

## Editorial

## Therapeutic Hypothermia in Cardiac Arrest

## Hipotermia terapéutica en la parada cardiaca

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## INTRODUCTION

Approximately 275 000 Europeans per year experience out-of-hospital cardiac arrest, with huge differences in survival ranging from more than 30% in some cities to just a few percent in others.<sup>1</sup> The main cause of these significant survival differences is differences in overall quality of the treatment, both pre-hospital during resuscitation and in-hospital after return of spontaneous circulation. Although cardiopulmonary resuscitation and defibrillation received the most attention and constituted the major research areas over the past 3 decades, in-hospital treatment and postresuscitation care have received much more attention during the last 10 years.

## THE POST CARDIAC ARREST SYNDROME

Sudden cardiac arrest survivors suffer from a global ischemia-reperfusion injury called post cardiac arrest syndrome,<sup>2</sup> which may lead to poor neurological outcome and death. This syndrome starts a cascade of deleterious inflammatory reactions in the body that may continue for several days. Treatment directed at minimizing the inflammatory response and cell death in the reperfusion period may improve outcome following cardiac arrest. One of the few proven in-hospital treatment strategies is induction of therapeutic hypothermia (TH).<sup>2</sup> Defined as a reduction of body temperature to 32°C to 34°C for 12 to 24 h, TH has been recommended by the International Liaison Committee on Resuscitation (ILCOR) since 2003.<sup>3</sup> The main protective effect of TH is to reduce the global cerebral injury through multifactorial pathways, body and cerebral metabolism in general, apoptosis, influx of Ca<sup>2+</sup> into the cell, intra- and extracellular acidosis, accumulation of the excitotoxic neurotransmitter glutamate, release of glycine, inflammation, nitric oxide production, and free radical production.<sup>2</sup>

## CLINICAL DATA ON THERAPEUTIC HYPOTHERMIA

The successful use of TH after cardiac arrest was first reported in 1959 by Benson et al. after cooling 12 patients<sup>4</sup> and

TH was recommended as an important part of postresuscitation care by the late Peter Safar in the early 1960s. However, not until 2002 did randomized controlled trials document a significant improvement in neurologically intact survival with TH compared with normothermia in comatose out-of-hospital cardiac arrest survivors.<sup>5,6</sup> Although proven beneficial only in patients with initial ventricular fibrillation,<sup>5,6</sup> ILCOR stated that such treatment might also be beneficial for other initial rhythms of cardiac arrest.<sup>3</sup> Importantly, cerebral reperfusion injury occurs in all comatose cardiac arrest patients, independently of initial rhythm; it seems reasonable to use TH independent of initial rhythm when active treatment is indicated. Although patients with nonshockable rhythms have worse prognosis and lower survival, in recent years TH also has contributed to improvements in survival with good outcome for these patients.<sup>7,8</sup>

The outcome benefit of cooling before and after implementation of TH in unselected patients is similar to that found in the randomised trials.<sup>7–12</sup> The largest such study to date is from a Dutch registry including more than 5000 resuscitated patients, in which in-hospital mortality decreased 20% after implementation of TH.<sup>10</sup> Based on the present evidence, it is highly recommended to use TH for 24 h as part of a standardized, goal-directed, high-quality postresuscitation care treatment plan in comatose cardiac arrest survivors when active treatment is indicated.<sup>9</sup> This standardized treatment plan includes early focus on optimizing hemodynamics, ventilation, and oxygenation; early treatment of the cause of the arrest, ie, coronary angiography and subsequent percutaneous coronary intervention (PCI) if indicated, avoiding hyperglycemia; and early seizure detection and treatment. At Oslo University Hospital Ullevål, after 2 years with such a treatment plan we were able to improve successful survival (defined as survival with cerebral performance category of 1–2) from 26% to 56%,<sup>11</sup> which was sustained during a 5-year follow-up.<sup>12</sup>

A recent Cochrane report concludes that TH seems to improve survival and neurologic outcome after cardiac arrest.<sup>13</sup> However, only a few hundred patients are enrolled in the small randomised trials to date and some researchers claim that more randomized trials are needed to strengthen the evidence, or to challenge the optimal target temperature, which is unknown. The Target Temperature Management After Cardiac Arrest [TTM] Study, already underway, is a multicenter trial that will enroll 900 patients and compare standard postresuscitation care with 33°C vs 36°C for 24 h in comatose cardiac arrest survivors

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irrespective of initial rhythm (<http://www.clinicaltrials.gov>, NCT01020916).

## WHEN AND HOW TO COOL

Treatment with TH can be divided into 3 parts: induction, maintenance, and rewarming. Although we have no clear evidence of the optimal target temperature, when active treatment is decided it is recommended to initiate cooling as fast as possible, attempt to maintain a stable 32°C to 34°C temperature for 24 h, and thereafter rewarm in controlled 0.3°C to 0.5°C per hour back to 37°C.<sup>9</sup> Induction can easily and inexpensively be induced with ice-cold fluids (30–40 mL/kg of NaCl 0.9% peripheral i.v.) in combination with traditional refrigerated cold-packs, placed in the groin, armpits and around the neck and head. With these techniques the patients can be transported cold to undergo coronary angiography and subsequent PCI.<sup>11,12</sup> The logistics within the hospital must be organized so that patients are cared for and monitored by emergency physicians/anesthesiologists/cardiologists/intensivists and dedicated nurses.

Numerous advanced cooling systems have been developed in recent years with the intention of achieving faster induction and more reliable temperature maintenance.<sup>9,14</sup> Some cooling devices have been compared, but no significant differences between them in outcomes or major side effects are reported.<sup>15</sup> Each institution should use a method or combination of methods appropriate to its infrastructure, logistics, treatment plan, and financial resources. No clear relationship between timing of cooling and outcome has been documented.<sup>7,9</sup> Furthermore, the feasibility of pre-hospital cooling has been extensively reviewed and investigated in recent years, without demonstrating that pre-hospital cooling further improves survival, despite being feasible and appropriate in some systems.<sup>16,17</sup> It is probably most important to initiate cooling in the hospital before patients become hyperthermic. Hyperthermia negatively affects outcome, and typically occurs within the first 2 h after cardiac arrest.<sup>2,18</sup> Another aspect to consider is that 10% to 20% of patients wake up some minutes after return of spontaneous circulation,<sup>12</sup> mainly after a short episode of arrest and resuscitation, and it is not necessary to cool these patients if they are awake and adequately obey commands. If all patients undergo early TH, requiring intubation and sedation, we will probably end up with more comatose patients than appropriate because continuous cooling requires deep sedation and mechanical ventilation. It is recommended to wait some 5 to 10 min after return of spontaneous circulation to see if patients wake up and obey commands. If so, they should be kept awake. If they don't wake up, or if in doubt, TH for 24 h should be initiated as fast as possible in a controlled fashion, including oral intubation, sedation of patients with controlled ventilation, and adequate monitoring.<sup>9–12</sup>

## SIDE EFFECTS OF THERAPEUTIC HYPOTHERMIA

Although TH has various effects on several organ systems, clinical studies show that TH does not increase the risk or number of complications compared to similar patients not treated with TH.<sup>5–7,9,11</sup> Pneumonia due to aspiration and/or mechanical ventilation may be the most important complication during the postresuscitation period, with up to 50% incidence in several studies, although it is not more frequent in patients treated with TH.<sup>5–7,9,11</sup> TH may cause renal tubular dysfunction and increased diuresis, which must be kept in mind during at least the first 24 h when the patient needs a positive fluid balance

due to the myocardial dysfunction and sepsis-like syndrome that occur in the early phase in cardiac arrest patients.<sup>2,9</sup> However, renal failure requiring invasive treatment is not more frequent in TH-treated patients.<sup>6,7,9</sup> TH may lead to hypophosphatemia, hypomagnesemia, hypocalcemia or hypokalemia.<sup>2,7,15</sup> Furthermore, TH may induce hyperglycemia by decreasing insulin sensitivity and secretion, but this is usually easy to control with insulin treatment.<sup>2,7,15</sup> Due to these mechanisms, close control of electrolytes and blood sugar is highly recommended, especially in the cooling and rewarming phases.<sup>9</sup> Importantly, due to the decreased metabolism during TH, tidal volumes must be reduced to avoid hyperventilation. Thus, frequent blood gas analyses are required, especially during the cooling and rewarming phases, to achieve the desired normoventilation. Prolonged drug effects due to decreased clearance must also be kept in mind.<sup>2,9</sup> Sedatives and opioids with very long half-life should be avoided and sedation must be discontinued as early as possible. In some cases, patients who are being discharged neurologically intact may not wake up for days.<sup>9,12</sup> Bleeding that requires transfusion is rare, with a rate of 4% of all patients reported in a registry study,<sup>7</sup> and the risk is significantly higher if angiography and PCI was performed (2.8% vs 6.2%, respectively).<sup>7</sup> However, early angiography and PCI were also predictors of good outcome, so the net effect of TH and PCI is obviously beneficial.<sup>7,9,11,12</sup>

Nielsen et al. described these adverse events occurring in the postresuscitation period in TH-treated patients and explored, in a multivariate model, their relation to mortality.<sup>19</sup> Importantly, the increased frequency of bleeding and sepsis after invasive procedures—coronary angiography, PCI, intravascular devices for cooling, intraaortic balloon pump—is not associated with increased mortality. On the other hand, sustained hyperglycemia and seizures treated with anticonvulsants are associated with increased mortality. If seizures occur, this alone cannot be used as a predictor for treatment survival because almost 20% of the patients survive.<sup>19</sup> Thus, monitoring of brain function and a prognostication protocol is of utmost importance, and requires special attention in future studies.

## THERAPEUTIC HYPOTHERMIA AND THE HEART

In the registry study, Nielsen et al. reported that the most common side effects in the postresuscitation period are severe arrhythmias. Tachycardia and bradycardia were present in 33% and 41% of patients, respectively.<sup>7</sup> It must be kept in mind that arrhythmias also occur in normothermic patients after cardiac arrest, due to the unstable cardiac situation.<sup>5,6,11</sup> Moreover, a reversible postresuscitation myocardial dysfunction appears early after cardiac arrest<sup>2</sup> and affects hemodynamics in the early postresuscitation period. However, even though bradycardia usually is considered as a side effect, in TH-treated patients after cardiac arrest it may have a positive beta-blocking effect on the ischemic heart. Recent studies even report improved contractility if the failing human myocardium is exposed to hypothermia.<sup>20,21</sup> In a pig model, Post et al.<sup>21</sup> demonstrated that TH negatively affects diastolic function but this is compensated by TH-induced bradycardia. Their model showed a positive inotropic effect and decreased whole body oxygen consumption during TH. This fits well with findings from a recent clinical study by Zobel et al.<sup>22</sup>: among patients in cardiogenic shock, TH provided circulatory support, increased systemic vascular resistance with reduced vasopressor use, and decreased oxygen consumption. This suggests that TH could be a therapeutic option in hemodynamically unstable

patients independent of cardiac arrest. It is questionable to what degree bradycardia should be treated in TH-treated patients. Since oxygen demand and consumption are markedly reduced during TH, the brain requires less cardiac output during TH.<sup>2</sup> Further clinical studies are of course needed in cardiogenic shock patients but also to explore the hemodynamic effects in the postresuscitation period, both with and without TH.

Finally, acute myocardial infarction is the single most common cause of cardiac arrest.<sup>2,9,11</sup> In a recent cardiogenic shock pig model,<sup>23</sup> cooling before reperfusion reduced mortality and improved myocardial function. The same group also documented reduced infarct size in humans if cooling is induced before reperfusion.<sup>24</sup> More human studies are required regarding the direct effects of TH on myocardial function and of ischemia/reperfusion injury on the heart, and some are underway.

## PROGNOSIS

A very important question that has become even more difficult after the introduction of TH, is when and how to prognosticate comatose patients.<sup>9,12</sup> Too early prognostication may result in too early treatment withdrawal in patients with a potential for successful survival. In the first 2 days after cardiac arrest there are no clinical predictors of poor outcome<sup>2,9</sup>; thus, when treatment with TH has been initiated the focus must be to optimize the standardized postresuscitation treatment as recommended<sup>9,11</sup> and follow the predefined plan. If patients don't wake up immediately, we must remember that it may take time, especially when sedatives and opioids have been used for many days. Although based on limited scientific evidence, the recommended timing to initiate active prognostication in still comatose patients after discontinuation of sedation seems to be 72 h after achieving normothermia.<sup>9</sup> Somatosensory evoked potential, measurement of neuron-specific enolase (in blood), electroencephalography (especially continuous electroencephalography<sup>25</sup>) and neurological clinical examination are the prognostic tools with the best scientific evidence.<sup>2,9</sup> We definitely need more studies on this difficult but important aspect of post cardiac arrest care.

## CONCLUSIONS

The increased use of TH as part of a standardized, goal-directed treatment protocol for postresuscitation care improves survival after out-of-hospital cardiac arrest. Treatment with TH is recommended by the European Guidelines of Resuscitation. Independently of the cooling method chosen, TH is easy to perform and is without severe side effects or complications associated with mortality. Not only are there beneficial effects on the brain, but several studies also indicate possible benefits of TH for the heart. Although TH is only proven beneficial for patients with initial ventricular fibrillation, the majority of centers also use it for comatose survivors with other initial rhythms if active treatment is decided. A combination of TH, coronary angiography, and PCI is associated with the best outcome. Some controversies still exist; the optimal target temperature, timing and duration of cooling have not yet been defined.

## CONFLICTS OF INTEREST

None declared.

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