

## EDITORIAL

# Therapeutic hypothermia: is it about the temperature?

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The publication in the *New England Journal of Medicine* in November 2013 of the Targeted Temperature Management (TTM) study,<sup>1</sup> which enrolled 950 comatose post-cardiac arrest (CA) patients and randomized these to a temperature of 33°C or 36°C, has raised many questions. One question was answered: there was no difference in outcome, either with regard to survival or neurological outcome when a comatose post-cardiac arrest patient was treated with a temperature of 33°C or 36°C. Discussion has now started about the role of therapeutic hypothermia (TH) or TTM as it is nowadays called, for the comatose post-CA patient.

After the evolution of modern cardiopulmonary resuscitation with the continuum of basic life support including closed chest compressions and mouth-to-mouth ventilation, as well as advanced life support including defibrillation, intubation and ventilation, and drugs such as epinephrine and anti-arrhythmics and their subsequent implementation, first in hospitals and later through community wide programmes, there came the realisation that despite all efforts, the outcome of unselected out-of-hospital cardiac arrest remained dismal. Furthermore, and not enthused by the overall grim outcome, critical care physicians adopted a wait-and-see approach, and for decades it was thought that in these patients the ‘damage was done’ and that there was no therapeutic intervention that could lead to a better outcome.

In 2002 however, in a single issue of the *New England Journal of Medicine*, two studies were published, both on therapeutic hypothermia. The study by Steven Bernard,<sup>2</sup> with 77 patients who remained unconscious after resuscitation from cardiac arrest (of presumed cardiac cause, with an initial shockable rhythm), was quasi-randomized, and the HACA trial,<sup>3</sup> that included similar patients, although highly selected (275 out of 3551 patients), were to be treated with therapeutic hypothermia (32°C to 34°C for 12 to 24 hours) and compared to standard treatment. These studies, whatever their flaws, changed the landscape of post-CA care dramatically. Post-anoxic

encephalopathy was now considered as a treatable condition, and survival of over 50% of comatose post-CA patients was reported regularly.

However, doubt remained about the effect of therapeutic hypothermia. Both 2002 TH studies had methodological flaws – no power calculations, no controlled randomization in the Bernard study, a very long inclusion period in the HACA trial, no clear protocol for prognostication, no data on sedation, ventilation, and other modes of treatment, that may have been different if the treatment group. So, while there was significant difference in outcome between the groups in these studies, it was not certain that this difference was due to temperature management alone. This doubt led to the study design behind the TTM study, which was to provide more solid proof for the use of TH/TTM by controlling all other circumstances and treatment modalities. In the protocol, the possibility of TTM having no effect or even an adverse effect was taken into account. The editorial by Rittenberger and Callaway accompanying the publication of the TTM paper<sup>4</sup> emphasizes the importance of temperature control: ‘*One interpretation of these results is that they reinforce the importance of controlling temperature, even while they question whether 33°C is the best temperature. For example, many patients in the “normothermia” group of the older trials actually became hyperthermic, which is deleterious. The exceptional rates of good outcomes in both the 33°C and 36°C groups in the present trial may reflect the active prevention of hyperthermia. Whatever the mechanisms, it seems clear that we should not regress to a pre- 2002 style of care that does not manage temperature at all. Perhaps the most important message to take from this trial is that modern, aggressive care that includes attention to temperature works, making survival more likely than death when a patient is hospitalized after CPR. In contrast to a decade ago, one half instead of one third of patients with return of spontaneous circulation after CPR can expect to survive hospitalization. Few medical situations have enjoyed such absolute improvement over the same time period.*’

While the statement concerning ‘modern, aggressive care’ is most probably true, the statement concerning temperature control is lacking evidence derived from properly controlled studies. Despite this lack of convincing evidence, the International Liaison Committee on Resuscitation (ILCOR) issued a statement,<sup>5</sup> in which they assert: *‘A key message from this study is that targeted temperature management (TTM) remains an important component of the post resuscitation care of the unconscious cardiac arrest patient and that similar results were obtained when either 33°C or 36°C were selected as target temperature. As detailed by the study investigators and the authors of the accompanying editorial, this study does not support a treatment strategy where TTM is abandoned. (...) Pending formal Consensus on the optimal temperature, we suggest that clinicians provide post-resuscitation care based on the current treatment recommendations.’*<sup>6,7</sup> We accept that some clinicians may make a local decision to use a target temperature of 36°C pending this further guidance.’

It was not only the TTM study that was unable to provide convincing proof for TH/TTM; but also the study by Kim et al.<sup>8</sup> recently published in *JAMA*, that did not show a positive effect of prehospital or hospital cooling on outcome. Although the investigators were able to reduce the time needed to reach a temperature of 34°C, the study did not show improved survival or neurological status in patients resuscitated from prehospital VF or those without VF.

This leaves us with the question as to what the role of TH/TTM really is. There is no doubt that cooling the brain is useful before a circulatory arrest occurs; there remains, however, doubt that it is useful after the circulatory standstill. But why then did both the Bernard study and the HACA trial show a positive outcome? One hypothesis may be that the TH resulted in other, unforeseen and unintended consequences. As TH/TTM leads to a disbalance of metabolism, much more attention to detail is needed while treating post-CA patients. As cooling most often demands sedation, the patients need to be properly ventilated, often in a controlled mode. Sedation leads to delaying prognostication, which in itself may lead to a better outcome:

physicians are notoriously bad in predicting outcome.<sup>9</sup> Most comatose post-CA patients who survive to the ICU, and who die of what we call ‘neurological complications’ die because we stop or limit treatment. We withhold life sustaining treatment based on the literature on prognostication which by definition is based on patients treated with less advanced protocols.

So, the most important questions are perhaps not whether we should continue to use TTM, or whether we should use 33°C or 36°C. We need to consider the possibility of the temperature not being the most crucial part of treatment. We should not lose sight of all other treatment details that may account for much of the progress we have made over the years: sedation, ventilation, hemodynamic optimisation, infection prevention, delay of prognostication, and more robust protocols for making predictions and probably other factors that we have not yet recognized to be important.

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