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Factors Associated With Rebound Hyperthermia After Targeted Temperature Management in Out-of-Hospital Cardiac Arrest Patients: An Explorative Substudy of the Time-Differentiated Therapeutic Hypothermia in Out-of-Hospital Cardiac Arrest Survivors Trial

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OBJECTIVES: To investigate rebound hyperthermia following targeted temperature management after cardiac arrest and its impact on functional outcome.

DESIGN: Post hoc analysis.

SETTING: Ten European ICUs.

PATIENTS: Patients included in the time-differentiated therapeutic hypothermia in out-of-hospital cardiac arrest survivors trial treated with targeted temperature management at 33°C for 48 or 24 hours. Favorable functional outcome was defined as a Cerebral Performance Category of 1 or 2 at 6 months.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of 338 included patients, 103 (30%) experienced rebound hyperthermia defined as a maximum temperature after targeted temperature management and rewarming exceeding 38.5°C. Using multivariate logistic regression analysis, increasing age (odds ratio, 0.97; 95% CI, 0.95–0.99; $p = 0.02$) and severe acute kidney injury within 72 hours of ICU admission (odds ratio, 0.35; 95% CI, 0.13–0.91; $p = 0.03$) were associated with less rebound hyperthermia, whereas male gender (odds ratio, 3.94; 95% CI, 1.34–11.57; $p = 0.01$), highest C-reactive protein value (odds ratio, 1.04; 95% CI, 1.01–1.07; $p = 0.02$), and use of mechanical chest compression during cardiopulmonary resuscitation (odds ratio, 2.00; 95% CI, 1.10–3.67; $p = 0.02$) were associated with more rebound hyperthermia. Patients with favorable functional outcome spent less time after rewarming over 38.5°C (2.5% vs 6.3%; $p = 0.03$), 39°C (0.14% vs 2.7%; $p < 0.01$), and 39.5°C (0.03% vs 0.71%; $p < 0.01$) when compared with others. Median time to rebound hyperthermia was longer in the unfavorable functional outcome group (33.2 hr; interquartile range, 14.3–53.0 hr vs 6.5 hr; interquartile range, 2.2–34.1; $p < 0.01$). In a predefined multivariate binary logistic regression model, rebound hyperthermia was associated with decreased odds of favorable functional outcome (odds ratio, 0.42; 95% CI, 0.22–0.79).

CONCLUSIONS: One-third of targeted temperature management patients experience rebound hyperthermia, and it is more common in younger male patients with an aggravated inflammatory response and those treated with a mechanical chest compression device. Later onset of rebound hyperthermia and temperatures exceeding 38.5°C associate with unfavorable outcome.

KEY WORDS: fever; out-of-hospital cardiac arrest; rebound hyperthermia; resuscitation; targeted temperature management

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Targeted temperature management (TTM) is a recommended treatment for out-of-hospital cardiac arrest (OHCA) (1). Rebound hyperthermia (RH) is a commonly observed phenomenon after cooling and guidelines recommend treating RH with antipyretics and active cooling (1–4). It is not known if RH causes or simply suggests a more severe anoxic brain injury, but studies have shown an association between fever and worse functional outcome (FO) and a lower survival after cardiac arrest (CA) (1, 5–11). Previous studies have reported diverse definitions for RH and have failed to demonstrate an unambiguous threshold value of temperature at which the risk of unfavorable outcome would be the highest (1–3, 10, 12). In addition, it is currently unknown whether certain patients are more likely to develop RH than others, even though the magnitude and timing of RH has been associated with FO in some studies (2, 3, 6, 10–14).

If the risk factors for RH and its clinical significance were better understood, patients who might benefit from longer controlled normothermia could be identified already during TTM. The primary aim of the current study was to determine the occurrence and factors associated with RH in patients treated with either standard (24 hr) (1) or prolonged (48 hr) duration of TTM at 33°C. Our secondary aim was to study associations between the development and timing of RH and functional long-term outcome in TTM patients.

MATERIALS AND METHODS

Study Population and Setting

This is a post hoc exploratory analysis of patients included in the time-differentiated therapeutic hypothermia in out-of-hospital cardiac arrest survivors (TTH48) trial (NCT01689077) (15). The protocol of the TTH48 study performed in 10 European ICUs has been described previously (16). The TTH48 study was approved by ethical committees and hospital boards at all study sites according to local practices. A full list of ethical and hospital approvals from all study sites is included in the **Supplementary Digital Content** (http://links.lww.com/CCX/A686). The inclusion criteria were age between 18 and 80 years, Glasgow Coma Scale of 8 or below, and a return of spontaneous circulation (ROSC) sustained for 20 minutes or longer prior to randomization. The exclusion criteria included: patients with terminal disease or a do-not-resuscitate order, ROSC delay over 60 minutes, systolic blood pressure less than 80 mm Hg, inhospital CA, persistent cardiogenic shock, acute stroke or intracerebral bleeding, acute coronary bypass surgery, severe coagulopathy, time from CA to cooling initiation of over 240 minutes, neurologic disease with cognitive impairment, and initial asystole following an unwitnessed OHCA. We selected patients who survived until normothermia and had temperature data collected after rewarming. Ethical and hospital approval of the TTH48 study was obtained at all sites (A list of the ethical approvals are included as a separate file in the Supplementary Digital Content, http://links.lww.com/CCX/A686).

Temperature Data and Outcomes

The study protocol mandated targeting a temperature of 33°C for 24 or 48 hours using intravascular or surface cooling and with rewarming at a rate of 0.5°C/hr until a temperature of 37°C was reached. Temperature was measured from the bladder, rectum, esophagus, or intravascular probes. The treating clinician could select to rewarm the patient to 36°C if the patient experienced severe complications. We defined RH as the occurrence of temperature exceeding 38.5°C after rewarming during ICU stay (2, 10, 12).

Demographic factors, data about ICU treatments, and laboratory findings were collected and compared between patient with and without RH. The magnitude of the inflammatory response included C-reactive protein (CRP) and WBC levels over time during ICU stay were compared in patients who experienced RH or not. Acute kidney injury severity within first 72 hours of ICU admission was evaluated using the Kidney Disease Improving Global Outcomes (KDIGO) classification (17).

The effect of the duration, magnitude, and time to RH on FO was studied with favorable FO defined as Cerebral Performance Category of 1 or 2 at 6 months. Time and area, defined as time multiplied by the difference between the threshold and actual value, spent over and under certain temperature thresholds as a percentage were compared between outcome groups. We studied the following threshold values over 37.5°C, 38°C, 38.5°C, 39°C, and 39.5° and under 37°C, 36.5°C, and 36°C. Analyses were performed separately for the first 72 hours after rewarming and for all the

measurements available after rewarming until ICU discharge.

Statistical Analysis

Categorical data are presented as counts and percentages and compared using the chi-square test. Continuous parameters were presented as medians (interquartile range [IQR]) and compared using the Mann-Whitney *U* test. Multivariable models were developed to identify the factors associated with RH. Variables were selected based on the presence of a *p* value of less than 0.20 in the univariate analysis. A second binary logistic regression analysis was conducted to determine the association of RH with FO at 6 months; this model included factors in the a priori-defined mortality model, that is, treatment center, age, gender, initial rhythm, ROSC delay, and bystander cardiopulmonary resuscitation (CPR). Patient temperatures were visualized using scatterplots with loess smoother curves separately for the patients with favorable FOs and the patients with unfavorable FOs. We compared temperatures over time in the patients with favorable and unfavorable FOs using a mixed linear model with compound symmetry as the covariance matrix accounting for repeated measurements and interaction between outcome group and time. The CRP and WBC for the first 100 hours after rewarming were also visualized using scatterplots with loess smoother curves. Different figures are presented for patients with and without RH. A *p* value of less than 0.05 was considered significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corporation, Armonk, NY).

RESULTS

Study Population

A total of 355 patients were randomized in the original TTH48 trial. Of these patients, 338 met the inclusion criteria and were therefore included in the study, inclusion flowchart is presented in **Supplemental Figure 1** (Supplemental Digital Content, http://links.lww.com/CCX/A684; legend, http://links.lww.com/CCX/A686). A total of 158,892 post-rewarm temperature measurements were obtained in the 338 patients, that is, a median of 115 (IQR, 30–679) measurements per patient. The median follow-up time was 182 days (IQR, 32–196 d) from randomization.

RH Prevalence and Predictors of RH

Of the 338 patients, 103 (30%) experienced RH. The patients who experienced RH were younger (median age, 59; IQR, 52–66 vs 64; IQR, 55–70; $p < 0.01$), taller (median, 180 cm; IQR, 175–185 cm vs 178 cm; IQR, 172–183 cm; $p = 0.03$), and more commonly male (93% vs 78%; $p < 0.01$). Length of ICU stay was not significantly different between patients that experienced RH and those that did not (median, 6 d; IQR, 4–9 d vs 5 d; IQR, 3–8; $p = 0.08$) (**Supplemental Table 1**, Supplemental Digital Content, http://links.lww.com/CCX/A685). Parameters at ICU admission are presented in **Supplemental Table 2** (Supplementary Digital Content, http://links.lww.com/CCX/A685). Of the patients who experienced RH, 8% had the highest KDIGO classification of 3 during the first 72 hours of ICU admission, compared with 16% of the patients in the group that did not experience RH ($p = 0.05$). The median highest ICU CRP measurement was 206 (IQR, 136–269) for the group that experienced RH and 163 (IQR, 112–240) for the group that did not experience RH ($p < 0.01$). The CRP measurements for the RH and the no RH groups are presented in **Supplemental Figures 4** and **5** (Supplemental Digital Content, http://links.lww.com/CCX/A684; legend, http://links.lww.com/CCX/A686). The CRP measurements for the RH and the no RH groups were separated for the different FO groups (**Supplemental Figs. 6–9**, Supplemental Digital Content, http://links.lww.com/CCX/A684; legend, http://links.lww.com/CCX/A686).

Results from ICU parameter analyses are presented in Supplemental Table 2 (Supplementary Digital Content, http://links.lww.com/CCX/A685). Highest measured ICU CRP was higher in the group that experienced RH (median, 163; IQR, 114–240 vs 206; IQR, 136–269; $p < 0.01$). There were no significant differences in the prevalence of pneumonia (47% vs 49%; $p = 0.95$), sepsis (7% vs 12%; $p = 0.18$), or other infections (35% vs 44%; $p = 0.09$) during hospital stay between the patient group that did not experience RH and the group that did. We found no significant difference in TTM duration between the groups (TTM for 24 hr 49% vs 52%; $p = 0.34$).

In the univariate analysis, age (odds ratio [OR], 0.97; 95% CI, 0.95–0.99; $p < 0.01$), male sex (OR, 3.51; 95% CI, 1.54–8.08; $p < 0.01$), height (OR, 1.04; 95% CI, 1.01–1.07; $p = 0.01$), use of a mechanical chest compression device (OR, 1.82; 95% CI, 1.09–3.05; $p = 0.02$), use of

TABLE 1.
Logistic Regression Model Predicting the Risk of Rebound Hyperthermia

Independent Variable	OR[a] in Univariate Analysis (95% CI)	*p*	OR[a] in Multivariate Analysis (95% CI)	*p*
Age (yr)	0.97 (0.95–0.99)	< 0.01	0.97 (0.95–1.00)	0.02
Male sex	3.51 (1.54–8.08)	< 0.01	3.94 (1.34–11.57)	0.01
Height (cm)	1.04 (1.01–1.07)	0.01	1.00 (0.96–1.04)	0.94
Previous percutaneous coronary intervention or coronary artery bypass graft	1.71 (0.86–3.39)	0.13	0.66 (0.30–1.46)	0.31
Mechanical chest compression used	1.82 (1.09–3.05)	0.02	2.00 (1.10–3.67)	0.02
Epinephrine given	1.48 (0.90–2.42)	0.11	1.57 (0.90–2.74)	0.11
ICU admission Na	0.98 (0.92–1.04)	0.52	0.98 (0.92–1.06)	0.66
Cooling method: surface	1.00 (reference)		1.00 (reference)	
Cooling method: invasive	1.67 (1.01–2.76)	0.05	1.44 (0.82–2.54)	0.21
Cooling method: both	1.37 (0.51–3.63)	0.53	0.94 (0.32–2.75)	0.91
Highest Kidney Disease Improving Global Outcomes classification 72 hr				
0	1.00 (reference)		1.00 (reference)	
1	1.71 (0.86–3.40)	0.12	1.40 (0.65–3.02)	0.39
2	0.74 (0.38–1.44)	0.38	0.74 (0.36–1.54)	0.42
3	0.47 (0.21–1.08)	0.07	0.35 (0.13–0.91)	0.03
Highest ICU C-reactive protein[b]	1.03 (1.01–1.06)	0.01	1.04 (1.01–1.07)	0.02

OR = odds ratio.
[a]Higher OR represents a higher risk of rebound hyperthermia.
[b]OR for every 10 mg/L increase of C-reactive protein.

invasive cooling (OR, 1.67; 95% CI, 1.01–2.76; $p = 0.05$), and highest ICU CRP (OR, 1.03; 95% CI, 1.01–1.06; $p = 0.01$) were significantly associated with RH. In the multivariate analysis, all the above-mentioned factors except height (OR, 1·00; 95% CI, 0.96–1.04; $p = 0.94$) and use of invasive cooling (OR, 1.44; 95% CI, 0.82–2.54; $p = 0.21$) were associated with RH. In the multivariate binary logistic regression model, the highest KDIGO AKI classification of 3 within 72 hours of ICU admission was significantly associated with decreased risk of RH (OR, 0.35; 95% CI, 0.13–0.91; $p = 0.03$) (**Table 1**). The regression model was repeated including the duration of TTM without any change in the results.

Temperature Threshold Analysis and Outcome

The median time spent in normothermia (36.5–37.5°C) as a percentage of all the measurements was similar between patients with favorable and the unfavorable outcome, either within the first 72 after rewarm end (46.7; IQR, 23.1–75.7 vs 48.0; IQR, 22.8–77.5) or in all the measurements available (46.4; IQR, 21.9–74.1 vs 50.4; IQR, 21.9–77.7). However, the mean time spent over the thresholds of 39°C and 39.5°C as a percentage of the first 72 hours after rewarm (**Supplemental Table 3**, Supplementary Digital Content, http://links.lww.com/CCX/A685) and the mean time spent over 38.5°C, 39°C, and 39.5°C were lower in patients with favorable outcome when compared with the others (**Table 2**). In addition, the percentage of time spent under 36.5°C and 37°C was also lower in the favorable FO group in all measurements available (Table 2). Results remained similar first 72 hours after rewarming ended (Supplemental Table 3, Supplementary Digital Content, http://links.lww.com/CCX/A685). Results from RH load comparison as minutes and minutes time degrees equaling the area are presented in **Supplemental Table 4** (Supplementary Digital Content, http://links.lww.com/CCX/A685).

All the temperature measurements for the patients with favorable FOs and the patients with unfavorable

TABLE 2.
Threshold Comparison Results in All Measurements After End of Rewarming

Threshold	*n*	All Patients, *n* = 317	CPC 1–2 at 6 mo, *n* = 216	CPC 3–5 at 6 mo, *n* = 101	*p*
% of time normothermia (36.5–37.5°C), median (IQR)/mean (range)	304	47.3 (21.9–74.5)/ 48.6 (0–100)	46.4 (21.9–74.1)/ 47.9 (0–100)	50.4 (21.9–77.7)/ 50.1 (0–100)	0.51
% of time spent under threshold, median (IQR)/mean (range)					
36°C	85	0 (0–0.1)/ 4.1 (0–100)	0 (0–0)/ 3.9 (0–100)	0 (0–0.6)/ 4.6 (0–100)	0.07
36.5°C	151	0 (0–9.6)/ 9.9 (0–100)	0 (0–6.3)/ 9.1 (0–100)	2.0 (0–13.3)/ 11.8 (0–100)	< 0.01
37°C	241	14.2 (0.4–38.6)/ 77/25.4 (0–100)	11.89 (0–33.6)/ 22.8 (0–100)	22.4 (2.8–47.5)/ 30.9 (0–100)	0.01
% of time spent over threshold, median (IQR)/mean (range)					
37.5°C	274	37.80 (11.1–70.1)/ 41.5 (0–100)	39.8 (13.7–72.0)/ 43.1 (0–100)	31.3 (8.6–62.5)/ 38.1 (0–100)	0.19
38°C	199	7.0 (0–24.2)/ 15.4 (0–94.4)	7.4 (0–21.7)/ 15.0 (0–94.4)	4.7 (0–29.5)/ 16.2 (0–77.3)	0.98
38.5°C	96	0 (0–2.3)/ 3.7 (0–63.2)	0 (0–0.6)/2.5 (0–51.0)	0 (0–5.8)/ 6.3 (0–63.2)	0.03
39°C	26	0 (0–0)/ 1.0 (0–48.0)	0 (0–0)/ 0.14 (0–9.6)	0 (0–0)/ 2.7 (0–48.0)	< 0.01
39.5°C	11	0 (0–0)/ 0.24 (0–26.2)	0 (0–0)/ 0.03 (0–2.9)	0 (0–0)/ 0.71 (0–26.2)	< 0.01

CPC = Cerebral Performance Category, IQR = interquartile range.

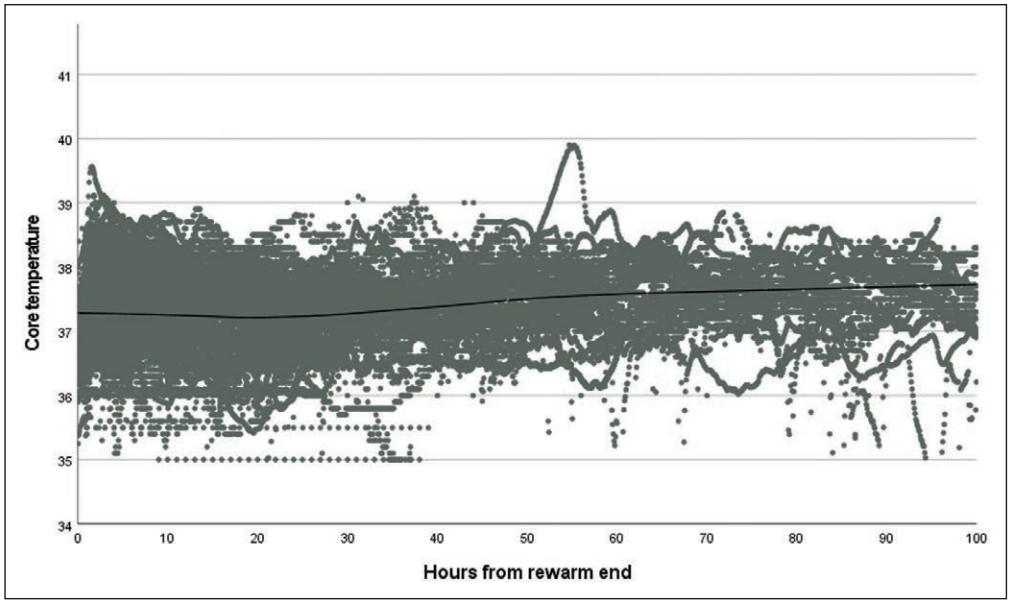

Figure 1. Loess smoother temperature scatterplot for favorable functional outcome patients (Cerebral Performance Category 1 or 2 at 6 mo).

FOs are presented in **Figures 1** and **2**. In a mixed linear model, temperatures were both higher over time after rewarm end ($p < 0.001$) and higher in patients with unfavorable FOs ($p < 0.01$). Median time to RH was longer in the unfavorable FO group (33.2 hr; IQR, 14.3–53.0 hr vs 6.5 hr; IQR, 2.2–34.1 hr; $p < 0.01$). The percentages of patients exceeding or falling under certain temperature thresholds at any point are presented

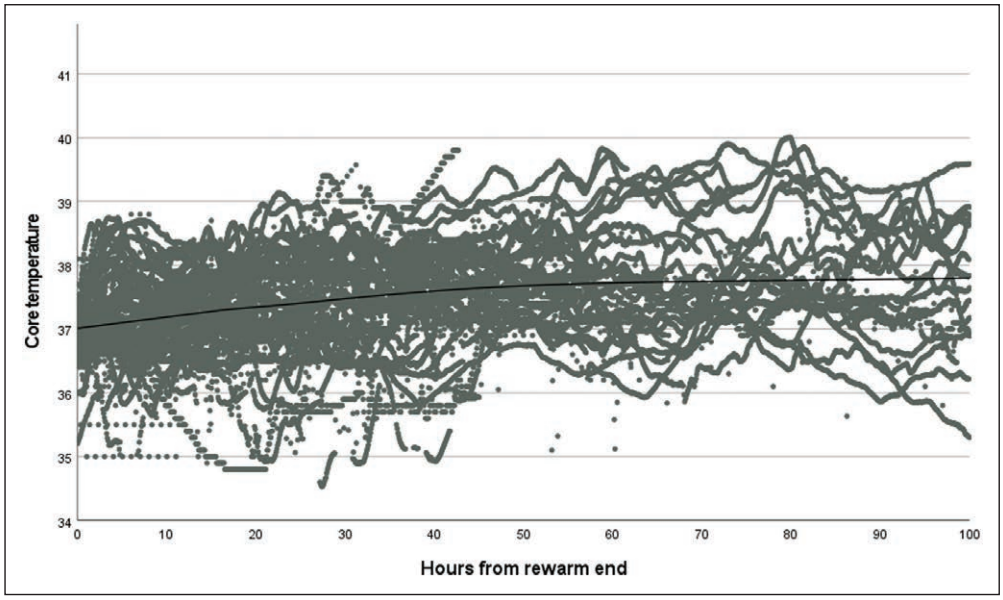

Figure 2. Loess smoother temperature scatterplot for unfavorable functional outcome patients (Cerebral Performance Category 3–5 at 6 mo).

in **Supplemental Figs. 2** and **3** (Supplemental Digital Content, http://links.lww.com/CCX/A684; legend, http://links.lww.com/CCX/A686).

Outcomes

We found no statistically significant difference in the prevalence of RH between FO groups (69% vs 62%; $p = 0.18$) or in hospital mortality (22% vs 22%; $p = 0.97$) between the group that experienced RH and the group that did not. In a multivariate binary logistic regression model, including age, gender, initial rhythm, treatment center, ROSC delay, and bystander CPR, RH was significantly associated with decreased odds of favorable FO at 6 months (OR, 0.42; 95% CI, 0.22–0.79) (**Table 3**). Inclusion of TTM duration did not change the results and remained statistically not significant. Same analysis was used to compare the effect of RH within first 72 hours after rewarm (OR, 0.40; 95% CI, 0.21–0.78) and total hours × degrees area spent over 38.5°C (OR, 0.77; 95% CI, 0.64–0.93) and both were significantly associated with decreased odds of favorable FO at 6 months while the effect of other factors did not significantly change.

DISCUSSION

One-third of the patients treated with TTM after OHCA experienced RH after rewarming, and it was more common in younger male patients, those treated with mechanical chest compression devices patients experiencing a more aggravated inflammatory

TABLE 3.
Logistic Regression Model Predicting Favorable Functional Outcome at 6 Months

Independent Variable	OR[a] in Univariate Analysis (95% CI)	*p*	OR[a] in Multivariate Analysis[b] (95% CI)	*p*
Rebound hyperthermia (yes)	0.72 (0.44–1.16)	0.18	0.42 (0.22–0.79)	0.01
Age	0.95 (0.93–0.97)	< 0.01	0.94 (0.91–0.97)	< 0.01
Male gender	1.83 (1.04–3.24)	0.04	1.70 (0.85–13.43)	0.14
Shockable rhythm	3.85 (1.94–7.63)	< 0.01	3.47 (1.54–7.81)	< 0.01
Return of spontaneous circulation delay (min)	0.94 (0.92–0.96)	< 0.01	0.94 (0.92–0.97)	< 0.01
Bystander cardiopulmonary resuscitation	2.57 (1.45–4.53)	< 0.01	1.98 (0.99–3.97)	0.06

OR = odds ratio.

[a]Higher OR represents higher probability for favorable functional outcome at 6 mo.

[b]Multivariate analysis was adjusted for treatment centers, but there were no significant between-center differences.

response. We found no difference in the development of RH in patients treated with 24 or 48 hours of TTM. Temperatures above 38.5°C were associated with unfavorable outcome, but less severe fever, or time spent as normothermic were not. Later occurring RH was more common in the unfavorable outcome group.

Previous studies have found similar RH prevalence, despite varying definitions for RH used between studies (3, 4, 12). In a study by Leary et al (3), the prevalence for RH was 41% using RH defined as a temperature greater than 38°C. In that study, a maximum temperature of greater than 38.7°C was associated with worse outcome. Gebhardt et al (4) found that fever is more common in CA patients not treated with TTM, and their findings suggest that if hyperthermia is delayed by TTM, it does not carry the same detrimental consequences. The definition for fever in their study was a temperature of greater than 38.0°C, and they found that 42% of OHCA patients experienced a fever of this magnitude.

In a meta-analysis by Makker et al (2), in which RH was defined as greater than 38°C and severe RH defined as greater than 38.5°C, both were significantly associated with worse FOs, and the authors speculated that the clinical impact of RH is likely proportional to the magnitude of RH. Indeed, in our study, RH was significantly associated with worse outcomes only with higher temperatures. Winters et al (10) used a definition of greater than 38.5°C for RH and found that 29.8% of their patients experienced RH and found that it was associated with increased risk for inhospital mortality and neurologic morbidity at discharge.

Previously, risk factors for RH have been unclear, but we identified younger age, male sex, and mechanical chest compression as risk factors. There are two dominant theories for the etiology of RH. First, it is possible that CA patients treated with TTM are at higher risk for developing infections; conversely, RH could be a physiologic result of ischemic injury and due to systemic inflammatory response (10, 18). We found higher CRP levels in patients experiencing RH, but WBC or clinically reported infections did not differ between the groups, indicating that the inflammatory component of RH may not necessarily be only due to infections. Mechanical chest compression is not routinely recommended, but it is useful for prolonged CPR (19) and may therefore be associated with more severe neurologic injuries and ultimately thermoregulation. The use of mechanical chest compression has been shown to result in a variable degree of lung injury (20), and we may speculate whether that could contribute to atelectasis and secondary pneumonia resulting in bacterial infection and fever. Regarding age, it is possible that the reason RH appears more common in younger patients could be a less marked inflammatory response and dysregulated thermoregulation among elderly patients (21).

We found that the percentage of time spent in the normothermia range was not associated with FO; however, the patients with worse FOs spent a higher percentage of time in low or high temperatures. Based on these results, it seems that favorable FO patients experience both high and low temperatures, whereas unfavorable FO patients undergo more isolated and severe post-TTM RH or hypothermia. In a study by Suffoletto et al (22), the patients who experienced an episode of hypothermia and those who had an episode of hyperthermia also had lower odds of survival. In an animal model, pharmacologically suppressed hyperthermia resulted in increased histopathological neuronal recovery in post-ischemic brain injury (23). As RH is clearly associated with worse outcomes, it could be beneficial to control it; however, further research is needed for definitive conclusions.

This study has several strengths: it is a large study on RH including data collected from multiple centers and with highly granular data on post-TTM temperatures. However, some limitations need to be kept in mind: there was no specific study protocol for temperature management after the end of rewarming, that is, antipyretics were given as suggested in European Resuscitation Council guidelines (1) and as deemed appropriate by the treating clinician. In addition, the means for measuring and recording temperatures varied between sites. Furthermore, we do not have detailed information on the use of antibiotics with regards to possible pneumonia and their effect on RH and inflammation. Finally, as patients were included in a randomized controlled trial with preset inclusion and exclusion criteria, the patient sample may not fully represent the majority of OHCA patients treated in ICUs.

CONCLUSIONS

Post-TTM RH developed in one-third of the patients, with a higher prevalence among younger male patients

and those treated with a mechanical chest compression device during CPR. We did not find any difference in the amount of RH based on the length of cooling. Post-TTM temperatures higher than 38.5°C and later onset of RH appear to be associated with worse FOs.

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The requirements regarding consent for participation from the next of kin and/or patients varied between study sites and the local principal investigator takes responsibility of this practice. Study monitoring was undertaken and the presence of the required informed consent documents was verified for all included patients during the monitoring process.

Ethical approvals for the TTH48 study: The Ethics Committee of Central Denmark Region on January 2, 2011 (journal number 20110022); the Regional Ethics Committee of Western Norway, October 9, 2013 (reference 2013/1486); the Ethical Committee of Helsinki and Uusimaa Hospital District on September 17, 2014 (§147), October 22, 2014 (§157), and October 21, 2015 (§212); the Tallinn Ethical Committee, Estonia, on March 10, 2015 (approval number 943); the Ethics Committee of the Hopital Erasme, Brussels, Belgium, March 9, 2015 (021/406); the Ethics Committee of the Charité-Universitätsmedizin, Berlin on August 2, 2015 (EA2/080/15); and it was also reported to the Danish Data Protection Agency and ClinicalTrials.gov (NCT01689077).

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