Therapeutic hypothermia and acute brain injury

Martin Smith

Abstract

The neuroprotective effects of therapeutic cooling of the brain have been recognized for decades, but these have generally failed to translate into improved outcomes in clinical studies. Targeted temperature management (TTM) has established roles in the management of post-cardiac arrest syndrome and neonatal hypoxic-ischaemic encephalopathy, but its role in other brain injury types remains controversial. 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; induced normothermia; intracerebral haemorrhage; intracranial pressure; subarachnoid haemorrhage; targeted temperature management; therapeutic hypothermia; traumatic brain injury

Royal College of Anaesthetists CPD Matrix: 1H02, 2F01, 3F00

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
- recognize 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 recognized 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 hypothermia-induced neuroprotection

Cerebral ischaemia is characterized 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.

Stabilization 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°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. Localized head cooling reduces the risk of systemic complications, but there is currently insufficient evidence to recommend it over whole body cooling for clinical use. Rewarming is the most dangerous phase of TTM, and rebound rises in ICP and hyperkalaemia are of major concern. Controlled rewarming is mandatory, and temperature increases of between 0.1°C and 0.25°C per hour are recommended to minimize the risks of complications.[3]

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]

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 randomized controlled trials published in 2002 demonstrated improved neurological outcome in comatose patients after out-of-hospital

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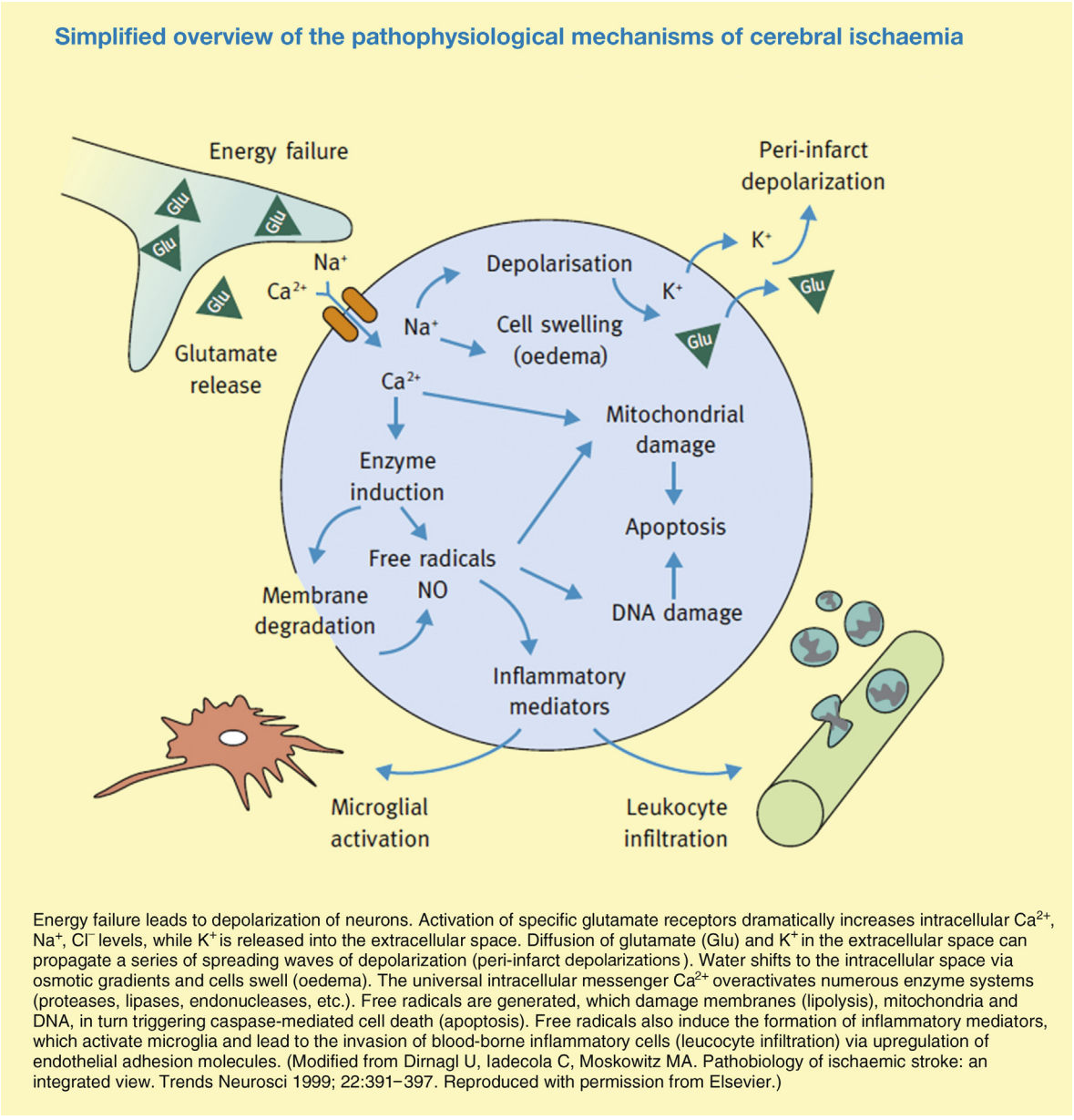

Energy failure leads to depolarization of neurons. Activation of specific glutamate receptors dramatically increases intracellular Ca^{2+}, Na^{+}, Cl^{-} levels, while K^{+} is released into the extracellular space. Diffusion of glutamate (Glu) and K^{+} in the extracellular space can propagate a series of spreading waves of depolarization (peri-infarct depolarizations). 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 (leucocyte 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; 22:391–397. Reproduced with permission from Elsevier.)

Figure 1

ventricular fibrillation (VF) cardiac arrest treated with TTM (32–34°C) within 2 hours of ROSC and maintained for 12–24 hours.[5] A more recent study confirmed that a target temperature of 36°C is as effective as 33°C in improving outcome 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 32–34°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 these were not confirmed in 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).[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,

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