TURKISH JOURNAL OF EMERGENCY MEDICINE

Invited Review Article

Access this article online

Quick Response Code:

Website: www.turkjemergmed.org

DOI: 10.4103/2452-2473.297466

Practical considerations for postarrest targeted temperature management

Isabelle Mullen, Benjamin S. Abella*

Department of Emergency Medicine, The Center for Resuscitation Science, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
**Corresponding Author*

Abstract:

Out-of-hospital cardiac arrest remains a major challenge worldwide, with survival to discharge rates of <20% in the great majority of countries. Advancements in prehospital care, including increasing deployment of automated external defibrillators and improvements in bystander cardiopulmonary resuscitation, have led to more victims achieving return of spontaneous circulation (ROSC), yet the majority of patients with ROSC suffer in-hospital mortality or significant neurologic injuries that persist after discharge. This postarrest morbidity and mortality is largely due to a complex syndrome of mitochondrial dysfunction, inflammatory cascades and cellular injuries known as the postcardiac arrest syndrome (PCAS). The management of PCAS represents a formidable task for emergency and critical care providers. A cornerstone of PCAS treatment is the use of aggressive core body temperature control using thermostatically controlled devices, known as targeted temperature management (TTM). This therapy, demonstrated to be effective in improving both survival and neurologic recovery by several randomized controlled trials nearly 20 years ago, remains a major topic of clinical investigation. Important practical questions about TTM remain: How soon must providers initiate the therapy? What TTM goal temperature maximizes benefit while limiting potential adverse effects? How long should TTM therapy be continued in patients following resuscitation? In this review, we will address these issues and summarize clinical research over the past decade that has added to our fund of knowledge surrounding this important treatment of patients following cardiac arrest.

Keywords:

Hypothermia, induced, postarrest syndrome, resuscitation

Introduction

It is estimated that there are more than 500,000 cases of out-of-hospital cardiac arrest (OHCA) in the United States and Europe each year and nearly 90% of them are fatal.[1] For patients who survive, neurologic injuries are common and often result in debilitating long-term consequences. Multiple strategies have been attempted in an effort to mitigate the neurologic damage that results from OHCA, including postarrest pharmacologic agents such as barbiturates, anti-inflammatory medications, and magnesium infusions, ventilator management strategies including oxygen titration, and temperature control approaches. Among these treatments, only targeted temperature management (TTM), sometimes referred to as "therapeutic hypothermia," has demonstrated long-term neurologic benefit in randomized clinical trials.[2-4] These trials applied lessons from a large body of laboratory research that demonstrated the role of lowering core body temperature to reduce cerebral edema, inflammatory changes, and other mechanisms of the postcardiac arrest syndrome in animal models of cardiac arrest.[5-8]

Despite the wealth of evidence to support TTM as an effective postarrest care strategy, many questions remain about

Submitted: 19-06-2020
Accepted: 21-06-2020
Published: 07-10-2020

ORCID:
IM: 0000-0002-1792-3149
BSA: 0000-0003-2521-0891

Address for correspondence:
Dr. Benjamin S. Abella, Department of Emergency Medicine, The Center for Resuscitation Science, School of Medicine, University of Pennsylvania, 3400 Spruce Street, Ground Ravdin, Philadelphia, PA 19104, USA.
E-mail: benjamin.abella@pennmedicine.upenn.edu

How to cite this article: Mullen I, Abella BS. Practical considerations for postarrest targeted temperature management. Turk J Emerg Med 2020;20:157-62.

its implementation. For example, in 2013, Nielsen *et al*. presented results from a multicenter OHCA cohort (known as the TTM trial), suggesting that the long-held postarrest target temperature of 33°C did not yield clinical benefit over a more modest target temperature of 36°C. This surprising finding, conflicting with prior trials and laboratory studies, led to changes in international TTM guidelines and impacted both hospital practices and post-OHCA outcomes.[9] The TTM trial and response to it demonstrate that there is much left to be studied about best practices in TTM. International resuscitation guidelines currently recommend maintenance of body temperature between 32°C and 36°C for patients with either shockable or nonshockable rhythms who remain unresponsive after return of spontaneous circulation.[10] Figure 1 illustrates other phases and parameters, in addition to target temperature, that remain the subject of investigation for the optimization of TTM. In the current review, we describe selected key research that informed these guidelines, the impacts of the TTM trial, and the questions that remain about the optimal timing, target temperature, duration and rewarming practices in TTM.

Timing of Targeted Temperature Management Intervention

An important parameter in the implementation of TTM is that of timing. TTM is typically initiated within the initial few hours following successful resuscitation, but in actual practice this timing has varied considerably. In one study of 570 cases, the time between postarrest admission and initiation of target temperature ranged from 20 to 319 min.[11] This variation raises the question: Does the benefit of temperature management depend on the timing of therapy? If earlier is better, should efforts be made to initiate cooling in the prehospital setting or at least in the Emergency Department before critical care admission? When earlier and later in-hospital cooling were compared, there was a trend that suggested cooling sooner was associated with improved neurologic outcome. While previous research suggests that administration of prehospital cooling does not improve survival or neurologic function, recent data on prehospital cooling using novel technology suggests that this question is still not settled science.[12]

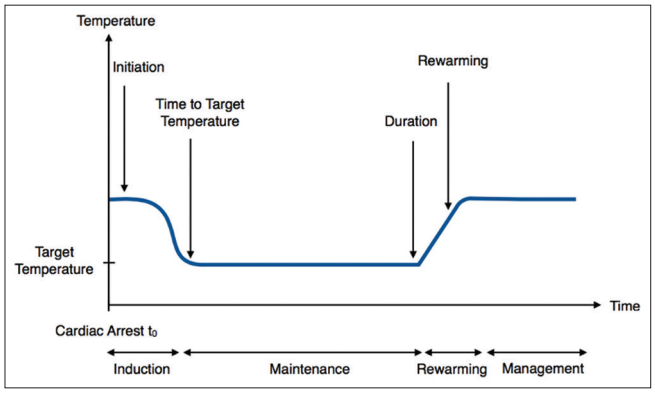

Figure 1: Phases and parameters of postarrest targeted temperature management

To address the question of timing, Stanger *et al*. investigated the impact of door-to-targeted temperature (DTT) management on neurologic outcome and survival by analyzing 570 patients resuscitated from OHCA. Investigators found that earlier TTM led to a significant increase in survival rates and trend toward better neurologic outcomes. Additional analysis based on DTT quartiles suggests that patients with the shortest DTT (average 36 min) had greater rates of survival and good neurologic outcome compared to even the second quartile (36–122 min). Of interest, rates of good neurologic outcome were decreased by a constant proportion with each quartile, whereas the decline in survival rates was greatest between the second and third quartile (2: 36–122; 3: >123–~219). This may point to a cut off time of 2 h following resuscitation, before which providers should aim to initiate TTM to achieve the greatest impact on survival rates.[11]

Given the potential importance of early TTM initiation, a number of investigations over the past decade have evaluated prehospital administration of TTM with largely negative results.[3,13-15] In the recent PRINCESS study, authored by Nordberg *et al*., there was no improvement in patient outcomes when cooling was initiated by emergency medical services prior to hospital admission compared to patients who received standard care of TTM initiation during subsequent hospital-based treatment.[12] Patients in the intervention group received trans-nasal evaporative intra-arrest cooling. Upon arriving to the hospital, patients in both groups received TTM with a goal temperature of 32°C–34°C. While the time to target temperature (below 34°C) was significantly shortened in the intervention group (105 min compared to 182 min average), this did not reflect improvements in neurologic outcomes or survival rates. However, there was a trend toward better survival in the group receiving evaporative prehospital cooling, suggesting that additional research is required for this intriguing technology. Taken together with the evidence from Stanger *et al*., prehospital TTM may be valuable in situations involving longer transport times; this question has not yet been the subject of rigorous clinical research.

There are a number of possible explanations for the discrepancy in the data regarding the importance of timing. In particular, the Stanger study measured the time from hospital presentation, while the PRINCESS study measured time from collapse to target temperature. Other confounders in the studies, including prehospital

care variables and postarrest protocol variations, may have also influenced outcomes. Different cooling methods and patient populations may have served to account for greater or diminished benefit. For example, the PRINCESS trial had a significantly lower portion of patients with shockable rhythm (40.8% average across both groups compared to 68.05% in the Stanger study).

Targeted Temperature Management Target Temperature

Of particular current interest is the question of the target temperature in TTM. Previously, the International Liaison Committee on Resuscitation (ILCOR) recommended TTM at 32°C–34°C for patients who remained comatose following cardiac arrest. Following the publication of the TTM Trial, the 2015 update to consensus ILCOR guidelines broadened the recommended target temperature to between 32°C and 36°C.[10] The question of optimal target temperature remains an active question, and some studies have suggested that a lower target temperature standard (33°C) may be more beneficial in certain populations and may even be associated with improved provider adherence.

Previous RCTs supported the administration of TTM between 32°C and 34°C in patients after resuscitation from cardiac arrest. Patients treated with TTM at 32°C–34°C had more favorable neurologic outcomes and a greater chance of survival.[2,3] In 2013, Nielsen *et al*. conducted the TTM Trial to determine if near-normothermic temperature control was equally as effective as the previously recommended 32°C–34°C range. Their study examined the impacts of TTM at 33°C compared with 36°C and found no significant difference in neurologic outcomes or mortality in either group.[9] However, in contrast to the TTM trial findings, a recent multicenter trial by Lascarrou *et al*. comparing postarrest TTM at 33°C with 37°C found significantly improved neurologic outcomes in the 33°C group.[16] Despite conflicting evidence regarding target temperature, the balance of evidence suggests that TTM is preferable to normothermia, and any changes to TTM guidelines should ensure use or quality of TTM therapy is not adversely affected.

The conflicting results from the Nielsen and Lascarrou trials illustrate the confusion around TTM: How low does target temperature have to be? Is the benefit derived from cooler temperatures or is aggressive fever prevention sufficient? A closer look at the studied populations in these two trials provides insight into the differing results. In the TTM trial, the first monitored rhythm in 80% of patients studied was a shockable rhythm (79% in the 33°C group; 81% in the 36°C group). In contrast, Lascarrou studied the impacts of TTM on patients with nonshockable rhythms. Patients with nonshockable rhythms generally represent patients with higher degrees of postarrest injury and worse outcomes. With these populations in mind, it may suggest that the difference between TTM at 33°C or 36°C is less impactful in patients whose condition is less severe at presentation, whereas patients with worse prognoses at time of evaluation benefit from a lower target temperature. In addition, patients in the TTM trial had higher rates of bystander cardiopulmonary resuscitation (CPR) than those that were analyzed in the seminal trials of temperature management at 32°C–34°C by Bernard *et al*. and the Hypothermia After Cardiac Arrest Study Group. The rates of bystander CPR between the trials of Nielsen *et al*. and Lascarrou *et al*. were, however, comparable.[2,3,9,16] In a recent editorial, Polderman and Varon theorized that other confounders may have impacted the results of the TTM trial. Specifically, the higher temperature group in the TTM trial had increased rates of bystander CPR and lower rates of comorbidities. Other confounders, such as cohort demographics and local treatment protocol differences may also make comparison between these different trials challenging.[17]

In addition to the conflicting scientific understanding of TTM "dose" (where "dose" can be thought of as a combination of goal temperature and duration of TTM) presented by these trials, there has been significant misinterpretation of the results of the TTM Trial, with a general interpretation by many providers that the trial suggests that TTM is ineffective by virtue of finding similar outcomes at 36°C versus 33°C. It is important to emphasize that both patient study arms received actively-controlled temperature management, and both groups were maintained at temperatures below normothermia, with high survival rates in both groups compared to previous studies with noncontrolled "usual care" controls. However, the misinterpretation that the TTM Trial proved that TTM was not beneficial may account for the decrease in use of TTM in real-world experience following the publication of the trial. In an analysis of 649 US hospitals, Bradley *et al*. found that use of postarrest TTM dropped from 52.5% in the last 3 months of 2013 – 46.0% in the first 3 months of 2014, following the publication of the TTM trial in December 2013.[18] In their analysis, Bradley *et al*. suggested that the results of the TTM trial imply that avoidance of fever and not hypothermia is protective against neurologic injury. The authors opined that this perspective may have driven providers to try other fever-prevention strategies such as administration of acetaminophen rather than a comprehensive TTM protocol. In Australia, Bray *et al*. examined changes in hospital practices when TTM protocol was changed from 33°C to 36°C, after the publication of the TTM Trial. Bray *et al*. found that the change to 36°C was associated with significantly

lower rates of achieving target temperature as well as a nonsignificant trend toward decreased rates of survival, discharge to home, and favorable neurologic outcome. Patients treated under the 36°C protocol also spent significantly less time at target temperature and had higher rates of fever.[19] Finally, these broadened guidelines, and inclusion of target temperatures closer to normothermia, may have led to the less rigid adherence to TTM protocols.

One other aspect of the debate on goal temperature following OHCA resuscitation is the rate of adverse events. Many studies suggest little to no difference in adverse events between groups with lower target temperatures than those with higher target temperature goals or normothermic patients.[2,3] While Bray *et al*. found a modest increase in rates of shivering ($P < 0.001$) and pneumonia ($P = 0.03$) in the 33°C group compared with the 36°C group, Nielsen *et al*. found no significant differences between adverse effects in the 33°C and 36°C groups of the TTM Trial, except for a slight increased risk of hypokalemia in the 33°C group ($P = 0.018$).[9,19] Furthermore, a sub-study of the patients of the TTM Trial revealed that the hemodynamic impacts of 33°C compared with 36°C – including increased vascular resistance, decreased cardiac output, and lower heart rate—were not present after rewarming.[20] Another sub-study of the TTM Trial demonstrated no difference in rates of bleeding or thrombotic events between 33°C and 36°C groups.[21] The slight variation in adverse events of 33°C compared to 36°C may be relevant in choosing the optimal target temperature for a patient with certain risk factors, but does not seem to affect overall outcomes.

Targeted Temperature Management Duration

In addition to depth of TTM, another component of TTM dose is how long the patient's temperature should be maintained at a specified goal temperature. While clinical trials on the subject are limited, animal studies have demonstrated that longer cooling may yield better outcomes. Che *et al*. performed histological analysis of neuronal survival in rats after cardiac arrest which demonstrated a benefit from longer TTM duration.[22] Rats that received TTM at 33°C for 24 h were found to have on average 42% of normal amounts of CA1 pyramidal neurons, whereas the rats who received the intervention for 48 h had on average 68% of the same neurons (normothermic (37°C), 9%), thus demonstrating greater limitation of brain injury with longer TTM duration.

Clinical studies have not definitively demonstrated the impact of longer TTM duration on clinical outcomes, however. In a study comparing the effects of TTM at 33°C for 24 h and 48 h, Kirkegaard *et al*. found there was a trend that suggested longer cooling (48 h) was associated with more favorable neurologic outcomes, though it was not statistically significant ($P = 0.33$).[23] A smaller study by Soga *et al*. demonstrated that cooling between 24°C and 48°C was associated with lower rates of poor neurologic outcomes compared with cooling for 72 h.[24] Current guidelines recommend TTM for at least 24 h. It may be that cooling is only necessary during an acute phase of care and the remainder of temperature management should be aimed at fever prevention for subsequent days after resuscitation. Further studies are needed to determine what combination of these practices is most beneficial.

Posttargeted Temperature Management Rewarming

Finally, the return to normothermia following TTM remains a poorly studied phase of care. There is little evidence that suggests a specific rewarming regimen. However, what evidence there is supports longer and slower rewarming.[25,26] Bouwes *et al*. found that patients who experienced "normal rewarming rates" (<0.5°C/h) trended towards better outcomes, although it was not significant ($P = 0.08$). In a study examining how the overall time spent rewarming affected outcomes, Hifumi *et al*. found that longer duration of rewarming was associated with favorable neurological outcomes.

In addition to rate of rewarming, some research has investigated the impact of post-TTM rewarming pyrexia, with some data suggesting some pyrexia is associated with better outcomes while others finding that amongst patients who experience pyrexia, higher temperatures are associated with worse outcomes.[27,28] While there is no consensus on rewarming protocols nor the implications of postrewarming pyrexia, it represents an area for further research to maximize the efficacy of post-OHCA care.

Summary

The complexity of the pathophysiology underlying postarrest neurologic damage is reflected in the complexity of treatment regimens like TTM. While evidence is strong that TTM is protective against poor neurologic outcome and in-hospital mortality, additional research is needed to evaluate the specifics of TTM execution to maximize its protective benefits. It is clear that TTM is effective to improve postarrest outcomes and that initiating early is likely beneficial. However, what remains to be agreed upon are the questions of what temperature we should target and for how long. The answer to these is likely more complex as they represent the dose being administered, and with any treatment, the dose may vary from patient to patient. It

may well be, as hinted at in a comparison of the trials of Nielsen *et al*. and Lascarrou *et al*., that patients with more severe presentation require lower temperatures or longer cooling. Patients who, develop fevers following TTM may be demonstrating a functional inflammatory response to injury, while those whose fevers exceed 38°C may be signaling a more severe condition wherein their own healing processes are dysfunctional and cause additional damage.

If this is the answer to the disparate data, reliable markers of injury severity to accurately prescribe the right "dose" of TTM would represent an important contribution. No markers have yet been identified as a fully reliable prognosticator for patients resuscitated from OHCA. Further studies are needed to investigate what these might be, followed by a stratification of patients based on disease severity to determine how the impact of TTM may vary in these populations. Through additional study of serologic and imaging markers of illness, it is possible that TTM in future years will become more "personalized", such that the parameters of TTM dose will be matched to patient physiology and clinical needs.

Author contributions
IM and BA contributed to the conception, drafting and editing of the work.

Conflicts of interest
Dr. Abella acknowledges funding support from the National Institutes of Health related to postarrest care, and speaking honoraria from Becton Dickinson.

Ethical approval
Not applicable for invited review.

Consent to participate
Not applicable, invited review article without human subjects.

Funding
None declared.

References

1. Nolan JP, Berg RA, Andersen LW, Bhanji F, Chan PS, Donnino MW, *et al*. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the utstein resuscitation registry template for in-hospital cardiac arrest: A consensus report from a task force of the international liaison committee on resuscitation (American Heart Association, European resuscitation council, Australian and New Zealand council on resuscitation, heart and stroke foundation of Canada, InterAmerican heart foundation, resuscitation council of Southern Africa, Resuscitation Council of Asia). Circulation 2019;140:e746-57.
2. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56.
3. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, *et al*. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
4. Soga T, Nagao K, Sawano H, Yokoyama H, Tahara Y, Hase M, *et al*. Neurological benefit of therapeutic hypothermia following return of spontaneous circulation for out-of-hospital non-shockable cardiac arrest. Circ J 2012;76:2579-85.
5. Nassal MM, Wan X, Dale Z, Deschênes I, Wilson LD, Piktel JS. Mild hypothermia preserves myocardial conduction during ischemia by maintaining gap junction intracellular communication and Na+ channel function. Am J Physiol Heart Circ Physiol 2017;312:H886-95.
6. Wu C, Xu J, Jin X, Chen Q, Li Z, Zhang M. Effect of mild hypothermia on lung injury after cardiac arrest in swine based on lung ultrasound. BMC Pulm Med 2019;19:198.
7. Gong P, Hua R, Zhang Y, Zhao H, Tang Z, Mei X, *et al*. Hypothermia-induced neuroprotection is associated with reduced mitochondrial membrane permeability in a swine model of cardiac arrest. J Cereb Blood Flow Metab. 2013 Jun;33:928-34.
8. Lei B, Tan X, Cai H, Xu Q, Guo Q. Effect of moderate hypothermia on lipid peroxidation in canine brain tissue after cardiac arrest and resuscitation. Stroke 1994;25:147-52.
9. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, *et al*. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197-206.
10. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, *et al*. Temperature management after cardiac arrest: An advisory statement by the advanced life support task force of the international liaison committee on resuscitation and the American heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation 2015;132:2448-56.
11. Stanger D, Kawano T, Malhi N, Grunau B, Tallon J, Wong GC, *et al*. Door-to-targeted temperature management initiation time and outcomes in out-of-hospital cardiac arrest: Insights from the continuous chest compressions trial. J Am Heart Assoc 2019;8:e012001.
12. Nordberg P, Taccone FS, Truhlar A, Forsberg S, Hollenberg J, Jonsson M, *et al*. Effect of trans-nasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest: The PRINCESS randomized clinical trial. JAMA 2019;321:1677-85.
13. Lindsay PJ, Buell D, Scales DC. The efficacy and safety of pre-hospital cooling after out-of-hospital cardiac arrest: A systematic review and meta-analysis. Crit Care 2018;22:66.
14. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, *et al*. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: A randomized clinical trial. JAMA 2014;311:45-52.
15. Kalra R, Arora G, Patel N, Doshi R, Berra L, Arora P, *et al*. Targeted temperature management after cardiac arrest: Systematic review and meta-analyses. Anesth Analg 2018;126:867-75.
16. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, *et al*. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med 2019;381:2327-37.
17. Polderman K, Varon J. Targeted temperature management after cardiac arrest: And the optimal target is ? Resuscitation 2020;146:263-5.
18. Bradley SM, Liu W, McNally B, Vellano K, Henry TD, Mooney MR, *et al*. Temporal trends in the use of therapeutic hypothermia for out-of-hospital cardiac arrest. JAMA Netw Open 2018;1:e184511.
19. Bray JE, Stub D, Bloom JE, Segan L, Mitra B, Smith K, *et al*. Resuscitation 2017;113:39-43.
20. Bro-Jeppesen J, Hassager C, Wanscher M, Østergaard M, Nielsen N, Erlinge D, *et al*. Circ Cardiovasc Interv 2014;7:663-72.
21. Jacob M, Hassager C, Bro-Jeppesen J, Ostrowski SR, Thomsen HR, Wanscher M, *et al*. Resuscitation 2015;96:260-7.
22. Che D, Li L, Kopil CM, Liu Z, Guo W, Neumar RW. Impact of therapeutic hypothermia onset and duration on survival, neurologic function, and neurodegeneration after cardiac arrest. Crit Care Med 2011;39:1423-30.

23. Kirkegaard H, Søreide E, Haas I, Pettilä V, Taccone FS, Arus U, *et al*. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: A randomized clinical trial. J Am Med Assoc 2017;318:341-50.
24. Soga T, Nagao K, Kikushima K, Wantanabe K, Tachibana E, *et al*. Duration of cooling and time from out-of-hospital cardiac arrest to spontaneous circulation in patients treated with mild hypothermia. Circulation 2007;116:II-436.
25. Bouwes A, Robillard LB, Binnekade JM, de Pont AC, Wieske L, den Hartog AW, et al. Resuscitation 2012;83:996-1000.
26. Hifumi T, Inoue A, Kokubu N, Hase M, Yonemoto N, Kuroda Y, *et al*. Association between rewarming duration and neurological outcome in out-of-hospital cardiac arrest patients receiving therapeutic hypothermia. Resuscitation 2020;146:170-7.
27. Leary M, Grossestreuer AV, Iannacone S, Gonzalez M, Shofer FS, Povey C, *et al*. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation 2013;84:1056-61.
28. Grossestreuer AV, Gaieski DF, Donnino MW, Wiebe DJ, Abella BS. Magnitude of temperature elevation is associated with neurologic and survival outcomes in resuscitated cardiac arrest patients with postrewarming pyrexia. J Crit Care 2017;38:78-83.