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Mid-term clinical outcomes of out-of-hospital cardiac arrest patients treated with targeted temperature management at 34–36 °C versus 32–34 °C

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ABSTRACT

Background: Targeted temperature management (TTM) in comatose survivors of out-of-hospital cardiac arrest has been associated with improved neurological outcomes. However, the optimal temperature target for TTM remains unclear.
Objectives: To compare a TTM protocol targeted at 34–36 °C with a protocol targeted at 32–34 °C with reference to both clinical outcomes and acute complications.
Methods: We analyzed a prospective registry of consecutive out-of-hospital cardiac arrest survivors who underwent TTM. We compared patients on a TTM protocol targeted at 34–36 °C ($n = 59$) with a historical cohort of patients treated at 32–34 °C ($n = 116$) according to the following parameters: six-month survival, cerebral performance category (CPC) scores, and acute complications.
Results: Survival and favorable neurological outcomes (CPC ≤ 2) at six months were 56% and 49%, respectively, in the higher target temperature group vs. 66% and 61%, respectively, in the lower target temperature group ($p = 0.18$ and 0.13). Acute clinical complications occurred in 1.5% vs. 12% of patients treated at the higher vs. the lower temperature range ($p = 0.02$).
Conclusions: Patients treated with TTM at 34–36 °C had similar mid-term survival and neurological outcomes as patients treated with TTM at 32–34 °C. However, patients treated within the higher temperature range had fewer acute complications.

Introduction

Comatose patients admitted to critical care units after successful resuscitation from an out-of-hospital cardiac arrest (OHCA) remain at high risk of death or permanent neurological damage.[1,2] These outcomes may be improved by decreasing body temperature to 32–36 °C for the initial 12–24 h after OHCA.[3-6] Known as targeted temperature management (TTM), this approach aims to minimize brain injury by decreasing the neuronal metabolism, systemic inflammation, and ischemia-reperfusion injury.[7]

While experimental studies and earlier clinical trials demonstrated the benefits of TTM aimed at 32–34 °C,[3,4,8] a recent randomized trial of OHCA patients found no difference in the clinical outcomes of patients maintained at 36 °C vs. 33 °C.[9] The results of this trial have prompted many centers to adopt higher temperature targets in their TTM protocol.

In this study, we evaluated acute complications, six-month survival, and neurological outcomes in OHCA patients who underwent TTM at a temperature target of either 34–36 °C or 32–34 °C. We hypothesized that the survival and neurological outcomes of these patients would not differ with regard to the intended or achieved body temperature.

Methods

Study population and design

We analyzed a prospective registry of consecutive OHCA survivors who underwent TTM ($n = 175$) at our cardiology intensive care unit between January 2007 and April 2016. The study was approved by the institution's ethics committee. Written consent from the patients was not required, as all of the procedures performed followed a routine clinical protocol.

Abbreviations: CPC, cerebral performance category; OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management

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In brief, all ambulance crews arriving at the scene of an OHCA were staffed by a physician. After recovery of spontaneous circulation, the ambulance physician consulted, by phone, with the attending physician at our institution. Patients with a suspected cardiac cause or an immediately unknown cause of cardiac arrest were admitted to our cardiology intensive care unit with the prospect of coronary angiography. Patients with an evident non-cardiac cause were primarily transported to general intensive care units at other institutions and were not included in the registry.

Coronary angiography was available at our institution 24/7. Patients with evident or highly probable acute coronary syndrome usually underwent urgent coronary angiography (< 2 h from admission). In the remaining patients, coronary angiography was usually performed after completion of TTM and after verification of a favorable neurological status.[10]

Cooling was initiated immediately after admission in all patients without contraindications (i.e., recurring life-threatening arrhythmias, severe bleeding, or hemodynamic deterioration requiring escalating doses of vasopressors). TTM was achieved using a hypothermia water blanket (PlastiPad, Blanketrol system, Cincinnati Sub-Zero, USA), ice packs, and cold infusions. Body temperature was measured using a thermistor-tipped urinary catheter and recorded hourly for at least 24 h. In the patients admitted before December 2013 ($n = 116$), the target was set at 32–34 °C for the initial 12–24 h in accordance with the contemporary evidence.[3,4] However, in the patients admitted after this period ($n = 59$), the protocol was amended to achieve a target of 34–36 °C based on the results of Nielsen et al.[9] The TTM protocol was considered complete when patients remained hypothermic (≤ 36 °C) for at least 12 h. Standard cardiology and intensive care management for comatose post-resuscitation patients was delivered according to the guidelines.[5,6]

All complications leading to the interruption or modification of the TTM protocol were recorded. End-of-life decisions were not made at our institution; patients with persisting severe neurological deficit were transferred to chronic care units.

Survival and cerebral performance category (CPC) scores were determined at the time of discharge from our intensive care unit and at six-month follow-up. CPC 1 (good cerebral performance) and CPC 2 (moderate cerebral disability) were regarded as favorable neurological outcomes. CPC 3 (severe cerebral disability), CPC 4 (coma or vegetative state), and CPC 5 (brain death) were regarded as unfavorable neurological outcomes. The six-month follow-up data were obtained as follows: an outpatient visit ($n = 82$), from a registry of insurance companies ($n = 39$), or by a phone call with the patient ($n = 4$) or the patient's relative or general practitioner ($n = 38$).

Statistical analysis

For the intention-to-treat analysis, we compared the historical patient cohort treated within a temperature target range of 32–34 °C with the more recent cohort of patients treated within 34–36 °C (Fig. 1). For the per-treatment analysis, we only included patients who had completed the TTM protocol, i.e. patients remaining at ≤ 36 °C for at least 12 h. The patients were divided according to the average body temperature reached during TTM (≥ 34 °C vs. < 34 °C).

Group comparisons were performed using the Student's *t*-test, Mann-Whitney U test, chi-square test, or Fisher's exact test, as appropriate. Factors associated with survival and favorable neurological outcomes were identified by univariate logistic regression analysis. Analyses were performed using JMP 10 (SAS Institute Inc., Cary, USA). A p-value < 0.05 was considered significant.

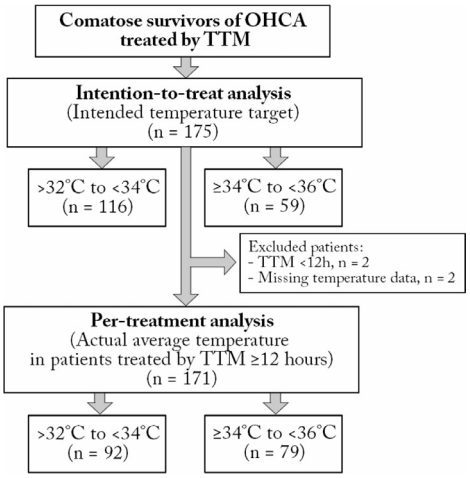

Fig. 1. A study flowchart. OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management.

Results

Baseline characteristics of the study population

The study comprised 175 OHCA patients who underwent TTM (Table 1). OHCA was witnessed in 89% of patients, with 78% exhibiting ventricular tachycardia/fibrillation upon initial medical contact. Although TTM was not actively initiated by the medical rescue service, 66% of patients were already hypothermic (< 36 °C) upon arrival at the hospital. OHCA was triggered by acute coronary syndrome in 61% of patients; of these, 77% underwent coronary revascularization.

Baseline comparison between the lower and higher temperature groups

There were no differences between patients in the higher temperature group (34–36 °C) and patients in the lower temperature group (32–34 °C) in any of the clinical characteristics, time of resuscitation, time to return of spontaneous circulation, or frequency of coronary revascularization (Table 1). It took expectedly longer to cool the patients to ≤ 34 °C compared to ≤ 36 °C (250 min [interquartile range 350–167] vs. 55 min [interquartile range 97–36]; $p < 0.001$). However, the time taken to achieve ≤ 36 °C did not differ between the groups, which suggests a similar approach to TTM. The average body temperature attained differed by 1.1 °C between the groups.

Acute complications during TTM

Seven patients in the lower temperature group regained consciousness spontaneously before completing the TTM protocol. Acute complications leading to the interruption or moderation of TTM occurred in 13 (8%) of the remaining 168 patients. The complications occurred in 12 of 101 (12%) patients treated at 32–34 °C at the time of the event vs. 1 of 65 (1.5%) patients with body temperatures of 34–36 °C (odds ratio 8.6, 95% confidence interval 1.1–68, Table 2).

Survival and neurological outcomes

In total, 163 (93%) patients survived acute cardiac care unit hospitalization, while 99 (57%) patients had CPC ≤ 2 (61% of survivors). Six months after OHCA, 110 (63%) patients were still alive, with 100 (57%) at CPC ≤ 2. Based on univariate logistic regression analysis, the following factors were significantly associated with six-month

Table 1
Clinical and demographic characteristics of the sample at baseline

	Targeted body temperature			Achieved body temperature		
	34–36 °C *n* = 59	32–34 °C *n* = 116	*p* value	34–36 °C *n* = 79	32–34 °C *n* = 92	*p* value
Clinical characteristics						
Age (years)	61 ± 12	59 ± 15	0.37	60 ± 12	60 ± 15	0.74
Male	49 (83)	93 (80)	0.65	66 (84)	73 (79)	0.48
Comorbidities[a]						
Diabetes mellitus	11 (19)	7 (33)	0.17	11 (18)	6 (33)	0.18
Arterial hypertension	36 (61)	14 (67)	0.65	37 (62)	11 (61)	0.97
Smoking	25 (42)	7 (33)	0.47	25 (42)	7 (39)	0.83
Dyslipidemia	20 (34)	7 (33)	0.96	21 (35)	5 (28)	0.57
Coronary artery disease	18 (31)	5 (25)	0.64	18 (30)	4 (24)	0.60
Markers of clinical severity						
Normal pupillary reflex on admission[b]	54 (92)	43 (94)	0.71	58 (92)	38 (95)	0.56
Lactate on admission (mmol/L)	3.9 [2.6–7.5]	4.1 [2.6–8.1]	0.84	3.7 [2.6–7.4]	4.0 [2.5–8.1]	0.87
High-sensitivity troponin T (ng/L)	124 [46–251]	113 [59–236]	0.97	113 [46–226]	129 [78–290]	0.15
Need for vasopressors[c]	32 (56)	64 (55)	0.90	44 (56)	51 (55)	0.97
Left ventricular ejection fraction (%)	36 ± 13	38 ± 14	0.36	36 ± 13	38 ± 14	0.27
Resuscitation-related characteristics						
Witnessed OHCA[d]	53 (90)	45 (88)	0.79	56 (88)	40 (91)	0.58
Basic life support performed	49 (83)	96 (83)	0.96	69 (87)	73 (79)	0.16
Basic life support time (min)	9 [5–10]	8 [5–10]	0.66	9 [5–10]	7 [5–10]	0.96
VT/VF upon first contact	43 (73)	93 (80)	0.32	60 (76)	74 (80)	0.48
Advanced life support time (min)	15 [10–22]	11 [6–22]	0.14	15 [9–22]	12 [6–23]	0.31
Time from OHCA to ROSC (min)	21 [17–30]	19 [14–29]	0.30	20 [15–30]	19 [15–29]	0.70
Electrocardiography						
ST-segment elevation or LBBB	32 (54)	56 (48)	0.46	43 (54)	43 (47)	0.32
ST-segment depression	22 (37)	50 (43)	0.46	32 (41)	39 (42)	0.80
Right bundle branch block	8 (14)	18 (16)	0.73	11 (14)	14 (15)	0.81
No ischemic ECG changes	7 (12)	17 (15)	0.61	9 (11)	15 (16)	0.36
Temperature management						
Body temperature on admission (°C)	35.6 ± 0.9	35.4 ± 1.1	0.29	35.6 ± 1.0	35.3 ± 1.1	0.04
Body temperature during TTM (°C)	34.7 ± 0.4	33.6 ± 0.5	<0.001	34.6 ± 0.4	33.4 ± 0.3	<0.001
Time from ROSC to ≤ 36°C (min)	55 [36–97]	73 [40–145]	0.09	65 [40–128]	69 [32–137]	0.79
Time within the temperature range (h)	21 [16–25]	22 [15–26]	0.97	18 [12–23]	24 [18–26]	<0.001
ICU care						
Revascularization urgent (≤ 2 h)	23 (39)	40 (34)	0.56	28 (35)	34 (37)	0.84
Revascularization delayed	9 (15)	14 (12)	0.56	13 (16)	10 (11)	0.29
Coronary angiography not performed	13 (22)	33 (28)	0.36	18 (23)	26 (28)	0.41
Length of stay at ICU (days)	7 ± 4	7 ± 5	0.42	7 ± 4	7 ± 4	0.84
Final diagnosis						
Myocardial infarction	38 (64)	69 (59)	0.53	48 (61)	57 (62)	0.87
Cardiomyopathy	5 (8)	14 (12)	0.47	9 (11)	9 (10)	0.73
Primary arrhythmogenic cause	1 (2)	9 (8)	0.10	2 (3)	8 (9)	0.09
Other	15 (25)	24 (21)	0.48	20 (25)	18 (20)	0.37

Targeted body temperature data were compared in intention-to-treat analysis, while achieved body temperature data in per-treatment analysis. The values are mean ± standard deviation, number (%) or median [Q1–Q3].
ICU, intensive care unit; LBBB, left bundle branch block; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, targeted temperature management; VT/VF, ventricular tachycardia/fibrillation.
[a] Data available for 80 patients.
[b] Data available for 105 patients.
[c] Data available for 173 patients.
[d] Data available for 110 patients.

survival and/or favorable neurological outcomes: lower age, lower initial lactate levels, ventricular tachycardia/fibrillation upon initial medical contact, shorter duration of advanced life support, shorter time to return of spontaneous circulation, and the absence of ST-segment depression upon admission (all $p < 0.001$). However, according to multivariable analysis (which includes all these factors), only the presence of ventricular tachycardia/fibrillation as the initial rhythm was significantly associated with favorable neurological outcomes ($p < 0.001$). There was no association between six-month survival or favorable neurological outcomes with the targeted temperature range or the average body temperature achieved during TTM (Table 3).

Table 2
Clinical complications associated with actual body temperature

	≥ 34 °C *n* = 65	< 34 °C *n* = 101
Significant bradycardia	1	3
Ventricular tachycardia	0	2
Hypotension requiring high doses of vasopressors	0	4
Major bleeding[a]	0	3
Total	1 (1.5%)	12 (12%)[b]

Groups are divided based on actual body temperature at the time of the event. Nine patients were excluded: seven patients regained consciousness spontaneously, while temperature data were unavailable in the case of the other two.
[a] Gastrointestinal bleeding (*n* = 2) and haemothorax (*n* = 1).
[b] *p* = 0.02 according to Fisher's exact test.

Discussion

This study showed no difference in six-month survival or neurological outcomes between OHCA patients treated with TTM at 34–36 °C vs. 32–34 °C, a finding based on observations of intention-to-treat analysis and confirmed by per-treatment analysis of the body temperature achieved. However, it would appear that maintaining patients at a

Table 3
Survival and neurological outcomes according to targeted and achieved body temperatures

	Targeted body temperature			Achieved body temperature		
	34–36 °C *n* = 59	32–34 °C *n* = 116	p	34–36 °C *n* = 79	32–34 °C *n* = 92	p
Upon discharge from ICU						
Alive	55 (93)	108 (93)	0.98	74 (94)	85 (92)	0.74
CPC	2 [1–4]	2 [1–4]	0.44	2 [1–4]	2 [1–4]	0.74
CPC 1–2	33 (56)	66 (57)	0.90	46 (58)	50 (54)	0.61
Six months after OHCA						
Alive	33 (56)	77 (66)	0.18	47 (59)	60 (65)	0.44
CPC	3 [1–5]	2 [1–5]	0.36	1 [1–5]	2 [1–5]	0.88
CPC 1–2	29 (49)	71 (61)	0.13	42 (53)	55 (60)	0.38

Values are numbers (%) or medians [Q1–Q3].
CPC, cerebral performance category; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest.

higher temperature range seems safer, as these patients developed fewer acute clinical complications.

Earlier experimental animal studies demonstrated that hypothermia induction (32–34 °C) shortly after an interrupted cardiac arrest can alleviate brain injury by decreasing the neuronal metabolism, systemic inflammation, and ischemia-reperfusion injury.[7,8,11,12] These findings were clinically confirmed by two randomized trials of OHCA patients: individuals cooled at 32–34 °C for an initial 12–24 h achieved better neurological outcomes compared to those who did not receive any TTM.[3,4] Based on these studies, TTM has become a standard therapy in all OHCA patients.[5,6]

However, controversy remains over the optimal temperature target during TTM.[5,6] While a decrease in body temperature leads to a proportional decrease in brain metabolism,[13] it also proportionally increases the risk of complications. The known side-effects of hypothermia include increased risk of infection ensuing from immunosuppression, relative hypovolemia leading to hypotension, bradycardia leading to decreased cardiac output, electrolyte disturbances leading to arrhythmias, impaired drug clearance, insulin resistance, and mild coagulopathy.[14] It is conceivable that some of these complications may nullify the clinical benefits of TTM.

In fact, a randomized trial by Nielsen et al. found no difference in survival or neurological outcomes between OHCA patients cooled at ~33 °C vs. ~36 °C.[9] The results of this trial instigated a change in the guidelines, allowing for a more liberal temperature range to be set during TTM (32–36 °C).[5,6] Likewise, a recent retrospective study by Kagawa et al. found similar neurological outcomes but fewer acute complications in OHCA patients cooled at ≥ 34 °C than in patients cooled at < 34 °C.[15] However, the results of this study are difficult to extrapolate, as 37% of the patients were treated by extracorporeal membrane oxygenation.

Our study adds to previous significant evidence based on real-world data. In agreement with Nielsen et al. and Kagawa et al.,[9,15] we demonstrate here that the targeting of lower temperatures (< 34 °C) during TTM did not provide any additional benefit for OHCA patients; conversely, it increased the risk of acute complications. In contrast to the study by Nielsen et al., however, we did not exclude patients with an extra-cardiac cause of OHCA or patients with unwitnessed OHCA and concomitant asystole.[9] Our results may thus be extrapolated to a broader patient population.

The emerging evidence prompts the question whether active induction of hypothermia itself has a greater neuroprotective effect on OHCA patients than merely preventing reactive hyperthermia.[16] This hypothesis is currently being tested as part of a randomized trial (NCT02908308), which plans to randomize 1900 OHCA patients between TTM at a target temperature of 33 °C and a strategy of only preventing fever. Meanwhile, in accordance with the current guidelines,[5,6] we next propose to cool OHCA patients for an initial 24 h at a temperature between 32 and 36 °C, but preferably at a higher temperature range to minimize the risk of acute complications.

Study limitations

This study was limited by the observational design and its relatively modest size. The patient population was biased towards cardiac causes of OHCA since patients with obvious extra-cardiac causes of circulatory arrest were transported to general intensive care units. The outcomes of the patients in the more recent cohort may have been theoretically biased by the more frequent use of drug-eluting stents and improvements in intensive care. Moreover, we cannot confirm the causality between the acute complications and TTM. Finally, we used only external cooling methods and cold infusions in our analyzed cohort. Although body temperature can be more tightly controlled by intravascular cooling catheters,[17,18] there is no clear evidence that this would affect the patient outcomes.

Conclusions

TTM targeted at 34–36 °C was associated with similar mid-term clinical outcomes but fewer acute complications than TTM targeted at 32–34 °C. Future studies are needed to clarify whether active induction of hypothermia is more beneficial for OHCA patients than the sole prevention of reactive hyperthermia.

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None.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the present study. Josef Kautzner serves as a scientific advisor and speaker for Biosense Webster, Boston Scientific Corporation/EP Technologies, Medtronic, LivaNova, and Abbott (St. Jude Medical), and as a speaker for Biotronik GmbH.

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Supplementary materials

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References

1. Hawkes C, Booth S, Ji C, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. *Resuscitation*. 2017;110:133–140.
2. Moulaert VR, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. *Resuscitation*. 2009;80:297–305.
3. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
4. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.
5. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation*. 2015;95:202–222.
6. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S465–S482.
7. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. *Nat Rev Neurosci*. 2012;13:267–278.
8. Geocadin RG, Koenig MA, Jia X, et al. Management of brain injury after resuscitation from cardiac arrest. *Neurol Clin*. 2008;26:487–506. ix.
9. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. *New Eng J Med*. 2013;369:2197–2206.
10. Kleissner M, Sramko M, Kohoutek J, et al. Impact of urgent coronary angiography on mid-term clinical outcome of comatose out-of-hospital cardiac arrest survivors presenting without ST-segment elevation. *Resuscitation*. 2015;94:61–66.
11. Gunn AJ, Thoresen M. Hypothermic neuroprotection. *NeuroRx*. 2006;3:154–169.
12. Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials and patient care. *J Neurol Sci*. 2007;261:118–126.
13. Fukuda T. Targeted temperature management for adult out-of-hospital cardiac arrest: current concepts and clinical applications. *J Intensive Care*. 2016;4:30.
14. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med*. 2009;37:S186–S202.
15. Kagawa E, Dote K, Kato M, et al. Do lower target temperatures or prolonged cooling provide improved outcomes for comatose survivors of cardiac arrest treated with hypothermia? *J Am Heart Assoc*. 2015;4: e002123.
16. Nielsen N, Friberg H. Temperature management after cardiac arrest. *Curr Opin Crit Care*. 2015;21:202–208.
17. Gillies MA, Pratt R, Whiteley C, et al. Therapeutic hypothermia after cardiac arrest: a retrospective comparison of surface and endovascular cooling techniques. *Resuscitation*. 2010;81:1117–1122.
18. Hoedemaekers CW, Ezzahti M, Gerritsen A, van der Hoeven JG. Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. *Crit Care*. 2007;11:R91.