

Targeted Temperature Management

Subjects: Critical Care Medicine

Contributor: Kazuya Kikutani

International guidelines recommend targeted temperature management (TTM) to improve the neurological outcomes in adult patients with post-cardiac arrest syndrome (PCAS). Several studies have indicated that the beneficial effect of hypothermic TTM differs according to the severity of PCAS, suggesting that there may be a subgroup of PCAS patients that is especially likely to benefit from hypothermic TTM.

Keywords: Targeted Temperature Management ; post-cardiac arrest syndrome ; large randomized controlled trial ; Clinical Factor

1. History of Randomized Controlled Trial (RCT) for the Setting Temperature during TTM

Fever after cardiac arrest and resuscitation is common ^[1] and can exacerbate brain damage in patients with post-cardiac arrest syndrome (PCAS), which is known as a severe syndrome caused by systemic ischemia-reperfusion after cardiac arrest resuscitation ^[2].

Hypothermic targeted temperature management (TTM) in adult post-cardiac arrest patients has been widely used in clinical practice, ever since the results of two trials published in 2002 suggested its therapeutic benefit ^{[3][4]}. In 2013, Nielsen et al. reported, on the basis of the results of a large randomized controlled trial (RCT) (TTM-1 trial), that there was no difference in the survival or likelihood of a favorable neurological outcome between TTM at 33 °C and TTM at 36 °C in post-cardiac arrest patients with presumed cardiogenic cardiac arrest ^[5]. The TTM-1 trial differed from the previous aforementioned RCTs in that measures were taken to control fever and to maintain normothermia (normothermic TTM), while in the previous two RCTs, no measures were taken for fever control. Considering the results of the TTM-1 trial, current guidelines recommend that the temperature setting for TTM should be in the range of 32 °C to 36 °C, with the actual temperature setting left to the preference of the treating physicians ^[6]. Therefore, many hospitals changed their protocols from hypothermic TTM to normothermic TTM, because normothermic TTM is generally less invasive and is associated with fewer complications. However, a few subsequent studies have reported interesting results in that the prognosis of the patients became worse in some of the hospitals that changed their protocol from hypothermic to normothermic TTM ^{[7][8]}. Thus, the optimal temperature setting temperature for TTM—hypothermic or normothermic—still remains unclear.

Two well-designed RCTs were conducted recently in an attempt to resolve the question. In the first RCT conducted in 2019 in 25 ICUs in France (HYPERION trial), the effects of TTM at 33 °C and 37 °C were compared in post-cardiac arrest patients with a non-shockable rhythm. In this trial, a higher survival rate and a higher rate of a favorable neurological outcome at 90 days (defined as Cerebral Performance Category ≤ 2) were observed in the group that received hypothermic TTM at 33 °C for 24 h compared to the group that received normothermic TTM at 37 °C for 24 h ^[9].

2. Differential Effectiveness of Hypothermic TTM According to the Severity of PCAS as Assessed by a Single Clinical Factor

The differential effect of hypothermic TTM according to the severity of PCAS as assessed by a single clinical factor has been well studied ^{[10][11][12][13]}. Kaneko et al. reported, based on a large database in Japan, that among patients who received hypothermic TTM, the neurological prognosis was better in patients with a time to ROSC of less than 30 min compared to those with a longer time to ROSC ^[10]. Another retrospective study reported that TTM at 32–34 °C improved the neurological outcome at 30 days compared to TTM at 35–36 °C in patients with severe hyperlactatemia (>12 mmol/L) and that the interaction for the outcome between the levels of lactate and the core temperature setting for TTM was significant ^[11]. The current retrospective study showed that PCAS patients who underwent hypothermic TTM had a better neurological outcome than PCAS patients who underwent normothermic TTM if they did not have any findings of hypoxic encephalopathy on brain CT ^[12].

In contrast, Kjaergaard et al. performed a secondary analysis of the data from the TTM-1 trial, which showed that TTM at 33 °C neither reduced the risk of mortality nor improved the neurological outcome as compared to TTM at 36 °C, regardless of the time to ROSC [13]. Therefore, as researchers have mentioned above, it may not be sufficient to consider any single clinical factor to determine the severity of PCAS, and risk classification based on a combination of clinical factors is needed for a more precise analysis of the differential effects of hypothermic TTM according to the severity of PCAS.

3. Differential Effects of Hypothermic TTM According to the Severity of PCAS as Assessed Using a Risk Score Based on Multiple Clinical Factors

To date, few studies have examined the differential effects of hypothermic TTM according to the severity of PCAS. Callaway et al. investigated whether the severity of PCAS—as determined using their risk classification system, PCAC—was associated with any change in the relationship between the target body temperature and patient prognosis [14]. In patients with mild to moderate coma (PCAC 1 or PCAC 2), TTM at 33 °C was associated with a lower survival rate than TTM at 36 °C; however, in patients with moderate coma and severe cardiopulmonary failure (PCAC 3) or severe coma (PCAC 4), TTM at 33 °C was associated with a better outcome than TTM at 36 °C [14]. In this analysis, the researchers excluded patients with severe cerebral edema or a highly malignant electroencephalogram, who are considered as belonging to the highest severity group in whom the outcomes seem to be poor, regardless of the TTM strategy used.

Researchers evaluated the association between the core temperature setting for TTM and the neurologic outcomes in PCAS patients classified according to the rCAST score as having PCAS of high, moderate, and low severity, and examined the effect of TTM at 33–34 °C on the neurological outcome in each group [15]. Among the patients with PCAS of moderate severity, those undergoing TTM at 33–34 °C showed a better neurological prognosis than patients undergoing TTM at 35–36 °C, while no such difference in the prognosis according to the core temperature setting was observed in patients with mild or severe PCAS. These results suggest that the benefit of hypothermic TTM varies according to the severity of PCAS.

4. Who Are the Most Suitable Candidates for Hypothermic TTM?

Considering that previous animal studies indicated that hypothermic TTM provided no benefit if the brain ischemia had progressed beyond a certain level [16][17], PCAS patients with a poor prognosis are unlikely to show a favorable neurological outcome regardless of the treatment adopted, including hypothermic TTM. It may also not be surprising to consider that hypothermic TTM would be of no benefit to those with minimal or non-existent brain damage. Thus, the patient group that is especially likely to derive benefit from hypothermic TTM is the group with PCAS of moderate severity. This hypothesis is partly supported by the two recent clinical studies mentioned above [14][15], while additional RCT(s) would be needed to confirm this hypothesis.

Not only has the optimal temperature setting of TTM for each severity not been studied yet, but neither has the optimal time to reach the target body temperature nor the optimal duration of the TTM for each severity, so future research addressing these issues is of great interest. Today, several new RCTs for TTM for post-cardiac arrest patients are ongoing, such as the ICECAP study, which is to compare the duration of hypothermic TTM [18]. These results are eagerly anticipated for a better understanding of the best strategy of TTM for post-cardiac arrest patients. Please also note that researchers focused on the beneficial effect of hypothermic TTM for patients with out-of-hospital cardiac arrest (OHCA) and did not mainly mention those with in-hospital cardiac arrest (IHCA). Because the characteristics of IHCA patients differ from OHCA patients [19][20], the evidence for hypothermic TTM in OHCA patients may not be directly applicable in IHCA patients. A large RCT to compare hypothermic TTM and normothermic TTM that focuses on the patients with IHCA is needed in the future.

References

1. Gebhardt, K.; Guyette, F.X.; Doshi, A.A.; Callaway, C.W.; Rittenberger, J.C.; Post Cardiac Arrest, S. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. *Resuscitation* 2013, 84, 1062–1067.
2. Stub, D.; Bernard, S.; Duffy, S.J.; Kaye, D.M. Post cardiac arrest syndrome: A review of therapeutic strategies. *Circulation* 2011, 123, 1428–1435.
3. 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.

4. Bernard, S.A.; Gray, T.W.; Buist, M.D.; Jones, B.M.; Silvester, W.; Gutteridge, G.; Smith, K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N. Engl. J. Med.* 2002, 346, 557–563.
5. Nielsen, N.; Wetterslev, J.; Cronberg, T.; Erlinge, D.; Gasche, Y.; Hassager, C.; Horn, J.; Hovdenes, J.; Kjaergaard, J.; Kuiper, M.; et al. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. *N. Engl. J. Med.* 2013, 369, 2197–2206.
6. Panchal, A.R.; Bartos, J.A.; Cabanas, J.G.; Donnino, M.W.; Drennan, I.R.; Hirsch, K.G.; Kudenchuk, P.J.; Kurz, M.C.; Lavonas, E.J.; Morley, P.T.; et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2020, 142, S366–S468.
7. Bray, J.E.; Stub, D.; Bloom, J.E.; Segan, L.; Mitra, B.; Smith, K.; Finn, J.; Bernard, S. Changing target temperature from 33 °C to 36 °C in the ICU management of out-of-hospital cardiac arrest: A before and after study. *Resuscitation* 2017, 113, 39–43.
8. Salter, R.; Bailey, M.; Bellomo, R.; Eastwood, G.; Goodwin, A.; Nielsen, N.; Pilcher, D.; Nichol, A.; Saxena, M.; Shehabi, Y.; et al. Changes in Temperature Management of Cardiac Arrest Patients Following Publication of the Target Temperature Management Trial. *Crit. Care Med.* 2018, 46, 1722–1730.
9. Lascarrou, J.B.; Merdji, H.; Le Gouge, A.; Colin, G.; Grillet, G.; Girardie, P.; Coupez, E.; Dequin, P.F.; Cariou, A.; Boulain, T.; et al. Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm. *N. Engl. J. Med.* 2019, 381, 2327–2337.
10. Kaneko, T.; Kasaoka, S.; Nakahara, T.; Sawano, H.; Tahara, Y.; Hase, M.; Nishioka, K.; Shirai, S.; Hazui, H.; Arimoto, H.; et al. Effectiveness of lower target temperature therapeutic hypothermia in post-cardiac arrest syndrome patients with a resuscitation interval of ≤ 30 min. *J. Intensive Care* 2015, 3, 28.
11. Okazaki, T.; Hifumi, T.; Kawakita, K.; Kuroda, Y.; Japanese Association for Acute Medicine out-of-hospital cardiac arrest registry. Targeted temperature management guided by the severity of hyperlactatemia for out-of-hospital cardiac arrest patients: A post hoc analysis of a nationwide, multicenter prospective registry. *Ann. Intensive Care* 2019, 9, 127.
12. Nishikimi, M.; Ogura, T.; Nishida, K.; Takahashi, K.; Fukaya, K.; Liu, K.; Nakamura, M.; Matsui, S.; Matsuda, N. Differential effect of mild therapeutic hypothermia depending on the findings of hypoxic encephalopathy on early CT images in patients with post-cardiac arrest syndrome. *Resuscitation* 2018, 128, 11–15.
13. Kjaergaard, J.; Nielsen, N.; Winther-Jensen, M.; Wanscher, M.; Pellis, T.; Kuiper, M.; Hartvig Thomsen, J.; Wetterslev, J.; Cronberg, T.; Bro-Jeppesen, J.; et al. Impact of time to return of spontaneous circulation on neuroprotective effect of targeted temperature management at 33 or 36° in comatose survivors of out-of hospital cardiac arrest. *Resuscitation* 2015, 96, 310–316.
14. Callaway, C.W.; Coppler, P.J.; Faro, J.; Puyana, J.S.; Solanki, P.; Dezfulian, C.; Doshi, A.A.; Elmer, J.; Frisch, A.; Guyette, F.X.; et al. Association of Initial Illness Severity and Outcomes After Cardiac Arrest With Targeted Temperature Management at 36 °C or 33 °C. *JAMA Netw. Open* 2020, 3, e208215.
15. Nishikimi, M.; Ogura, T.; Nishida, K.; Hayashida, K.; Emoto, R.; Matsui, S.; Matsuda, N.; Iwami, T. Outcome Related to Level of Targeted Temperature Management in Postcardiac Arrest Syndrome of Low, Moderate, and High Severities: A Nationwide Multicenter Prospective Registry. *Crit. Care Med.* 2021, 49, e741–e750.
16. Nozari, A.; Safar, P.; Stezoski, S.W.; Wu, X.; Kostelnik, S.; Radovsky, A.; Tisherman, S.; Kochanek, P.M. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation* 2006, 113, 2690–2696.
17. Janata, A.; Bayegan, K.; Sterz, F.; Weihs, W.; Holzer, M.; Sipos, W.; Springler, G.; Behringer, W. Limits of conventional therapies after prolonged normovolemic cardiac arrest in swine. *Resuscitation* 2008, 79, 133–138.
18. Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients. Available online: <https://ClinicalTrials.gov/show/NCT04217551> (accessed on 18 November 2021).
19. Engsig, M.; Soholm, H.; Folke, F.; Gadegaard, P.J.; Wiis, J.T.; Molin, R.; Mohr, T.; Engsig, F.N. Similar long-term survival of consecutive in-hospital and out-of-hospital cardiac arrest patients treated with targeted temperature management. *Clin. Epidemiol.* 2016, 8, 761–768.
20. Andersen, L.W.; Holmberg, M.J.; Berg, K.M.; Donnino, M.W.; Granfeldt, A. In-Hospital Cardiac Arrest: A Review. *JAMA* 2019, 321, 1200–1210.

