

Door-to-Targeted Temperature Management Initiation After Out-of-Hospital Cardiac Arrest: A New Quality Metric in Postresuscitation Care?

Aldo L. Schenone, MD; Venu Menon, MD

The administration of targeted temperature management (TTM) is considered standard of care in the treatment of comatose cardiac arrest survivors, particularly those with out-of-hospital cardiac arrest stemming from a shockable rhythm.^{1,2} Despite the lack of high-quality evidence, current resuscitation guidelines encourage that TTM also be considered for unresponsive survivors of in-hospital cardiac arrest or cardiac arrest stemming from a nonshockable rhythm² as the intervention appears to provide a net overall benefit.³ Despite advances in postresuscitative care and routine use of TTM, the prognosis of comatose arrest survivors continues to be dismal. The dominant mechanism of death after a cardiac arrest is related to brain injury arising because of the combination of ischemia during the arrest and ensuing ischemia-reperfusion injury on return of spontaneous circulation (ROSC).^{4,5} The remaining deaths after an arrest are a consequence of circulatory collapse in the setting of shock, resulting from initial cardiac dysfunction that is accompanied by a profound vasodilation and multiorgan failure.^{4,5} The observed benefits of TTM in cardiac arrest are mainly attributed to the reduction of brain metabolism and attenuation of the ischemia-reperfusion cascade, whereas others propose an adjunctive cardioprotective effect.⁶

Although a class I recommendation, the optimal TTM prescription for unresponsive arrest survivors remains largely unknown, and current practice predominantly mirrors landmark trial proceedings with minor adaptations. Endovascular and surface cooling remain the most used methods to

decrease and maintain core temperature (surface and endovascular) during TTM and have been associated with similar clinical outcomes. Current guidelines discourage the routine infusion of large volumes of ice-cold solution before hospital admission and immediately after ROSC because of concerns for harm, whereas high-quality clinical data are lacking for novel methods, such as the cooling helmet and intranasal cooling.^{7–9} Recent trials have established that active cooling is associated with similar outcomes when using temperature targets of 32°C to 36°C,^{2,10} and prolonged duration of cooling appears to confer no additional benefit and is rather associated with higher complication rates and longer intensive care length of stay.¹¹

The timing of hypothermia initiation after ROSC has been extensively evaluated. Although animal data suggested an incremental benefit with cooling initiated as early as within 15 minutes from ROSC, human observation studies have reported mixed results.¹² Although some reports suggested that TTM administration in this setting was time sensitive, others failed to identify such an association.^{13–16} The excitement about faster TTM initiation after ROSC was tempered by the negative results of 7 randomized studies comparing prehospital cooling, either during arrest or shortly after, against standard hospital initiation of TTM.¹⁷ The interpretation of these trials was hampered by important design flaws, including small sample sizes, lack of blinding of outcomes assessment, absence of mandated rewarming protocols, and a significant proportion of patients who did not receive the intended treatment. In addition, concerns exist that the prehospital induction with large volumes of ice-cold solution, as the designated test intervention, might have adverse consequences that confounded the results.^{17,18} Consequently, whether earlier initiation with TTM provides incremental benefit in cardiac arrest survivors remains debatable.

The report by Stanger et al¹⁹ in this issue of the *Journal of the American Heart Association (JAHA)* offers relevant evidence to the ongoing debate about the ideal timing of TTM initiation. Using data collected in British Columbia, Canada, from the CCC (Trial of Continuous or Interrupted Chest

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From the Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH.

Correspondence to: Venu Menon, MD, Cleveland Clinic Lerner College of Medicine, 9500 Euclid Ave, Cleveland, OH 44195. E-mail: menonv@ccf.org
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Compression During cardiopulmonary resuscitation), the investigators conducted a post hoc analysis evaluating the association between the time from hospital admission to TTM initiation (namely, door-to-TTM time [DTT]) and survival with favorable neurological outcome.

A total of 570 patients from the 3805 patients who experienced out-of-hospital cardiac arrest met inclusion criteria. Enrollment was restricted to those surviving to hospital admission and undergoing TTM. The cohort was mainly composed of middle-aged men presenting with a shockable rhythm. Patients underwent TTM using surface cooling (99.7%) and were dichotomized into those with DTT shorter than (early DTT) or longer than (delayed DTT) the median DTT of 122 minutes. The early DTT group exhibited a median DTT of 35 minutes (interquartile range, 20–81 minutes), whereas the delayed group had a median DTT of 218 minutes (interquartile range, 167–319 minutes). The early DTT group was a slightly less sick cohort given the marginally higher proportion of shockable rhythm, witnessed arrest, cardiopulmonary resuscitation by bystander with slightly shorter time to ROSC, and associated higher pH on admission. After adjustment for age, sex, initial rhythm, witnessed status, location of arrest, and time to ROSC, early DTT was associated with higher survival to hospital discharge (adjusted odds ratio, 1.56; 95% CI, 1.02–2.38), although it was not associated with good neurological outcome (adjusted odds ratio, 1.45; 95% CI, 0.94–2.22); this was a likely function of power rather than treatment effect. When restricting analysis to those with shockable rhythm, early DTT was independently associated with higher rates of both survival (adjusted odds ratio, 1.82; 95% CI, 1.1–3.0) and favorable neurological outcomes (adjusted odds ratio, 1.79; 95% CI, 1.09–2.95). On the basis of these findings, the authors hypothesized that an expedited initiation of in-hospital TTM, specifically in those presenting with shockable rhythm, would translate into better survival and neurological outcomes at hospital discharge.

As a post hoc analysis, this study used high-quality data that were subjected to the most rigorous controls expected from a randomized clinical trial. It included a relatively large sample size for a study involving a postarrest cohort undergoing TTM, and appropriate statistical analyses and adjustment for relevant available covariates were conducted. Authors acknowledged the limitations related to the post hoc study design and recognized that important comorbidities, such as cardiac risk factors and left ventricular ejection fraction, among others, were not available for analysis. The implications of missing comorbidities are uncertain as the association between comorbidity burden before cardiac arrest and postarrest outcomes remains debatable, with mixed results.^{20,21} An important limitation of this study is the lack of reporting of complications (eg, rearrest and hemodynamic instability) and/or interventions (eg, mechanical support and

percutaneous coronary intervention) within the DTT that could have forced a delay. Although the authors enumerated the potential reasons behind DTT delays (lack of streamlined postarrest care, competing procedures, inexperience, or contraindication for hypothermia), the specific reasons behind the delay (forced versus system) in TTM initiation are not reported. As a result, the sceptic could argue that DTT delays are simply a surrogate for a sicker population with higher in-hospital complications (rearrest and hemodynamic instability) that delay TTM initiation and result in worse observed outcomes. Postarrest management is not limited to initiation of cooling alone; and fever prevention, controlled rewarming, hemodynamic goals after resuscitation, neurological prognostication, ventilator care, and seizure management all influence outcome. Initiation of early TTM may, thus, simply be a marker of the availability of high-quality postresuscitative care and not a direct cause of the benefit observed.

The findings of this study have potential implications in clinical practice. Given the absence of harm, the study should encourage the early initiation of TTM after hospital admission. It is sobering to note that in the current era, a large number of patients were excluded from study participation because they were never offered TTM despite achieving ROSC and initially surviving out-of-hospital cardiac arrest. The study is also a clarion call for developing centers of expertise in postresuscitative care and creating protocols that will drive consistent and timely care in this population. Over the past 20 years, patient outcomes in ST-segment–elevation myocardial infarction, like trauma in the past, have dramatically improved by the creation of regional systems of care. Although similar systems for out-of-hospital cardiac arrest have been proposed, these remain few and far between.²² The time to act is now.

Disclosures

None.

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