown in Table 2. The patients in the late period (2009 to 2014) were older, had more initial nonshockable rhythms, had a higher usage of ECMO, had a longer duration from cardiac arrest to ROSC, and had a shorter duration from ROSC to 34°C. Regarding the TTM protocols, the prevalence of a target temperature <34°C was similar; however, prolonged durations of cooling (62% versus 2%, $P<0.001$) and rewarming (64% versus 3%, $P<0.001$) were used less often in the late period.

Favorable Outcomes

Among the study patients, 110 patients (46%) survived up to 30 days, 106 patients (45%) were discharged alive, and 108 patients (46%) survived up to 90 days. At 90 days, 84 patients (35%) had a CPC of 1, 3 (1%) had a CPC of 2, 9 (4%) had a CPC of 3, 12 (5%) had a CPC of 4, 129 (54%) had a CPC of 5, and 87 patients (37%) had favorable outcomes. The prevalence of TT <34°C (36% versus 40%, $P=0.589$), durations of cooling ≥28 hours (35% versus 29%, $P=0.284$), and durations of rewarming ≥28 hours (35% versus 32%, $P=0.580$) were similar between the patients who survived
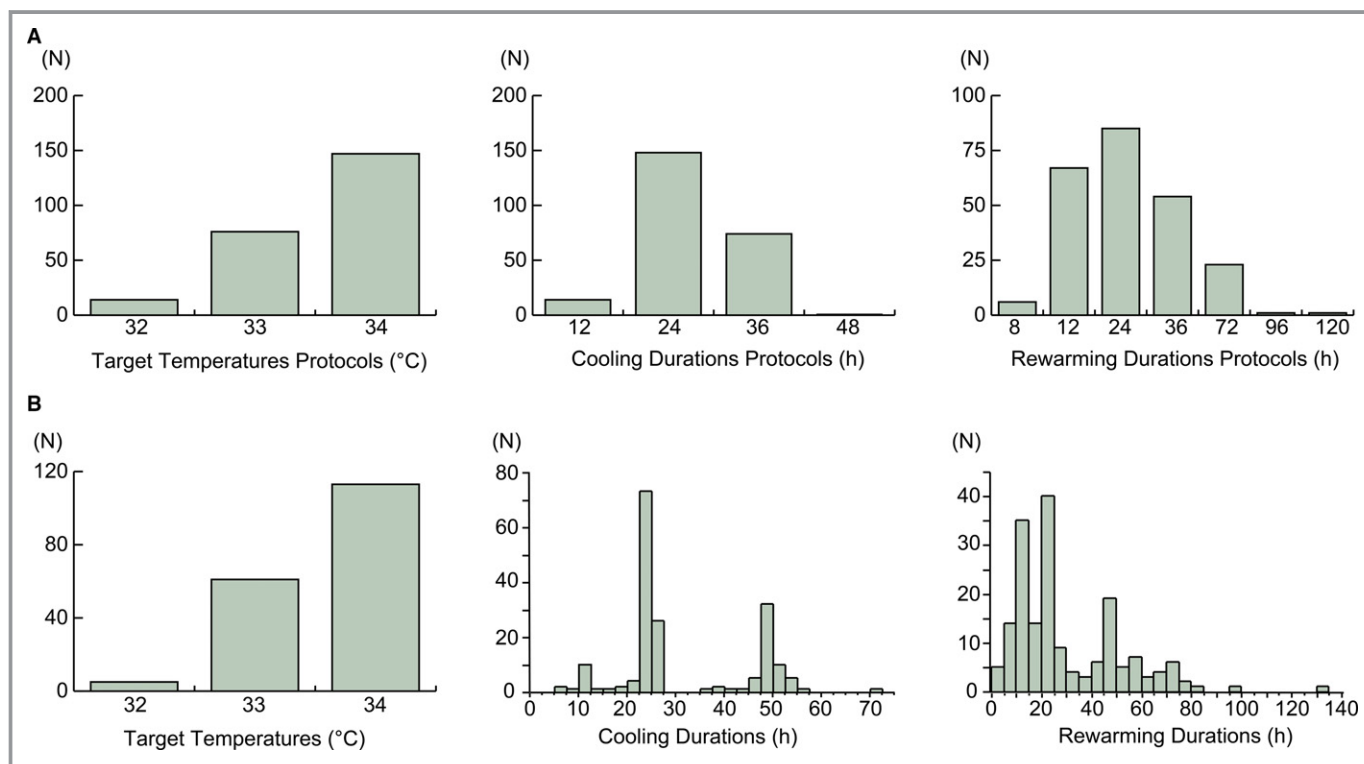

Figure 2. The distributions of cooling and rewarming durations (in hours, h) and target temperatures. A, The distributions of all of the patients according to the protocols. B, The distributions of the patients who survived up to the completion of rewarming according to the practical durations and temperatures.

Table 2. The Clinical Characteristics, Protocols, and Outcomes According to the Study Period

	Early Period (2003 to 2008, n=118)	Late Period (2009 to 2014, n=119)	*P* Value
Age, y	58 (49 to 69)	64 (54 to 73)	0.016
Male	96 (81)	84 (71)	0.053
Out-of-hospital cardiac arrest	103 (87)	90 (76)	0.021
Witnessed arrest	92 (78)	101 (85)	0.171
Bystander cardiopulmonary resuscitation	57 (48)	70 (59)	0.105
Initial shockable rhythm	72 (61)	54 (45)	0.016
Acute coronary syndrome	53 (45)	44 (37)	0.214
Immediate coronary angiography	65 (55)	79 (66)	0.075
Subsequent percutaneous coronary intervention	35 (30)	41 (34)	0.429
Extracorporeal membrane oxygenation	29 (25)	58 (49)	<0.001
Patients survived up to completion of rewarming	99 (84)	80 (67)	0.003
Cardiac arrest to CPR, min	6 (1 to 11)	3 (1 to 11)	0.541
Cardiac arrest to ROSC, min	32 (19 to 45)	43 (24 to 57)	0.004
ROSC to 34°C, min	190 (116 to 343)	70 (15 to 135)	<0.001
Protocol			
Target temperature <34°C	44 (38)	46 (39)	0.823
Cooling ≥28 h	73 (62)	2 (2)	<0.001
Rewarming ≥28 h	75 (64)	4 (3)	<0.001
90-Day survival	64 (54)	41 (34)	0.002
Favorable outcomes	55 (47)	32 (27)	0.002

Data presented as number (%) of patients or median (interquartile range). CPR indicates cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

up to 90 days and those who did not. The durations and TTs of TTM by favorable or unfavorable outcomes are shown in Table 3. The durations from cardiac arrest to ROSC in the patients with favorable outcomes were significantly shorter than those in the patients with unfavorable outcomes (22 minutes versus 45 minutes, *P*<0.001). The durations from ROSC to 34°C were significantly longer in patients with favorable outcomes than in those with unfavorable outcomes (209 minutes versus 98 minutes, *P*<0.001). The TT and the cooling and rewarming durations protocols were similar between the patients with favorable and unfavorable outcomes. We conducted a post-hoc power calculation, and we had a 99.6% statistical power to detect such an effect size of Cohen's w 0.3 at an α level of 0.05. The results were consistent across all subgroups, except for the significantly higher rate of TT <34°C in ECPR patients with favorable outcomes than in those with unfavorable outcomes (82% versus 49%, *P*=0.01, Table 4). There were no significant interactions between TT <34°C and the subgroups. In the ECPR subsets, the baseline characteristics were similar between the patients with TTs of <34°C and those with TTs >34°C (Table 5); however, the rates of favorable outcomes in patients with TTs <34°C were significantly higher than those with TTs of ≥34°C (29% versus 8%, *P*=0.01). The rate of

favorable outcomes was higher in the patients in the early period compared with those of the late period (47% versus 27%, *P*=0.002, Table 2). In the subsets of ACS patients, favorable outcomes were similar between the patients who received immediate coronary angiography and subsequent coronary revascularization and those who did not (31% versus 36%, *P*=0.615). The ORs for favorable outcomes in the subgroups with TTs <34°C are shown in Figure 3. In the subsets of patients who were treated with ECPR, TTs <34°C were significantly more favorable (OR 4.94, 95% CI 1.46 to 22.81, *P*=0.009). The univariable and multivariable analyses for predicting favorable outcomes are shown in Table 6. The TTM protocols of TTs <34°C, durations of cooling ≥28 hours, and durations of rewarming ≥28 hours were not independently associated with favorable outcomes. The covariates that reached statistical significance included a shockable initial recorded rhythm, time intervals from collapse to ROSC ≥32 minutes, and time intervals from ROSC to 34°C ≥167 minutes.

Complications

The complications during the first 7 days after the index cardiac arrest are shown in Table 7. Episodes of lethal

Table 3. Durations and Target Temperatures With or Without Favorable Outcomes

	Favorable (n=87)	Unfavorable (n=150)	P Value
Cardiac arrest to CPR, min	5 (2 to 9)	4 (1 to 13)	0.556
Cardiac arrest to ROSC, min	22 (15 to 32)	45 (32 to 58)	<0.001
ROSC to 34°C, min	209 (114 to 340)	98 (35 to 164)	<0.001
Protocol			
Target temperature <34°C	36 (41)	54 (36)	0.411
Cooling ≥28 h	33 (38)	42 (28)	0.113
Rewarming ≥28 h	32 (37)	47 (31)	0.391
Practical temperatures and durations			
Target temperature <34°C	36 (41)	54 (36)	0.411
Cooling, h	24.5 (23.7 to 48.0)	24.0 (11.1 to 26.6)	0.002
Rewarming, h	24.0 (12.0 to 48.0)	13.0 (0.0 to 25.0)	<0.001

Data presented as number (%) of patients or median (interquartile range). CPR indicates cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

arrhythmia and pneumonia were more frequent in patients with protocols cooling and rewarming durations ≥28 hours than in those with durations <28 hours. The rates of lethal arrhythmia and pneumonia were similar among patients with protocols TTs <34°C and those with TTs ≥34°C. The rate of bleeding was significantly higher in patients treated with protocols TTs <34°C than in those with TTs ≥34°C (53% versus 31%, P<0.001).

Discussion

Our study showed that there were no significant differences in the neurological outcomes of patients treated with or without prolonged cooling and rewarming durations. In all of the study patients, similar neurological outcomes were observed in patients who were treated with TTs <34°C and ≥34°C; however, TTs <34°C were associated with improved outcomes in patients treated with ECPR. Prolonged cooling and rewarming durations and lower TTs were associated with more frequent complications including lethal arrhythmia, pneumonia, and/or bleedings.

This study has several strengths for hypothesis generation to provide some light on doubts concerning the optimum TT and durations, although it was observational. First, the majority of study patients were evaluated with the use of immediate coronary angiography and subsequent coronary intervention. Many observational studies reported that immediate coronary angiography and revascularization were associated with improved outcomes, and the current guidelines recommended immediate coronary angiography and revascularization for resuscitated patients when indicated.[19–21] Our study patients received the current optimal care for ischemic heart disease and revascularization.

Second, this study includes patients treated with novel CPR using ECMO and analyzed the difference of associations of TTs and durations between the patients treated with or without ECPR.[22,23] Recently, Nielsen et al reported that there were no differences between the mortality rates of patients treated with TTs of 33°C and 36°C, and our data in non-ECPR patients support these results.[24] However, in patients treated with ECPR in our study, TTs <34°C was associated with significantly improved neurological outcomes compared with patients treated with TTs ≥34°C.

The possible cause of the different lower TT results between patients treated with and without ECPR may be as follows: first, optimal target temperatures may vary by the severity of ischemic injury. However, if only the severity of illness plays a role, different outcomes should have been observed in the TTM trial.[24] Therefore, other factors/mechanisms must be present in the differences of outcomes in our study. Second, the early application of hypothermia increased intact survival, and the timing of hypothermia determined the organ protective effect of hypothermia in animal studies.[25,26] Rapid cooling by ECMO may be able to provide more neuroprotective and cardioprotective effects at lower temperatures that depend on the depth of cooling compared with the non-ECMO technique.[27] Third, ECMO could provide hemodynamic stability just after the initiation of ECMO, and the neuroprotective effect may be different between TTs in such conditions.[28] Fourth, reperfusion with ECMO may be closer to "controlled reperfusion," and in such conditions, the organ-protective effects may vary by the TTs.[28] In patients treated with ECMO, reperfused blood was oxygenated and carbon dioxide was removed by using a membrane oxygenator, and the blood was relatively cold due to a loss of heat by heat radiation and conduction at the ECMO circuit, which was

Table 4. Durations and Target Temperatures With or Without Favorable Outcomes

	Initial Recorded Rhythm Was Shockable (n=126)			Out-of-Hospital Cardiac Arrest (n=193)			Acute Coronary Syndrome (n=97)			Conventional Cardiopulmonary Resuscitation (n=150)			Extracorporeal Cardiopulmonary Resuscitation (n=87)		
	Favorable (n=64)	Unfavorable (n=62)	P Value	Favorable (n=72)	Unfavorable (n=121)	P Value	Favorable (n=31)	Unfavorable (n=66)	P Value	Favorable (n=70)	Unfavorable (n=80)	P Value	Favorable (n=17)	Unfavorable (n=70)	P Value
Cardiac arrest to CPR, min	6 (2 to 9)	6 (2 to 12)	0.274	7 (2 to 9)	6 (1 to 14)	0.522	7 (1 to 11)	4 (1 to 10)	0.658	7 (2 to 10)	10 (2 to 15)	0.057	0 (0 to 5)	2 (1 to 9)	0.058
Cardiac arrest to ROSC, min	21 (15 to 29)	49 (33 to 60)	<0.001	23 (15 to 35)	48 (37 to 61)	<0.001	25 (19 to 36)	44 (24 to 58)	0.001	21 (15 to 30)	42 (31 to 53)	<0.001	25 (18 to 44)	51 (34 to 62)	0.002
ROSC to 34°C, min	231 (127 to 401)	108 (55 to 189)	<0.001	231 (136 to 373)	109 (55 to 168)	<0.001	178 (105 to 320)	94 (22 to 148)	0.002	237 (151 to 394)	153 (98 to 242)	<0.001	28 (6 to 90)	34 (10 to 90)	0.805
Protocol															
Target temperature <34°C	26 (41)	26 (42)	0.881	26 (36)	43 (36)	0.936	17 (55)	27 (41)	0.199	22 (31)	20 (25)	0.381	14 (82)	34 (49)	0.012
Cooling ≥28 h	25 (39)	19 (31)	0.322	32 (44)	38 (31)	0.068	16 (52)	20 (30)	0.043	29 (41)	31 (39)	0.738	4 (24)	11 (16)	0.48
Rewarming ≥28 h	24 (38)	21 (34)	0.671	31 (43)	43 (36)	0.299	15 (48)	24 (36)	0.26	28 (40)	32 (40)	1.000	4 (24)	15 (21)	1.000
Practical															
Target temperature <34°C	26 (41)	26 (42)	0.881	26 (36)	43 (36)	0.936	17 (55)	27 (41)	0.199	22 (31)	20 (25)	0.381	14 (82)	34 (49)	0.012
Cooling, h	24.6 (23.8 to 48.0)	24.0 (6.4 to 26.4)	0.009	25.8 (24.0 to 48.0)	24.5 (12.9 to 36.5)	0.002	26.0 (23.8 to 48.0)	23.7 (6.2 to 31.9)	0.005	24.9 (24.0 to 48.0)	24.5 (23.1 to 48.0)	0.269	23.7 (12.0 to 25.8)	19.6 (5.6 to 25.1)	0.13
Rewarming, h	23.0 (12.0 to 48.0)	12.0 (0 to 24.3)	<0.001	25.3 (17.3 to 48.8)	15.5 (0 to 29.5)	<0.001	26.0 (15.5 to 66.3)	12.0 (0 to 45.8)	<0.001	24.0 (15.4 to 48.0)	21.0 (11.0 to 46.1)	0.052	12.0 (11.5 to 42.3)	5 (0 to 19.0)	0.002

CPR indicates cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

Table 5. Baseline Characteristics in Patients Treated With Extracorporeal Cardiopulmonary Resuscitation According to the Target Temperature Protocols

	Target Temperatures <34°C (n=48)	Target Temperatures ≥34°C (n=39)	*P* Value
Age, y	60 (54 to 69)	64 (60 to 72)	0.138
Male	36 (75)	28 (72)	0.736
Out-of-hospital cardiac arrest	28 (58)	26 (67)	0.426
Witnessed arrest	45 (94)	37 (95)	1.000
Bystander cardiopulmonary resuscitation	38 (79)	28 (72)	0.424
Initial shockable rhythm	22 (46)	18 (46)	0.976
Acute coronary syndrome	26 (54)	22 (56)	0.834
Immediate coronary angiography	37 (77)	31 (79)	0.787
Subsequent percutaneous coronary intervention	22 (46)	21 (54)	0.457
Patients survived up to completion of rewarming	20 (42)	20 (51)	0.371

cooled by a using heat exchanger at the time of initiation of ECMO. On the other hand, in patients treated with conventional CPR, the blood was relatively hypoxic, hypercapnic, and acidic, and the blood temperature was equal to the core temperature at the time of ROSC.

The TTM protocols in our study resulted in longer durations of cooling and rewarming, which were less frequent after 2009. This finding may be caused by the guideline's recommendation. The patient characteristics treated with TTM were also altered so that the patients with more severe conditions, such as nonshockable rhythms, longer duration from cardiac arrest to ROSC, or refractory cardiac arrest treated with ECMO, were treated with TTM in the late period. The more severe conditions of the patients in the late period may cause a lower rate of favorable outcomes compared with those in the early period (Tables 2 and 6).

In our study, a shockable initial recorded rhythm, a time interval from collapse to ROSC <32 minutes, and a time interval from ROSC to 34°C ≥167 minutes were independently associated with more favorable outcomes. Predictors, such as a shockable rhythm and the time interval from collapse to ROSC, were reported previously.[5,16,29] Nagao et al reported that early attainment of 34°C was associated with

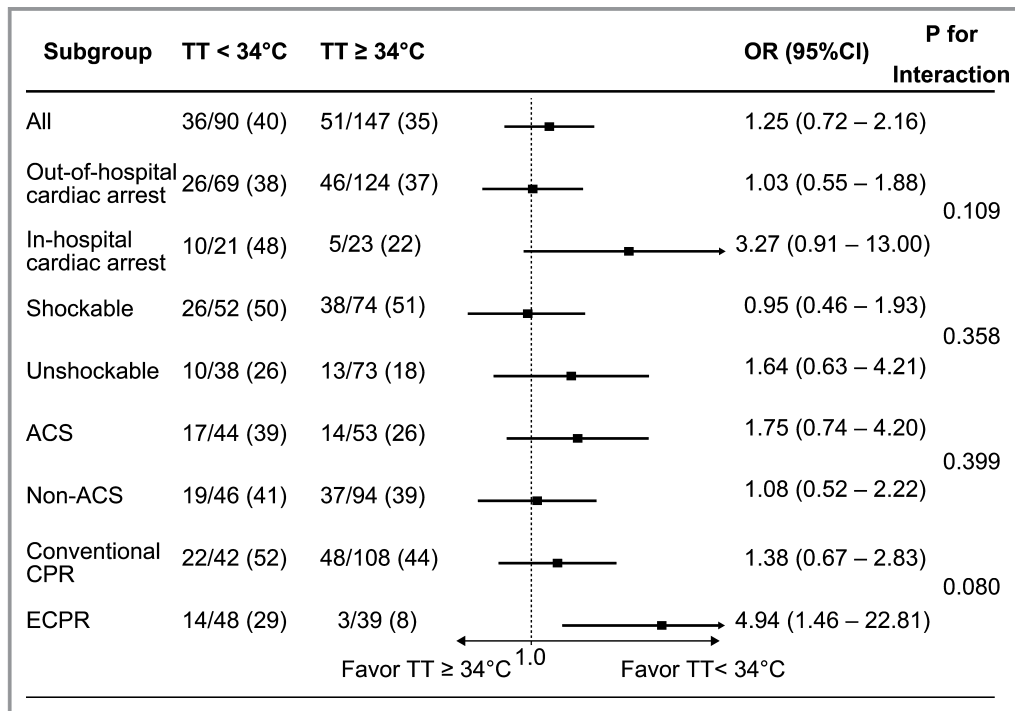| Subgroup	TT < 34°C	TT ≥ 34°C	OR (95%CI)	P for Interaction
All	36/90 (40)	51/147 (35)	1.25 (0.72 – 2.16)	
Out-of-hospital cardiac arrest	26/69 (38)	46/124 (37)	1.03 (0.55 – 1.88)	0.109
In-hospital cardiac arrest	10/21 (48)	5/23 (22)	3.27 (0.91 – 13.00)	
Shockable	26/52 (50)	38/74 (51)	0.95 (0.46 – 1.93)	0.358
Unshockable	10/38 (26)	13/73 (18)	1.64 (0.63 – 4.21)	
ACS	17/44 (39)	14/53 (26)	1.75 (0.74 – 4.20)	0.399
Non-ACS	19/46 (41)	37/94 (39)	1.08 (0.52 – 2.22)	
Conventional CPR	22/42 (52)	48/108 (44)	1.38 (0.67 – 2.83)	0.080
ECPR	14/48 (29)	3/39 (8)	4.94 (1.46 – 22.81)	

Favor TT ≥ 34°C — 1.0 — Favor TT< 34°C

Figure 3. Odds ratio of favorable outcomes of TT <34°C or ≥34°C in the subgroups. The odds ratios were evaluated using a univariable logistic regression. Patients with out-of-hospital cardiac arrest, in-hospital cardiac arrest, shockable initial recorded rhythms, unshockable initial recorded rhythms, acute coronary syndrome, nonacute coronary syndrome, conventional cardiopulmonary resuscitation, and extracorporeal cardiopulmonary resuscitation were included in the subgroups. ACS indicates acute coronary syndrome; ECPR, extracorporeal cardiopulmonary resuscitation; OR, odds ratio; TT, target temperature.

Table 6. Univariable Analysis for Favorable Outcomes

	Univariable			Multivariable		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
All patients (n=237)						
Age ≥55 y	0.50	0.28 to 0.87	0.015	0.53	0.26 to 1.07	0.078
Initial recorded rhythm was shockable	3.95	2.24 to 7.14	<0.001	2.59	1.31 to 5.19	0.006
Out-of-hospital cardiac arrest	1.15	0.59 to 2.34	0.689			
Acute coronary syndrome	0.70	0.41 to 1.21	0.205			
Cardiac arrest to CPR ≥5 min	0.93	0.55 to 1.57	0.777			
Cardiac arrest to ROSC ≥32 min	0.11	0.06 to 0.21	<0.001	0.16	0.08 to 0.30	<0.001
ROSC to 34°C ≥167 min	5.49	3.11 to 9.89	<0.001	4.07	1.86 to 9.22	<0.001
Protocol of targeted temperature management						
Target temperature <34°C	1.25	0.73 to 2.16	0.412	1.80	0.86 to 3.85	0.120
Duration of cooling ≥28 h	1.57	0.89 to 2.75	0.115	3.20	0.37 to 70.83	0.312
Duration of rewarming ≥28 h	1.28	0.73 to 2.22	0.393	5.13	0.61 to 113.23	0.142
The late period (after 2009)	0.42	0.24 to 0.72	0.002	0.72	0.30 to 1.75	0.467

CPR indicates cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

improved outcomes.[30] On the other hand, Haugk et al reported that a faster decline in body temperature to 34°C was associated with unfavorable outcomes.[31] Though it seems contradictory, this discrepancy may be caused by the patient populations and the cooling methods used in the studies. Preserved homeostasis may act to better maintain body temperature in patients whose neurological injuries are minor and who had favorable outcomes, resulting in a delay to the TT. The patients in the study by Haugk et al were cooled by using nonextracorporeal cooling methods, and the median duration from ROSC to 34°C was 144 minutes. On the other hand, ECMO and its attached heat exchanger could provide faster cooling and easy and precise temperature control.[32] One-half of the patients in Nagao et al's study were cooled by cold infusion and ECMO, and their duration from the initiation of ECMO to 34°C was ≈30 minutes less than that of Haugk et al's study. In Nagao et al's study, the difference of the time to TT between patients with and without favorable outcomes might be relatively small due to powerful cooling by ECMO, and the major differences between the times to TT were

based on the timing of initiation of cooling between post-ROSC cooling and intra-arrest cooling. Our study supports both results. Recent studies reported that the early attainment of hypothermia did not result in favorable outcomes in patients treated with or without prehospital cooling under conventional CPR.[33] We were able to generate a hypothesis that the early attainment of TT could result in more favorable outcomes with ECPR but not with conventional CPR.

Possible explanations, implications, and hypotheses for clinicians and future trials from this study are that optimal durations of cooling in TTM may be <28 hours. In patients treated with conventional CPR, TTs <34°C and ≥34°C may provide similar outcomes, and if extrapolated from the report by Nielsen et al, the optimal TT may be 36°C[24]; however, in selected patients such those treated with ECPR, this study could generate a hypothesis that TTs <34°C provide improved outcomes, and the optimal TT may be different according to the patient conditions after cardiac arrest. Can what was old be new again? Randomized controlled trials are necessary to clarify these issues. We calculated that forthcoming random-

Table 7. Complications During the First 7 Days After Cardiac Arrest

	Target Temperature Protocol			Cooling Duration Protocol			Rewarming Duration Protocol		
	<34°C (n=90)	≥34°C (n=147)	*P* Value	<28 hours (n=162)	≥28 hours (n=75)	*P* Value	<28 hours (n=158)	≥28 hours (n=79)	*P* Value
Lethal arrhythmia	14 (16)	16 (11)	0.294	15 (9)	15 (20)	0.021	12 (8)	18 (23)	<0.001
Pneumonia	25 (28)	37 (25)	0.658	31 (19)	31 (41)	<0.001	29 (18)	33 (42)	<0.001
Bleeding	48 (53)	45 (31)	<0.001	62 (38)	31 (41)	0.654	60 (38)	33 (42)	0.573

Data are presented as number (%) of patients.

ized trials would need to enroll 100 patients in each group to have 80% power to show favorable outcomes 15% higher in the TT <34°C group than those in the TT ≥34°C group with a 2-sided α level of 0.05, assuming that the frequency of favorable outcomes at TTs <34°C is 25%.

Limitations

This study was a nonrandomized controlled study and had the inherent limitations of any observational investigation. The study was prone to biases related to unmeasured factors. The TTs and durations were decided at the time of initiation of TTM by the treating physicians, and there could be selection biases, such as longer durations of cooling or lower TTs for patients treated with prolonged resuscitation. However, the baseline characteristics, such as time interval from collapse to ROSC, of the study patients were similar between the TT and duration subsets, and the severity of illness might not affect the discretion of the treating physicians. Patient selection for ECPR might have the potential to include selection biases, but the choice of protocols for TTM and selection of candidates for ECPR were different, while the baseline characteristics in patients treated with ECMO were similar (Table 5).

Conclusions

Prolonged cooling and rewarming durations ≥28 hours were not associated with improved outcomes and were associated with higher rates of lethal arrhythmia and pneumonia. TTs <34°C were not associated with improved outcomes and were associated with a higher prevalence of bleeding in patients treated with conventional CPR. However, TTs <34°C may be beneficial for patients who were CPR nonresponders and were treated with ECPR. On the basis of these findings, randomized studies are needed to answer the question of whether we should turn down the thermostat in patients treated with ECPR.

Acknowledgments

Disclosures

None.

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