

Targeted temperature management in neurocritical care: Boon or bust

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Abstract

Temperature management in neurocritical care is important and has gained due importance in recent years. Targeted temperature management (TTM) includes deliberate reduction of core body temperature to a range of 32–34°C in comatose survivors of cardiac arrest after return of spontaneous circulation and also therapeutic hypothermia (33–35°C) in normothermic patients or controlled normothermia (cooling patients to 37°C) in hyperthermic patients. This review focuses on the practical aspects of cooling and temperature management in neurocritical care. An electronic search of Google Scholar, MEDLINE (OVID), EMBASE and the Cochrane library was performed. The physiological changes, potential side effects along with significant research and clinical applications in the field of temperature management are main highlights. Currently, the research evidence is available for TTM in adults following cardiac arrest, neonatal hypoxic ischaemic encephalopathy and raised intracranial pressure. Controlled normothermia in neurocritical care population is rapidly gaining popularity. However, data on disease specific therapeutic markers, therapeutic depth and duration and prognostication of this modality are limited. Overall in experienced hands, the technique is safe to execute without the major morbidity and a potential to improve the outcome. Though over the years, clinical applications are unable to consistently demonstrate its benefits, but TTM in neurological insult has become an established and promising concept.

Key words: Adverse effects, controlled normothermia, cooling, indications, targeted temperature management, therapeutic hypothermia

INTRODUCTION

The global burden of neurological injury is gigantic. The constant need to improve outcome following the neurological insults has given birth to desperate yearning for cerebroprotective agents. Though the magic pill for the same is missing, but a range of agents with the assorted mechanism of action are being tested. By virtue

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of its versatile mechanism of action, hypothermia (HT) has been looked upon as one of the most eligible contenders among these agents. Its foundation is based on the rich history of experimental and clinical research. It has fascinated the mankind by anecdotal reports of remarkable neurological recovery despite prolonged resuscitation in victims of near-drowning in ice-cold water.^[1] Targeted temperature management (TTM) after neurological insult is now a well-established and enticing concept. This review focuses on the practical aspects of cooling and temperature management in neurocritical care. The physiological changes, potential side effects along with significant research and clinical applications in the field of temperature management are main highlights. An electronic search of Google scholar, MEDLINE (OVID), EMBASE and the Cochrane library

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was performed. The search terms used included 'HT', 'cooling' or targeted temperature management in various combinations with 'methods', 'devices', 'induction', 'indications', 'arrhythmias', 'haemodynamic', 'bleeding', 'side effects', 'coagulopathy', 'infection', 'immune suppression' and various others were used.

Physiology of temperature regulation

The human body is roughly divided into two thermal compartments: A 'core' compartment consisting of the trunk and head and a 'peripheral' compartment consisting of the skin and extremities. Under normal physiological conditions, core body temperature (CBT) is strictly regulated around a set point of $36.6^{\circ}\text{C} \pm 0.38^{\circ}\text{C}$. The temperature of the peripheral compartment is less strictly controlled and under normal circumstances is $2\text{--}4^{\circ}\text{C}$ lower than the core temperature. The brain temperature is slightly higher than the CBT. The mean gradient ranges from 0.3°C to 1.1°C . This difference may increase to $2\text{--}4^{\circ}\text{C}$ during fever and other events of neurological insults. Conversely, it may disappear or reverse in cases with an abrupt rise in systemic temperature or suppression of cerebral activity.^[2,3] There is a spatial variation in temperature within the brain itself. Deeper and areas with higher metabolic activity have a higher temperature. High brain temperature following neurological insult has a deleterious effect and potentiates excitotoxic brain injury.

CBT is measured from core body sites such as the oesophagus, pulmonary artery, nasopharynx or tympanic membrane or intermediate sites such as oral (sublingual), rectal or bladder. Peripheral temperature measurements are obtained from forehead skin or axilla. CBT is less affected by vasomotor or thermoregulatory mechanisms. Temperature measurement site must be chosen according to need and feasibility. Brain temperature cannot be predicted accurately from CBT. It can be measured in brain parenchyma (sensor coupled with brain tissue oxygen sensors or intracranial pressure [ICP] probes), cerebral ventricle or in the subdural space. Measuring brain temperature is complex and invasive that is why even during aggressive HT therapies it's often guessed from CBT only. Brain temperature was not measured even in the most important studies of HT after cardiac arrest and perinatal asphyxia. Many non-invasive devices to measure brain temperature are being developed, but none is widely available for clinical use. Though brain temperature is the therapeutic target, but CBT continues to be used as a surrogate.

DEFINITION

HT is defined as $\text{CBT} < 36^{\circ}\text{C}$ while fever is $\text{CBT} > 38^{\circ}\text{C}$. Deliberately inducing HT is often referred to as therapeutic HT (TH) or induced HT (IH). Accidental HT is

an involuntary drop in $\text{CBT} < 35^{\circ}\text{C}$. TH is broadly divided into mild HT ($\text{CBT } 35.9\text{--}34.0^{\circ}\text{C}$), moderate HT ($\text{CBT } 33.9\text{--}32.0^{\circ}\text{C}$), moderate deep HT ($\text{CBT } 31.9\text{--}30.0^{\circ}\text{C}$) and deep HT ($\text{CBT} < 30.0^{\circ}\text{C}$).^[4] Previously, the hypothermic neuroprotection was thought to be solely due to temperature dependent reduction in metabolism; lower the temperature, greater the protection consequently deep HT were practised. The associated complication burden was huge. Over the years, other mechanism of action of HT became known and mild to moderate temperature drop gained popularity. It had a low incidence of unfavourable effects. The recommended temperature range of $32\text{--}34^{\circ}\text{C}$ is widely used clinically and has been extrapolated from animal experiments.^[5] The term targeted temperature management (TTM) was coined to refer to deliberate reduction of the CBT to a range of $32\text{--}34^{\circ}\text{C}$ in comatose survivors of cardiac arrest after return of spontaneous circulation (ROSC). Now, the term also includes TH in normothermic patients (mild HT of $33\text{--}35^{\circ}\text{C}$) or controlled normothermia (cooling patients to 37°C) in hyperthermic patients.^[6]

MECHANISM OF PROTECTION BY THERAPEUTIC HYPOTHERMIA

Traditionally, HT was thought to be neuroprotective as it decreased cerebral metabolism, but alone it could not explain the non-linear protective effects so offered. Countless destructive processes such as excitotoxicity, neuroinflammatory reactions, apoptosis, free radical production, seizure activity, blood - brain barrier disruption, blood vessel leakage, cerebral thermo pooling, etc., begin in brain following neurological insult. The severity of this destructive cascade and body's response to it determines the outcome. Experimentally, TH has the potential to inhibit or mitigate this chain of events following the neurological insult. It influences multiple aspects of brain injury during acute, sub-acute and chronic periods, that is, weeks to months after the injury, well after cooling has stopped!

Acute phase

In the acute period, the predominant effect is on cerebral metabolism, blood flow and excitotoxicity. Cerebral oxygen and glucose consumption decreases by $5\%/^{\circ}\text{C}$ fall in brain temperature.^[7] By preserving the metabolic reserves, HT prevents adversities associated with increased lactate production and subsequent acidosis during anaerobic metabolism. Probably this mechanism plays a role during global hypoxia. Under injury conditions such as ischaemic stroke, HT helps during reperfusion. At the time of reperfusion, HT blunts immediate hyperaemia and later prevents a gradual reduction in cerebral blood flow (CBF) following stroke. It also prevents the release of excitotoxic amino acids.^[8] Cooling also attenuates acute inflammatory

processes, induction of immediate early genes, cellular stress response and induction of heat shock proteins-70. Currently, the effect of HT on microRNA (non-coding RNA) expression is under investigation. MicroRNA expression increases following ischaemia and these play a significant role in stroke pathogenesis. Cooling favourably alters the expression of microRNA.^[9]

Sub acute phase

A period somewhere from 1-day to 1-week following an injury. It is actually the period when secondary insult occurs through a cascade of events. Reperfusion, inflammatory and cell death pathways are activated during this time and result in propagation of ischaemic injury.^[10,11] There is disruption of blood brain barrier, oedema formation or haemorrhage. HT offers protection by influencing the apoptotic and endogenous survival pathways, suppression of inflammation and preservation of vascular morphology. It reduces glutamate release, inflammation and free radical generation. HT may impair glutamate-mediated calcium influx or directly inhibit calcium-mediated effects of calcium/calmodulin kinase.^[12,13] The effect on ICP may be explained by stabilisation of vascular morphology and decreased oedema formation.^[14] HT is shown to be protective in large models of ischaemic stroke but less commonly in models of haemorrhagic stroke. As it inhibits coagulation pathways by decreasing fibrinogen and thrombin generation, it might increase the chances of bleeding and thus correlate to poorer outcome in such cases.^[15]

Chronic stage

The chronic effects are seen over a period of weeks to months, well after the cooling has stopped. HT is believed to help the injured brain to regenerate and reorganise. The exact mechanism is yet not understood but is related to protection and proliferation of stem cells by HT. It is proposed that HT influences recovery and repair mechanisms and helps in neurogenesis, gliogenesis, angiogenesis and restoration of neural circuitry.^[12,13,16,17]

Institution of therapeutic hypothermia

The institution of TH can be divided into three main phases: Induction, maintenance and rewarming. Each one has its own risk and management issues [Table 1]. The speed and duration of cooling and rate of rewarming are the key factors in determining affectivity of TH.

Induction of cooling

The aim of this phase is to decrease the CBT to a targeted range, as quickly as possible by available means and to deal with physiological and pathological changes associated with it. During this phase, slight overshoot is acceptable, but the temperature should not fall to <30°C.^[4,13] The risk of complications such as hypotension, electrolyte disturbances and hyperglycaemia are the greatest during

induction.^[4,13,18] Hypokalaemia is common due to the intracellular shift of potassium. Shivering is the major adverse effect and active intervention is required to treat it. To curtail side effects, duration of induction phase should be minimised, and more stable temperatures should be achieved quickly.

The cooling equipment

The body can lose heat by means of convection, conduction, radiation or evaporation. Consequently, HT can be attained by different devices using a combination of these principles. The rate of heat loss is dependent on the temperature gradient, conductive properties of environment and body composition. A number of devices are commercially available for achieving TH and range from the whole body to selective cerebral cooling systems [Table 2].

Whole body cooling

The methods of the whole body cooling are extensively studied and commonly used in clinical practise. The prerequisites of ideal cooling device are the rapid speed of induction, tight temperature control during maintenance and slow rewarming rates.^[4,13] Grossly, the methods to attain whole body cooling can be divided into non-invasive methods and invasive methods [Table 1].

Non-invasive methods

Ice packs, water/alcohol sprays, skin exposure, etc., are cheap, readily available, non-invasive methods to achieve TH.^[4,19] However, these methods are cumbersome and produce erratic temperature reductions. Water or air cooling blankets with temperature feedback systems are better and have been used in large clinical trials to attain TH.^[19-21] These blankets wrap around patients body with/without adhering and automatically cool and rewarm gradually according to preset modes. They control temperature by using feedback temperature sensors from the patient's core and skin. They have been used even in awake patients.^[21] The equipment consists of a separate machine for temperature control and air/water circulated blanket. The conventional water (Blanketrol, Gaymar Meditherm, etc.)/air (Polar Air, Bair Hugger) cooling blankets induce cooling by conduction and convection, respectively. A new non-invasive temperature management system (Arctic Sun, Medivance) uses hydrogel-coated pads circulating temperature-controlled water under negative pressure and adheres to the patient's abdomen, back and thighs [Figure 1]. This is different than conventional water blankets or wraps, in which air is trapped between the cooling source and the skin and the patient is cooled by cold air (convection). The cooling rate is reported to be 1.5°C/h or better with it. However, overall cooling and rewarming rates with blankets are less predictable and alone they take a long time to attain HT. Decreasing

Table 1: Different phases of targeted temperature management

Phase	Induction (37-35°C)	Maintenance (32-35°C)	Rewarming (hypothermia-37°C)
Aim	Maximise speed of cooling for optimal neuroprotection	Continue cooling Avoid wide fluctuations in temperature	Slow rewarming Active Passive
Duration	Preferably within 30 min	24 h, or more depending upon indication	0.25°C/h
Caution	Watch for Haemodynamic instability Shivering Coagulation abnormalities Electrolyte disturbances (specially hypokalaemia) Hyperglycaemia Metabolic acidosis Diuresis	Thermal burns Shoot down Infectious complications Altered drug metabolism	Vasodilatation and haemodynamic instability Electrolyte disturbances (especially hyperkalaemia) Avoid post-rewarming fever Shivering

General care

- Ventilator care: Adjust settings according to EtCO₂ production, interpret temperature corrected ABG
- Feeding requirement may be decreased
- Maintain normoglycaemia
- Maintain intravascular volume status
- Drug level monitoring for important drugs
- Standard operating protocols for infection control

ABG= Arterial blood gas analysis

Table 2: Methods for institution of hypothermia

Whole body hypothermia	Selective cerebral hypothermia
Noninvasive/surface cooling	Noninvasive
Air/water circulated cooling blankets	Surface cooling
Ice packs	Cooling helmets/caps
Water/alcohol sprays	Fans
Skin exposure	Surface cooling after hemicraniectomy
Immersion in cold water	Cooling through upper airway Transnasal devise
Invasive/core cooling devices	Invasive
Intravascular catheters	Vascular cerebral cooling methods
Infusion of ice-cold saline	Extraluminal anterograde cerebral perfusion
Extracorporeal circulation	Intraluminal anterograde cerebral perfusion
Antipyretics	Retrograde jugular venous cooling Compartmental cooling (epidural, subarchanoid, subdural, intraventricular)

temperature from 37°C to 32°C may take up to 8 h and temperature fluctuations are common.

Invasive methods

Using intravascular cooling catheters are gaining popularity^[22] [Figure 2]. They attain TH rapidly, maintain a narrow temperature range and rewarm in a well-controlled manner. The device consists of a central line with two or three balloons filled with temperature controlled saline and can be inserted through subclavian, superior caval or femoral vein.^[23,24] Cooling rate is 2–2.5°C/h and temperature can be maintained within a narrow range of ± 0.5°C. Rapid (30 min) intravenous infusion of a large volume (30 ml/kg) of cold (4°C) lactated Ringer’s solution has also been described as an effective method of inducing TH. In patients without cardiac shock, it can reduce CBT from 36.9°C ± 1.9°C to 34.6°C ± 1.5°C at 30 min and to 32.9°C ± 0.9°C at 60 min.^[25] In order to attain quick cooling, combined methods (infusion of cold saline and cooling blankets) have been described.

Despite advances in surface and core cooling devices, the average period of 2–3 h is still required to reach a temperature of 32–34°C. Among water or air circulating external cooling device, gel-coated adhesive system, endovascular cooling, conventional cooling with cold saline bolus and surface cooling with ice, the intravascular cooling system attain TH the fastest and maintain temperature within a narrow range. These devices are also user-friendly.^[26,27] Cooling catheters change CBT and thus peripheral cooling and its consequences such as cutaneous vasoconstriction and shivering are avoided.

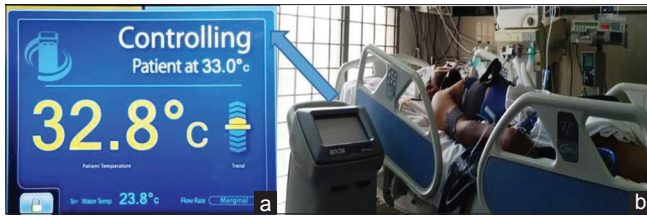


Figure 1: (a) Temperature control panel (b) Patient with surface cooling blanket *in situ*

Antipyretics

Heat generation in patients with hyperthermia can be reduced by antipyretics, but patients with elevated temperatures caused by impaired thermoregulation (central fever/stroke) antipyretics are often ineffective.^[28] A few preclinical have suggested the pharmacological agents such as neurotensin and its analogues, 3-iodothyronamine and hydrogen sulphide to decrease body temperature for given depth and duration.^[29]

- Selective cerebral cooling is emerging to potentially overcome logistical obstacles and systemic complications of whole body HT. A number of invasive and non-invasive methods are developed to induce selective cerebral cooling [Table 1]. Human research in selective HT is limited to non-invasive cooling methods
- Surface cooling of the head: Forced air-cooling helmet, cooling caps have been used in some trials to produce selective cerebral HT, but these are associated with superficial brain cooling only and regional temperature gradients are likely.^[30,31] A best of 2°C drop in intraparenchymal temperature at a depth of 2 cm has been achieved. Scalp temperature does not correlate with deep brain temperature in these cases.^[30] The first cooling helmet was designed by National Aeronautics and Space Administration technology. The device has 2 components: A head/neck liner and a conditioning unit.^[30] While surface cooling of brain in adults has disadvantage of not cooling brain parenchyma uniformly, cooling caps have been successfully used for selective HT in neonates with hypoxic ischaemic encephalopathy (HIE) owing to the unique neonatal anatomy and intracranial dynamics^[32]
- Selective cerebral cooling through upper airway: It is another emerging technique to provide selective cerebral HT.^[33,34,35] Transnasal evaporative cooling uses a mixture of liquid coolant and oxygen sprayed into nasopharynx through disposable nasal catheter [Figure 3]. The liquid undergoes rapid evaporation under the administration of high flow oxygen. Rhinochill (BeneChill International AG, Switzerland) is a portable device which utilises the principle of transnasal cooling.^[33] It consists of a

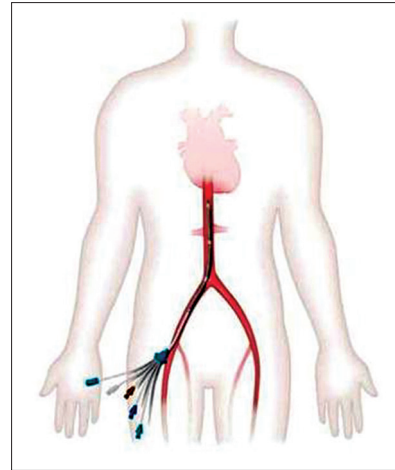


Figure 2: Endovascular cooling catheter

nasal cannula connected to battery operated control unit which controls cooling rates and switches of the device in case of high intranasal pressures. It has been successfully tested in clinical trials and results in rapid cooling of nasal passages and brain. It is especially helpful for pre-hospital and intra-arrest cooling. Device related complications are few and include periorbital emphysema, epistaxis and nasal discoloration.^[33,34] It is a safe and feasible technique and may result in significant improvement in the time required to cool the patients

- Invasive methods of cerebral cooling: Far few clinical trials are currently utilising this modality. It is an understudied approach to TH. Vascular cerebral cooling methods or conductive or convective heat transfer between various intracranial compartments can be exploited to achieve selective cerebral cooling. Injections of cooled saline or blood into an extracranial internal carotid artery (intraluminal anterograde cerebral perfusion) or retrograde venous perfusion and extraluminal cooling of the extracranial carotid artery (extraluminal anterograde cerebral perfusion) are under exploration. Transcutaneous cooling in patients with decompressive craniectomies has been used in animal models. Selective cooling can also be attained by irrigating the intracranial spaces with chilled saline.^[35,36]

Among the selective cerebral cooling techniques only surface cooling methods and intranasal cooling systems have been tested in humans. Potential concerns regarding the uneven cooling of the brain is a concern with some regional methods including surface, epidural and intranasal cooling. On the other hand, endovascular cooling and extra-luminal cuffs can provide uniform cooling of the brain. The least invasive and most selective methods of TH hold the greatest promise.

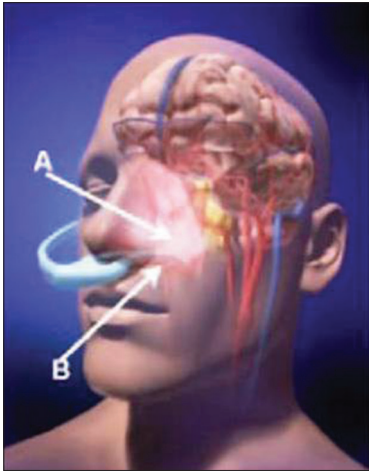


Figure 3a: Rhinochill: Transnasal evaporative cooling device, (A) coolant spray (B) nasal catheter. Reprinted with permission from BeneChill, Inc.

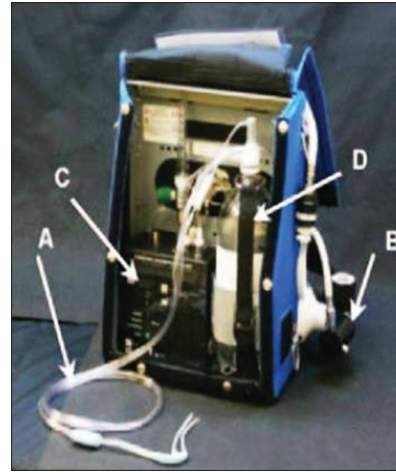


Figure 3b: (A) Nasal catheter, (B) oxygen tank, (C) control unit and (D) coolant bottle

Maintenance phase

The aim of this phase is to maintain HT and tightly regulate the body temperature with minimal fluctuations (0.2–0.5°C). It requires keeping the temperature in desired range for the appropriate length of time. There is less risk of hypotension, electrolyte disturbance or fluid shifts during this phase and once the CBT <33.5°C, shivering decreases dramatically but complications such as pneumonia, wound infections, bed sores and coagulation abnormalities are common.^[4,13,18] Drug dosage needs to be adjusted according to metabolism.

The timing and optimal duration of HT are not well defined. The timing of induction and duration of HT generally depend upon its indication. International Liaison Committee on Resuscitation (ILCOR) and American Heart Association (AHA) guidelines recommend patients with ROSC after out-of-hospital cardiac arrest (OHCA) should be cooled to 32–34°C within 2 h for 12–24 h.^[37,38] Similarly, for neonatal HIE, IH (33.5–34.5°C) within 6 h of birth for 72 h is recommended in infants born at ≥36 weeks gestation. In trials on traumatic brain injury (TBI), TH for cerebral protection has to be started as early as possible and at least for 48 h, while TH to treat refractory intracranial hypertension can be started late and can be given for longer duration (48 h–10 days), as premature termination of HT can cause rebound increase in ICP.^[37–41]

Rewarming

During rewarming phase, the cooled body returns to normal body temperature. Rewarming may be passive or active. Passive rewarming involves removal of the source for cooling and allowing the patient to warm on his own. Alternatively, active rewarming may be programmed into the same devices as used for cooling. Rewarming is a critical step. It should be gradual, the rate of rewarming should be 1°C/4 h (0.25°C/h) until the core temperature is ≥36°C. Rapid rewarming

may increase neurologic injury and not only negate protective effects of HT but also exacerbate neural pathology. Rewarming is associated with vasodilatation, hypotension, hypovolaemia, hyperkalaemia and arrhythmias. These can be mitigated by slow rewarming. These side effects should be managed effectively. Rebound intracranial hypertension is common due to rewarming induced vasodilatation.^[4,42] Watch for temperature after drop and overshoot during the early and late stages of rewarming, respectively.

PHYSIOLOGICAL CHANGES OF HYPOTHERMIA

There is a difference between pathophysiological adaptations to cooling and its side effects. While it is important to register physiological consequences of cooling, insufficient management of side effects may result in negation of protective effects. Mild HT induced a slight decrease in cardiac output, mild acidosis; the rise in lactate or amylase levels might only represents the physiological consequences of cooling and may not require treatment. However, shivering as a consequence of HT is deleterious and needs early treatment. Moderate HT is usually not associated with major complications, but deep HT adds to major morbidity. Pathophysiological changes can become major side effects with increasing depth of cooling.

- Shivering is an anticipated consequence but a major adverse effect of TH. Cooling is initially met with the resistance of counter-regulatory homeostasis mechanisms which try to maintain CBT to near normal. During use of surface cooling, there is increased sympathetic tone which leads to peripheral vasoconstriction and shivering which prevents fall in temperature. Shivering during TH induction generates significant heat and thus significantly

reduces cooling rates. Shivering can increase oxygen consumption by 40–100% and may result in acidosis and myocardial ischaemia. It is highly undesirable, especially in patients with neurological/post-hypoxic insult. Even mild HT can elicit a vigorous thermoregulatory defence. In healthy humans, peripheral vasoconstriction is triggered at 36.5°C and shivering at 35.5°C. These thresholds are often higher than normal in brain-injured patients; therefore, these thermoregulatory defences may occur more vigorously and at higher temperatures. Younger age, male gender and lower body surface area are associated with increased shivering episodes. It is difficult to cool younger patients with higher body mass index (BMI) and robust vascular response to changes in temperature in contrast to elderly patients with a lower BMI and less effective vascular response.^[43] The bedside Shivering Assessment Scale helps in the quantification of shivering. Various methods such as deep sedation, active skin counter warming, opioids, pethidine, clonidine and magnesium have been recommended for the treatment of shivering. In awake, non-ventilated patients meperidine and buspirone have been used to control shivering in clinical trials. Therapy for shivering should suppress the central thermoregulatory reflex rather than just uncoupling of skeletal muscle response. Use of muscle relaxant stops clinical manifestations of shivering but does not mitigate the on-going cerebral and systemic stress response. Only if not controlled by sedation, muscle relaxants should be used in intensive care settings. Conversely, muscle relaxants are highly effective in controlling shivering without associated vasodilatation and hypotension. They may be superior in settings of haemodynamic instability and emergency room. Shivering is markedly depressed or absent at temperature <33.5°C consequently it becomes less bothersome during the maintenance phase

- CBF and metabolism: The uninjured brain has closed coupling of CBF and CMRO₂ between temperatures of 33°C and 35°C. Reduction in CBF nearly parallels reductions in CMRO₂. CMRO₂ decreases by 8%/°C falls in temperature. However, below 28°C there is uncoupling between the two and studies report the development of both ischaemic and hyperaemic states.^[7,43] The cerebral vasculature retains its responsiveness to CO₂ even at reduced temperatures but in the diseased state the coupling may be disturbed. The literature demonstrates inconsistent changes in CBF during various diseases states such as TBI, subarachnoid haemorrhage (SAH), stroke, etc., due to loss of autoregulation.^[44] Clinically, mild HT causes confusion, dysarthria, ataxia and amnesia. Below 28°C, there is a loss of reflexes and

diminishing electroencephalogram (EEG) activity with complete EEG silence below 26°C. In a study conducted in survivors of cardiac arrest treated with HT, mean flow velocity in middle cerebral artery was low with normal jugular venous oxygenation. It indicates a reduction in cerebral metabolic activity as a neuroprotectant in these patients^[45]

- Cardiovascular changes: TH has a variable impact on cardiovascular status. It can affect cardiac rhythm, output and peripheral vascular resistance. The magnitude of effect increases with decreasing temperature. During moderate TH, these changes warrant close monitoring and do not require medical management in most of the cases. Cooling is initially associated with tachycardia followed by bradycardia. Tachycardia is because of initial increased myocardial oxygen demand relative to supply and TH induced increased catecholamine levels. With the further decrease in temperature decreased metabolism and depressant effect of TH on heart results in bradycardia. Cold induced vasoconstriction leads to increased vascular resistance and thus after load. This may result in increased vascular permeability and extravasation of fluid into extravascular circulation and manifests as increased haematocrit and blood viscosity. (4–6%/°C temperature reduction). Mild TH may decrease cardiac output by up to 25%. Cardiac function is more suppressed with increasing levels of HT.^[46,47] Direct effect of HT on the myocardium, HT induced endogenous catecholamines or electrolyte abnormalities have a significant bearing on cardiac rhythm. Temperatures below 32°C have a tendency to develop atrial fibrillation and even lower temperatures are associated with the development of refractory, spontaneous ventricular fibrillation (VF). The occurrence of Osborn wave is also seen at these temperatures. Such rhythms are dangerous and warrant urgent management
- Notably, the influence of TH on the myocardium is conflicting. Even mild TH reduces cardiac contractility inducing systolic and diastolic dysfunction. Coronary vasoconstriction was reported in patients with pre-existing coronary artery disease during HT. This can be taken as the theoretical risk of myocardial insult, especially in patients with cardiovascular disease.^[47,48] On the other hand, there is evidence of increased inotropy due to catecholamine release and decreased myocardial infarct size with TH
- Coagulation abnormalities: Coagulation cascade is temperature dependent. With fall in temperature, there is increased tendency to bleed. It is due to whole host effects of HT on coagulation cascade. There is decreased the production of clotting enzymes, tissue plasminogen activator inhibitor enzyme and

inhibition of other steps in the coagulation cascade. The platelet function and number are decreased. Throughout HT, platelets become sequestered in the spleen and liver and re-enter the circulation after rewarming. Similar to blood gas analysis, standard blood coagulation studies are reported normal in TH, as they are interpreted at 37°C in the lab. They may be prolonged if done at CBT. A meta-analysis of clinical trials of mild TH for traumatic head injury determined that partial thromboplastin time was slightly increased (0.02 s) in the TH.^[4,49] Despite these disturbances, the incidence of bleeding is reported to be very low, in major clinical trials including TBI. The role of TH in patients with trauma is controversial, as HT itself is a poor prognostic indicator in these patients. Spontaneous HT is bad as it indicates exhaustion of energy stores and, therefore, correlates more with severe injuries. The same may not hold true for TH, as it is implied in controlled manner and associated with decreased metabolic and oxygen demands in tissues and other beneficial effects.^[49] No human studies have been performed to evaluate the effect of HT in haemorrhagic shock

- Metabolic effects: TH can induce a number of metabolic effects. It shifts the oxyhaemoglobin saturation curve to the left subsequently, decreases the availability of oxygen in tissues; thus, it is not uncommon to see acidosis in hypothermic patients. HT can increase synthesis of glycerol, free fatty acids and lactate. This slight fall in pH may not be of clinical relevance and does not need any special treatment.^[24] Overall, metabolic rate decreases by 5–8%/°C fall in body temperature. The reduction in metabolic rate leads to decreased oxygen consumption and carbon dioxide production. The production of CO₂ is decreased by 30% when the core temperature is 33°C, this requires a reduction in minute ventilation as guided by EtCO₂ readings and arterial blood gas (ABG) analysis.^[4,50-52] At 37°C, the arterial partial pressure of oxygen and carbon dioxide increase (due to increased solubility of gases following an increase in temperature) and there is a false increase in blood hydrogen ion concentration. When ABGs are corrected for temperature, the patient may have a respiratory alkalosis. Therefore, temperature corrected ABG should be analysed. Hypothermic patients have lower feeding requirements. *Per se*, HT or use of muscle relaxant does not call for cessation of feeding
HT leads to hypokalaemia due to the intracellular shift of potassium, especially during the induction and maintenance phases. This may require frequent monitoring and replacement of serum potassium. During rewarming potassium returns to the intravascular compartment and may produce

dangerously high levels of serum potassium. Keeping serum potassium around 3.0 mEq is desirable during this phase. Besides potassium, calcium, phosphate and magnesium levels may alter and need to be monitored. Hyperglycaemia, blood glucose variability and insulin resistance are seen in hypothermic phase as compared to the post-rewarming normothermic conditions.^[53] It requires frequent monitoring and treatment as hyperglycaemia is an independent predictor of mortality in patients with neurological injury. Understanding the impact of TH on drug disposition is necessary to optimise its application and prevent drug toxicity. Cooling affects drug metabolism. This becomes, especially important during resuscitation when it may render many agents used in cardiopulmonary resuscitation ineffective or delay their response. Antiarrhythmic agents (especially amiodarone) may fail to act. The half-life of non-depolarising muscle relaxants may be prolonged. Due to depression of cytochrome p450 (CYP) related drug metabolism, commonly used antiepileptic drugs, phenytoin and fosphenytoin metabolism is depressed. TH may reduce the elimination of these drugs and lead to accumulation and toxicity.^[54,55] Monitoring plasma levels of anticonvulsants are logical

To summarise, HT may induce many metabolic changes, which are usually self-limiting but particular attention should be drawn to electrolyte disturbances, prevention of shivering and altered drug metabolism

- Infection: The suppression of inflammation by HT is like a double edged sword. On one hand inhibition of inflammatory response is beneficial for the prevention of neurological insult but at the same time it renders patient susceptible to infectious complications. It inhibits neutrophil and macrophage function, suppresses inflammatory reactions and inhibits the release of proinflammatory cytokines.^[4,51,56] HT induced insulin resistance, suppression of inflammatory response, decreased gastrointestinal motility make the patient vulnerable to pneumonia, vascular device, blood stream as well as wound-related infections. Largely, these complications are dependent on the depth and duration of HT. Shorter the duration lesser the worries! A trend towards increased the incidence of sepsis and pneumonia is seen in studies using HT. Even HACA researchers reported sepsis as the most important complication of TH, but its occurrence was not statistically significant between normothermia and HT group (7% vs. 13%).^[57,58] ICTuS-L study, which used endovascular cooling along with intravenous thrombolysis for stroke also reported an increased incidence of pneumonia.^[59] Good intensive care, careful follow of protocols for

infection control and early calculated antibiotic therapy is required to lower the risk of these complications. The use of prophylactic antibiotics is not recommended.

CLINICAL APPLICATIONS OF TTM

Therapeutic hypothermia after cardiac arrest

In 2002, two landmark prospective randomised controlled trials confirmed the efficacy of TH for cerebral protection. An 11-center European trial reported 16% improvement in outcome in patients with witnessed arrest following ventricular tachycardia/VF, and a similar four-centre Australian study found improved outcome in 23% patients. Many other non-randomised studies have also reported improved outcomes with TH.^[57,58,60] In October 2002, the ILCOR recommended TH after cardiac arrest in unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm was VF, other rhythms or in-hospital cardiac arrest.^[37] AHA recommends cooling to 32–34°C within 2 h for 12–24 h in comatose patients with ROSC after cardiac arrest when the initial rhythm was VF (Class I). It may be considered as a reasonable option in comatose patients with cardiac rhythm which does not respond to defibrillation or patients after in hospital cardiac arrest (Class II b).^[38] The European Resuscitation Council guidelines for resuscitation recommend TH for all comatose survivors of cardiac arrest regardless of initial rhythm, although the guideline acknowledges a lower level of evidence for TH in patients with a cardiac arrest from non-shockable rhythms.^[61]

Though the international guidelines and reviews support the use of TH but questions regarding its use have been raised. Limitations of reported TH studies like, no strict temperature management in controls, who had an average temperature of 37.8°C, lack of prior power calculation and a low rate of enrolment drew attention of health care professionals. The available evidence in support of HT may be considered weak, owing to bias and small sample size.^[62] Neilson *et al.* conducted a large, multicentric and randomised controlled trial which evaluated the effect of TTM at either 33°C or 36°C in 950 unconscious adults after OHCA of presumed cardiac cause. In their study, targeted temperature of 33°C had no benefit as compared to targeted temperature of 36°C, and thus, questioned the role of cooling. This study too had some inherent flaws with its methodology and selection.^[63] Though these conclusions cannot be ignored but till now there is not enough evidence for discarding/favouring TH for strict fever management (or, worse, no temperature management). All pertinent issues need to be satisfactorily addressed. Pre-hospital and critical care management have changed during the past decade

so is the associated mortality. Clinically relevant benefit of controlling the body temperature at 36°C or lower, instead of allowing the fever to develop in patients following resuscitation after cardiac arrest needs to be investigated in detail.

Therapeutic hypothermia in traumatic brain injury

Two possible paradigms currently tested for TBI are titrated TH to reduce ICP and TH for cerebral protection. Fay described the concept of cooling traumatic brains in 1945.^[64] As he used very low temperatures (28°C) for long duration (4–7 days), he encountered too many side effects. The method did not gain popularity until 1990 when experimental data again showed less neurological damage with its use. Overall the results of TH in TBI are not as encouraging as in post-cardiac arrest patients, due to the obvious disparity in the patient population. In OHCA global ischaemia and reperfusion injury play a dominant role, whereas in TBI pathology is heterogenous with a variable degree of necrosis, midline shift, etc., Hence, the same results need not be expected. No high-quality evidence supports the role of this modality as a neuroprotectant and only a trend towards reduced mortality and improved outcome is seen, but a large body of evidence suggests affectivity of TH for controlling refractory intracranial hypertension.^[41,65-67] The previous studies differ in their study protocol (individualised onset/duration of cooling, the rate of rewarming), enrolling different categories of patients and diverging treatment protocols. However, from existing literature the beneficial effects of TH were significantly the greatest when it was maintained for >48 h, to those who have not received barbiturate therapy and had slower rewarming rates of 24 h or 1°C/4 h.^[39-41] However a recent study, planned to address the pitfalls of previous trials, failed to demonstrate the beneficial effects of prolonged HT alongwith slow rewarming and tight hemodynamic monitoring over strict fever control in patients with TBI.^[68] Another computed tomography based Japanese study reported favourable outcome with TH in young patients with evacuated haematomas as compared to controlled normothermia but patients with diffuse brain injury deteriorated with TH.^[68,69] Nonetheless the current studies do not put an end to HT in TBI. The existing meta-analyses point towards the need of high quality randomised controlled trials for further demonstration of its effects and defining the depth and duration may be depending upon individual needs.^[70] Two large new trials Eurotherm3235 trial (www.eurotherm3235trial.eu) and POLAR (<http://clinicaltrials.gov/ct2/show/NCT00987688>) are testing the efficacy of titrated HT for raised ICP and early HT as a cerebral protectant. The studies planned to incorporate described optimised cooling protocols and to enrol specialised centres only. Eurotherm 3235 which had initially planned to recruit 600 patients has stopped

enrollment prematurely for unknown reasons and the results are awaited. POLAR trial is currently recruiting with a focus on early cooling (<3 h) post-injury.

Therapeutic hypothermia in ischaemic stroke

Several experimental studies have demonstrated beneficial effects of HT in animal models of ischaemic stroke, but it is less described in haemorrhagic stroke. The institution of HT is associated with unique challenges in stroke patients. There is an innate disparity between stroke pathology and cardiac arrest. Successful resuscitation resulting in ROSC following cardiac arrest is also associated with the return of cerebral perfusion but in stroke, the affected vessel often remains occluded for a long time in the absence of reperfusion therapies. Most of the stroke patients are awake and un-intubated. Thus, discomfort associated with deliberate cooling is high and the management of shivering difficult. Pharmacological or mechanical approaches are required for early recanalisation. Recombinant tissue plasminogen activator (rt-PA) is currently the only beneficial proven therapy for stroke. The safety of combining HT with rt-PA is not well proven. Both fibrinolytic therapy and HT are associated with haemorrhagic complications and the efficacy of fibrinolytic agents is temperature dependent, lower temperatures associated with decreased activity.^[71,72] The rt-PA was effective in improving recanalisation, and cooling can reduce infarct size, but the combination of the two did not clearly show synergy. Due to late presentation of patients with stroke, the therapeutic window for the institution of TH needs to be determined.^[73] The application of combination therapy such as using HT to expand the temporal therapeutic window of rt-PA should be explored.

The ICTuS-L study is a recent randomised multicentre trial of HT and rt-PA in acute stroke patients.^[59] Here, 58 patients were randomised, 28 to HT at 33°C for 24 h and 30 to normothermia. In the HT group, 24 were also given rt-PA. Cooling was well tolerated in this study and did not affect the occurrence or severity of brain haemorrhage in patients given rt-PA. There were no differences in 90-day outcomes, although the study was not powered to determine efficacy.

Therapeutic hypothermia in subarachnoid haemorrhage

The largest randomised trial of intraoperative HT for aneurysm surgery (Intraoperative Hypothermia for Aneurysm Surgery Trial) applied HT in 1001 patients with good-grade SAH. In this trial, no difference in neurological outcome was seen between hypothermic and normothermic groups, 3 months post-surgery.^[74-76] However, these results may not be extrapolated to patients with poor-grade SAH. The most important and potentially treatable complication of SAH is intracranial

hypertension and delayed cerebral ischaemia leading to progressive cerebral infarction. The strength of TH in SAH is thought to be directed towards ischaemia rather than haemorrhage itself. TH has shown to attenuate the degree of cerebral vasospasm up to 14 days after SAH possibly by regulating the levels of ET-1 and NO. Good outcome following the application of prolonged HT within 24 h in poor-grade SAH is reported in few case series. Similarly, HT either during delayed aneurysm clipping or in cases with vasospasm refractory to hyperdynamic and endovascular therapy has shown to help.^[77-79] Available data suggests that HT may improve outcome in a carefully selected subgroup of SAH patients. The patients developing intracranial hypertension and/or symptomatic vasospasm refractory to conventional treatment may benefit from it. More evidence on this subject is required to draw fruitful conclusions.

Hypothermia in perinatal hypoxic-ischaemic encephalopathy

Even with major advances in monitoring and knowledge of perinatal medicine, HIE is one of the significant causes of mortality and long-term morbidity. The pioneer studies described the feasibility of TH in neonates with HIE more than a decade ago.^[80] Data from large randomised clinical trials indicate that cooling is an effective therapy for HIE. Both whole body cooling and selective head cooling have been successfully implemented since then.

Randomised controlled trials showing decreased death or disability in neonates treated within 48 h of birth with the whole body HT have been published.^[81-84] Meta-analysis of these trials suggests positive effect of TH. Although the trials had some differences in the method of cooling and selection of subjects, but infants enrolled were at least 35 weeks gestation at birth; randomised within 6 h of birth, cooled to a target temperature of 33.5–34.5°C for 72 h, followed by slow rewarming (0.5°C/h). The primary outcome measure was the combined rate of death or disability, assessed at 18–22 months of age. Adverse effects of TH in the target temperature range were infrequent. The most common adverse effects were sinus bradycardia and prolongation of QT interval on electrocardiogram, both of which are physiologic responses to HT. Reddening or hardening of the skin (systemic HT) and on the scalp (selective head cooling) and subcutaneous fat necrosis occurred rarely. The reported rates of coagulopathy, sepsis and pneumonia were same in treated and control infants. When published studies were aggregated in a meta-analysis, the adverse effects of HT included an increase in sinus bradycardia and a significant increase in thrombocytopenia (platelet count 150,000/mm³). The adverse effect of pyrexia on

neurologic outcome among infants allocated to standard care was obvious.^[84,85] ACLS guidelines recommend TH in infants born at ≥ 36 weeks of gestation with evolving moderate to severe hypoxic-ischaemic encephalopathy.^[39]

Still there are unanswered questions regarding the use of this modality in neonates. Optimal timing for initiation of cooling and the depth and duration of therapy needs further evaluation. As cooling and its management are preferably done in higher centres and many neonates are unable to reach higher centres within 6 h so clinical trials designed to assess the efficacy of initiating cooling between 6 and 12 h of age are required. There is uncertainty regarding the safety and efficacy of initiating cooling before transfer to a centre offering TH. Safety and efficacy of cooling treatment of encephalopathic infants born at < 35 weeks of gestational age are currently lacking.

Other applications

Clinical evidence has demonstrated TTM to be effective in treating refractory status epilepticus. Cortical spreading depression (CSD) has been described as one of the causes in the development of ischaemia in TBI and stroke and TH has been shown to suppress CSD. Other applications include use in experimental and clinical spinal cord injury, myocardial infarction and cardiogenic shock. It is also used for the management of hepatic failure.

Controlled normothermia

To avoid the negative effects of fever and TH, controlled normothermia was introduced. Fever is an independent predictor of poor outcome for several neurological diseases.^[86] Symptomatic fever control is becoming the popular goal of therapy in neurocritical illness. Controlled normothermia is bringing down core temperature in patients with fever and maintaining temperature within a range of 36.0–37.5°C with potentially deleterious effects such as shivering, being controlled or suppressed. Most of the HT trials conducted in past failed to effectively manage body temperature in controls. Controls had fever episodes and were not actually normothermic throughout the study time. Satisfactory normothermia cannot be achieved in a fever by drug treatment alone.^[87] Reasonable treatment of fever must be combined with general measures of infection control and supportive treatment protocols. Routine antipyretics have a limited role in controlling neurological fever. The average decrease in CBT with the use of acetaminophen is only about 0.3–0.4°C. Surface, endovascular cooling and new pharmacological methods are being increasingly used for the treatment of fever. The methods used to treat fever depend upon the availability, expertise and relevant resources. Though there is no superiority of one method over other and a combination of these techniques

make a reasonable option. In few trials, endovascular methods of controlling temperature have been found to be superior to conventional temperature control methods (combination of nonsteroidal anti-inflammatory drugs and surface cooling) in patients with the severe cerebrovascular disease.^[88] Controlled HT has its own set of limitations, important being shivering and effect on immune response. During fever, hypothalamus resets the CBT to a higher target value and body heat preservation methods are maximally activated to achieve this new set point. For this reason, it is not easy to attain controlled normothermia.

Future directions

TTM can be a boon for treating millions of life worldwide. Currently, the strongest evidence for TTM in adults is following cardiac arrest, neonatal HIE and ICP control. Controlled normothermia in neurocritical care population is rapidly gaining recognition. Data on disease specific therapeutic markers, therapeutic depth and duration and prognostication of this modality is limited. The optimal speed and time to initiate; duration of cooling and rewarming rates in different pathologies need to be more defined.^[43] Modern Intensive Care Unit protocols for HT follow a 'one temperature fits all' mentality. Newer studies are correlating temperature management and brain metabolism or surrogate markers may answer important questions pertaining to this modality in neurological insult. Overall in experienced hands the technique is safe without major morbidity but a potential to improve outcome.

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Conflicts of interest

Authors are investigators of EURO THERM3235 trial.

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