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Short paper

Change of target temperature from 36 °C to strict fever avoidance only in comatose cardiac arrest survivors – A before and after study

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Abstract

Aim: The guidelines on temperature control for comatose cardiac arrest survivors were recently changed from recommending targeted temperature management (32–36 °C) to fever control (≤37.7 °C). We investigated the effect of implementing a strict fever control strategy on prevalence of fever, protocol adherence, and patient outcome in a Finnish tertiary academic hospital.

Methods: Comatose cardiac arrest survivors treated with either mild device-controlled therapeutic hypothermia (≤36 °C, years 2020–2021) or strict fever control (≤37 °C, year 2022) for the first 36 h were included in this before-after cohort study. Good neurological outcome was defined as a cerebral performance category score of 1–2.

Results: The cohort consisted of 120 patients (≤36 °C group n = 77, ≤37 °C group n = 43). Cardiac arrest characteristics, severity of illness scores, and intensive care management including oxygenation, ventilation, blood pressure management and lactate remained similar between the groups. The median highest temperatures for the 36 h sedation period were 36.3 °C (≤36 °C group) vs. 37.2 °C (≤37 °C group) ($p < 0.001$). Time of the 36 h sedation period spent >37.7 °C was 0.90% vs. 1.1% ($p = 0.496$). External cooling devices were used in 90% vs. 44% of the patients ($p < 0.001$). Good neurological outcome at 30 days was similar between the groups (47% vs. 44%, $p = 0.787$). In multivariable model the ≤37 °C strategy was not associated with any change in outcome (OR 0.88, 95% CI 0.33–2.3).

Conclusions: The implementation strict fever control strategy was feasible and did not result in increased prevalence of fever, poorer protocol adherence, or worse patient outcomes. Most patients in the fever control group did not require external cooling.

Keywords: Cardiac arrest, Temperature management, Therapeutic hypothermia, Fever control

Introduction

Over the last decade, there have been major changes in our knowledge surrounding hypothermia after cardiac arrest.[1–5] The TTM1 trial in 2013 resulted in practice change and a shift to targeting mild hypothermia.[4,5] Subsequently, several cohort studies reported poorer overall protocol adherence, higher incidences of fever, and a few studies also reported association with worse patient outcomes.[6–10]

Since the publication of the TTM2 trial comparing the targeted hypothermia treatment (33 °C) with early fever control in 2021, both the updated European Resuscitation Council (ERC) - European Society of Intensive Care Medicine (ESICM) guidelines and the Finnish national guidelines on resuscitation have recommended actively preventing fever (>37.7 °C) as opposed to previously recommended temperature control between 32–36 °C among comatose cardiac arrest survivors.[1–4]

While temperature protocols are today, although variably, changing from hypothermic targets to fever control, concerns have risen on how fever control targets translate into practice.[2,11] No real-life pragmatic patient data on this transition exist. In this before-after study we investigated, how this change impacted the overall protocol adherence, prevalence of fever, and patient outcomes in a Finnish tertiary hospital.

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Methods

Study design

This is a single center observational before-after cohort study, and it is reported according to the STROBE Statement guidelines for observational studies.[12]

Ethics

The Ethics Committee of Tampere University Hospital (TAYS) approved the research protocol (R21143R). Informed patient consent was waived as the study design was purely observational.

Hospital and intensive care unit

TAYS is one of the five university level tertiary hospitals in Finland. The hospital has approximately 550 beds and 65.000 annual somatic admissions. The mixed surgical-medical intensive care unit (ICU) has 20 beds with annual 1,600 admissions.

Treatment protocol for comatose cardiac arrest survivors

Out of hospital cardiac arrest patients were attended by local helicopter emergency medical service doctor, and in-hospital cardiac arrest patients were attended by hospital's medical emergency team. All unconscious cardiac arrest survivors were intubated and transferred directly to primary percutaneous angiography and / or computed tomography scans where clinically indicated, and subsequently admitted to the ICU.

The ICU's standard operating procedure and multimodal neurological prognostication for comatose cardiac arrest survivors followed the ERC 2015 and Finnish 2016 guidelines,[4,13] which both were updated in 2021–2022.[2,3] In short, patients were sedated and mechanically ventilated for 36 hours after the cardiac arrest. All care bundles but the first 36 h temperature control targets remained unchanged between 1.1.2020–31.12.2022. Body temperatures were recorded by bladder temperature catheters. The COVID-19 pandemic did not affect these care bundles.

Since the publication of ERC 2015 guidelines, patients' core temperatures were to be maintained ≤36 °C with external cooling pads (Arctic Sun®) or endovascular catheter cooling (CoolGard®) during the 36 h sedation period.[4] On 1st January 2022 the temperature target for the sedation period was changed to ≤37 °C, and mechanical cooling was to be used only when conservative methods (exposing, paracetamol, wet towels) were deemed insufficient. All staff members received lectures and information on this protocol change between 1st November and 31st December 2021. The ≤37 °C target was chosen, because it was hypothesized that the risk of fever, defined as body temperature >37.7 °C in the current guidelines, would be effectively avoided with this small 0.7 °C margin.

Data collection

The ICU staff were unaware of this study protocol. Data were prospectively collected for the ≤37 °C cohort and retrospectively for the ≤36 °C cohort. The non-ICU data were collected from the electronic patient records (including patients' cerebral performance category, CPC, 30 days after the arrest), and the ICU data, such as the first 24 h ICU severity-off-illness scores, from the Centricity Critical Care Clinisoft® system. The system captures data on all vital signs continuously and compresses the data for averaged two-minute intervals for storage purposes.

Outcome measure

The primary outcome measure was the prevalence of fever (>37.7 °C). The secondary outcomes were protocol adherence (defined indirectly as following respiratory, haemodynamic and sedation targets), patient CPC 1–2 at day 30 post cardiac arrest, and external cooling device usage.

Exclusion criteria

Cardiac arrest patients under 18 years of age, patients with treatment limitations (do-not-attempt-resuscitation/ do-not-increase level of life-sustaining treatments) and not subjected to 36 h sedation protocol, and conscious cardiac arrest survivors were excluded.

Statistical analyses

Data are presented as counts (percentages) and continuous variables as medians (Q_1, Q_3), except for the hourly temperature data that are presented as means with 95% confidence intervals in Fig. 2. The Chi–square test and the Mann–Whitney U-test were used for the comparisons between groups. A multivariable logistic regression model using the 'enter' method was used to investigate variables associated with 30-day neurological survival. Two-sided p-values are reported. $P < 0.05$ was considered statistically significant. Odds ratios with 95% confidence intervals are reported where appropriate. The SPSS Statistics software (version 27 for Windows, SPSS Inc., Chicago, IL, USA) was used.

Results

Study cohort

The final study cohort consisted of 120 patients (77 patients in the ≤36 °C cohort and 43 patients in the ≤37 °C cohort, Fig. 1.). Cardiac arrests were more frequently witnessed in the ≤37 °C cohort; all other variables were comparable between the groups (Table 1).

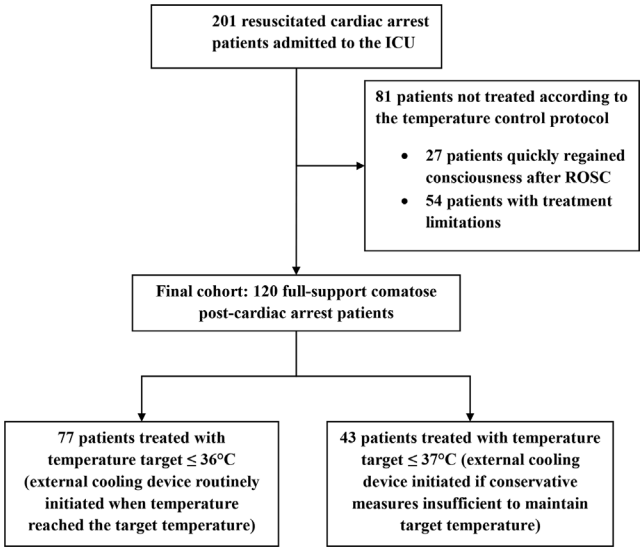

Fig. 1 – The study cohort. ICU, intensive care unit.

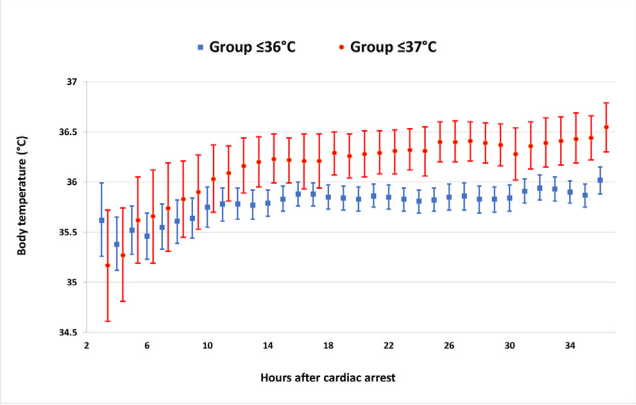

Fig. 2 – The mean hourly body temperatures with 95% confidence intervals for the ≤36 °C and the ≤37 °C groups. Body temperatures for the 1 h and 2 h are not presented as only a few patients had been admitted <3 h after the cardiac arrest.

Protocol adherence, body temperatures and patient outcomes

The usage of sedatives, noradrenaline (norepinephrine) and muscle relaxants were comparable across the groups (Table 2). The median blood oxygen saturations, mean arterial pressures, arterial blood gases and lactate levels were similar.

External cooling devices were utilized in 90% vs. 44% of the ≤36 °C vs. ≤37 °C patients, and if a device was utilized in the ≤37 °C cohort it happened median 7.9 h later than in the ≤36 °C cohort. Paracetamol was more frequently prescribed in the ≤37 °C cohort (Table 2).

Table 2 and Fig. 2 present the body temperatures for the 36 h sedation period. In general, the target temperatures were well maintained in both groups. Fewer was avoided 99% of the time in both groups.

The body temperatures rose in both groups 37–72 hours after the cardiac arrest (median temperatures 37.3c vs. 37.6c, $p = 0.176$). Fever was recorded in majority of patients in both groups (68% vs. 74%, $p = 0.481$). Detailed data are presented in Appendix A.

Table 1 – Patient characteristics, cardiac arrest characteristics and outcome.

	≤36 °C Group (n = 77)	≤37 °C Group (n = 43)	*p*-value
Patient characteristics			
Age	65 (55, 74)	68 (54, 74)	0.568
Sex (male)	65 (84)	36 (84)	0.920
Body mass index (kg/m^2)	26 (23, 29)	26 (24, 31)	0.945
Charlson comorbidity index	0 (0, 2)	1 (0, 2)	0.629
Independent in activities of daily living	72 (94)	40 (93)	0.919
Cardiac arrest characteristics			
Out of Hospital Cardiac Arrest	73 (95)	41 (95)	0.896
Primary rhythm			
VT/VF	55 (71)	31 (72)	
PEA	14 (18)	9 (21)	0.794
ASY	8 (10)	3 (7.0)	
Witnessed arrest	63 (82)	41 (95)	0.037
Basic life support provided	61 (79)	35 (81)	0.775
Time to advanced life support (min)	8 (6, 11)	8 (5, 10)	0.675
Return of spontaneous circulation (min)	21 (17, 28)	22 (15, 29)	1.000
Immediate primary coronary angiography	51 (66)	24 (56)	0.258
Cardiac aetiology for the cardiac arrest	65 (84)	31 (72)	0.106
Intensive care admission characteristics			
Time from cardiac arrest to ICU arrival (min)	183 (138, 237)	177 (130, 228)	1.000
APAHCE II score (first 24 h)	27 (23, 31)	28 (24, 32)	0.891
SAPS II score (first 24 h)	63 (53, 67)	60 (54, 66)	0.463
SOFA score (first 24 hours)	11 (9, 12)	11 (10, 11)	0.912
Pneumonia	61 (82)	35 (81)	0.954
Sepsis (blood culture positive)	3 (3.9)	3 (7.0)	0.458
Intensive care unit length of stay (days)	4 (3, 6)	4 (3, 6)	0.916
Outcome			
Highest NSE-value	24 (16, 41)	32 (17, 107)	0.198
Conscious immediately after sedations stopped[a]	32 (42)	14 (33)	0.331
Discharged alive and without treatment limitations from the ICU	44 (57)	22 (51)	0.528
Survival to hospital discharge with CPC 1–2	33 (43)	19 (44)	0.888
30-day survival with CPC 1–2	36 (47)	19 (44)	0.787

Data are presented as numbers (percentages) and continuous data as medians (Q_1, Q_3). [a] Glasgow coma motor score 6 (obeys commands). VT, ventricular fibrillation; VF, ventricular tachycardia (non-perfusing); PEA, pulseless electrical activity; ASY, asystole; APACHE, the acute physiology and chronic health evaluation; SAPS, the acute physiology and chronic health evaluation; SOFA, the sequential organ failure assessment; NSE, neuron specific enolase (taken 24 h, 48 h and 72 h after the cardiac arrest); ICU, intensive care unit; CPC, cerebral performance category.

Table 2 – General patient treatment and temperature management characteristics during the 36 h sedation protocol.

	≤36 °C Group (n = 77)	≤37 °C Group (n = 43)	*p*-value
Sedation and noradrenaline (norepinephrine)			
Propofol (g)	8.7 (6.5, 10)	8.8 (6.6, 10)	1.000
Midazolam (mg)	19 (3.0, 43)	28 (9.0, 50)	0.446
Fentanyl (mg)	1.7 (0.53, 3.6)	1.8 (0.53, 4.0)	0.703
Noradrenaline (mg)	13 (5.0, 26)	14 (5.9, 24)	1.000
Neuromuscular blockade (>2 boluses and/or infusion)	11 (14)	6 (14)	0.960
Vital signs and arterial blood gases and lactate (median values during the 36 h sedation protocol)			
Peripheral blood oxygen saturation (%)	99 (96, 99)	98 (96, 98)	0.174
Mean arterial pressure (mmHg)	71 (69, 74)	72 (69, 75)	0.336
PaO_2 (kPa)[a]	13 (12, 15)	13 (12, 14)	0.914
$PaCO_2$ (kPa)[a]	5.0 (4.8, 5.4)	5.1 (4.9, 5.5)	0.446
Lactate (mmol/l)[a]	1.3 (1.1, 1.7)	1.1 (0.90, 1.7)	0.446
Body temperature management during the 36 h sedation protocol			
External cooling device used			
No	8 (10)	24 (56)	
Arctic Sun®	40 (52)	19 (44)	< 0.001
CoolGard®	29 (38)	0 (0.0)	
Time from ICU arrival to external cooling initiation if used (min)	160 (95, 388)	633 (250, 967)	< 0.001
Paracetamol prescribed	7 (9.1)	17 (40)	< 0.001
Total paracetamol dose if prescribed (g)	0.5 (0.5, 0.5)	1.5 (1.0, 4.0)	0.020
Patient body temperatures (°C) during the 36 h sedation protocol			
ICU arrival	35.4 (34.6, 36.0)	35.1 (34.2, 35.9)	0.253
Highest measured	36.3 (36.2, 36.7)	37.2 (36.8, 37.5)	< 0.001
Lowest measured	34.9 (34.2, 35.4)	34.8 (33.8, 35.6)	0.914
Median	35.9 (35.8, 36.1)	36.5 (35.9, 36.8)	< 0.001
Time spent over the target temperature (%)[b]	9.0	4.1	< 0.001
Highest measured >37.7 °C	4 (5.2)	8 (19)	0.027
Time spent >37.7 °C (%)[c]	0.90	1.1	0.496

Data are presented as numbers (percentages) and continuous data as medians (Q_1, Q_3). [a]Median eight measurements during the sedation protocol. [b]Time presented as percentage spent >0.2 °C over the target temperature during the 36 h treatment protocol. [c]Time presented as percentage of the 36 h treatment protocol spent >37.7 °C. IHCA, in-hospital cardiac arrest; CCI, Charlson comorbidity index; Malignancy, malignant solid tumor or hematologic malignancy; ROSC, return of spontaneous circulation.

There were no differences in patient outcomes between the two groups (Table 1). Using a multivariable regression model, immediate basic life support (OR 4.4, 95% CI 1.2–16), shockable primary rhythm (8.8, 1.4–56) and low SAPS II score (0.92, 0.88–0.98) were associated with cerebral performance category (CPC) 1–2 at 30 days. Target temperature group did not predict outcome. The full model is presented in Appendix A.

Discussion

The key findings of this study are as follows: transition from mild device-controlled hypothermia to strict fever control did not result in higher prevalence of fever among comatose cardiac arrest survivors. Protocol adherence concerning oxygenation, ventilation, mean arterial pressure, lactate levels and sedation remained comparable. Most patients in the ≤37 °C group did not require external cooling. Patient outcomes did not change.

Large multicentre registry studies have reported that the overall adherence to temperature management guidelines decreased after the publication of TTM1 trial, and it has been speculated that some clinicians may have interpreted the TTM1 study results as 'hypothermia vs. no intervention'.[5,7–9,14] The translation of high fidelity RCT results to every-day clinical work may be challenging.[10] Indeed, while the TTM1 and TTM2 studies compared 33 °C with 36 °C and <37.7 °C, these RCTs had otherwise strict treatment protocols and the patients in higher temperature groups actually received high-quality treatment interventions with appropriate neuroprognostication, etc.[1,5] Our study presents the first real-life data on transition from hypothermia protocol to fever control. While the data imply that the transition can be successful in practice, the results on the other hand suggest that when other aspects of the ICU treatment and neuroprognostication of comatose cardiac arrest survivors remain unchanged, hypothermia vs. strict fever control does not impact patient outcome outside RCT setting either.

Using external cooling devices inevitably increase the treatment costs as compared with simple conservative measures.[2] Interestingly, while our strict fever control target was 0.7 °C lower than the limit used in the TTM2 fewer control group, the percentages of device use were identical (46%) and endovascular system was never utilized in our cohort.[1] It seems that most patients remain afebrile during the sedation period. The incidence of fever increased substantially after sedations were stopped, but at this point most survivors had swiftly regained consciousness and their fever treatment

followed normal ICU protocols. Moreover, a recent high-quality RCT found no benefit in using external cooling devices after the first 36 h.[15]

Our study has several limitations. This was a single center study from a Nordic country, the cohort population had many cardiac arrest characteristics associated with favorable outcome as did the TTM2 trial[1] (high rates of shockable rhythms, witnessed arrest and basic life support) and the cohort size was relatively small. The data on ≤36 °C group were retrospectively collected. Further, the limit in our fever control protocol was ≤37 °C, which presumably left margin for conservative measures before the ESICM-ERC definition for fever >37.7 °C was reached.

Conclusions

Transition to strict normothermia protocol did not result in higher prevalence of fever, lower protocol adherence, or worse patient outcomes among comatose cardiac arrest survivors in a large academic ICU.

Conflict of interest statement

Markus Skrifvars reports speaker fees from INVOS COVIDIEN and BARD Medical (Ireland) and a research grant from GE Healthcare in 2015–2016. Joonas Tirkkonen declares that no financial or non-financial conflicts of interests exist.

CRediT authorship contribution statement

Joonas Tirkkonen: Conceptualization, Methodology, Investigation, Data curation, Validation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Markus B. Skrifvars:** Conceptualization, Resources, Methodology, Visualization, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109796.

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