

Therapeutic Hypothermia and Acute Brain Injury

Martin Smith

Author details:

Martin Smith MBBS FRCA FFICM is Consultant and Honorary Professor in Neuroanaesthesia and Neurocritical Care at the National Hospital for Neurology and Neurosurgery, University College London Hospitals

Corresponding author:

Martin Smith MBBS FRCA FFICM

Box 30

The National Hospital for Neurology and Neurosurgery

Queen Square

London WC1N 3BG

Tel: +44 (0)20 3448 4711

Email: martin.smith@ucl.ac.uk

Acknowledgement: Martin Smith is part funded by the UCLH National Institute for Health Research Biomedical Research Centre.

Conflicts of interest: none declared.

Royal College of Anaesthetists CPD matrix codes: 1H02, 2F01, 3F00.

Abstract

The neuroprotective effects of therapeutic cooling of the brain have been recognised for decades, but these have generally failed to translate into improved outcomes in clinical studies. Targeted temperature management (TTM) has been investigated in a variety of clinical conditions, but has confirmed roles only in the management of post-cardiac arrest cerebral hypoxia-ischaemia and neonatal hypoxic-ischaemic encephalopathy. It is a therapeutic option in the management of intracranial hypertension, and fever control after brain injury. Many questions remain regarding the logistics of cooling (including length of treatment), and how best to manage complications of therapy, particularly shivering.

This article will review the putative mechanisms of hypothermia-induced neuroprotection, the technical considerations for the clinician wishing to use TTM, and review the evidence for the clinical application of TTM after acute brain injury.

Keywords

Acute ischaemic stroke; hypoxic-ischaemic encephalopathy; intracerebral haemorrhage; intracranial pressure; subarachnoid haemorrhage; targeted temperature management; therapeutic hypothermia; traumatic brain injury

Learning objectives

After reading this article, you should be able to:

- Understand the mechanisms of hypothermia-induced neuroprotection
- Evaluate the role and evidence for targeted temperature management after acute brain injury
- Recognise the effect of hypothermia on intracranial pressure

- ❑ Understand the indications for induced normothermia
- ❑ Discuss the complications associated with therapeutic targeted temperature management

The neuroprotective effects of therapeutic cooling of the brain have been recognised for decades, but positive preclinical studies have generally failed to translate into improved outcomes in humans. Therapeutic hypothermia was the term previously used to describe intentional lowering of body temperature, but targeted temperature management (TTM) is now preferred since it implies a broad range for managing body temperature including maintenance of normothermia.

Pathophysiology of brain ischaemia and neuroprotection

Cerebral ischaemia is characterised by cellular energy failure, depolarization of cell membranes, release of excitatory amino acids and cytosolic calcium overload.¹ These events cause irreversible injury if ischaemia is prolonged, and also set the stage for subsequent reperfusion-related injury. Resumption of oxidative metabolism as perfusion is restored leads to release of reactive oxygen species, mitochondrial calcium overload, altered gene expression, inflammation and triggering of cell death pathways. In preclinical studies, hypothermia has a multifactorial neuroprotective action, exerting its influence on virtually all pathways that lead to cell death including excitotoxicity, apoptosis, inflammation and free radical production (figure 1).² Hypothermia also preserves the integrity of the blood-brain barrier (BBB), and possibly influences tissue regeneration through neurogenesis, gliogenesis and angiogenesis.

Figure 1 near here

Stabilisation of the BBB decreases the risk of cerebral oedema and intracranial hypertension, and reduction in intracranial pressure (ICP) is the most robust clinical manifestation of TTM when body temperature is $\leq 35.5^{\circ}\text{C}$.³

Practical aspects of targeted temperature management

TTM is typically separated into three phases – induction, maintenance and rewarming.

Intravascular or whole body surface cooling techniques, with feedback loops to maintain a set temperature, are widely used in the clinical setting.³ Rapid induction of hypothermia can be achieved with the application of ice packs and cold intravenous fluids.

There are several important adverse effects associated with TTM (table 1), and close monitoring and management of shivering, blood glucose, electrolyte levels and fluid balance is essential. Localised head cooling reduces the risk of systemic complications, but there is currently insufficient evidence to recommend it over whole body cooling. Rewarming is the most dangerous phase of TTM, and rebound rises in ICP and hyperkalaemia are of major concern. Controlled re-warming is mandatory, and temperature increases of between 0.1°C to 0.25°C per hour are recommended to minimize the risks of complications.³

Table 1 near here

Clinical applications of targeted temperature management in acute brain injury

TTM has been investigated in a variety of brain injury types, but has confirmed roles only in the management of post-cardiac arrest syndrome and neonatal hypoxic-ischaemic encephalopathy (HIE) (table 2).^{3;4}

Table 2 near here

Cardiac arrest

Cardiac arrest results in global cerebral ischaemia, and return of spontaneous circulation (ROSC) in reperfusion injury. Neurological sequelae are major contributors to mortality and severe morbidity after cardiac arrest. Data from two randomised controlled trials published in 2002 demonstrated improved neurological outcome in comatose patients after out-of-hospital ventricular fibrillation (VF) cardiac arrest treated with TTM (32 - 34°C) within two hours of ROSC and maintained for 12 to 24 h.⁵ A more recent study confirmed that a target temperature of 36°C is as effective as 33°C in unconscious survivors of out-of-hospital cardiac arrest. Evidence from observational case series also suggests benefit of TTM in patients with rhythms other than VF, or after in-hospital cardiac arrest. The incorporation of TTM into post-resuscitation care is now standard, with an option to target a temperature of 36°C instead of the previously recommended 32 to 34°C.

Traumatic brain injury

Neuronal damage after traumatic brain injury (TBI) is caused not only by the initial trauma but also by subsequent pathophysiological cascades which are precipitated by, and perpetuate, the primary injury. The mechanisms of secondary injury include cerebral hypoxia-ischaemia, excitotoxicity, inflammation, metabolic dysfunction, electrophysiological disturbances, and brain oedema and raised ICP.¹ TTM has theoretical potential to ameliorate all aspects of TBI-related secondary injury, but positive results in preclinical studies have failed to translate into clinical benefit.

Multiple observational and phase II clinical trials have identified potential outcome benefits from TTM in TBI, but two large phase III trials in adults (the National Acute Brain Injury Study: Hypothermia I and II trials) and two in children (the Hypothermia Paediatric Head Injury trial and Cool-Kids trial) failed to confirm such benefit.⁶ The reasons for the failure of

TTM in clinical studies of TBI are multifactorial. All aspects of the complex pathophysiology of TBI are likely to contribute to outcome, but not all may be modifiable by TTM. In some studies rewarming occurred between 24 and 48 hours after injury, and this is the period of maximal cerebral oedema and therefore greatest risk of intracranial hypertension. To control for this the EURO THERM3235 trial incorporated TTM (32-35°C) as a component of ICP management in TBI patients with ICP > 20 mmHg resistant to initial ICP-lowering therapies.⁷ Although TTM was effective in reducing ICP, the study was terminated early because cooling was associated with higher mortality and worse functional outcome compared to standard care.

Therapeutic temperature reduction consistently reduces ICP after TBI, and TTM is often incorporated into management protocols for ICP control despite lack of evidence of improved outcomes.⁸ Whether the results of the recent EURO THERM3235 trial will change clinical practice in this regard remains to be seen.

Acute ischaemic stroke

TTM to 35°C reduces infarct size by about 33% and improves neurological outcomes in animal studies of acute ischaemic stroke (AIS), but evidence of benefit in humans remains inconclusive.⁹ EuroHYP-1, a randomized controlled trial evaluating the efficacy of TTM (34 to 35°C maintained for 24 h) after AIS, has completed enrollment but not reported at the time of writing (<http://www.eurohyp1.eu/>). There are several practical difficulties in implementing TTM after AIS, including control of shivering in awake patients, and prevention of complications such as pneumonia.³ Phase II clinical trials have demonstrated that cooling awake stroke patients is feasible, and that it does not reduce the effectiveness of thrombolysis.⁹

Intracerebral haemorrhage

Preclinical data suggest that cooling to 35°C reduces BBB disruption and perihematoma oedema after intracerebral haemorrhage (ICH), but these findings have not been correlated with improved neurological outcomes.⁴ A small observational clinical study confirmed these findings, and demonstrated that the oedema-reducing effects of TTM are not lost during rewarming. The targeted temperature management after intracerebral hemorrhage (TTM-ICH) trial is investigating the safety and feasibility of TTM (32-34°C for 72 h) after ICH, and whether it improves outcome compared to normothermia (<https://clinicaltrials.gov/ct2/show/NCT01607151>).

Subarachnoid haemorrhage

The use of hypothermia after aneurysmal subarachnoid haemorrhage (SAH) dates back to the 1950s when cooling was first used for neuroprotection during aneurysm surgery. The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) subsequently demonstrated that intraoperative hypothermia has no clinical benefit, and increases the risk of infection.⁴ Only small observational case series have investigated the effects of TTM in the intensive care management of SAH, most commonly in patients with intracranial hypertension and cerebral vasospasm refractory to medical therapy, with limited evidence of benefit.¹⁰

Neonatal hypoxic-ischaemic encephalopathy

Neonatal HIE occurring before or around the time of birth is associated with a high risk of death or lifelong disability. The underlying pathophysiology of HIE is cerebral hypoperfusion and ischaemia, and subsequent reperfusion injury. There is compelling

evidence that TTM improves survival and reduces the risk of disability in full-term infants with severe HIE, and that hypothermia is most protective when started as early as possible after the insult.¹¹ Current protocols recommend beginning treatment within the first 6 h of life, cooling to $34.5 \pm 0.5^{\circ}\text{C}$ and continuing treatment for 48 to 72 h. There is evidence that lower temperatures and longer duration of cooling are associated with adverse outcomes.

Targeted normothermia

Fever (variably defined as core body temperature exceeding 37.5 to 38.5°C) is reported in 50% to 70% of critically ill brain-injured patients, and associated with worse outcomes. An infective cause of pyrexia should always be excluded or treated (pneumonia is particularly common after ABI), but fever may be related to non-infective causes such as hypothalamic dysfunction secondary to ischaemia or the effects of subarachnoid blood. Whether the association between fever and clinical outcomes is an epiphenomenon, or increased temperature a direct contributor to poor outcome after ABI, remains unresolved. Despite limited evidence linking targeted normothermia with improved clinical outcomes, consensus guidelines recommend maintenance of normothermia in several brain injury types.¹² There are several issues that require clarification, including which patients might benefit from targeted normothermia, the temperature defining normothermia, the optimal duration of targeted normothermia, and the optimal way to control shivering.

Summary

TTM has established roles in the management of post-cardiac arrest syndrome and neonatal HIE, but its role in other brain injury types remains controversial. Questions remain regarding the optimal methods of cooling, length of treatment and rewarming, and how best

to manage complications of therapy, particularly shivering. High-quality studies are needed to address these issues.

References

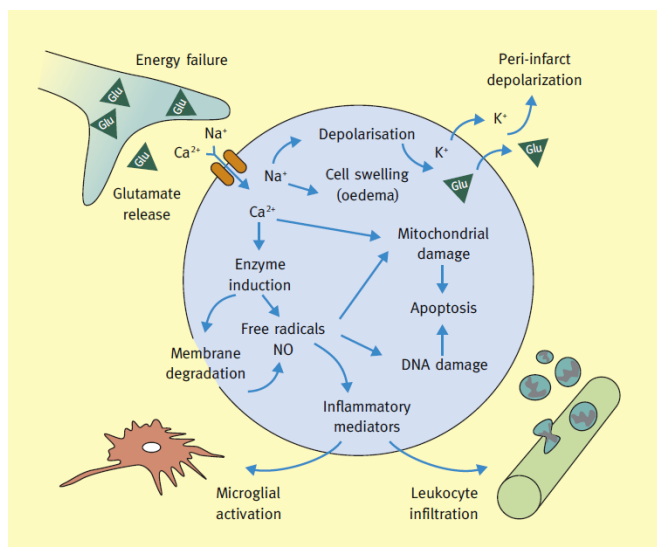
1. Kunz A, Dirnagl U, Mergenthaler P. Acute pathophysiological processes after ischaemic and traumatic brain injury. *Best Pract Res Clin Anaesthesiol* 2010; 24: 495-509
2. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. *Nat Rev Neurosci* 2012; 13: 267-78
3. Choi HA, Badjatia N, Mayer SA. Hypothermia for acute brain injury--mechanisms and practical aspects. *Nat Rev Neurol* 2012; 8: 214-22
4. Andresen M, Gazmuri JT, Marin A, Regueira T, Rovegno M: Therapeutic hypothermia for acute brain injuries. *Scand J Trauma Resusc Emerg Med* 2015; 23: 42
5. Mahmoud A, Elgendy IY, Bavry AA. Use of targeted temperature management after out-of-hospital cardiac arrest: a meta-analysis of randomized controlled trials. *Am J Med* 2015; Epub ahead of print, 14 November
6. Georgiou AP, Manara AR. Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review. *Br J Anaesth* 2013; 110: 357-67
7. Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JK, Murray GD.: Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. *N Engl J Med* 2015; 373: 2403-12
8. Corry JJ. The use of targeted temperature management for elevated intracranial pressure. *Curr Neurol Neurosci Rep* 2014;14: 453
9. Wu TC, Grotta JC. Hypothermia for acute ischaemic stroke. *Lancet Neurol* 2013; 12: 275-84
10. Badjatia N. Hypothermia in neurocritical care. *Neurosurg Clin N Am* 2013; 24: 457-67

11. Davidson JO, Wassink G, van den Heuvel LG, Bennet L, Gunn AJ. Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy - where to from here? *Front Neurol* 2015; 6: 198
12. Bohman LE, Levine JM. Fever and therapeutic normothermia in severe brain injury: an update. *Curr Opin Crit Care* 2014; 20: 182-8

Figure 1

Simplified overview of the pathophysiology of cerebral ischaemia

Energy failure leads to depolarisation of neurons. Activation of specific glutamate receptors dramatically increases intracellular Ca^{2+} , Na^+ , Cl^- levels, while K^+ is released into the extracellular space. Diffusion of glutamate (Glu) and K^+ in the extracellular space can propagate a series of spreading waves of depolarization (peri-infarct depolarisations). Water shifts to the intracellular space via osmotic gradients and cells swell (oedema). The universal intracellular messenger Ca^{2+} overactivates numerous enzyme systems (proteases, lipases, endonucleases, etc.). Free radicals are generated, which damage membranes (lipolysis), mitochondria and DNA, in turn triggering caspase-mediated cell death (apoptosis). Free radicals also induce the formation of inflammatory mediators, which activate microglia and lead to the invasion of blood-borne inflammatory cells (leukocyte infiltration) via upregulation of endothelial adhesion molecules.



Modified from Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999; 22:391-7. Reproduced with permission from Elsevier.

Table 1**Complications and adverse effects of targeted temperature management**

Complication/adverse effect	Explanation and comments
Shivering	Shivering counteracts the cooling process, increases energy consumption and metabolic demand, and is uncomfortable for awake patients. First-line treatments include paracetamol, buspirone, intravenous magnesium, and forced warm air (40°C) skin counter-warming. Second-line treatments include α 2-receptor agonists (e.g. dexmedetomidine), opioids, propofol and, in sedated patients as a last resort, paralysis (using vecuronium or cisatracurium).
Acid-base balance disturbance	'Alkaline shift' results from the increased solubility of CO ₂ and resultant fall in PaCO ₂ during cooling.
Deranged electrolytes	Decreased levels of serum potassium, phosphate and magnesium can occur during cooling. Conversely, rewarming can cause release of intracellular electrolyte stores. Careful replacement of electrolytes is important during cooling, being mindful to avoid potentially life-threatening hyperkalaemia in the rewarming phase.
Impaired cardiac function	Mild-moderate hypothermia (33-35°C) is well-tolerated by the heart. With shivering controlled, hypothermia results in bradycardia, reduced myocardial contractility, and thus cardiac output and blood pressure. Hypothermia < 32°C is associated with atrial fibrillation, ventricular fibrillation, and ventricular tachycardia. Ensuring the body temperature does not fall below 33°C is therefore important.
Insulin resistance	Hypothermia results in a state of insulin resistance. During rewarming insulin sensitivity may rapidly increase, with the risk of hypoglycaemia.
Impaired immune function	Hypothermia is associated with immunosuppression and impaired leucocyte phagocytosis, explaining the increased risk of bacterial infections (particularly pneumonia) during TTM. Coagulopathy and platelet abnormalities can occur even with temperatures > 35°C but no evidence of an increased risk of serious bleeding exists, even in those with intracranial haemorrhage.

Table 2**Targeted temperature management in acquired brain injury**

	Recommendation	Level of evidence
Cardiac arrest	Strong evidence in favour of improved outcomes. Incorporation of TTM into post-resuscitation care is now standard, with an option to target a temperature of 36°C instead of the previously recommended 32 to 34°C.	Level I
Traumatic brain injury	No role for early TTM as a neuroprotectant in adult or paediatric traumatic brain injury.	Level I
Management of intracranial hypertension	TTM (33 - 36°C) is often incorporated into protocols for the treatment of intracranial hypertension resistant to first-line interventions.	Level II
Neonatal hypoxic-ischaemic encephalopathy	Babies born at term (or near term) with moderate or severe hypoxic ischaemic encephalopathy should be treated with TTM to 34.5 ± 0.5°C. Treatment should be initiated within the first 6 h of life, and continued for 48-72 h	Level I
Acute ischaemic stroke	Encouraging evidence of benefit, albeit from small underpowered feasibility trials. Data from on-going Phase II/III trials are awaited.	Level III
Intracerebral haemorrhage	No proven indications for neuroprotection. TTM can be considered as a treatment option for management of intracranial hypertension and reducing symptomatic mass effect in the presence of peri-haematoma oedema. Data from on-going Phase III trials are awaited. Can be used for refractory pyrexia.	Level III
Subarachnoid haemorrhage	No proven indications for TTM as a neuroprotectant. May have a role in refractory pyrexia, but the incidence of complications is high.	Level III

TTM, targeted temperature management