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# From therapeutic hypothermia towards targeted temperature management: a decade of evolution

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**Abstract**

More than a decade after the first randomised controlled trials with targeted temperature management (TTM), it remains the only treatment with proven favourable effect on postanoxemic brain damage after out-of-hospital cardiac arrest. Other well-known indications include neurotrauma, subarachnoidal haemorrhage, and intracranial hypertension. When possible pitfalls are taken into consideration when implementing TTM, the side effects are manageable. After the recent TTM trials, it seems that classic TTM (32–34°C) is as effective and safe as TTM at 36°C. This supports the belief that fever prevention is one of the pivotal mechanisms that account for the success of TTM. Uncertainty remains concerning cooling method, timing, speed of cooling and rewarming. New data indicates that TTM is safe and feasible in cardiogenic shock, one of its classic contra-indications. Moreover, there are limited indications that TTM might be considered as a therapy for cardiogenic shock per se.

**Key words:** therapeutic hypothermia, targeted temperature management, cardiogenic shock, cardiac arrest, indications, limitations

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Cardiac arrest (CA) has a dismal prognosis. More than half of the patients with out-of-hospital cardiac arrest (OHCA) die at the scene [1]. The mortality of patients after CA who are admitted to the intensive care unit (ICU) is mainly determined by their neurological outcome. In the last decade, the mortality of this group has decreased significantly to 40–60% [2]. This progress is largely due to increased attention being paid to the post cardiopulmonary resuscitation (CPR) phase. Therapeutic hypothermia (TH) in particular is the main innovation in this field.

The goal of this review is to give a state-of-the-art oversight in the field of TH and how TH has evolved over recent years towards targeted temperature management (TTM) avoiding hyperthermia. The results of the recent TTM trials reinforce the importance of controlling temperature [3]. Many patients in the 'normothermia' group of the older trials in fact became hyperthermic, which is deleterious [4]. The exceptional rates of good outcomes in both the 33°C and 36°C groups in the TTM trials may just reflect the avoidance of hyperthermia. This narrative review will give an overview on the definitions, physiology, rationale and current evidence for TH which in our opinion should be referred to as TTM.

## DEFINITIONS

The term 'targeted temperature management' (TTM) has largely replaced 'therapeutic hypothermia' (TH), after the publication of the landmark TTM trial last year [5]. Un-

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like TH, TTM also includes maintaining normothermia. The use of TTM in this review refers to inducing hypothermia of 32–34°C. If other temperatures are intended, this will be made explicit.

## PHYSIOLOGY AND RATIONALE FOR TTM

Ischaemia triggers different complex and destructive processes that can be reinforced by the restoration of normal circulation, through reperfusion injury. Most of these processes are temperature mediated and vary depending on the duration of the insult and underlying patient conditions.

The most widely known beneficial effect of TTM is a decrease of the basic metabolism by 6–10% per degree of hypothermia, which leads to diminished oxygen consumption [6]. Also neuro-exitotoxicity, where rising calcium influx in the ischaemic neuron and massive release of glutamate reinforce each other to induce brain damage, can be prevented, interrupted, or diminished by TTM [7]. The physiological immune response, which arises after tissue damage, with recruitment of leucocytes and macrophages and activation of the complement system, induces additional damage in ischaemic conditions through release of free radicals [8]. TTM can also positively modulate this immune response [7]. Furthermore, TTM decreases brain oedema, a complication of ischaemia that carries a very poor prognosis [9]. All these destructive cascades, caused by ischaemia, induce increased heat production in the brain. Global or localised brain oedema impedes efficient heat removal by the venous and lymphatic structures, contributing to a relative temperature increase of up to 2°C in ischaemic brain tissue compared to core body temperature. This concept, known as cerebro-thermopooling, is a very important factor influenced by TTM [10].

Hyperthermia and fever on the other hand have a stimulatory effect on the above-mentioned destructive processes. Hyperthermia increases oxygen consumption, reinforces neuro-excitotoxicity, and intensifies the detrimental immune response to ischaemic damage [11]. Recent data has shown that the clinical effect of targeting 33°C or 36°C is equal, suggesting that fever prevention alone is one of the main explanations of the clinical success of TTM [5]. This suggests that some of the above-described physiological pathways are less important than was previously thought. It is thus clear that the new information from the TTM trial has uncovered substantial knowledge gaps in the physiology behind TTM.

## CLINICAL EVIDENCE TTM

In 2002, two simultaneously published trials reported a significantly beneficial effect of TTM compared to a placebo in 356 comatose patients after successful CPR, due to ventricular fibrillation (VF) [12, 13]. In both trials, TTM was associated with better neurological prognosis, while in the largest trial a > 25% decrease in mortality was noted in the TTM group. The price of TTM is estimated at 50,000 USD per quality adjusted life year, which is considered acceptable in most developed countries [14].

Based on these findings, the European Resuscitation Council guidelines consider TTM to be part of the post-resuscitation care for patients who remain comatose after OHCA [15]. The European guidelines recommend using TTM irrespective of the presenting rhythm. One could argue that patients with ventricular tachycardia (VT) or a non-shockable rhythm (NSR) were not included in the two seminal trials in 2002; however, one can — at least theoretically — also expect a favourable effect in these populations. In the NSR population, the very high mortality in this group must be taken into account when deciding to start TTM.

The two pioneer trials published in 2002 applied classic TTM with cooling temperatures of between 32°C and 34°C [12, 13]. Recently, two studies re-addressing this issue were published [3, 5]. In the first of these studies, the induction of hypothermia using 2 L of ice-cold normal saline in patients with return of spontaneous circulation (ROSC) after OHCA did not improve survival to hospital discharge compared to those in whom cooling was delayed until arrival at hospital [3]. Prehospital cooling reduced mean core temperature by 1.2–1.3°C compared to those not cooled prehospital. The proportion of patients re-arresting during transfer to hospital or with pulmonary oedema on the first chest radiograph was significantly greater in the prehospital cooled group.

The second study published recently was a very large Swedish trial (TTM trial) that included more than twice as many patients than the two previous trials combined. The TTM trial compared a target temperature of 33°C to 36°C and showed no significant differences in mortality between both groups [5]. This unexpected negative result has been ascribed by some authors to selection bias or to too rapid rewarming [16]. Also, neuroprognostication happened at the same time in the 33°C and 36°C groups, whereas one should expect much slower metabolisation of sedatives in the 33°C group, which could have negatively impacted upon the outcome in this group. Nevertheless, the negative result of the TTM study, together with well-known methodological flaws in the two pioneer trials (i.e. no power calculations, no data on sedation, ventilation or other modes of treatment, no clear prognostication protocol) raised doubt about the need for any kind of temperature management post CA [17]. Registry data however show clearly improving mortality after CA in the last decade since implementation of TTM [18]. A likely explanation for the conflicting results of the TTM trial and the two previous trials is that many patients in the normothermia group in the older trials in fact became hyperthermic, which is known to be deleterious [4]. This

finding indicates that TTM remains important and that fever prevention, more than anything else, is a pivotal mechanism in the success of TTM. The TTM trial however does not provide us with hard evidence for or against a specific target temperature. In an update of its guidelines, following the publication of the TTM trial, the International Liaison Committee on Resuscitation (ILCOR) confirms the importance of TTM post OHCA and advises the maintenance of target temperature at 32–34°C, with an option to increase the temperature to 36°C, for example when hypothermia related complications arise [19]. So in conclusion, for the time being we should not abandon TTM post CA [16].

With regard to the method of cooling (internal or external), multiple devices are on the market, but randomised controlled evidence to support the use of one superior method is not available [7]. The timing of TH also remains an area of uncertainty, as the recommendations in guidelines concerning this topic are based on expert opinion.

## PITFALLS IN TTM

### TIMING OF COOLING AND REWARMING

Based on data from animal experiments, the consensus is that TTM should be commenced as soon as possible after CA [20]. However, a recent trial in which prehospital cooling did not incur benefit contradicts this finding [3]. The three large randomised controlled trials in the field of TTM employed a protocol of TTM during 12 to 36 hours [5, 12, 13]. We suggest that the best choice would be a cooling period of 24 to 36 hours with fast induction and slow and controlled rewarming. After rewarming, aggressive prevention and treatment of fever should be the norm for at least 72h.

### HAEMODYNAMIC ALTERATIONS

Hypertension may arise at induction of TTM. This may be caused by insufficient sedation. Hypotension is more common and this is frequently caused by hypovolemia, as is often the case in post CPR patients [21]. Hypovolemia can be aggravated by the diuretic effect of hypothermia. In euvolemic patients, TTM will have little or even a positive effect on blood pressure [7, 21–23]. In a case of persistent hypotension, vasoplegia due to sepsis must not be overlooked in view of the increased sepsis risk in patients treated with TTM.

### ARRHYTHMIA

In contrast to deep hypothermia (< 30°C), TH is virtually not arrhythmogenic. In a case of inadequate sedation, tachycardia may arise in the induction phase. After induction of TTM, bradycardia may develop. This bradycardia usually does not require treatment, since cardiac output remains unchanged due to increase in stroke volume [7, 23]. It is unclear whether this also applies to patients with diastolic dysfunction, in whom a rise in stroke volume at slower heart rates may not occur.

### COAGULATION AND BLEEDING DISORDERS

Ample physiological explanations exist to suggest that TTM causes coagulopathy and platelet dysfunction [24, 25]. This raises obvious concern in a post CA population already at risk for bleeding due to dual antiplatelet therapy after myocardial infarction or disseminated intravascular coagulation due to critical illness post CPR. The guidelines highlight pre-existing coagulation disorders as contraindications for the implementation of TTM [26]. Nonetheless, several large RCTs, including the recent TTM trial, did not show any additional bleeding in the hypothermia group [5, 13]. A recent large systematic review also did not observe an increased bleeding risk in patients receiving TTM [27]. This data suggests that the clinical bleeding risk due to TTM is non-existent or very small, if patients with known bleeding diathesis are excluded from receiving TTM.

### NEED FOR SEDATION

Shivering slows down the cooling process and increases the basic metabolism of the patient. Shivering should be treated aggressively by administering a bolus of morfinomimetics, increasing sedation or even muscle relaxants. Short working agents and boluses are preferred. Animal models indicate that inadequate sedation may neutralise the positive effects of TTM, by inducing a detrimental stress reaction [28].

### INFECTION RISK

A recent systematic review including 2,820 patients showed a significant increase in pneumonia and sepsis in patients treated with TTM [29]. This increased infection risk however does not seem to be related to an increased mortality [30]. Nevertheless, clinicians should have a low threshold to initiate antibiotic therapy during TTM, since classic signs of infection are difficult to interpret.

### PHARMACODYNAMICS AND PHARMACOKINETICS

Most enzyme related reactions are temperature mediated. Therefore the hepatic metabolism of drugs is usually slowed down during TTM and plasma levels of drugs with hepatic metabolisation (e.g. beta-blockers, benzodiazepines, opioids) are usually elevated during TTM [31]. Because of this, the effect of sedative drugs may be more pronounced and may influence the neuroprognostication. On the other hand, the efficiency of clopidogrel, which needs conversion to its active component by hepatic metabolisation, is dramatically diminished by TTM [32, 33]. Moreover, a recent trial also reported 30% non-responders to prasugrel, in acute coronary syndrome (ACS) patients, treated with TTM after PCI [34]. This all leads to

an elevated risk of acute stent thrombosis. Possibly ticagrelor, which does not need hepatic metabolisation, should be preferred when using TTM. Hard data is lacking on this subject.

ELECTROLYTES AND GLYCAEMIA

TTM lowers serum potasium levels by promoting in ward cellular potasium flux. Renal excretion of magnesium and phosphate is also increased during TTM. Finally, TTM causes insulin resistance and decreased insulin production, which triggers hyperglycaemia. During rewarming the inverse mechanisms can lead to hyperkalaemia and hypoglycaemia. Consequently, frequent monitoring of electrolytes and glycaemia is required [35].

NEUROLOGICAL PROGNOSTICATION

To date, we have only very rudimentary tools to predict neurological prognosis after CA. Only patients with bad neurological prognosis can be identified with an acceptable false positive rate. Discrimination in the majority of patients, those who are not classified as having bad neurological prognosis, remains difficult. Many of these patients are left with substantial permanent neurological impairment. In view of the increased use of sedatives during TTM, the situation is further complicated by the fact that many trials in this field date from the pre-TTM era. Nonetheless, a recent systematic review of patients receiving TTM identified the absence of pupillary light reflexes, corneal reflexes and absence of N20 motor response at 72 hours after CA as strong predictors of bad outcome even after the use of TTM [36]. Probably, a multimodal approach including clinical, electrophysiological and newer biochemical (or imaging) modalities, as proposed by Oddo et al., will prove most effective [37].

ORGANISATION OF CARE

In 2008, the International Liaison Committee on Resuscitation (ILCOR) statement on a treatment bundle for the post-cardiac-arrest syndrome was published [38]. Several studies showed that the implementation of such a treatment bundle, facilitating standardised and multidisciplinary care for post CA patients, was able to reduce mortality and to improve neurologic outcome after cardiac arrest [39–41]. This approach was also included in the most recent guidelines on resuscitation in 2010 [26].

A thorough knowledge of the possible pitfalls and the physiological repercussions of hypothermia is a prerequisite for its safe use. When these conditions are met, TTM is a valid therapy with few complications.

## TTM IN CARDIOGENIC SHOCK

As described above, the neuroprotective effects of TTM are based on reduction of oxygen consumption, inhibition of inflammation and decreased production of free radicals. These same mechanisms also play a central role in the pathophysiology of cardiogenic shock. Based on this knowledge, one could presume a positive influence of TTM on cardiogenic shock, and in the last decade evidence to support this hypothesis has been mounting.

Hitherto, our knowledge on the exact evolution of haemodynamic parameters in patients with cardiogenic shock treated with TTM has been incomplete. Nevertheless, the limited evidence available indicates a possible advantageous effect of TH in cardiogenic shock. Two recent trials showed in a total in 29 patients that TTM in cardiogenic shock is not only feasible and safe, but also has a beneficial effect on haemodynamic parameters such as blood pressure and cardiac output [22, 23]. There is also evidence that TTM has a positive effect on myocardial damage in acute coronary syndromes, the most common cause of cardiogenic shock. For instance, a significant reduction in infarct size has been noted in lab animals treated with TTM [42]. A small randomised Swedish trial demonstrated a reduction in infarct size of 38% on MRI compared to controls after treatment with TTM in STEMI patients, accompanied by significantly reduced biochemical markers for myocardial damage [43]. In the recently presented randomised, controlled TTM trial, TTM with a target temperature of 33° was compared to a target temperature or 36°C in 939 patients, of whom 136 were in cardiogenic shock at the moment of inclusion. In a predefined post hoc analysis on these cardiogenic shock patients, serum lactate was significantly higher in the 33°C group, but mortality did not differ between groups [44]. On the other hand, patients with severe cardiogenic shock (systolic blood pressure < 80 mm Hg despite fluid administration, vasopressors and/or intra aortic balloon pump) were excluded from the TTM trial. Based on this data, TTM can be considered feasible and safe in patients with cardiogenic shock, with some remaining uncertainty about the most severe cases. According to international guidelines, neither cardiogenic shock nor severe cardiogenic shock are contraindications for TTM [15].

This new data contains two key messages. The first finding is that TTM is safe and feasible in cardiogenic shock. This is important, since the two original randomised, controlled trials on TTM excluded all patients in cardiogenic shock. Consequently, in clinical practice, TTM was withheld in many patients in cardiogenic shock. At this moment, especially given the recent data from the TTM trial, there is enough evidence to implement TTM irrespective of the presence of cardiogenic shock, so this group can also enjoy the well-known neuroprotective effects of TTM.

A second key message is that major haemodynamic parameters such as cardiac output and blood pressure, but also

myocardial infarct size, are probably favourably influenced by TTM. TTM could thus be viewed as a myocyte-protective, anti-ischaemic and positive inotropic treatment of cardiogenic shock per se. A number of smaller trials are enrolling patients at this moment to establish the clinical relevance of this presumption (NCT01890317), but a large-scale trial with clinical endpoints is needed.

## CONCLUSIONS

Mortality after cardiac arrest remains very high, but there has been a significant improvement in outcomes over the last decade. The implementation of TTM is a major contributor to this progress. When the physiological consequences and the possible pitfalls of TTM are taken into consideration and anticipated, it is a safe treatment. After the publication of the TTM trial last year, it seems that a target temperature of 33°C or 36°C is equally safe and effective, which supports the pivotal role of fever prevention in the pathophysiology surrounding TTM. Guidelines however still explicitly advise the use of classic TTM (32–34°C). Other classic pathophysiological benefits of TTM, next to fever prevention, are a decrease in metabolic rate and production of free radicals, immunosuppression and interruption of neuro-excitotoxicity. This broad spectrum of beneficial pathophysiological mechanisms suggests a role for therapeutic hypothermia beyond its current clinical use. In recent years, evidence has accumulated proving that the use of therapeutic hypothermia in cardiogenic shock, a classic contraindication, is safe and feasible. Moreover, therapeutic hypothermia may be beneficial in cardiogenic shock per se, due to its positive inotropic and anti-ischaemic properties. So over the past decade, therapeutic hypothermia has evolved towards targeted temperature management and retained its place in the therapeutic armamentarium of post CA patients.

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