Targeted temperature management after cardiac arrest: when, how deep, how long?

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Improving outcomes for patients who are resuscitated from cardiac arrest but remain comatose has been challenging. Over 50 years ago, Peter Safar, when describing what we now know as the ABCs of cardiopulmonary resuscitation, included the induction of hypothermia for patients who do not show signs of neurologic recovery within 30 minutes, utilizing this in a case report (1). At the time, it was felt that cooling below 32 ℃ was necessary for benefit as these temperatures were already utilized for preservation during cardiac surgery. The idea was that if blood flow to the brain was absent or inadequate, decreasing brain metabolic needs with hypothermia could allow better matching of oxygen delivery and consumption. Maintaining these temperatures was challenging and fraught with complications, such as bleeding and infections. Consequently, induction of post-resuscitation hypothermia did not become widespread for many years.

In the 1980s, laboratory studies demonstrated that mild cooling (33–34 ℃) was beneficial compared to normothermia or cooling to lower temperatures, though it seemed that cooling had to be induced very quickly after restoration of spontaneous circulation (ROSC) (2,3). In 2002, two randomized clinical trials demonstrated that cooling to 32–34 ℃ for 12–24 hours improved outcomes, even though cooling didn't begin for over 1.5 hours and target temperature wasn't achieved until 8 hours after ROSC (4,5). The results of these trials had an almost immediate impact upon the care of comatose survivors of cardiac arrest. Clinicians who had previously been very frustrated with poor outcomes after cardiac arrest and failures of previous trials (6) were eager to implement a therapy that had great potential for improved outcomes. Adherence to the hypothermia protocols outside of clinical trials showed benefit. Various techniques and devices for cooling were studied, but none appeared to be better than others.

More recently, the results of the two landmark studies of 2002 have been questioned because many patients in the normothermic groups may have actually been hyperthermic, which is well accepted to be associated with worse neurologic outcomes. Subsequently, in the targeted temperature management (TTM) trial temperature was actively controlled at either 33 or 36 ℃ (7). Over 900 patients were enrolled, making this study much larger than the previous studies combined. Similar to the previous studies, target temperature was not reached for several hours after randomization. Since patients were admitted with temperatures near 35 ℃, patients in the 36 ℃ were actually warmed to reach the target temperature. Nonetheless, the study demonstrated no outcome differences between the 33 and 36 ℃ groups. Subsequently, the American Heart Association and the European Resuscitation Council recommended that comatose patients after cardiac arrest should be treated with TTM at 33–36 ℃ for 24 hours (8,9).

Though previous laboratory studies and clinical trials have explored different temperatures, they almost

universally have included only one time for initiation of cooling and one duration of hypothermia. In essence, a "one size fits all" approach to timing has been applied in these studies, leaving clinicians with important questions about the most appropriate timing, duration, and depth of hypothermia.

The optimal duration for TTM remains unclear. In one laboratory study, 48 hours of hypothermia reduced neuronal degeneration more than 24 hours (10). In an attempt to define the optimal duration of TTM in patients, Kirkegaard *et al.* have recently compared 24 *vs.* 48 hours of cooling to 33 °C for comatose survivors of cardiac arrest (11). Testing of this doubling of the cooling duration makes sense as it would be easy to implement clinically and could answer the question of whether or not longer cooling is better. In a sense, this is doubling the "dose" of hypothermia. The time from ROSC to achievement of target temperature was around 5 hours overall, but was shorter in the 48 hours group. They found no difference in long-term favorable neurologic outcome (Cerebral Performance Category 1 or 2), mortality, or hospital length of stay. Adverse outcomes were more common with more prolonged cooling.

This study included several high quality aspects. Clinicians were required to continue patient management for at least 72 hours unless brain death or refractory shock ensued. Multimodal assessments were conducted by independent clinicians at 72 hours. This approach is critical to avoid self-fulfilling prophecies with early withdrawal of life sustaining therapies. The clinical teams could not be blinded to the group assignments, however, but the final outcome analysis was performed by a blinded assessor.

The only significant limitation of this trial is its size. The study was powered to detect a 15% absolute difference in favorable neurologic outcomes, perhaps too ambitious a goal. Consequently, only 355 patients were enrolled. Perhaps a significant difference would have been found with a larger sample size, but this study did not reveal much of a signal.

Comparing the 33 °C for 24 hours group in the study by Kirkegaard *et al.* (11), with the equivalent group in the TTM trial (7), there appears to be better outcomes in terms of good functional outcome at 6 months in the former compared to the latter. It's difficult to develop a clear hypothesis as to why this may be true. The study inclusion criteria and patient demographics were similar. Though the TTM trial does not explicitly state the time to target temperature (the temperature figure begins at the time of randomization, already well after ROSC), it appears that this timing may have been longer than that in the study by Kirkegaard *et al.* (11). One could speculate that earlier cooling had an impact, though the general consensus is that the literature does not support earlier cooling. Previous studies of early, or even prehospital, cooling have not demonstrated clear benefit. Time to target temperature has not correlated with outcome in numerous trials. One of the confounders with looking at cooling time is that patients with more severe neurologic deficits tend to cool faster than those with lesser deficits (12).

What do the findings of the Kirkegaard mean? It is certainly possible that there actually is a difference in outcomes between 24 and 48 hours of TTM and this study was underpowered to demonstrate this difference. Would it actually be appropriate to repeat this study with a larger sample size? It seems unlikely that one would find a truly clinically-relevant difference even if such a study demonstrated a statistical difference.

Another possibility is that there is no difference between 24 and 48 hours, but 72 hours is actually better. Without good laboratory data to substantiate this hypothesis, it would be difficult at this juncture to justify a study of even more prolonged TTM. There are clearly risks associated with therapeutic hypothermia, including shivering, coagulopathy, and infections. These risks would likely increase with more prolonged cooling. The current study already suggests an increase in complications at 48 hours.

For future studies related to dose of an intervention in resuscitation trials, Callaway has made several important recommendations (13): (I) the use of continuous measures, rather than dichotomous variables, can improve power and thus reduce sample size; (II) ancillary care provided by the critical care team may counter the detrimental effects of a less efficacious intervention. While ancillary care may be very difficult to control, measuring these interventions may be possible; (III) dose-finding trials may be more relevant if the dose of the intervention is titrated to different targets, rather than set to a specific dose. The challenge for studies focused on good neurologic outcome after cardiac arrest is that there are no established targets. One could monitor intracranial pressure or cerebral oxygenation, but this may necessitate invasive procedures that would not be justified otherwise.

In conducting clinical trials to demonstrate the utility of a particular intervention, it's typical to utilize fairly narrow inclusion criteria to make the groups as uniform

and equivalent as possible. For example, one might conduct a clinical trial in cancer patients with tumors that have the same cellular morphology and same clinical staging. When dealing with emergency situations, this approach becomes impossible. A patient must be enrolled in a timely fashion, without the opportunity to obtain detailed information. Thus the groups become heterogeneous, resulting in the possibility that some patients may have benefited from the intervention, while others may have suffered harm. When it comes to cardiac arrest victims, is it possible that the patients with more severe ischemic insults would benefit more than those with lesser insults? The challenge will be to determine the best biomarker to differentiate these patients. Right now, we don't know.

One of the scientific problems with implementing TTM is that we are not sure of the pathophysiologic basis for its benefit. Certainly cooling by only 3–4 ℃ does not have a significant impact upon oxygen metabolism. There is evidence that hypothermia affects a multitude of biochemical pathways and organ systems, including free radical production, apoptosis and mitochondrial dysfunction, inflammation, neuroexcitotoxicity, and vascular permeability (14). Perhaps the finding that hypothermia is beneficial after cardiac arrest despite the failures of other therapies is specifically because it targets multiple pathways. Each of these pathways have different timing. If we had a better idea of which of these pathways are most important, we could better target the timing and depth of hypothermia.

TTM as currently recommended improves outcomes in comatose survivors of cardiac arrest compared to no temperature control. So far, we have not determined any timing of initiation, specific temperature targets, or duration of TTM that have a definitive impact. As basic science research into the mechanisms of action of hypothermia gives us better answers, we can hopefully use biomarkers to personalize the temperature targets for each patient in order to maximize the patient's chances of good functional neurologic outcome.

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None.

Footnote

Conflicts of Interest: SA Tisherman is a co-author of a patent for "Emergency Preservation and Resuscitation Method".

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