Letter to the Editor

How long should comatose patients resuscitated from cardiac arrest be cooled?

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Patients resuscitated from cardiac arrest (CA) suffer to a greater or lesser degree from post CA syndrome due to ischaemia and reperfusion injuries. In order to minimize the detrimental cerebral effects of this syndrome it is recommended that resuscitated patients be cooled to a temperature within the range 32 to 36 ℃ for at least 24 hours. The use of hypothermia has been implemented in clinical practice after the publication of two landmark studies in 2002. Although many experimental studies suggested beneficial effects since decades in different forms of brain injury, there are still many unanswered questions to be investigated concerning hypothermia or the targeted temperature management (TTM), as it is defined nowadays. How fast should we cool, how long can we wait to start before the effectiveness of the treatment is lost, how low should we go, how fast should we rewarm, and how long should we cool? Remarkably, neither of the two landmark studies argues or discusses why they selected to cool for 12 and 24 hours, respectively, nor do they discuss whether another choice of cooling time could result in a better or worse outcome. It seems as though the duration of cooling was somewhat arbitrarily chosen.

Nevertheless, beneficial effect of prolonged cooling has been demonstrated in animal studies. In a CA swine model, Suh *et al.* showed that 48-hour cooling was more effective in attenuating brain apoptosis than 24-hour duration (1). In another study, Che *et al.* likewise demonstrated that neurodegeneration after CA was reduced in rats cooled for 48 hours compared to 24 hours (2). In human adults there are case series reporting on cooling for more than 24 hours, while the resent TTH48 trial (3) was thus far the only randomized clinical trial (RCT) evaluating this question. Observational studies reported conflicting results, Bisschops *et al.* nicely demonstrated in a prospective study that 72 hours of hypothermia following CA was associated with a lower inflammatory response during rewarming (4). In a Japanese study that included 237 patients, however, there was no difference in favorable outcome rates when patients were cooled for either more, or less, than 28 hours (5). In children resuscitated from CA, TTM was investigated in the randomized THAPCA trial comparing 48 hours of TTM to normothermia. The conclusion of this study was that hypothermia did not confer a significant benefit in this setting. The study has been largely criticized because a lack of power analysis and survival in the hypothermia group was 8% higher than the control group. In neonates, the message is clear. A meta analyses including 11 randomized controlled trials and, comprising 1,505 term and late preterm infants cooled for 72 hours (in two studies for 48 hours) found a statistically significant reduction in the combined outcome

of mortality or major neuro-developmental disability at 18 months of age (6). However, the pathophysiology may be different in neonates compared to adults and these data cannot be extrapolated to other settings that neonatal CA.

In an editorial published in this journal, Poldermann nicely discusses this specific question: how long should we cool? He begins by describing the detrimental effect of hyperthermia. Several papers have shown an association between fevers and poor outcome following rewarming from TTM in CA (7), and it is generally accepted that fever should be actively treated. However, whether the association of fever with poor outcome is causal or just represents a sign of severe hypoxic brain damage, remains unknown. Thereafter, Poldermann explains the metabolic consequences of hypothermia and exposes the pathophysiology behind animal studies. Importantly the majority of destructive processes last for a period of 48 to 72 hours. This may explain why the neonatal studies investigated and recommended 72 hours of hypothermia. It may also supports studies of 48–72 hours in adults as proposed by Poldermann although data remain scarce.

If the results from the TTM trial (8), that showed no difference in neurological outcome between groups cooled to 33 or 36 ℃, are considered together with the results from the TTH48 trial (3), showing no difference between 24 and 48 hours of cooling, one may argue whether it is more appropriate to speak in terms of optimal "dose" of TTM rather than depth and duration. Hypothermia "dose" would represent the combination of time and depth during which a patient is exposed to cooling procedures. As an example, a combination of longer cooling and deeper cooling (i.e., high cooling dose) was associated with a higher risk of harm in neonatal CA (9). Similarly, a change in TTM protocols with a higher temperature target (i.e., 36 ℃ instead of 33 ℃) was associated to a lower compliance to keep patients within target temperatures over time, which resulted in low cooling dose and a trend towards worse outcomes (10).

Finally, Polderman discusses about the safety of prolonged cooling for 48 hours after CA as well as the results and power calculation of the TTH-48 trial. If a larger beneficial effect should be expected in a trial comparing different durations of cooling, it is possible that TTM methods should be pre-defined, as more recent and effective devices could provide a better quality of TTM than older methods. It is also possible that a larger beneficial effect could be seen in identified specific subgroup of patients' population (i.e., shockable rhythm with younger age). Alternatively, if the severity of the initial insult is better stratified, using some available scales, such as the hypothermic-ischemic ratio (i.e., the ratio between the time to return of spontaneous circulation and the total time from this point to the time the patient reached 37 ℃) (11). In the light of the TTM-2 study that just has started and will randomize 1,900 patients to cooling or just avoiding fever after CA, TTM for 48 hours is a safe therapy in resuscitated patients after CA and deserves further analysis in future studies.

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Footnote

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