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Rapid rewarming rate associated with favorable neurological outcomes in patients with post–cardiac arrest syndrome patients treated with targeted temperature management

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Abstract

Aim: To determine whether the rewarming rate is associated with neurological outcomes in patients with post–cardiac arrest syndrome treated with targeted temperature management (TTM) at 34°C.

Methods: We conducted a retrospective analysis of a nationwide cohort study of out-of-hospital cardiac arrest in Japan. Adult patients who experienced a return of spontaneous circulation and completed TTM at 34°C between June 2014 and December 2019 were divided equally into three groups (slow, moderate, and rapid) according to their rewarming rates from 34°C to 36°C. The rates of favorable neurological outcomes (Cerebral Performance Category of 1–2 after 30 days) were compared among the groups, and the adjusted odds ratios for a favorable neurological outcome were calculated for the groups.

Results: We analyzed 348, 357, and 358 patients in the slow, moderate, and rapid groups, respectively. The periods of rewarming from 34°C to 36°C were 41.9 ± 10.5, 22.4 ± 1.8, and 12.2 ± 3.6 h, respectively. The number of favorable neurological outcomes after 30 days was 121 (34.8%), 125 (35.0%), and 147 (41.1%), respectively, with no significant differences among the three groups ($p = 0.145$). Rapid rewarming was independently associated with a favorable neurological outcome compared with slow rewarming (adjusted odds ratio 1.57 [95% confidence interval 1.04–2.37]; $p = 0.031$).

Conclusions: Rapid rewarming after TTM at 34°C was associated with a more favorable neurological outcome than slow rewarming.

KEYWORDS
complication, neurological outcome, post–cardiac arrest syndrome (PCAS), rewarming rate, targeted temperature management

INTRODUCTION

Although several randomized controlled trials (RCTs) have been conducted in recent years to evaluate the efficacy of targeted temperature management (TTM), including therapeutic hypothermia, in patients with post–cardiac arrest syndrome (PCAS),[1–5] there is also an interest in the rate of rewarming after therapeutic hypothermia, and several RCTs have been conducted.[6–8] As the European Resuscitation Council guidelines once recommended a slow rewarming rate of 0.25–0.5°C/h,[9,10] this rate has been investigated in these and many other RCTs.[1–8] Bouwes et al[6] showed that rewarming rates faster than 0.5°C/h were associated with worse neurological outcomes for patients with PCAS, but a subsequent RCT reported no difference in outcomes between rewarming rates of 0.15 and 0.25°C/h.[7]

Several animal studies have shown that slow rewarming rates have a neuroprotective effect,[11–16] and slow rewarming (such as at 1.0°C/day) has long been considered to exert a neuroprotective effect and is generally used in Japan.[17] Slow rewarming was also applied in a previous RCT of hypothermia for severe traumatic brain injury in Japan,[18] and a secondary analysis reported that longer rewarming times were associated with better neurological outcomes.[19] Hifumi et al[20] showed that a longer rewarming time (median 44 h from 34°C to 36°C) after therapeutic hypothermia in patients with PCAS with cardiogenic causes was associated with better neurological outcomes. However, they noted that the sample size was small and that it was an observational study, so further verification was desirable.[21]

The purpose of the present study was to determine whether the rewarming rate, including the traditional Japanese slow rewarming rate, is associated with the neurological outcome and the occurrence of complications in patients with PCAS treated with TTM at 34°C, using the data from the Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest (JAAM-OHCA) Registry, a nationwide multicenter prospective cohort in Japan.[22]

METHODS

Study design

This study was a retrospective analysis of data from the JAAM-OHCA Registry, a nationwide multicenter prospective cohort in Japan.[22] This prospective multicenter cohort included patients with out-of-hospital cardiac arrest (OHCA) transferred directly to 101 hospitals in Japan. The registry included only patients who had sustained cardiac arrest in a prehospital setting, for whom resuscitation had been attempted, and who had been transported to a participating institution. The registry excluded patients with OHCA who did not receive cardiopulmonary resuscitation (CPR) by a physician, those who suffered in-hospital cardiac arrest, and those who refused to participate in the registry, either personally or through family members. The registry was approved by the ethics committees of each participating institution.

Data collection

The data from the JAAM-OHCA Registry included prehospital resuscitation data obtained from the All-Japan Utstein Registry of the Fire and Disaster Management Agency of Japan and in-hospital data collected prospectively by each institution participating in the JAAM-OHCA Registry. From these data sets, we obtained the following data: age, sex, cause of arrest, witness of collapse, layperson bystander CPR, documented initial rhythm, time course of resuscitation including time from collapse to return of spontaneous circulation (ROSC; ROSC time), Glasgow Coma Scale (GCS) score at ROSC, data from arterial blood gas analysis at ROSC, treatment details including TTM, and outcome. The outcome included the Glasgow–Pittsburgh Cerebral Performance Category (CPC) after 30 days and any complications of TTM. We defined a favorable neurological outcome as a CPC score of 1–2 after 30 days.

Participants

For this analysis, we analyzed data for patients aged 18 years or older who experienced ROSC and completed TTM at 34°C between June 2014 and December 2019. TTM was performed according to the protocols used at each institution, including the duration maintained at 34°C and the rate of rewarming from 34°C to 36°C. Patients whose rewarming rates were outliers were excluded. The upper and lower limits for an outlier were set at 1.5 times the interquartile range. After excluding the outliers and visually inspecting the data distribution, the eligible patients were divided equally into three groups according to their rewarming rates from 34°C to 36°C: the slow, moderate, and rapid groups.

Statistical analysis

The background characteristics, types of treatment, and outcomes of the patients were compared among the three groups. Variables are shown as means ± standard deviations or numbers (percentages). Univariate analyses employed an χ^2 test for categorical variables and a one-way analysis of variance for continuous variables. Multivariable logistic regression analyses were performed to determine the adjusted odds ratios (ORs) for a favorable neurological outcome in the rapid and moderate groups compared with the slow group by using all data from the rapid, moderate, and slow groups. Variables used for adjustment included age, sex, cause of cardiac arrest, initial rhythm on electrocardiography (ECG), bystander CPR, witness/ROSC time, GCS score, pH, partial oxygen pressure, partial carbon dioxide pressure, lactate, glucose, use of percutaneous cardiopulmonary support, time from the start of cooling to 34°C, and duration maintained at 34°C. The same multivariable analyses were performed in subgroups divided according to sex, age, cause of cardiac arrest, initial rhythm on ECG, bystander CPR, and severity based on the revised post–Cardiac Arrest Syndrome for Therapeutic Hypothermia (rCAST) score.[23] A p value <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows version 22.0 (IBM, New York, NY).

RESULTS

Patients and their characteristics

Of the 1319 patients aged 18 years or older who completed TTM at 34°C, 1063 were analyzed in the present study (Figure 1). The major reason for exclusion was a lack of data. As the median rewarming rate and interquartile range were 0.095 and 0.070–0.174°C/h, respectively, among the patients included, 122 patients for whom the rewarming rate was >0.32875°C/h were excluded. Patients with rewarming rates of ≤0.0831°C/h, 0.0833–0.1180°C/h, and 0.1180–0.32875°C/h were assigned to the slow, moderate, and rapid groups, respectively.

The background characteristics of the patients in the three groups are shown in Table 1. Overall, the patients were 60 ± 16 years old, and 828 patients (77.9%) were male. The

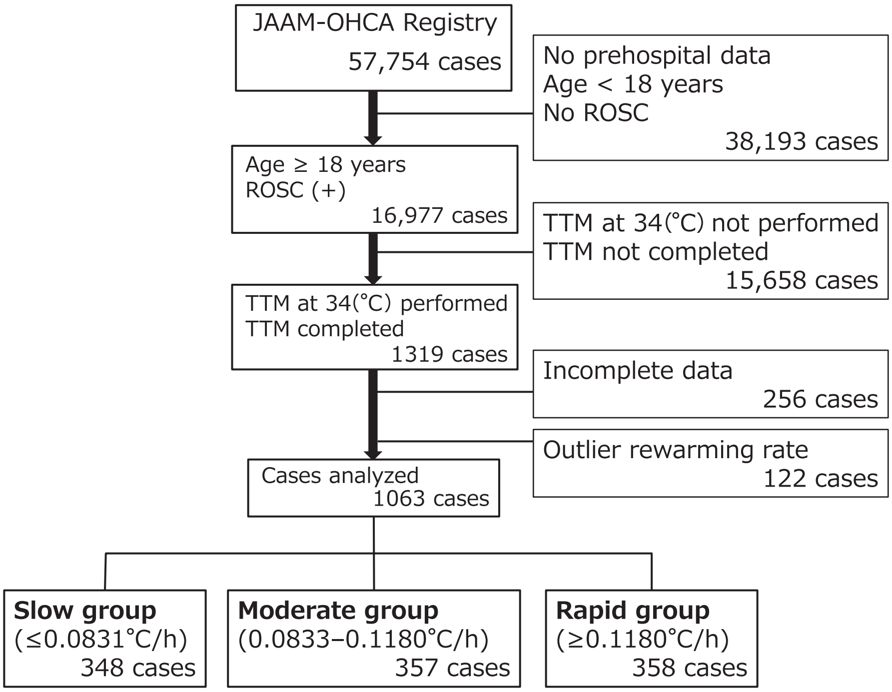

FIGURE 1 Patient selection flow chart. JAAM-OHCA, Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

TABLE 1 Patient characteristics.

	Slow group (n = 348)	Moderate group (n = 357)	Rapid group (n = 358)	p value
Age	61 ± 16	61 ± 15	59 ± 16	0.078
Sex, male, n (%)	277 (79.6)	281 (78.7)	270 (75.4)	0.372
Glasgow Coma Scale score at ROSC	3.5 ± 1.4	3.5 ± 1.5	3.4 ± 1.2	0.568
Blood gas analysis at ROSC				
pH	7.10 ± 0.21	7.09 ± 0.21	7.10 ± 0.21	0.743
$PaCO_2$ (mmHg)	58 ± 32	61 ± 31	59 ± 31	0.576
PaO_2 (mmHg)	210 ± 153	218 ± 168	214 ± 160	0.788
HCO_3^- (mmol/L)	16.2 ± 5.0	16.4 ± 5.2	16.4 ± 6.1	0.829
Lactate (mmol/L)	9.5 ± 4.8	9.8 ± 6.4	10.1 ± 4.8	0.358
Glucose (mg/dL)	277 ± 104	269 ± 95	273 ± 92	0.614
Witness, n (%)	262 (75.3)	263 (73.7)	281 (78.5)	0.306
Bystander CPR, n (%)	192 (55.2)	183 (51.3)	186 (52.0)	0.541
Cardiogenic, n (%)	275 (79.0)	283 (79.3)	284 (79.3)	0.994
Initial ECG, shockable, n (%)	210 (60.3)	210 (58.8)	227 (63.4)	0.440
ROSC time (min)	34 ± 26	32 ± 25	33 ± 30	0.754
rCAST score	11.1 ± 4.5	11.5 ± 4.7	11.4 ± 4.2	0.481

Abbreviations: CPR, cardiopulmonary resuscitation; ECG, electrocardiography; HCO, bicarbonate; $PaCO_2$, partial carbon dioxide pressure; PaO_2, partial oxygen pressure; rCAST, revised post–Cardiac Arrest Syndrome for Therapeutic Hypothermia; ROSC, return of spontaneous circulation.

Variables are shown as means ± standard deviations or numbers (percentages).

cardiac arrest of 806 patients (75.6%) was witnessed and 561 patients (52.8%) were provided with bystander CPR. The cause of cardiac arrest was diagnosed as cardiogenic in 842 patients (79.2%), and the initial ECG showed a shockable rhythm in 647 patients (60.9%). The mean ROSC time was 33 ± 27 min. These background characteristics did not differ significantly among the slow, moderate, and rapid groups, including GCS at ROSC, data from an arterial blood gas analysis, and glucose levels. The mean rCAST score was 11.3 ± 4.5, indicating moderate severity,[23] and did not differ significantly among the three groups.

Details of therapeutic interventions, including TTM at 34°C

Details of the therapeutic interventions, including TTM, in each group are shown in Table 2. Percutaneous cardiopulmonary support was applied to 77 (22.1%), 102 (28.6%), and 87 (24.3%) patients in the slow, moderate, and rapid groups, respectively. The use of intra-aortic balloon pumping differed among the three groups: 106 (30.5%), 136 (3.81%), and 106 (29.6%) patients in the slow, moderate, and rapid groups, respectively ($p = 0.030$). In total, coronary angiography and percutaneous coronary intervention were performed on 688 patients (64.7%) and 323 patients (30.4%), respectively, and the differences in coronary angiography and percutaneous coronary intervention among the three groups were not significant.

For TTM at 34°C, the time from the start of cooling until 34°C was significantly different among the three groups (4.8 ± 6.8 h, 3.4 ± 4.5 h, and 4.0 ± 4.8 h in the slow, moderate, and rapid groups, respectively; $p = 0.003$). The mean period of maintenance at 34°C was 24.5 ± 9.9 h in all patients and did not differ significantly among the three groups. The periods

TABLE 2 Details of therapeutic interventions, including targeted temperature management, in each group.

	Slow group ($n = 348$)	Moderate group ($n = 357$)	Rapid group ($n = 358$)	p value
PCPS, n (%)	77 (22.1)	102 (28.6)	87 (24.3)	0.134
IABP, n (%)	106 (30.5)	136 (38.1)	106 (29.6)	0.030
CAG, n (%)	220 (63.2)	237 (66.4)	231 (64.5)	0.675
PCI, n (%)	101 (29.0)	118 (33.1)	104 (29.1)	0.408
Time from the start of cooling to 34°C (h)	4.8 ± 6.8	3.4 ± 4.5	4.0 ± 4.8	0.003
Duration maintained at 34°C (h)	23.9 ± 12.3	25.3 ± 8.1	24.4 ± 9.0	0.184
Duration of rewarming from 36°C (h)	41.9 ± 10.5	22.4 ± 1.8	12.2 ± 3.6	<0.001
Gastric cooling, n (%)	33 (10.2)	30 (8.9)	46 (13.4)	0.165
Cooling infusion, n (%)	108 (33.1)	137 (39.9)	177 (51.3)	<0.001
Surface cooling, n (%)	218 (67.1)	243 (70.2)	251 (73.0)	0.251
Intravascular cooling, n (%)	70 (20.9)	35 (10.3)	49 (14.3)	0.001
Extracorporeal heat exchanger, n (%)	72 (22.0)	84 (24.5)	61 (17.7)	0.089

Abbreviations: CAG, coronary angiography; IABP, intra-aortic balloon pumping; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support. Variables are shown as means ± standard deviations or numbers (percentages).

TABLE 3 Neurological outcomes after 30 days, and complications during targeted temperature management.

	Slow group ($n = 348$)	Moderate group ($n = 357$)	Rapid group ($n = 358$)	p value
Favorable neurological outcome after 30 days, n (%)	121 (34.8)	125 (35.0)	147 (41.1)	0.145
Cerebral Performance Category score after 30 days, n (%)				0.068
1	83 (23.9)	97 (27.2)	114 (31.8)	
2	38 (10.9)	28 (7.8)	33 (9.2)	
3	46 (13.2)	35 (9.8)	32 (8.9)	
4	78 (22.4)	102 (28.6)	75 (20.9)	
5	103 (29.6)	95 (26.6)	104 (29.1)	
Complications of targeted temperature management, n (%)	44 (16.1)	41 (16.1)	45 (15.5)	0.974
Bleeding, n (%)	10 (5.9)	8 (5.9)	12 (6.4)	0.977
Hypotension, n (%)	16 (9.4)	15 (11.0)	27 (14.4)	0.335
Arrhythmia, n (%)	12 (7.1)	7 (5.1)	17 (9.1)	0.392
Hyperglycemia, n (%)	7 (4.1)	7 (5.1)	13 (6.9)	0.500
Infection, n (%)	15 (8.8)	25 (18.4)	14 (7.4)	0.007
Electrolyte imbalance, n (%)	12 (7.1)	15 (11.0)	32 (16.9)	0.014

Variables are shown as numbers (percentages).

of rewarming from 34°C to 36°C were 41.9 ± 10.5, 22.4 ± 1.8, and 12.2 ± 3.6 h in the slow, moderate, and rapid groups, respectively. For the cooling method, the frequencies of gastric cooling, surface cooling, and extracorporeal heat exchanger did not differ significantly among the three groups. Cooling infusion was most frequently used in the rapid group (108 patients [33.1%] in the slow group, 137 patients [39.9%] in the moderate group, and 177 patients [51.3%] in the rapid group; $p < 0.001$), whereas intravascular cooling was most frequently used in the slow group (70 patients [20.9%] in the slow group, 35 patients [10.3%] in the moderate group, and 49 patients [14.3%] in the rapid group; $p = 0.001$).

Neurological outcomes and their associations with rewarming rate

Neurological outcomes after 30 days and the complications during TTM are shown in Table 3. The numbers of patients with favorable neurological outcomes after 30 days were 121 (34.8%), 125 (35.0%), and 147 (41.1%) in the slow, moderate, and rapid groups, respectively, and the differences among the three groups were not significant ($p = 0.145$). There tended to be more patients with a CPC score of 1 in the rapid group than in the slow group (31.8% vs. 23.9%, respectively; $p = 0.068$).

Complications during TTM occurred in 44 (16.1%), 41 (16.1%), and 45 (15.5%) patients in the slow, moderate, and rapid groups, respectively, and the differences among the three groups were not significant ($p = 0.974$). The frequency of bleeding, hypotension, arrhythmia, and hyperglycemia did not differ significantly among the three groups. The incidence of infection was highest in the moderate group (15 patients [8.8%] in the slow group, 25 patients [18.4%] in the moderate group, and 14 patients [7.4%] in the rapid group; $p = 0.007$), and that of electrolyte imbalance was highest in the rapid group (12 patients [7.1%] in the slow group, 15 patients [11.0%] in the moderate group, and 32 patients [16.9%] in the rapid group; $p = 0.014$).

The results of multiple logistic regression analysis for a favorable neurological outcome are shown in Table 4. The adjusted OR for a favorable neurological outcome for the rapid group compared with the slow group was 1.57 (95% confidence interval [CI] 1.04–2.37]; $p = 0.031$), whereas that for the moderate group compared with the slow group was 1.276 (95% CI 0.841–1.935; $p = 0.252$).

A subgroup analysis of the adjusted OR for a favorable neurological outcome in the rapid group compared with the slow group is shown in Figure 2A. In the subgroup analysis, rapid rewarming was preferable to slow rewarming in the subgroups of patients who were male (adjusted OR 1.88 [95% CI 1.18–3.00]; $p = 0.008$), aged <65 years (adjusted OR 1.91 [95% CI 1.10–3.32]; $p = 0.022$), had a cardiogenic cause (adjusted OR 1.65 [95% CI 1.06–2.57]; $p = 0.026$), had an initial shockable rhythm (adjusted OR 1.83 [95% CI 1.12–2.98]; $p = 0.015$), underwent bystander CPR (+) (adjusted OR 1.90 [95% CI 1.05–3.42]; $p = 0.032$), or had a moderate rCAST score (adjusted OR 1.78 [95% CI 1.09–2.92]; $p = 0.021$).

The subgroup analyses of the adjusted OR for a favorable neurological outcome in the moderate group compared with the slow group are shown in Figure 2B. These analyses revealed that no subgroups were associated with a favorable neurological outcome.

TABLE 4 Multivariable logistic regression analysis for a favorable neurological outcome.

Variables	OR	95% CI	*p* value
Slow group	Reference	Reference	Reference
Moderate group	1.276	0.841–1.935	0.252
Rapid group	1.570	1.042–2.365	0.031
Age	0.961	0.949–0.972	<0.001
Sex, male	1.009	0.654–1.558	0.967
Cardiogenic cause	2.688	1.465–4.931	0.001
Shockable rhythm	4.323	2.768–6.751	<0.001
Bystander CPR (+)	1.800	1.284–2.523	0.001
Witness (−) with ROSC time >20 min	Reference	Reference	Reference
Witness (+)	3.023	1.891–4.831	<0.001
Witness (−) with ROSC time <20 min	1.014	0.665–1.547	0.948
GCS	1.272	1.104–1.466	0.001
Blood gas analysis at ROSC			
pH	3.695	0.867–15.754	0.077
PaO_2 (mmHg)	0.999	0.998–1.000	0.142
$PaCO_2$ (mmHg)	0.984	0.974–0.994	0.002
Lactate (mmol/L)	1.000	0.996–1.004	0.916
Glucose (mg/dL)	0.998	0.996–1.000	0.028
PCPS (+)	0.286	0.186–0.438	<0.001
Time from the start of cooling to 34°C (h)	1.000	1.000–1.001	0.262
Duration maintained at 34°C (h)	1.000	1.000–1.000	0.915

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; OR, odds ratio; $PaCO_2$, partial carbon dioxide pressure; PCPS, percutaneous cardiopulmonary support; ROSC, return of spontaneous circulation.

DISCUSSION

In this study, rapid rewarming was more closely associated with a favorable neurological outcome 30 days after patients with PCAS were treated with TTM at 34°C than slow rewarming. However, rapid rewarming was associated with more instances of hypotension and electrolyte abnormalities than slow rewarming.

In this study, rapid rewarming was associated with better neurological outcomes than slow rewarming, which is

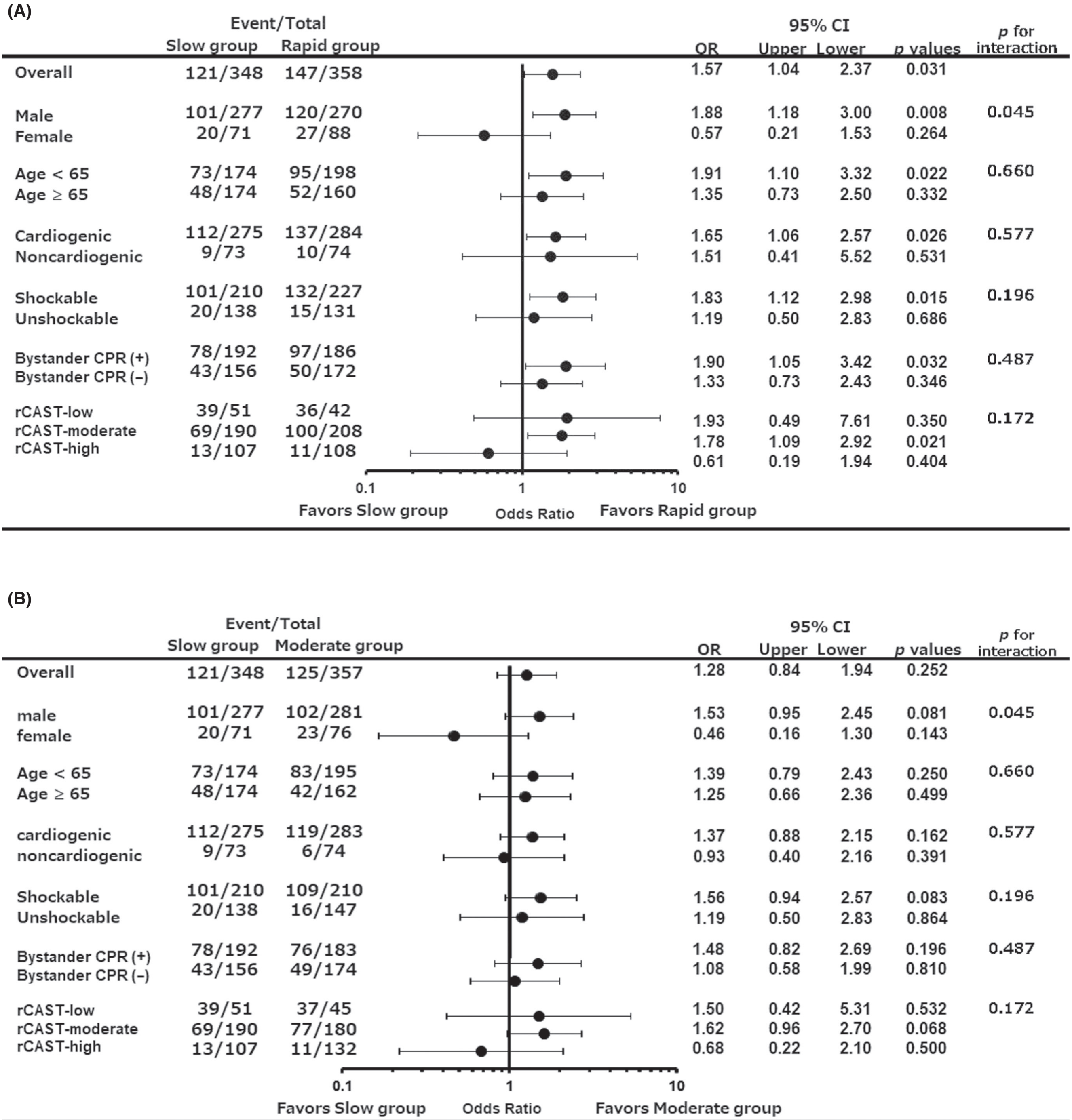

FIGURE 2 Results of subgroup analyses for a favorable neurological outcome. Multivariable logistic regression analyses were performed to determine the adjusted ORs for a favorable neurological outcome in the rapid and moderate groups compared with the slow group using all data from the rapid, moderate, and slow groups. Subgroups were defined according to sex, age (<65 or ≥65 years), cause of cardiac arrest, initial rhythm, layperson bystander CPR, and rCAST score. Adjustments were made for sex, age, cause of cardiac arrest, initial rhythm, bystander CPR, witness/ROSC time, Glasgow Coma Scale score, pH, partial oxygen pressure, partial carbon dioxide pressure, lactate, glucose, use of percutaneous cardiopulmonary support, time from the start of cooling to 34°C, and duration maintained at 34°C. Values of *p* for interaction were calculated in each subgroup, including data from the rapid, moderate, and slow groups. (A) Influence of rapid rewarming compared with slow rewarming on favorable neurological outcomes in patient subgroups. (B) Influence of moderate rewarming compared with slow rewarming on favorable neurological outcomes in patient subgroups. CI, confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; rCAST, revised post–Cardiac Arrest Syndrome for Therapeutic Hypothermia; ROSC, return of spontaneous circulation.

traditionally used in Japan.[17,18] The rate of rewarming investigated in previous RCTs was the rate of rewarming used in the rapid group in the present study,[6–8] but no RCTs have examined slower rates, such as that used in the slow group in this study. In an observational study from Japan similar to the present study, Hifumi et al[20] reported results contrary to ours, that is, a longer period of rewarming was associated with a better neurological outcome in patients with cardiogenic PCAS who underwent TTM at 34°C, with a median rewarming period of 44 h (interquartile range 24–50 h). The study by Hifumi and colleagues included only patients with cardiogenic PCAS, whereas our study included patients with both cardiogenic and noncardiogenic PCAS. However, rapid rewarming was associated with better neurological outcomes in the present study, even in the subgroup of patients with a cardiogenic cause (Figure 2A). The reasons for the different results are not clear, but one possible explanation is that the duration of the study and the number of participating institutions differed between our study and that by Hifumi et al.[20] The study by Hifumi et al was conducted between 2005 and 2011 and only 14 institutions participated, whereas our study used data collected between 2014 and 2019 from 101 institutions. It is possible that differences in the protocols between institutions and differences in treatment strategies for TTM between our study and that by Hifumi et al may be due to the different times at which the studies were conducted.

In our study, a rapid rewarming rate was associated with better outcomes, especially in the subgroup of patients with a cardiogenic cause (Figure 2A). Slow rewarming is thought to be neuroprotective, as rapid rewarming was reported to exacerbate brain injury in several animal models of traumatic brain injury by exacerbating cerebral contusions,[11] axonal injuries,[12,13] and microvascular damage and dysfunction.[14] In the rodent temporary middle cerebral artery occlusion model, slow rewarming after hypothermia was reported to have a neuroprotective effect by reducing the extent of infarction compared with rapid rewarming.[15] Regarding TTM itself, therapeutic hypothermia, such as TTM at 33°C, has not been shown to be superior to normothermia in cardiogenic PCAS, which is considered to have a relatively good prognosis.[3,5] However, therapeutic hypothermia at 33°C was reported to improve the functional outcome at 90 days compared with normothermia in a study of patients with PCAS with nonshockable rhythm, which is a severe condition.[4] Considering these results, it seems possible that patients with a cardiogenic cause who do not show advantages of therapeutic hypothermia have less brain damage and are less likely to experience the deterioration that might be caused by rapid rewarming. Furthermore, rapid rewarming was associated with improved outcomes in patients with a cardiogenic cause, and in the following subgroups: males, <65 years, shockable rhythm, and bystander CPR (+) (Figure 2A). Therefore, this explanation may also be true for these subgroups.

Other unmeasured confounding factors may also exist. For example, we cannot exclude the possibility that the rapid group in this study included patients whose prognoses only became clear during rewarming (e.g., improved level of consciousness) and were then rewarmed promptly because the TTM protocol, including the rate of rewarming, was not fixed and was chosen at the discretion of each institution. Therefore, further RCTs are required to clarify the impact of the very slow rate of rewarming traditionally practiced in Japan on the outcome of patients with PCAS treated with TTM.

In this study, there was no increase in the total incidence of complications in the slow group (Table 3); even in the study by Hifumi et al,[20] a longer rewarming period was not associated with increased complications. These findings may suggest that complications based on slow rewarming are reduced by quality TTM management. However, rapid rewarming resulted in more cases of hypotension and electrolyte abnormalities in the present study (Table 3). Rapid rewarming may cause redistributive hypotension arising from vasodilation and rebound hyperkalemia because the renal excretion of potassium is inadequate.[24] Therefore, rapid rewarming is associated with a favorable neurological outcome, but caution must be exercised because hypotension and electrolyte abnormalities are still possible.

This study had several limitations. First, it is possible that a faster rewarming rate was selected in patients predicted to have a more favorable outcome. The reverse is also possible, and a slower rewarming rate may have been selected for patients expected to have poorer outcomes. Second, the rate of rewarming was calculated from the start and end of the rewarming period as a constant rate, but the actual rate of rewarming during the whole process is unknown because the actual protocol differs at each institution. Furthermore, no data were available on temperature control after the completion of rewarming. Third, it is unclear whether the difference in the frequency of complications due to TTM is related to the direct effects of the rate of rewarming itself or indirectly to differences in treatment strategies, including the rate of rewarming. Furthermore, this study did not include data on the timing of complications, and the relationship with the time of onset was unknown.

CONCLUSIONS

Rapid rewarming after TTM at 34°C was associated with a more favorable neurological outcome than slow rewarming. However, rapid rewarming was associated with more cases of hypotension and electrolyte abnormalities.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

JAAM-OHCA registration data belong to JAAM and are not available to the public.

ETHICS STATEMENT

Approval of the research protocol: This study was approved by the Ethics Committee of Kyoto University, as the corresponding institution. All participating hospitals, including

Yamaguchi University Hospital, approved the JAAM-OHCA Registry protocol.
Informed consent: The requirement for informed consent of patients was waived.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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