

# Therapeutic hypothermia

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Pioneer works on therapeutic hypothermia (TH) half a century ago already showed promising results but clinical application was limited by a lack of understanding of the underlying pathophysiology, lack of reliable method for temperature control and lack of intensive care facilities to deal with possible complications. More recently, 2 studies in 2002 supported the application of moderate TH (32.0–34.0°C) in post-cardiac arrest patients. Although the studies included only patients suffering from out-of-hospital VF, many ICUs world-wide are applying the therapy to all post-cardiac arrest patients irrespective of site or presenting rhythm. While primary coagulopathy and cardiogenic shock are usually stated as relative contraindications, evidences are accumulating to support the application of TH in patients with cardiogenic shock. TH can be divided into 4 phases: Induction, maintenance, de-cooling and normothermia. Induction is usually achieved by infusion of cold isotonic fluid. The precautions included avoidance of over-cooling, hypokalaemia, hyperglycaemia, and shivering. TH can be maintained by many different methods, varying in their level of invasiveness, cost and effectiveness. Issues including changes in pharmacokinetics and haemodynamics, and susceptibility to infection need to be addressed. The optimal duration of maintenance is unknown but the usual practice is 12–24 hours. De-cooling and rewarming is especially challenging because complications can be serious if temperature rise by more than 1°C every 3–5 hours. Life-threatening hyperkalaemia can occur especially if patient suffers from renal insufficiency. Fever is a frequent complication either due to infection or post-cardiac arrest syndrome but patient must be kept normothermic for 72 hours. (Korean J Anesthesiol 2010; 59: 299-304)

**Key Words:** Cardiac arrest, Hypothermia, Post-cardiac arrest syndrome, Therapeutic hypothermia.

## Introduction

Although the basic principles of resuscitation were described by Versalius more than 500 years ago, the practice of cardiopulmonary resuscitation in its modern form only starts 50 years ago [1,2]. Despite advances in the understanding

and practices of airway management, ventilatory support, external cardiac compression and drug therapy the outcome of patients undergoing cardiopulmonary resuscitation remained poor [3]. Patients may have spontaneous circulation restored and admitted to the intensive care unit, but then developed complications related to ischaemic insult to the brain as well

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as to the rest of the body. The term post-resuscitation disease was coined by the Russian resuscitologist Vladimir A. Negovsky in 1972 to describe the constellation of pathological processes caused by ischaemia and reperfusion associated with cardiac arrest and the subsequent resuscitation. This is more recently renamed post-cardiac arrest syndrome [4] because “the term resuscitation is now used more broadly to include treatment of various shock states in which circulation has not ceased...(and) the term postresuscitation implies that the act of resuscitation has ended...” 4 key components contribute to the development of this syndrome: 1) post-cardiac arrest brain injury; 2) post-cardiac arrest myocardial dysfunction; 3) systemic ischaemia/reperfusion response; and 4) persistent precipitating pathology [4]. There is evidence to support that proper management in the post-resuscitation phase can improve outcome of these patients [5] and therapeutic hypothermia is one important component of such management.

To avoid confusion, there is a need to define terminology used in relation to manipulation of body temperature [6]:

- Hypothermia is defined as core body temperature of less than 36°C regardless of the cause.
- Induced hypothermia is defined as an intentional reduction of a patient’s core temperature below 36°C.
- Therapeutic hypothermia is defined as controlled induced hypothermia; i.e. induced hypothermia with the potentially deleterious effects such a shivering, being controlled or suppressed.
- Controlled or therapeutic normothermia is defined as bringing down core temperature in a patient with fever, and maintaining temperature within a range of 36–37.5°C, with the potentially deleterious effects such a shivering, being controlled or suppressed.

The degree of therapeutic hypothermia can mild (34.0–35.9°C), moderate (32.0–33.9°C), moderately deep (30.0–31.9°C) or deep (<30.0°C) according to the target temperature as stated within the brackets.

Early studies showed that induced hypothermia improved outcome in cardiac arrest patients [7,8]. Although both studies were small (12 patients had induced hypothermia in each study) case series. However, further progress was hindered by 1) lack of understanding of the underlying pathophysiology, 2) lack of reliable methods to control body temperature, and 3) lack of intensive care facilities to manage possible complications. The early hypothesis that beneficial effect of hypothermia was due to reduction of metabolism leads to the adoption of more profound cooling (around 30°C). The result was serious complications which cannot be handled effectively without the support of intensive care, which was then only at its infancy. Further studies in the recent decades showed that the mechanism of cerebral protection by hypothermia is more

complicated and neurological outcome can be improved by mild to moderate degree of hypothermia. Two studies published in 2002 [9,10] provided the evidence basis that hypothermia can improve neurological outcome. Coupled with advances in technology in hypothermia and intensive care in general, therapeutic hypothermia is now a standard for management of post-cardiac arrest patient.

## Indications and Contraindication

The study population of both the study by Bernard et al. [9] and the HACA study Group [10] are patients suffering from out-of-hospital ventricular fibrillations. There is evidence that cooling patients with presenting rhythms other than VF or VT following out-of-hospital arrests does no harm [11]: 2 retrospective cohort studies found that the outcomes for patients presenting with PEA/systole did not differ from those observed among the group presenting with VF or VT. There is little published evidence to support the use of therapeutic hypothermia following in-hospital cardiac arrest. An analysis of patients entered into Arrich and ERCHACARS Group [12] found that 13% of procedures were performed post in-hospital cardiac arrest. 43% of these were cooled and although the initiation of hypothermia was faster than that for the out-of-hospital arrests, there was no difference in outcome between the patients treated with hypothermia and those with normothermia. The HACA in-hospital multi-center trial is currently investigating whether therapeutic hypothermia is beneficial for patients following in-hospital cardiac arrest.

In both the HACA and Bernard studies, patients who are hypotensive (MAP < 60 mmHg [10] or SBP < 90 mmHg despite adrenaline infusion [9]) were excluded. Coagulopathic patients were also excluded in the HACA Study Group [10]. The underlying reason being the possible deleterious effect of hypothermia on cardiovascular function and coagulation. However, there are several publications suggesting that post-cardiac arrest patients in cardiogenic shock could actually also benefit from moderate therapeutic hypothermia [11,13].

Reduction in platelet count and platelet dysfunction is noted when body temperature is dropped to <35°C; and when temperature is below 33°C, synthesis and kinetics of clotting enzymes and plasminogen activator inhibitors are also affected [14]. However, it was found in a recent study which assessed the risk and severity of bleeding during simultaneous use of mild hypothermia and thrombolysis that bleeding risks were similar to historical controls treated with thrombolytics alone, although there was a trend toward more red blood cell units being required to reach target hematocrit in hypothermic patients who developed bleeding complications and needed transfusions [15]. This, however, is a small study and more data

is required. The current practice is still to avoid induction of hypothermia in patients with coagulopathy.

The procedures of therapeutic hypothermia can be divided into 4 phases: induction, maintenance, de-cooling (or re-warming) and normothermia.

## Induction

This is the initial phase during which the patient's body temperature is lowered to the target of 32–34°C. Continuous core temperature measurement should be started before induction of therapeutic hypothermia to ensure that the patient's body temperature is within the target range and to avoid overshoot. This is preferably achieved by bladder, rectal, central venous, or oesophageal measurement. However, it should be noticed that bladder temperature may poorly reflect core temperature if the patient is oliguric, and other monitoring sites are preferred.

This phase is associated with many possible complications most of which can be minimized by rapid cooling. Rapid cooling can be achieved by rapid bolus administration of 30 to 40 ml/kg cold (4°C) isotonic resuscitation fluid over 1 hour. Despite theoretical problems this method is proven to be safe [16].

When core temperature drops to 32°C, metabolic rate decreases to 50–65% of normal. Oxygen consumption and carbon dioxide production are reduced accordingly. It is important to adjust ventilator settings to avoid hypocapnia. The issue of how to interpret arterial blood gases in hypothermic patients (alpha-stat versus pH-stat) is a topic of some controversy and readers are referred to review articles for detailed discussion [17]. Cold-induced diuresis is common in these patients and can lead to hypovolemia. This may be related to increased venous return, tubular dysfunction and hormonal changes [14]. Hypothermia can lead to hypokalaemia, hypophosphataemia and hypomagnesaemia as a result of intracellular shift as well as urinary loss because of tubular dysfunction. It is particularly important to monitor and replace potassium in order to avoid arrhythmia [18]. On the other hand, mild metabolic acidosis is common yet do not usually require treatment. It is the result of increased fat metabolism, leading to an increase in the levels of glycerol, free fatty acids, ketonic acids, and lactate. pH rarely fall below 7.25 [19]. Hyperglycaemia due to reduction of insulin secretion and insulin resistance should be controlled by close monitoring and insulin therapy.

The haemodynamic effect of hypothermia is more complicated. The main sources of relevant data come from patients with hypothermia induced during cardiac surgery. All patients studied developed bradycardia but blood pressure usually remained stable. Cardiac output decreased along with the heart

rate; however, the hypothermia-induced decrease in metabolic rate usually equaled or exceeded the decrease in cardiac output, so that the balance between supply and demand remained constant or improved [20]. However, the actual cardiac output is also affected by the volume status and effect of sedation. Systolic function of myocardium may actually be improved during mild to moderate hypothermia but diastolic function is usually impaired. It is important to note that the effect of hypothermia on myocardial contractility is strongly dependent on heart rate. If the heart rate is allowed to decrease along with the temperature, myocardial contractility as measured by systolic function usually increases, although there may be a mild degree of diastolic dysfunction. However, if the heart rate is artificially increased through administration of chronotropic drugs or a pacing wire, myocardial contractility decreases significantly. This phenomenon has been demonstrated in animal studies and also in patients undergoing cardiothoracic surgery. Thus, the effect of hypothermia on myocardial function strongly depends on whether the heart rate is allowed to decrease [20–22]. Maintaining euvoemia is one important aspect of management during therapeutic hypothermia and one challenge is cold induced diuresis. The underlying mechanisms leading to cold-induced diuresis include increased venous return caused by constriction of peripheral vessels (particularly in the skin) due to hypothermia-induced increases in plasma noradrenaline levels and activation of the sympathetic nerve system, activation of atrial natriuretic peptide, decreased levels of antidiuretic hormone and renal antidiuretic hormone receptor levels, and tubular dysfunction [23,24]. If uncorrected, diuresis can cause hypotension as well as electrolyte depletion and increase in blood viscosity. The risk for hypovolemia increases significantly if the patient is simultaneously treated with diuretic agents such as mannitol. However, hypotension can be quite easily prevented by avoiding or promptly correcting hypovolemia, and by avoiding excessive stimulation of heart rate. While profound hypothermia of <28°C is associated with severe arrhythmia, mild to moderate hypothermia could stabilize membranes. One study showed that mild and moderate hypothermia actually improves success of defibrillation [25].

Hypothermia will activate homeostatic mechanisms of the body: vasoconstriction and shivering. Study in normal human showed that the threshold for vasoconstriction is about 36.5°C and that for shivering is 35.5°C. The threshold is slightly higher in female but the difference is <0.5°C [26]. Shivering of postoperative patients may lead to increased risk of morbid cardiac events especially in older patients with heart disease: the result of increased rate of metabolism and oxygen consumption, leading to excess work of breathing and tachycardia [27,28]. However, the situation may be different

in sedated patients. While hypothermia in an awake patient causes tachycardia, inducing hypothermia intentionally in sedated patients has the opposite effect. Shivering will increase oxygen consumption, but as the patient is on mechanical ventilation, there will be no increase in the work of breathing [29]. Nevertheless, it is important to prevent or aggressively treat shivering because it significantly complicates hypothermia induction, and leads to an undesirable increase in metabolic rate and oxygen consumption.

Shivering may be controlled by one and more of the following methods: 1) drugs lowering shivering threshold, e.g. acetaminophen (paracetamol), aspirin, and nonsteroidal anti-inflammatory drugs; 2) drugs suppressing shivering response paralyzing agents, sedatives, opiates, and others; and/or 3) skin counterwarming. Drugs lowering shivering threshold are not quite effective in general. Of the drugs which suppress shivering, meperidine is the most effective [30]. In a recent systematic review, it was found that there is significant variation in sedation protocols amongst the 68 ICUs included in the selected studies [31]. Midazolam (5 mg/h to 0.3 mg/kg/h) being most commonly used, followed by propofol (up to 6 mg/kg/h). A quarter of ICUs do not use any analgesic, the rest use either fentanyl (0.5–10 mcg/kg/h) or morphine. Most ICUs routinely use neuromuscular blocking agents. Use of neuromuscular blocking agents, however, is associated with several disadvantages some of which can be reduced by adequate sedation: 1) attempts of the brain to generate a shivering response will not cease; 2) they can mask seizure; 3) they lack of vasodilating effect of sedatives; and 4) their use is associated with development of critical illness polyneuromyopathy [14]. The importance of adequate sedation and suppression of hypothermia-induced stress responses is underscored by observations from animal experiments suggesting that some or all of hypothermia's neuroprotective effects can be lost if cooling is used in non-sedated animals [32]. Skin counterwarming is an interesting phenomenon. It was found that 4°C increase in skin temperature could "compensate" for 1°C drop in core temperature to prevent a shivering response. Some areas of the body (hands, feet and face) have a higher concentration of "temperature sensors" and warming of those areas could have a greater effect on suppressing shivering [33]. By reducing shivering, counterwarming can reduce metabolic rate and oxygen consumption of hypothermic patients [34].

## Maintenance

During this phase, the goal is to maintain core temperature at 32–34°C for 12–24 hours [9,10]. The patient is usually more stable during this phase with fewer disturbances in their haemodynamic, volume or electrolyte status, as well as less

shivering. However, the patient is subjected to other hazards including changes in pharmacokinetics, nosocomial infections and bedsores.

Conventionally, patients are maintained cool by surface cooling through exposure, placing ice packs to the neck, groins and axillae, and/or spraying with water. Rubber cooling blankets can also be used but should be placed over the patient. Placing those blankets under the patient can lead to skin damage due to vasoconstriction in already pressurized areas. Although widely available and inexpensive, conventional surface cooling is difficult to control as there is no internal feedback mechanism. Overcooling is common despite extreme nursing vigilance. Nursing workload can also be high. This has brought about the emergence of many commercial cooling devices. These may be classified as non-invasive surface cooling devices such as hydrogel-coated water circulating pads or water-circulating wrapping garments, and invasive core cooling devices using intravascular catheters. A problem with surface cooling is that 40–90% the patient's surface area needs to be covered and carries a risk of skin lesions. But they can be started immediately using nurse-driven protocols without direct physician intervention. Cooling rate is 1.0–1.5°C/hour. Core-cooling methods, on the other hand, are highly reliable once the catheter is in place, with a cooling rate of 2.0–4.5°C/hour. However, insertion of catheter is required and it can lead to complications such as thrombosis and infection [35].

Cautious medication dosing during this phase is required due to change in drug metabolism. For example, CYP450 activity has been found to be temperature dependent [36]. Hypothermia can increase the risk of infection. Even short duration of hypothermia during perioperative period for intracranial aneurysm increase the risk of postoperative bacteraemia [37]. A study has shown that 3 days of prophylaxis with ampicillin-sulbactam can reduce early onset nosocomial pneumonia but not the incidence of late-onset nosocomial pneumonia [38]. Nursing care to prevent bedsores is important. Sedation should be continued during this phase.

## De-cooling/Rewarming

After 12–24 hours of cooling, patient can be allowed to warm up slowly. The goal should be 0.2–0.33°C per hour until the patient is 36.5–37.0°C. More rapid warming must be prevented to avoid electrolyte disturbance due to transcellular shift, hypoglycaemia due to increased insulin sensitivity, as well as aggravated brain destruction [35].

Hyperkalaemia can develop during this phase due to release of intracellular potassium. This can be prevented by slow rewarming, allowing the kidneys to excrete the excess potassium. However, this should not be a reason to accept hypokalaemia

in the induction or maintenance phase. For patients with renal dysfunction, renal replacement therapy should be started before rewarming to avoid life-threatening hyperkalemia.

## Normothermia

Fever can develop after cessation of cooling. This may be the result of nosocomial infection or part of the post-cardiac arrest syndrome. Fever is independently linked to adverse outcome in all types of neurological insults. Furthermore, cerebrovascular reactivity may be impaired following hypothermia treatment and thus increase the potential harmful effects of fever even more [38,39]. There was a case report in which a post-cardiac arrest patient who initially improved after rewarming deteriorated after development of fever and subsequently died. Autopsy showed massive brain swelling and tentorial herniation [40]. It is recommended that patients should be maintained normothermic after decooling until 72 hours have elapsed since restoration of spontaneous circulation [35]. Patients who develop fever should be actively cooled again.

## Conclusion

Current evidence supports that induction of therapeutic hypothermia in selected patients after cardiac arrest can improve neurological outcome [41]. However, not all ICUs are currently taking up the practice. Lack of familiarity and lack of a concrete protocol are the most important amongst the list of perceived barriers [42]. It is hoped that by summarizing the current state of knowledge on the subject and highlighting issues on clinical management will enable more patients to benefit from the therapy.

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