Post cardiac arrest therapeutic hypothermia in adult patients, state of art and practical considerations

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ABSTRACT

The importance of therapeutic hypothermia in selected categories of patients has been widely demonstrated. Laboratory, animal, and human studies permitted to understand the molecular mechanisms underlying cooling and its importance in preventing the ischemia/reperfusion injury of the brain. The development of new technologies offered the possibility to reach the desired temperature effectively and rapidly, reducing related side effects. Nevertheless, the application of systematic protocols of cooling has not been adequately reached in many hospitals. In this paper the most recent findings regarding hypothermia, its physiological bases and ways of application are reviewed.

Keywords: therapeutic hypothermia, cardiac arrest, ischemia-reperfusion injury, neuroprotection, cooling, re-warming.

Out-of-hospital cardiac arrest claims 225,000 lives each year in the United States and a similar number in Europe, accounting for about half of all deaths due to cardiovascular disease (1). Even when resuscitation efforts are successful, recovery is too often limited by post-anoxic encephalopathy. The interest regarding hypothermic therapy to protect brain after cardiac arrest started in late 1950s of the past century and the first publication dates 1959 (2). In spite of promising evidences, mostly because of the absence of simple and reliable cooling methods, apart from some farseeing and lonely voices as Peter Safar (3), the curtain falls over therapeutic hypothermia (TH) in the following decades. After almost forty years of oblivion, interest in cooling was rekindled in the early 1980s by the positive results from animal experiments suggesting that neurological outcome could be improved by using mild to moderate hypothermia (31°C-35°C) rather than deep hypothermia (30°C), with far fewer and less severe side effects (4-6). Following the promising results obtained from laboratory and animal models, in 2002 two important randomized multicentric studies on humans were realized (7, 8). In the first, the European Hypothermia after cardiac arrest study group enrolled 275 patients, with 137 patients randomly as-
signed to the hypothermia group and 138 to the normothermia group. (i.e., the group that received standard care after resuscitation). The study included only patients who had been resuscitated after witnessed out-of-hospital cardiac arrest due to ventricular fibrillation (VF) that were randomly assigned to undergo TH (target bladder temperature, 32°C to 34°C) over a period of 24 hours or to receive standard treatment with normothermia. The temperature was maintained at 32°C to 34°C for 24 hours from the start of cooling, followed by passive rewarming, which was expected to occur over a period of 8 hours. This study demonstrated that systemic cooling increases the chance of survival and of a favorable neurological outcome, as compared with standard normothermic life support without significant differences in terms of complications in the two groups.

In the second study 77 patients who remained unconscious after resuscitation from out of hospital cardiac arrest were randomly assigned to treatment with hypothermia (33°C core body temperature for 12 hours) or normothermia. In the TH group 49% survived with a good outcome (home or rehabilitation facility discharge) compared with the 26% (P = 0.046) of the normothermia group.

Considering these results, the 2005 American Heart Association guidelines for cardiopulmonary resuscitation and post resuscitation support concluded that clinicians should not actively rewarm hemodynamically stable patients who spontaneously develop a mild degree of hypothermia (33°C) after resuscitation from cardiac arrest (9). The same guidelines state that mild hypothermia may be beneficial to neurologic outcome and is likely to be well tolerated without significant risk of complications. In a select subset of patients who were initially comatose but hemodynamically stable after a witnessed VF cardiac arrest of presumed cardiac etiology, active induction of hypothermia was beneficial (class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (class IIb).

Although eight years passed from the original publications and several studies clarified many mechanism of TH and described feasibility and efficacy of different cooling methods (10, 11), this therapeutic approach is far from being extensively and widely used in everyday practice.

In a survey carried out in 2005 in the US (12), of 265 physician (practicing emergency medicine, critical care and cardiology) who were asked if they had ever used TH after cardiac arrest, 87% answered no. Among reasons for non-use they mentioned not enough data to support TH, non-inclusion in ACLS protocol or technical difficulties.

While a recent survey carried out on all UK intensive care units showed that 85% of departments considered TH as a part of post cardiac arrest management with a major implementation in use on the last three years (13), another recent review underlined that an informal online survey of cardiology conference attendees showed that 20% of respondents were even aware of the American Hospital Association guidelines (14).

Many studies tried to identify the reasons why, despite scientific evidence, TH fatigues to reach a routinely utilization. A recent study conducted on a 43 Canadian hospital network identifies some pivotal elements: lack of familiarity and availability of concrete TH protocols, availability of equipment, equipment costs, and higher workload demands for emergency nurses are the most perceived barriers. Awareness of these general, individual and local barriers may improve adherence to evidence-based practice (15).

Moreover, the majority of out-of-hospital
cardiac arrest patients nowadays are conducted to emergency medical services with non-VF (pulseless electrical activity, asystole) as the initial cardiac rhythm. For this reason, clinicians have to decide whether or not to use TH in this patient group, considering the feasibility, possible benefit, and potential adverse side effects of hypothermia in patients with neurological injury who have been resuscitated from non-VF cardiac arrest (16).

Some studies tried to evaluate feasibility and efficacy of TH in other medical emergency situations and with cardiac arrest presentation rhythms different from VF (17-19), although some authors believe that it will be difficult to find significant evidence due to the low incidence and poor outcome of this condition. As Bernard maintains, these trials would require a very large sample size to detect a significant change in an important outcome measure such as survival with good neurological function. Bernard et al suggest that, considering the few adverse effects related to the use of hypothermia and their relatively easy management, it would appear reasonable for clinicians to cool most patients with suspected neurological injury following prolonged cardiac arrest, whatever the initial cardiac rhythm (20).

Since a recent retrospective study (21) conducted on 491 patient shows no significant improvement in neurologic outcomes in patients whose initial rhythm was different from VF, further prospective studies are needed to clarify whether TH is effective also in asystole and pulseless electrical activity or not.

Another key point for the future is the identification of poor and good outcome predictors after TH post cardiac arrest. Glasgow Coma Scale monitoring and particularly motor response from third day after cardiac arrest remains a powerful tool to predict outcome of patients treated with TH (22).

Promising data come from the utilization of bispectral index (BIS) and suppression ratio during TH as an early predictor of neurologic outcome (23, 24).

For the future, larger prospective studies are needed to re-assess the validity of traditional clinical, biochemical and instrumental outcome predictors in patients treated with hypothermia and the identification of good outcome predictors is of paramount importance.

**MECHANISMS OF ACTION**

Animal and laboratory findings during 1980s and 1990s allowed a better knowledge of the molecular mechanisms underlying hypothermia, helping to define adequate strategies of cooling and to prevent possible side effects.

In the 1950s and 1960s, when the first procedures of cooling were realized, it was presumed that the beneficial effects of hypothermia were related to the reduction of brain metabolic requests (25). Although this statement is correct (a decrease in cerebral metabolism by 6% to 10% for each grade of body temperature reduction has been observed) this is not the unique involved mechanism (26).

Brain damages after a cardiac arrest may be considered as a model of ischemia-reperfusion injury. Animal and laboratory findings during ’80s and ’90s showed an increase in apoptosis, a dysfunction in mitochondrial activity, and an alteration in ion pump function controlling the influx of calcium into cells (27). During cooling an inhibition of caspase enzyme activation, a prevention of mitochondrial dysfunction, a decreased overload of excitatory neurotransmitters, and a modification of intracellular ion concentrations were observed, (28, 29). Immune system is also activated in the injured brain. One hour after the ischemic insult
an increase of inflammatory molecules (interleukin-1, tumor necrosis factor alpha) released by microglia, endothelial cells and astrocytes is detectable (26). This phenomenon is associated to chemotaxis and complement system activation facilitating neutrophil, macrophages and monocytes passage through the endothelium (30).

Numerous animal experiments and some clinical studies showed that hypothermia suppresses ischemia-induced inflammatory reactions and release of pro-inflammatory cytokines and decreases the production of nitric oxide, which is a key agent in the development of post-ischemic brain injury (31). In addition, hypothermia can impair neutrophil and macrophage function, reducing white blood cell count (32).

Another mechanism of damage is related to the increase of free radicals such as superoxide, peroxynitrite, hydrogen peroxide, and hydroxyl radicals that play an important role in determining whether injured cells will recover or die (33). Cooling seems to reduce the production of free radicals and to mitigate the damage, allowing the cells a better recovery after injury. This function and the ability in preserving the integrity of blood-brain barrier also determine a reduction of cerebral edema and the consequent intracranial hypertension (34).

In addition, brain glucose utilization is affected by ischemia-reperfusion, and there is evidence suggesting that hypothermia can improve brain glucose metabolism; in particular the ability of the brain to utilize glucose (35).

A disruption in equilibrium of vaso-active substances such as endothelin, thromboxane A2 (TxA2), and prostaglandin I2, following an ischemic or traumatic event, can lead to vasoconstriction, hypoperfusion, and thrombogenesis in injured areas of the brain (36, 37).

Several studies showed how hypothermia affects the local secretion of these agents in the brain and in other sites reproducing the natural haemostasis of vasoactive agents (38).

In some patients, during the post-ischemic phase, it is also detectable an epileptic activity, probably associated to the ongoing brain damage. Hypothermia is associated to a reduction in the convulsive activity, providing an adequate neuro-protection (39). Hypothermia increases the expression of the so called immediate early genes, which are a part of the protective cellular stress response to injury, and stimulates the induction of cold shock proteins, which can protect the cell from ischemic and traumatic injury (40). Ischemia-reperfusion also leads to substantial rises in cerebral lactate levels that are shown to be reduced during cooling (41). The importance of the protective effect of hypothermia on the brain can also be deduced by the observation that fever is associated with an increase risk for adverse outcome, worsening mortality in brain injures (42).

**Cooling strategy**

Thanks to a better knowledge of hypothermia mechanisms a rationale approach and management of cooling strategy was established and three main phases identified (43).

The first is the induction phase, with the target to reach a mild hypothermia (a core temperature between 32°C-34°C), as soon as possible. Some animal experiments suggest that neuro-excitotoxicity can be blocked or reversed only if the treatment is initiated in the very early stages of the neuro-excitatory cascade (44). Other studies have reported somewhat wider time frames, ranging from 30 minutes to up to 6 hours (45). The possibility of reaching hypothermia in the field for out-hospital cardiac arrest is still object of debate. One not adequately powered trial demonstrated a trend toward a better neurological outcome
when cooling was started out-of-hospital with 4°C saline rapid infusion (17), and preliminary data from the PRINCE study showed that cooling before ROSC with a nasal cooling device is feasible, and in selected groups of patients allowed higher neurologically intact survival rate when compared with TH started in hospital (19). The second phase is the maintenance one, with the aim to maintain core temperature as close as possible to the target (maximum fluctuation 0.2-0.5°C).

The third phase is the rewarming period, which consists in a slow and controlled return to normothermia (0.2-0.3°C/h). This phase starts 24 hours after hypothermia induction and ends when the patient reaches normothermia. Slow de-cooling avoids violent hemodynamic fluctuations and electrolyte disorders and prevent hypoglycemia due to increased insulin sensitivity. Moreover some studies (46, 47) suggest that rapid rewarming could reverse some protective effects of hypothermia while a significant decrease in jugular venous oxygen saturation during rapid rewarming of patient following cardiac surgery is demonstrated (48, 49), and the incidence and severity of jugular bulb desaturation may be lessened by a slower rewarming.

Each TH phase is characterized by physiological changes. Shivering is a protective strategy activated by human organism in contrast to temperature loss and leads to an undesirable increase in metabolic rate and oxygen consumption (50).

Its prevention and aggressive treatment requires subsequent steps: a rapid cooling below 34°C, magnesium administration, adequate sedation and analgesia, and eventually neuromuscular blockade (51). Some authors describe benefits from skin warming during cooling (52). Shivering prevention and treatment is of paramount importance to avoid TH benefits loss.

During mild to moderate hypothermia (32°C-34°C), cardiac output decreases by 25% to 40%, mainly due to a decrease in heart rate; since metabolic decrease exceeds cardiac output reduction, overall circulatory system result unchanged or improved. At 32°C heart rate usually decrease around 40-45 beats per minute and when heart rate is allowed to decrease, systolic function usually increases. Conversely myocardial contractility decreases when chronotropic agents are administrated or a pacing is placed; if an increase in heart rate is necessary rewarming the patient to a slightly higher temperature may be sufficient. Occurrence of malignant arrhythmias is described only for severe hypothermia (53, 54).

The increase in venous return induced by hypothermia can lead to activation of atrial natriuretic peptide and a decrease in the levels of anti-diuretic hormone leading to a marked increase in diuresis, which may lead to hypovolemia, renal electrolyte loss, and hemoconcentration with increased blood viscosity (55). Hypovolemia is the most frequent cause of haemodinamic instability during the induction phase, its prevention and prompt treatment is of pivotal importance (56).

Hypothermia also induces electrolytic disorders: during the induction phase potassium and magnesium levels decrease due to urinary loss and intracellular shift. While electrolytes correction may prevent arrhythmias, it is necessary to consider that in the rewarming phase electrolytes movement occur in the opposite direction (57). In cooled patients a reduction in metabolism is also observed. Caloric intake and mechanical ventilation should be decreased in order to balance O₂ and CO₂ and to avoid alterations that can worsen the ischemic/reperfusion injury (58).

A decreased insulin secretion and, in many patients, a moderate (and sometimes severe) insulin resistance is observed. This
can lead to hyperglycaemia and/or a significant increase in doses of insulin required to maintain glucose levels within an acceptable range (59).

Despite standard coagulation tests will show no abnormalities unless they are performed at the patient’s actual core temperature, due to effects on platelet count and function, kinetics of clotting enzymes and other steps in the coagulation cascade, hypothermia produces a mild bleeding diathesis (60-64).

Hypothermia begins to affect platelet function only when temperature decrease below 35°C, and other coagulation factors are affected when temperature decrease below 33°C (60-64); the risk of clinically significant bleeding induced by hypothermia in patients who are not already actively bleeding is very low.

Drugs clearance is affected by cooling, the half-life is increased and higher plasmatic concentrations are achieved with the same doses (64). This must be kept on mind while administrating sedatives, analgesics, neuromuscular blockade agents or other required medicaments.

Multiple evidences show that hypothermia can suppress epileptic activity (65-67), even if during TH antiepileptic medicaments are administered for patient sedation, continuous EEG monitoring is recommended when seizures or non-seizures epileptic activity is suspected, especially when muscle relaxant are required for shivering control.

Hypothermia impairs immune functions and inhibits various inflammatory responses, increasing the risk of infections (68). Incidence of pneumonia is described to increase in some cases, particularly for prolonged hypothermia and some authors suggest prophylactic treatments. Appropriate attention must be taken in wound care (68).

Other minor alteration, like transient impaired bowel function or amylase count occurs but they normalize once normothenmia is reached.

In *table 2* a list of laboratory and instrumental tests we use in our department to monitor and prevent changes, side effects and potential complications due to TH.

### Cooling methods

After having identified patient to cool and excluded conditions that contraindicate TH (*Table 1*), clinicians should start cooling as soon as possible and should consider the different options to get the target temperature.

Needs for other procedures such as percutaneous coronary intervention shouldn’t delay cooling, as TH during percutaneous transluminal coronary angioplasty is shown to be feasible and safe (69).

| **INDICATIONS:** |
|---|
| Return Of Spontaneous Circulation (ROSC) after cardiac arrest (any rhythm of presentation, any location) |
| Coma (does not open eyes to pain, does not follow verbal command) |
| Age ≥18 |

| **CONTRAINDICATIONS:** |
|---|
| Time from ROSC > 6 h |
| Other possible causes for coma (stroke, intoxication, head trauma, hypoglycaemia, seizures) |
| Significant pre-existing neurologic impairment |
| Systolic arterial pressure < 90 mmHg despite fluids and vasopressors |
| Refractory Ventricular Arrhythmia |
| Pre-existing coagulopathy or severe bleeding (Disseminated Intravascular Coagulation, severe thrombocytopenia, liver failure) |
| NOTE: anticoagulant and antiplatelet therapy are not a contraindication |
| Pregnancy |
| Sepsis |
| Known pre-existing terminal illness |

| **SUSPEND COOLING PROTOCOL WHEN:** |
|---|
| sepsis or pneumonia |
| refractory haemodynamic instability |
| severe refractory arrhythmia |
Table 2 - Timetable for laboratory and instrumental tests in use in our institute.

| Time from TH induction (h) | 0   | 2   | 8   | 12  | 16  | 24  | 36  | 48  | 72  |
|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Blood Urea Nitrogen Creatinine | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Albumin, Proteinaemia     | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Creatine Phosphokinase    | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Aspartate Transaminase    | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Alanine Transaminase      | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Lactate dehydrogenase     | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Creatine Kinase           | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Myocardial Band isoenzyme | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Troponin                  | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Coagulation tests         | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Amylase, lipase           | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Lactate                   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Complete Blood Count      | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Arterial Blood Gas        | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| + electrolytes + glycaemia| ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Electrocardiography       | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Echocardiography          | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Chest X-Ray               | ⊗   | ⊗   |   |   |   |   |   |   |   |
| Electroencephalography    | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| (continuous when needed)  | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Evoked potential          | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| Computed Tomography scan  | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |
| (if need to exclude other causes for coma) | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   | ⊗   |

First of all a temperature probe must be positioned. The site chosen to measure core temperature is of key importance. Pulmonary artery catheter is the gold standard for core temperature detection but risks linked to the procedure must be considered; oesophageal and bladder probes are less precise and slower in detecting temperature changes but widely used due high correlation to core temperature, relative simple positioning and few side effects. Tympanic probes are also used, particularly indicated for out-of-hospital measurements, they are quick and easy to place, may reflect brain temperature but readings sometimes may be inaccurate. The best way to achieve rapid cooling, temperature maintenance and a slow and controlled rewarming is to integrate different cooling methods. Administration of cold fluids in the induction phase is a common, practical, effective, safe and cheap procedure. A rapid bolus of 20-30 ml/kg 4°C isotonic saline solution is effective in decreasing temperature and its use is supported by multiple evidences in pre-hospital setting as in emergency department (70-74). Modern cooling devices work in a controlled feedback manner, continuously measuring patient’s temperature and consequently changing the temperature of the cooling elements (catheters, pads, or blankets). Intravascular cooling devices permit to achieve a tight temperature control but are
affected by risks and complications of central venous catheterization (75, 76). Surface cooling devices allow a good temperature control, are well tolerated and relative safe because of the infrequency of overcooling and lack of vascular catheterization complications and are useful for maintenance of normothermia after cooling (70). Both this kind of devices represent, at the moment, the best and preferred choice for the maintenance and rewarming period. Preliminary data from the PRINCE study show that intranasal cooling is feasible and effective and more studies are needed to confirm benefits on outcome when used in out-of-hospital setting (19).

Low cost methods as covering the patient with ice or placing ice packs on groin, neck and axillas are also used. Those techniques are cheap but lack in loop control with the core body temperature and expose the patient to an overcooling risk, don’t allow a tight temperature control, don’t allow a controlled rewarming and produce an extra workload for nurses.

Other methods like body cavity lavage, whole-body ice water immersion, cooling helmets or extracorporeal devices are less used due to lack in efficacy or higher risks and costs/effectiveness (77).

**CONCLUSIONS**

Beneficial effects of mild TH in patients with a witnessed FV cardiac arrest are clearly demonstrated. However, a widespread use of TH in daily practice is still far to be reached, as demonstrated by several surveys. Reasons may be related to general, individual and local barriers. Lack of institutional protocols, lack of agreement with supporting evidence, absence of adequate instrumentation useful to reduce nurse work load and optimize management are the most perceived barri-

ers. Extensive and rapid diffusion of protocols and process issues, further training and more studies in this field are essential key points for new developments and TH application increasing.

No conflict of interest acknowledged by the authors.

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