JOURNAL CLUB COMMENT

How to target temperature after cardiac arrest: insights from a randomized clinical trial

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ABSTRACT

Implementation of treatments able to improve survival and neurological recovery of cardiac arrest (CA) survivors is a major clinical challenge. More than ten years ago, two pivotal trials showed that application of therapeutic hypothermia (TH, 32-34 °C) to patients resuscitated from an out-of-hospital CA (OHCA) with an initial shockable rhythm significantly ameliorated their outcome. Since then, TH has been used also for non-shockable rhythms and for in-hospital CA to some extent, even if the quality of evidence supporting TH in such situations remained very low. The objective of this randomized, controlled, multicenter study (named "Targeted Temperature Management" TTM study) was to compare two different strategies of temperature control after CA; patients were randomized to be treated either at 33 °C or at 36 °C for 24 hours, while fever was accurately avoided for the first 3 days since randomization. Inclusion criteria were: Glasgow Coma Score <8, presumed cardiac origin of arrest, randomization occurring within the first 4 hours from the return of spontaneous circulation. Patients were excluded if they had an unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke, and a body temperature of less than 30 °C. A specific algorithm was used to decide for withdrawal of care in patients remaining comatose after 72 hours since normothermia was achieved. The primary outcome was 6-month mortality. After the enrollment of 939 patients, the authors did not find any significant difference between groups in primary outcome (235/473 [50%] and 225/466 [48%] of patients died in 33 °C and 36 °C group, respectively; HR for death if in the 33 °C group, 1.06 [95% CI 0.89 to 1.28; P=0.51]). Similarly, the analysis of the composite outcome of death or poor neurologic function yielded similar results between the two groups. This is the largest study evaluating the effects of two different strategies of temperature management after CA. Some important concerns have been raised on the real benefit of keeping CA patients at 33 °C and major changes in clinical practice are expected. We discussed herein the main differences with previous randomized trials and tried to identify possible explanations for these findings. *(Minerva Anestesiol 2014;80:736-43)*

Key words: Heart arrest - Hypothermia, induced - Shock

In the last years, many efforts have been done to improve outcome among cardiac arrest (CA) survivors. Although the development of standardized resuscitation bundles has progressively brought to an increased rate of return of spontaneous circulation (ROSC) and hospital admission,[1-3] many patients will eventually die after CA because of extended brain injury.[4, 5] Thus, a rising interest has been directed towards strategies able to improve survival with intact neurological outcome in this patients' population. Amongst all, the use of therapeutic hypothermia (TH, 32-34 °C) immediately after witnessed CA due to shockable rhythms (*i.e.* ventricular fibrillation or tachycardia, VF/VT) was shown to increase the number of patients with good neurological recovery in two randomized clinical trials (RCT).[6, 7] Since then, TH was included in international guidelines for post-resuscitation care and has been applied to all patients who survived CA, regardless of the initial rhythm and characteristics of arrest.[8, 9] Subsequent non-randomized

studies also confirmed that the use of TH was associated with a better neurological outcome than standard-of-care in CA patients.[10] Nevertheless, the optimal timing and duration of cooling as well as the most effective temperature to achieve in this setting remain unknown.[11, 12] Moreover, TH appeared to be largely underused in clinical practice because of the lack of standardized protocols and of the inadequacy of available cooling methods.[13, 14] Also, Nielsen *et al.* underlined how the evidence regarding the use of TH after out-of-hospital cardiac arrest (OHCA) was still inconclusive and associated with non-negligible risks of systematic and random errors.[15] In particular, the number of patients included in previous RCTs was not large enough to give the statistical power, according to the trial sequential analysis. Importantly, as control patients developed early fever after hospital admission, it remained unclear whether TH was effective *per se* or whether fever may have contributed to burden the postanoxic brain injury in previous studies.[7]

The study

Nielsen *et al.*[16] investigated the effects of two different levels of hypothermia after CA in a randomized, controlled, multicentrer, phase 3 trial (from November 2010 to January 2013 – named "Targeted Temperature Management", TTM study), including 36 Intensive Care Units (ICUs). Patients were randomized within 4 hours after ROSC to be treated either at 33 °C or to 36 °C for 24 hours; thereafter, temperature was slowly increased up to 37 °C and kept below 37.5 °C for 72 hours. The main hypothesis was that TH at 33 °C would have resulted in a 20% reduction of overall mortality when compared to 36 °C. Patients included were unconscious at hospital admission (Glasgow Coma Score, GCS<8) and suffered from an OHCA of presumed cardiac cause, regardless of the initial rhythm. Exclusion criteria were an unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke, and a body temperature of less than 30 °C. No specific cooling methods were suggested. At 72 hours after the end of TH, a neurological evaluation was performed by a physician who was unaware of the group assignment and who proposed to continue or withdraw life-sustaining therapies, according to a specific prognostication algorithm. All surviving patients were followed until 6 months after the enrollment in the study. The primary outcome was all-cause 6-month mortality. The main secondary outcome was a composite outcome including death or poor neurological status, defined as a Cerebral Performance Category (CPC) of 3-5 and/or a score of 4-6 on the modified Rankin scale.[17, 18] A total of 1431 patients were considered as eligible during the study period (53 patients/month - 1.5 patient/month/ICU) and 950 were eventually randomized (35 patients/month - 0.9 patient/month/ICU); a total of 939 patients, 473 in the 33°C group and 466 in the 36°C group, were considered in the final intention-to-treat analysis. Groups were similar at baseline, while median temperatures well separated according to group assignment after few hours (Figure 1). At the end of the study period, 235/473 (50%) and 225/466 (48%) of patients died in the 33 °C and 36 °C group, respectively (HR 1.06 [95% CI 0.89-1.28; P=0.51]). Similarly, the analysis of the composite outcome of death or poor neurologic at 6 months yielded similar results (CPC 3-5=54% in 33 °C *vs.* 52% in 36 °C, P=0.78; modified Rankin Scale 4-6=52% in 33 °C *vs.* 52% in 36 °C, P=0.87). Predefined sub-group analyses showed no differences between groups according to age, gender, time to ROSC and initial rhythm. A trend towards a better outcome in the 36 °C was observed in the small group of patients with shock on admission (N.=137; HR 1.35 [0.90-2.03] P=0.17). One or more serious adverse events occurred in 93% in 33 °C group as compared to 90% in 36 °C group (RR, 1.03 [95% CI, 1.00 to 1.08], P=0.09).

Discussion

The TTM trial gave some relevant insights on the benefits of TH in a large population of OHCA patients, including all rhythms. The main characteristics of the three RCTs on TH [6, 7, 16] after CA are shown in Table I.

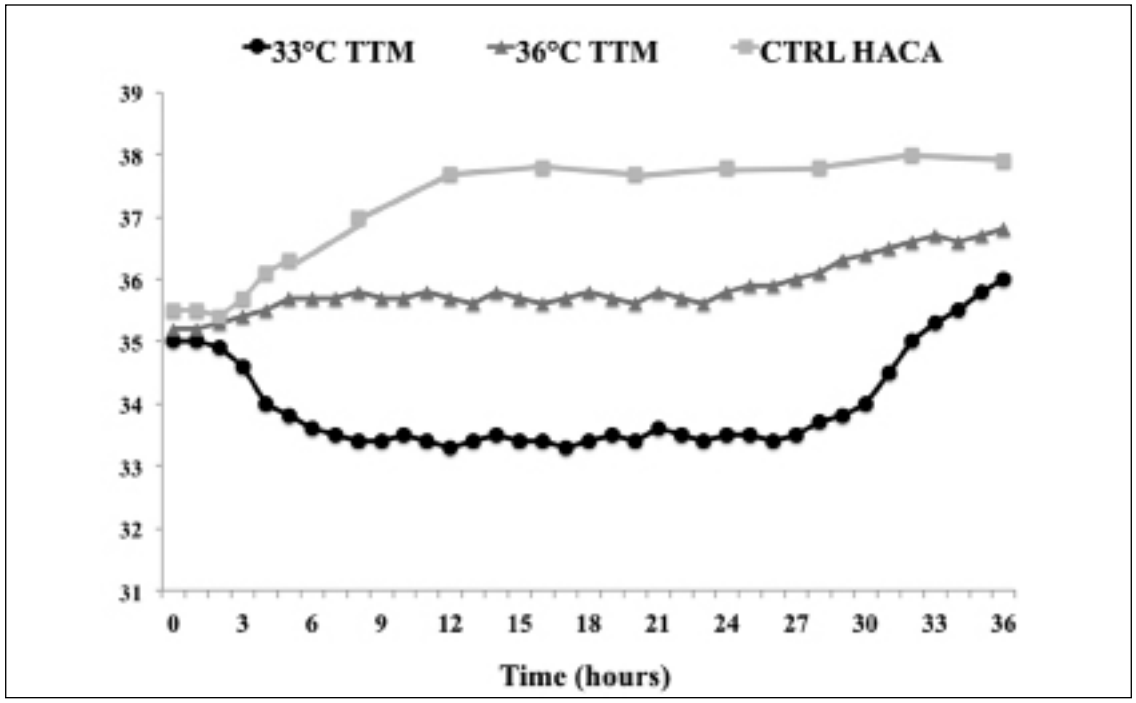

Figure 1.—Median temperature over the first 36 hours after arrest in the Targeted Temperature Management (TTM) study (33 °C and 36 °C) and the control group of the Hypothermia After Cardiac Arrest (HACA) Study. Data are adapted from the two studies.[7, 15]

Table I.—*Major differences among the three randomized trials on the use of therapeutic hypothermia after cardiac arrest.*

	HACA (2002) [7] N.=275	Bernard (2002) [6] N.=77	TTM (2013) [16] N.=939
Median age (years)	59	66	64
Gender, N. (%)	210/275 (76%)	52/77 (68%)	761/939 (81)
Initial Rhythm	VF/VT	VF	VF/VT = 752/939 (80%)
Witnessed CA, N. (%)	99%	95%	90%
Study period	1996-2001	1996-1999	Nov 2010 – Jan 2013
Bystander CPR, N. (%)	127/275 (46%)	45/77 (58%)	683/939 (73%)
Epinephrine, mg	3 [1-6]	2.2 ± 2.1	NA
Median time to ROSC, min	22	26	25
Thrombolysis, N. (%)	51/275 (19%)	NA	20/930 (2%) *
Hypothermia, hrs	24	12	24
Duration of rewarming, hrs	8	6	8
Post-resuscitation care	No	Yes	No
Prognostication	No	No	Yes
Survival			
All cohort	52%	41%	52%
VF/VT	52%	41%	60%
Hypothermia	59%	49%	50% #
Intact Neurological outcome			
All cohort	47%	31%	48%
VF/VT	47%	31%	NA
Hypothermia	55%	49%	NA

VF: ventricular fibrillation; VT: ventricular tachycardia; CA: cardiac arrest; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; NA: not available.
*44% of patients had percutaneous coronary intervention (PCI)
#33 °C Group

Strenghts

The TTM study has some important strengths which should be highlighted. First, the authors were able to recruit a sample size of 950 patients, which provided 90% power to detect the expected reduction in outcome between groups, thus avoiding any potential recruitment limitation. The Hypothermia after Cardiac Arrest (HACA) study [7] had no specific power calculation and was prematurely interrupted because of limited funding; the Bernard's trial [6] randomized patients according to the day of the month, which explained an imbalance in the number of enrolled patients in the two groups (43 in the hypothermia group and 34 in the normothermia group) and subsequent selection bias. Second, Nielsen *et al.*[16] included 66% of the eligible patients, while the two previous trials had largely limited the patients eventually selected; in the HACA trial,[7] only 275 out of 3551 (8%) patients were randomized, while in the Bernard's study [6] only 84 patients were found to be eligible over 4-year period. Third, as the allocation to hypothermia or to a specific target temperature was not blinded, a clear prognostication algorithm is mandatory to avoid rapid and unclear withdrawal of care among patients remaining comatose few days after arrest.[19] In the TTM study, an independent neurologist proposed for limiting life-sustaining therapies in case of: a) brain death due to cerebral herniation; b) severe myoclonus status in the first 24 hours after admission and a bilateral absence cortical response on median nerve somatosensory evoked potentials (SSEPs); c) persisting coma at 72 hours with a GCS motor response 1-2 and bilateral absence of cortical response on SSEPs; d) persisting coma with a GCS motor response 1-2 and refractory status epilepticus. In all other patients, daily clinical evaluation was recommended and withdrawal of care was considered only in those patients without neurological recovery in absence of potential confounders. Thus, as early and reliable neurological examination can be performed only in a limited number of patients after TH,[20] the TTM study used a rigorous methodology to avoid any bias in the clinical judgment on withdrawal of care, while the first two RCTs may have been flawed by the lack of this decisional process on the primary outcome evaluation.

Controversial issues and limitations

Although this trial clearly challenges the actual recommendations on cooling after CA, some important issues needs to be discussed to identify possible explanations for the differences with previous studies. First of all, the management of critically ill patients has dramatically changed in the last decade; early-goal directed management of sepsis, sedation interruption, tight glycemic control and reduced tidal volume in case of acute lung injury [21-24] are only some of the interventions that were not available at the moment the first two trials on TH after CA were conducted. Thus, it is possible that the improved quality of care delivered to such patients has blunted any potential benefit of TH in this setting. Second, the two TTM groups had a significant lower median temperature than the control group in the HACA study (Figure 2);[7] thus, it is difficult to compare their results, as temperature management was totally different. Third, the TTM study was designed to evaluate all patients surviving OHCA, regardless of the initial rhythm, while the two pivotal trials enrolled only patients with shockable rhythms. Nearly 80% of patients in the TTM study had VF/VT, which is in contrast with recent epidemiological data showing

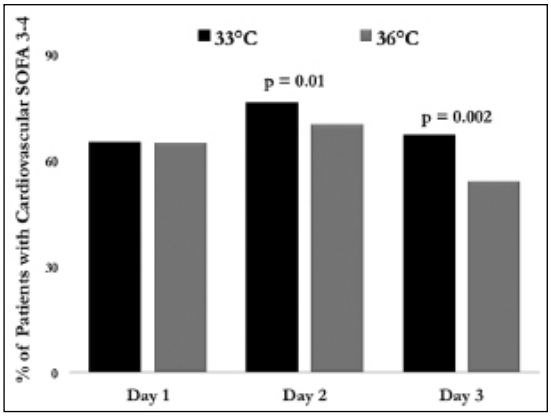

Figure 2.—Proportion of patients with cardiovascular failure, as determirned by the cardiovascular Sequential Organ Failure Assessment (SOFA) subscore of 3-4 during the first 3 days since arrest in the TTM study, according to target temperature at 33 °C or 36 °C.

that non-shockable rhythms account for more than 70% of OHCA.[25] Whether this is the result of the high by-stander cardiopulmonary resuscitation (CPR) rate or to a selection bias, it is impossible to evaluate from the published data. Recent studies suggested no benefit for TH in the treatment of non-shockable rhythms. In a 10-year retrospective OHCA cohort (N.=1145), Dumas *et al.* found an improved outcome when TH was used only for patients with VF/VT but not for non-shockable rhythms.[26] A large observational study in 548 patients from Finland showed that only 31% of patients with PEA/asystole were actually cooled and that TH had no impact on neurological outcome among them.[27] Similarly, a meta-analysis of RCTs and observational studies found no significant improvement in neurological outcome when TH was applied in CA due to non-shockable rhythms.[28] Thus, it is possible that in non-shockable rhythms, with a presumed longer time of anoxia and impaired tissue perfusion, the use of TH may not influence outcome and should not be considered.

Furthermore, in the TTM study, hypothermia at 33 °C did not confer any benefit when compared with 36 °C even for VF/VT (HR for death if in 33 °C 1.06 [95% CI 0.84-1.34]). Which are the potential confounders that might explain these discrepancies with previous data? First of all, no specific recommendations were provided on the different cooling strategies to achieve target temperature. Recent studies suggested that the use of cold fluids may be associated with increased adverse events after CA.[29, 30] Cold fluids were not used in the HACA trial and may have an unpredictable impact on patients included in the TTM study. Also, a significant variability in target temperature was observed over time in the two groups, with some patients in the 33 °C group having over-cooling (*i.e.*<32 °C) and some in the 36 °C group having normothermia (*i.e.*>37 °C). Whether over-cooling and/or normothermia may have influenced the final results of this study, it remains unknown; however, it would be interesting to know the survival rate in the sub-group of patients treated with endovascular devices (24% of all cohort), as this method allow a precise and constant body temperature around the target threshold and may have limited temperature variability in this setting.[31] As such, Lopez-de-Sa *et al.* showed that, using an endovascular cooling device, a lower temperature level was associated with a better outcome in OHCA patients with a shockable rhythm.[32] Thus, the effects of targeted temperature management using specific cooling methods will be investigated in future clinical trials in CA patients (FROST Study, NCT02035839).

Second, the type of sedative agents and their daily dose were not collected. As such, the association propofol/remifentanil provides a faster recovery of consciousness than midazolam/fentanyl but is associated with the need of more vasopressors to maintain stable hemodynamic. Also, high dose of these drugs may significantly prevent the development of seizures when compared to lower daily regimens. Moreover, drug metabolism is often altered during TH so that drug accumulation may significantly influence the neurological recovery and be associated with more adverse events.[33] As it may be expected that higher sedative doses were used in the 33 °C group to maintain target temperature and avoid shivering, the role of sedation on the outcome of patients after CA may be considered as an important confounder. Third, the proportion of patients receiving a by-stander CPR was surprisingly higher than in other studies (Table I) and was associated with a median time to CPR of 1 minute; interestingly, Testori *et al.* showed that the beneficial effect of TH for OHCA was evident starting from 2 minutes of no-flow, with the larger benefit for patients who experimented more than 8 minutes without CPR.[34] Thus, the very short no-flow time in this study may have substantially limited the extension of brain injury in these patients and blunted the potential benefits of TH. Also, the generability of such results may be questioned in a scenario with a longer time to CPR. Finally, patients randomized in the 33 °C group had more hemodynamic instability, as assessed by the cardiovascular Sequential Organ Failure Assessment (SOFA) score, than the others (Figure 2). As the TTM study lacked of a specific protocol to manage all the cardiovascular and respiratory variables, including PaO_2, $PaCO_2$, mean arterial pressure and cardiac output, which may influence outcome in

this setting,[35-37] one may argue that the systemic alterations associated with a lower body temperature may have contributed to impaired tissue perfusion. This was supported by the higher proportion of patients having an early death because of cardiac failure or multiple organ failure (54/235 in the 33 °C *vs.* 39/225 in the 36 °C group, P=0.13) and a trend for a better outcome for the 36 °C group in the subgroup of patients with shock on admission.

Impact of these findings on daily practice

How the results of the TTM study will change our daily practice? First of all, patients remaining comatose after CA must be always considered for hypothermia. The target temperature level should be set between 33 °C and 36 °C and all patients should be sedated and shivering controlled, as proposed in previous studies.[6, 7, 16] Probably, 33 °C could be considered in case of cooling device which are not so effective to maintain a constant body temperature over time; indeed, if 36 °C would be selected, some patients could easily have body temperature above 37.5 °C, which was the temperature observed in the control group of the HACA trial (Figure 2) and associated with a poorer outcome. On the opposite, patients with cardiovascular instability should be considered for 36 °C. Importantly, a rapid coronary reperfusion and/or a tight infection control in these patients is mandatory. As such, immediate coronary angioplasty was associated with improved hospital survival in patients with or without ST-segment elevation.[38] Also, positive blood cultures for bacteria were found in nearly 40% of patients immediately after CA,[39] suggesting that early antibiotic administration could potentially influence the hemodynamic optimization in this setting. Whether these two interventions may contribute to reduce adverse events associated with lower temperature targets after CA, it remains to be evaluated. Finally, the TTM study gave no information on the optimal time to initiate TH. Experimental studies yielded that TH was more effective when it was applied immediately after the ischemic event.[40] Nevertheless, pre-hospital hypothermia with cold fluids provided no benefit on patients' outcome when compared to standard in-hospital cooling.[29] The use of intra-arrest hypothermia (IATH), *i.e.* cooling initiated during CPR, may further reduce both hypoxic and reperfusion injury after global cerebral ischemia.[41] In the only human RCT,[42] IATH using a trans-nasal evaporative cooling was associated with a significantly lower temperature at hospital admission and a lower time to target temperature than standard cooling. However, IATH did not improve survival rate or good neurological outcome; only in the subgroup of patients with a time from collapse to CPR below 10 minutes, IATH was associated with higher rate of good neurological recovery (43.5% *vs.* 17.6% P=0.03). An ongoing RCT will try to demonstrate if transnasal cooling during the early phase of CPR may improve neurological outcome in OHCA patients.[42]

Conclusions

The TTM study showed that a decrease in body temperature below 36 °C in the post-resuscitative phase after CA does not provide any further benefits on survival. More importantly, it seems that lower body temperature are associated with more adverse events and cardiovascular instability. Untreated fever could have worsened outcome in previous studies and must be avoided. Future studies should consider these issues to provide a better post-resuscitation care in this setting; also, the optimal timing to initiate TH remains to be defined.

Key messages

— In comatose patients after CA, hypothermia at 33 °C does not provide any benefit when compared with 36 °C.

— The major strengths of the TTM study are the large cohort of patients included, the high percentage of eligible patients who were eventually randomized and the strict protocol to assess prognosis in this population.

— Some potential confounders are the concomitant evaluation of both shockable and non-shockable rhythms, the lack of data on the type and dose of sedation, the use of

different cooling methods to maintain target temperature and the absence of specific protocols to manage the post-cardiac arrest syndrome.

— The optimal timing to initiate cooling after CA needs to be further evaluated.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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