Editorial

Cooling after cardiac arrest—the longer the better?

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Provenance: This is an invited Editorial commissioned by the Section Editor Lei Huang (Cardiac Center of Tianjin Third-Central Hospital, Tianjin, China).

Comment on: Kirkegaard H, Søreide E, de Haas I, *et al.* Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA 2017;318:341-50.

Submitted Feb 06, 2018. Accepted for publication Feb 27, 2018.
doi: 10.21037/jtd.2018.07.96
View this article at: http://dx.doi.org/10.21037/jtd.2018.07.96

Temperature plays a key role in the development of acute neurological injuries. Numerous animal experiments have convincingly demonstrated that temperature elevation (either spontaneous/infection related or induced by external warming) can significantly exacerbate all types of neurologic injury; in fact, the magnitude of fever-induced increase in injury is similar to the effects of severe hypoperfusion or severe hypoxia (1-4). This effect has been demonstrated in numerous animal models including rodents, cats, dogs, sheep, pigs, and primates, and in all types of neurologic injury (cardiac arrest, ischemic stroke, traumatic brain injury and haemorrhagic stroke). More than 40 observational studies have confirmed a link between temperature elevations and increased neurological damage and adverse outcome in various types of neurological injury (3-9). Some of these studies have shown that the effects of fever are dose-dependent, i.e., the greater the fever burden/time spent at high temperatures, the greater the extent of injury and likelihood of poor outcome (4-9). Such observations strongly suggest that the link is causal, i.e., fever is directly causing the additional injury. In these studies, the differences persist on multivariate analysis, and occur regardless of the presence of infection (i.e., are present both for infectious and non-infectious fever). Hyperthermia has also been linked to increased risk of complications such as haemorrhagic conversion in patients with ischemic stroke (6). Preliminary evidence suggests that controlling fever could improve neurological outcome (10), although there are as yet no conclusive data from randomized controlled trials (RCTs) proving this.

In animal experiments fever prevention decreases neurological injury, while induction of hypothermia further mitigates the damage. In other words, hypothermia has more protective effects than fever control. When looking at the more than 20 processes that underlie post-ischemic neurologic injury [described in detail in reference 2 (2)], the following fundamental factors should be considered.

(I) In the temperature range between 30 and 40 ℃, the destructive processes are mitigated with decreasing temperature in a more or less dose-dependent fashion. For example, the metabolic rate decreases by between 7% and 10% per degree Celsius drop in temperature; thus, the cellular oxygen demand at a core temperature of 32 ℃ is between 50% and 65% of the demand at 37 ℃, and between 38.5% and 53.7% of what it would be at 40 ℃ (3,4). Other destructive processes such as neuroinflammation, apoptosis, mitochondrial and ion pump dysfunction, cellular membrane leakage etc. are affected in a similar way;

(II) In most animal models (especially smaller animals such as rodents), the therapeutic window (i.e., the time before which hypothermia treatment must be initiated in order to achieve benefits) is shorter than in humans, probably indicating that although post-ischemia mechanisms are basically the same, the relative importance of these mechanisms may vary between different species (1,2,4). This

is probably due to differences in basic brain anatomy, mechanisms for heat dissipation, and perhaps other factors (2,4). Rodents have a much smaller brain (relative to body size) than humans, with a lissencephalic structure that has different rheological and metabolic properties and appears to be more (easily) responsive to neuroprotective interventions than the much more complex gyrencephalic human brain. Most mammalian species have a carotid rete[1] that is a key factor in brain temperature regulation and heat removal, which the human brain does not possess (13). Neuroexcitotoxicity is a key destructive mechanism following brain injury in rodents; this mechanism begins within minutes after ischemic injury and continues for around 2 hours (2,4). In rodents, inhibiting neuroexcitotoxicity significantly improves outcome, but in other animal models and in humans this is far less effective (2,4). Moreover, the therapeutic window for affecting this mechanism is relatively short (<2 hours), yet many clinical trials using therapeutic hypothermia (TH) and initiating cooling beyond this window have achieved positive results. For example, in the HACA trial cooling was initiated 109 minutes after cardiac arrest, and target temperature was achieved only after 8 hours (14); in rodents this would be well beyond the therapeutic window, yet the therapy was effective in humans. This indicates that other mechanisms such as neuroinflammation, apoptosis, suppression of spreading depolarisations and seizures, and other "later" mechanisms must be far more important in humans than in rodents. This is one of the reasons why treatments aimed at neurologic recovery should always be tested in multiple animal models, before clinical trials are initiated;

(III) Brain temperature exceeds core temperature in physiological conditions (by 0.1–0.5 ℃) and especially following brain injury (by 1.0–2.0 ℃, with temperature in injured area's being even higher, up to 4 ℃ higher than measured core temperature) (2-4). This is due to the excessive heat generated by the destructive processes in the injured areas of the brain, and trapping of this heat due to impairment of the mechanisms that under normal circumstances immediately remove excess heat;

(IV) The majority of the destructive processes take place over a period of 48–72 hours; therefore, in theory the optimal period for application of hypothermia treatment would be 48–72 hours (2-4). This applies to some but not to all mechanisms; excitotoxicity, cell membrane leakage and free radical production usually cease after a few hours, though the processes can be reactivated by a new episode of ischemia (2-4), and the potential benefit must be weighed against the risk of side effects (15). The required "dose" (i.e., both depth and duration) of hypothermia is unclear, and likely varies from patient to patient.

The original studies using hypothermia in cardiac arrest selected a temperature of 32–34 ℃ and a cooling period of 12–24 hours in an attempt to balance potential benefits against the risks of what was at that time thought to be a potentially risky therapy (3,4,12,16). Subsequent studies have mostly used 24-hour cooling periods and temperatures of 32–34 ℃, though as stated the optimal target temperature (part of the "dosing") is not completely clear. A large trial by Nielsen and co-workers reported that protective effects of hypothermia at 36 ℃ were equivalent to 33 ℃ (17); however, this study has been criticized by the undersigned and others for up to 4-hour delays in initiation of cooling, time to target temperature of 10 hours in the 33 ℃ group, possible selection bias and other potential problems (18,19).

[1] The internal carotid artery is absent, or rudimentary, in many mammalian species (cats, dogs, sheep and goats). In those species blood flows to the base of the brain from the systemic circulation via the external carotid artery. Before entering the circle of Willis, the external carotid artery branches into a series of small arteries; this is the carotid rete. The rete lies within a venous lake, the cavernous sinus. Under normal conditions, with ambient temperature being lower than core body temperature, the temperature of air entering the nose is lower than the core body temperature. This allows heat exchange to occur between the warmer incoming arterial blood and the "cooled" blood draining the nasal cavity. This leads to a cooling of arterial blood arriving at the circle of Willis (the point of entry to the base of the brain). In this way the carotid rete provides an anatomical structure that can cool the brain, via a mechanism sometimes referred to as "selective brain cooling" (11,12). Rodents, rabbits and primates (including humans) do not have a carotid rete, therefore blood is not cooled before entering the brain.

Thus, optimal target temperature continues to be debated; current AHA and ERC guidelines recommend choosing and maintaining a target temperature between 32 and 36 ℃ (20).

Apart from cardiac arrest, the best clinical evidence for active temperature management comes from studies in neonatal asphyxia, where several large multicenter trials have compared hypothermia (temperatures ranging from 32–33.5 ℃ for 48–72 hours) to strict normothermia (37.0 ℃), and reported significant improvements in neurological outcome with hypothermia (3,4). At least for this indication, the evidence clearly shows that hypothermia provided clinical benefits beyond "just" maintaining normothermia (3,4).

Returning to cardiac arrest, apart from the debate on optimal temperature there is discussion regarding optimal duration of therapeutic cooling. A recently published study by Kirkegaard and co-workers addressed this issue by comparing the effects of 24-hour cooling following witnessed cardiac arrest (the current "standard" treatment) to a longer cooling period of 48 hours, followed by rewarming at 0.4 ℃/hour (21). A total of 355 patients were enrolled in this multicentre RCT, of whom 351 patients completed the trial. Although there was a trend towards reduced mortality and more favourable neurologic outcome in the 48-hour group this did not reach statistical significance; favourable neurologic outcome [defined as Glasgow Outcome Score (GOS) of 1 or 2] was 69% (n=120/175) in patients cooled for 48 hours *vs.* 64% (n=112/176) in controls, absolute difference 4.9%, 95% CI: −5% to +14.8%, odds ratio (OR) for improved outcome 1.08 (95% CI: 0.93–1.25) (21). Mortality was 27% (n=48/175) *vs.* 34% (n=60/176), OR −16.1 to +3.1, relative risk (RR) 0.81 (95% CI: 0.59–1.11). The median length of ICU stay was longer in patients treated for 48 hours (151 *vs.* 117 hours, P<0.001), but length of hospital stay did not differ (11 *vs.* 12 days, P=0.50).

How should we interpret these findings?

The first question should be what difference we would expect. The power calculation for this study was based on a predicted effect magnitude of 15%; i.e., the authors expected to find an absolute difference of 15% (so a relative improvement of 30%) in rates of good neurologic outcome, based on a predicted baseline favourable outcome of 50% (which is about the average of the two pivotal studies published in 2002 (12,16), and from subsequent studies performed in experienced centers using hypothermia in patients following witnessed cardiac arrest) (3,4). In the event, the actual rate of favourable outcome in patients cooled for 24 hours was 64%, which is outstanding and superior to outcomes reported in most centers; it is equal or better than the best results reported in recent literature, with large trials reporting favourable outcomes ranging from 46.5% to 57.5% (17,18,22). Outcomes in patients cooled for 48 hours were even better, but as stated above not significantly so. The absolute difference in rates of good neurologic outcome was 5% (relative 13.9%). Mortality was 7% lower in the 48-hour group (representing a relative reduction of 21%), a non-statistically significant difference (21).

In my opinion the projected 50% baseline rate of favorable outcome was realistic based on the published literature, but the projected 15% absolute (30% relative) increase in rates of favourable outcome seems optimistic. Data from animal studies does not support such a large effect of longer cooling, though as explained above there may be important differences between humans and animals. Looking at the clinical evidence, the HACA trial (which compared hypothermia to no active temperature management) reported an absolute difference of 16% between patients receiving active temperature management at 32–34 ℃ and those with no active temperature management (14). The absolute rate of good outcome in cooled patients was 55%; in the study by Bernard *et al.* where patients were cooled for 12 hours the rate of good outcome was 49% (16). Is the 6% absolute difference in rates of good outcome between the two trials attributable to the difference in duration of cooling (12 *vs.* 24 hours)? Perhaps, but the studies had many other differences, such as speed of cooling (time to target temperature 480 *vs.* 120 minutes), active temperature control to normothermia in the control group in the Bernard study *vs.* subfebrile temperatures (37.8 ℃) in controls in the HACA trial, and others differences that might have partially "compensated" for greater effects of longer cooling in the HACA trial (14,16,18).

The studies in neonatal asphyxia (which used longer cooling periods, 48–72 hours) reported absolute differences in outcome ranging from 11% to 32% (2-4); however, this was in comparison to patients kept at normothermia (37.0 ℃), not to patients receiving hypothermia of shorter duration as happened in the Kirkegaard trial.

The bottom line is that with all the above information, in the end the authors had to make an assumption, as no comparative studies had previously been performed in CA

patients (though some studies had used 48-hour cooling periods); perhaps they decided on 15% in part because planning for a much larger trial did not seem feasible.

The authors are to be commended for taking on this challenge, for achieving a phenomenal rate of favourable outcome in both arms of their trial, and for showing us what number of patients will likely be required to answer the question of whether longer duration of cooling does, or does not, improve outcome. Based on a projected baseline rate of good outcome of 50% and an effect size of 5% (the difference in rates of favorable neurological outcome in the Kirkegaard study) or 7% (the difference in mortality), the numbers required would be 2,030 or 1,061 patients, respectively. With a baseline rate of 64% (the actual rates of good outcome in the Kirkegaard study) these numbers would drop slightly, to 1,866 or 935 patients (based on a P value <0.05).

Thus, there are numerous unanswered questions regarding the optimal temperature and duration of therapeutic cooling. Large studies will be required to answer them. The answer may lie in a single large study using an adaptive trial design (22), where the questions of optimal temperature (testing a range of 31–37 ℃) and duration (24 to 72 hours) could be analysed in sequential fashion. Cooling should be initiated quickly and rewarming should be done slowly, preferably at a maximum of 0.15–0.25 ℃/hour as there is evidence for detrimental effects of rapid re-warming (3,4,23,24). In this way the current controversies could perhaps be addressed in a single, cooperative study. Until we have more information it appears reasonable to continue to use therapeutic cooling for 24 hours in most patients, though 48 hours can be an option as the Kirkegaard study (though not proving benefit) showed a favourable trend and found no evidence that this would be detrimental or harmful.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Polderman KH. Cooling after cardiac arrest—the longer the better? J Thorac Dis 2018;10(Suppl 26):S3300-S3304. doi: 10.21037/jtd.2018.07.96