Therapeutic hypothermia: Benefits, mechanisms and potential clinical applications in neurological, cardiac and kidney injury

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ABSTRACT

Therapeutic hypothermia involves the controlled reduction of core temperature to attenuate the secondary organ damage which occurs following a primary injury. Clinicians have been increasingly using therapeutic hypothermia to prevent or ameliorate various types of neurological injury and more recently for some forms of cardiac injury. In addition, some recent evidence suggests that therapeutic hypothermia may also provide benefit following acute kidney injury.

In this review we will examine the potential mechanisms of action and current clinical evidence surrounding the use of therapeutic hypothermia. We will discuss the ideal methodological attributes of future studies using hypothermia to optimise outcomes following organ injury, in particular neurological injury. We will assess the importance of target hypothermic temperature, time to achieve target temperature, duration of cooling, and re-warming rate on outcomes following neurological injury to gain insights into important factors which may also influence the success of hypothermia in other organ injuries, such as the heart and the kidney. Finally, we will examine the potential of therapeutic hypothermia as a future kidney protective therapy.

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Introduction

Therapeutic hypothermia (TH) involves the controlled reduction of a patient’s core temperature in an attempt to protect an organ at risk of injury. To date, TH has principally been used as a protective therapy following various brain insults; however there
is emerging evidence that it may also be useful in the protection of other organs when at risk of injury.

The current main clinical indications for TH for cerebral protection in adults are out-of-hospital cardiac arrest and, in neonates, hypoxic ischaemic encephalopathy with randomised clinical trials showing the neurological benefit of TH. Furthermore, recent meta-analyses have suggested potential outcome benefit with TH following traumatic brain injury (TBI). The safety and efficacy of TH have resulted in TH being increasingly applied by clinicians to comatose patients of various etiologies (i.e. stroke, hepatic encephalopathy, etc.) in an attempt to decrease brain injury. These new but as yet unproven indications follow from the established use of TH to improve outcomes in operations involving significant risk of cerebral ischaemia during circulatory arrest in cardiac and neurosurgery. In addition to its protective neurological effects, hypothermia may decrease infarct size in patients with acute myocardial infarction after emergency percutaneous coronary intervention and reduce the risk of renal failure after renal ischaemia–reperfusion injury in animals.

Although evidence is limited, studies suggest five key factors that could explain the failure of these previous studies and need to be addressed in future studies of TH: time to induction of hypothermia after injury, target temperature attained, duration of cooling, rate of re-warming and prevention of side effects/complications from hypothermia. In this article we will review the evidence for potential clinical applications of TH, describe its mechanisms of action and side effects, and, within this setting, discuss optimal methods for its implementation in future clinical trials. The focus is on TBI and on how the lessons learned with TBI may help effectively apply TH to the treatment of acute kidney injury.

**Cooling: physiological aspects of induced hypothermia**

In order to successfully and safely implement cooling, awareness of the physiological effects and appropriate management of the side effects of hypothermia are required. There are three commonly recognized phases of hypothermia management: induction, maintenance and re-warming.

In the induction phase the aim is to reduce the temperature to target as quickly as possible. In TBI, clinical studies indicate that the temperature range associated with better outcomes appears to be 32–35 °C (Table 1). As this phase involves the highest risk for immediate side effects such as electrolyte disorders, hyperglycaemia and shivering (Table 1), it is preferable to reach the stable maintenance phase quickly. Continual monitoring of ventilation, blood pressure, sedation, blood sugar, and electrolytes is required in this phase.

Several methods are used to induce hypothermia:

**Surface cooling by air:** Traditional methods such as exposing the skin to air, which may be combined with sponge baths, are effective, and air-circulating cooling blankets are also available.

**Surface cooling by fluid:** This includes methods from ice packs to water-circulating cooling blankets, pads, and wrapping garments, as well as hydrogel-coated-water-circulating pads.

**Core-cooling:** The infusion of ice-cold fluids is effective in inducing hypothermia. Invasive devices such as intravascular catheters with saline-filled cold balloons or coated metal components are also used for core-cooling as well as antipyretic agents.

By combining different cooling methods the target temperature is more rapidly achieved.

In the maintenance phase, core temperature should be tightly controlled to ensure patient stability. During this period, prevention of side effects such as nosocomial infections and pressure ulcers is important particularly if the duration of hypothermia is prolonged.

The re-warming phase involves the very slow increase of the temperature of the patient to normal levels. This is done slowly for several reasons: to minimise electrolyte disturbances caused by shifts between intra- and extracellular compartments, and to reduce insulin sensitivity and the risk for hypoglycaemia if the patient is receiving insulin. Very slow re-warming is also necessary to prevent the exacerbation of damaging mechanisms in the injured brain which are associated with rapid re-warming; and to minimise the degree of vasodilation with warming in an attempt to maintain systemic blood pressure and cerebral perfusion pressure. Following re-warming, hyperthermia is commonly seen. However, normothermia should be maintained since fever is independently associated with adverse outcomes in many forms of brain injury.

**Potential mechanisms of the neuroprotective effects of therapeutic hypothermia and common side effects**

In out-of-hospital cardiac arrest, hypoxic ischaemic encephalopathy in neonates, traumatic brain injury (TBI), stroke and hepatic encephalopathy, TH is used to reduce the potential neurological complications of evolving secondary brain tissue injury. The mechanisms of action of hypothermia are complex (Table 1) but principally they act to attenuate the cascade of destructive processes (secondary injury), which occurs in the minutes to hours following initial tissue injury (primary injury). We will discuss these processes with particular regard to cerebral insults, where the majority of the research to date has focused, however, these protective processes are expected to be replicated in other organs during TH. Side effects which consequently affect patient management are also addressed (Table 1).

**Metabolism/electrolytes:** Until the 1990s, it was assumed that the neurological protective effects of hypothermia were solely due to a reduction in cerebral metabolism. Whilst there is indeed a decrease in metabolism, it is now understood that this is only one of many mechanisms behind the protective effects of hypothermia. As the core temperature drops and the metabolic rate decreases, oxygen and glucose consumption, and carbon dioxide production also decrease, thus helping to prevent or ameliorate injury when oxygen supply is interrupted or limited.

The reduction in metabolic rate induced by hypothermia may require adjustments in ventilator settings to maintain normocapnia. Decreases in insulin sensitivity and secretion may also require changes to insulin infusion rates. The rate of these changes depends on the rapidity of induction and re-warming.

Electrolyte levels are also affected by hypothermia due to tubular dysfunction and intracellular shift. Considering that magnesium may ameliorate cerebral injury; that low phosphate levels are linked to higher risk of infection; and that low magnesium and potassium levels can increase the risk of arrhythmias, these electrolytes should be kept in the high-normal range during and after hypothermia. However, caution is required with potassium supplementation during cooling as there is a risk of rebound hyperkalaemia during re-warming.

**Apoptosis and mitochondrial dysfunction:** Following ischaemia with subsequent reperfusion, cells may recover to varying degrees, become necrotic, or enter a pathway to programmed cell death (apoptosis).Whilst hypothermia appears to block the apoptotic pathway in its early stages there is a finite window for interventions such as hypothermia to affect this process.

**Ion pumps and neuroexcitotoxicity:** Hypothermia is thought to inhibit damaging neuroexcitatory processes that occur with ischaemia–reperfusion injury (Fig. 1 and Table 1). When cerebral oxygen supply is interrupted, levels of adenosine triphosphate...
Potential mechanisms of action, risks and changes with hypothermia.

<table>
<thead>
<tr>
<th>Mechanism/change</th>
<th>Explanation</th>
<th>When/treatment</th>
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<tbody>
<tr>
<td>Metabolic changes</td>
<td>Cerebral metabolic rate by 6–8% per 1°C in core T → ↓ in O₂ consumption and CO₂ production. Excessive ↓ in CO₂ can ↑ cerebral oedema, and excessive ↓ in CO₂ can ↑ ischaemia.</td>
<td>Acute in induction/frequent BGs and ventilator setting adjustments to maintain normocapnia, slow rewarming</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Cooling → ↑ renal tubular dysfunction → ↑ electrolyte excretion Cooling → intracellular electrolyte shift → ↓ K⁺, Mg⁺⁺, PO₄⁻ → ↑ risk for arrhythmias Rewarming → intracellular K⁺ released → hyperkalaemia</td>
<td>Keep electrolytes in high-normal range, slow rewarming (0.25°C/h post cardiac arrest, slower for severe TBI)</td>
</tr>
<tr>
<td>Apoptosis and mitochondrial dysfunction</td>
<td>Post IR injury mitochondrial dysfunction (mitochondria = cells’ energy source), disturbed energy metabolism in cell, and caspase enzymes can → apoptosis Hypothermia blocks apoptotic pathway early by: ↓ caspase enzyme activation, ↓ mitochondrial dysfunction, ↓ excitatory neurotransmitters, and modifying intracellular ion concentrations</td>
<td>Starts late in post-reperfusion phase, can continue for 72 h or more → In theory wide window for treatment</td>
</tr>
<tr>
<td>Ion pumps and neuroexcitotoxicity</td>
<td>IR injury → ↓ brain O₂ supply → ↓ ATP and phosphocreatine levels. This initiates a complex cascade of events involving excessive calcium influx into brain cells, excessive glutamate receptor activation and neuronal hyperexcitability (excitotoxic cascade) which can lead to further injury and cell death even after reperfusion and normalisation of glutamate levels. Hypothermia can ↓ damage from neuroexcitatory cascade</td>
<td>Disturbed Ca²⁺ homeostasis begins minutes after injury and may continue for many hours → may be treatable. Animal studies suggest to initiate treatment early in the neuroexcitatory cascade</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Brain injury → Proinflammatory mediators released ++ → leukocytes drawn across BBB → inflammatory cells in brain → passage of neutrophils, phagocytic monocytes and macrophages into brain → phagocytic action and toxin production → further injury by stimulating further immune reactions Some of this is neuroprotective, but if continual and excessive → ↑ injury. Hypothermia → ↓ ischaemia-induced inflammatory and immune reactions, ↓ NO production (key agent in developing brain injury post-ischaemia), ↓ neutrophil/macrophage function and ↓ WCC</td>
<td>Begins ~ 1 h after ischaemia and persists for up to 5 days, suggesting a therapeutic window for these mechanisms</td>
</tr>
<tr>
<td>Free radicals</td>
<td>IR injury →↑ free radicals that oxidise and damage cell components → brain’s defence mechanisms likely overwhelmed. Hypothermia → ↓ release of free radicals → endogenous antioxidants more able to meet demand</td>
<td></td>
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<tr>
<td>Blood–brain barrier/vascular permeability</td>
<td>Traumatic/IR injury can disrupt BBB → brain oedema. Mild hypothermia ↓ BBB disruptions and vascular permeability after IR injury → ↓ brain oedema. Brain oedema and ICH play key role in neurological injury in severe TBI and ischaemic stroke, and ICH is a marker for neurological injury → plausible that therapies to ↓ ICP may also improve neurological outcome Hypothermia has been used to ↓ ICP in neurological injury including TBI, ischaemic stroke, meningitis and SAH</td>
<td>Brain oedema peaks after 24–72 h → this mechanism could offer a wide therapeutic window</td>
</tr>
<tr>
<td>Acidosis and cellular metabolism</td>
<td>Ion-pump failure, mitochondrial dysfunction, cellular hyperactivity and ↓ in cell membrane integrity → intracellular acidosis → ↑ oxidative processes. Hypothermia can alleviate this, may improve brain glucose metabolism and when induced early enhances speed of metabolic recovery → ↓ toxic metabolic accumulation → ↓ acidosis</td>
<td></td>
</tr>
<tr>
<td>Brain temperature</td>
<td>Brain temperature slightly higher than core temperature and can ↓ 0.1–2.0°C post-injury (more with fever). Injured areas are hotter than uninjured areas due to cellular hyperactivity. Dissipation of heat by lymph/venous drainage is hampered by local brain oedema (cerebral thermo-pooling) → ↑ hyperthermia-related injury Hypothermia in brain-injured patients may ↓ potential hyperthermia-related adverse effects</td>
<td></td>
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<tr>
<td>Coagulation</td>
<td>Activation of coagulation seems to be involved in developing IR injury Its reversal, whilst targeting other mechanisms, could improve outcomes Hypothermia induces anticoagulatory effects: mild platelet dysfunction at 33–35°C can affect clotting factors at ≤33°C, and a potential reduction in platelet count, may influence synthesis and kinetics of clotting enzymes and plasminogen activator inhibitors. This anticoagulation effect could provide protection, but not investigated. Cooling to 35°C → no effect on coagulation</td>
<td>Assess risk versus benefit</td>
</tr>
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</table>

glutamate levels. Hypothermia seems to prevent or ameliorate damage from this neuroexcitatory cascade. Some animal studies suggest interventions need to be initiated early in the neuroexcitatory cascade for treatment to be effective, and again implying a narrow therapeutic time window for effective TH.

**Table 1 (Continued)**

<table>
<thead>
<tr>
<th>Mechanism/change</th>
<th>Explanation</th>
<th>When/treatment</th>
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<tr>
<td><em>Vasoactive mediators</em></td>
<td>Secretion of vasoactive substances endothelin and TxA2 (vasoconstrictors) and prostaglandin I2 (vasodilator) is affected by hypothermia. TxA2 and prostaglandin I2 regulate cerebral blood flow. Their balanced production is required to maintain homeostasis. If disrupted by ischaemia/trauma TxA2 production increases which can → vasoconstriction and hyperperfusion in injured brain. Hypothermia → imbalance, but regulation of cerebral perfusion is complex and influenced by cerebral autoregulation and patient management. Influence of hypothermia on secretion of vasoactive mediators in brain-injured patients requires further investigation.</td>
<td></td>
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<tr>
<td><em>Improved tolerance of ischaemia</em></td>
<td>In animal models 'preconditioning' with hypothermia improves tolerance for ischaemia. As brain injury is frequently complicated by ischaemic events after the initial insult, this could be a valuable neuroprotective mechanism.</td>
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<tr>
<td><em>Reduction of epileptic activity</em></td>
<td>Epileptic activity without signs and symptoms (non-convulsive) occurs frequently in brain-injured patients and if it occurs in the acute phase of brain injury the combined effect is destructive. Evidence indicates that hypothermia; epileptic activity; another mechanism through which it could provide neuroprotection.</td>
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<tr>
<td><em>Early gene activation</em></td>
<td>Hypothermia → early gene activation which is part of the protective cellular stress response to injury and → production of cold shock proteins that can be cytoprotective in the presence of ischaemic and traumatic injury.</td>
<td></td>
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<tr>
<td><em>Shivering</em></td>
<td>↑ metabolic rate, O2 consumption, work of breathing, heart rate and myocardial O2 consumption.</td>
<td>34–35°C opioids, sedation, paralysis if required, other agents.</td>
</tr>
<tr>
<td><em>Insulin sensitivity and secretion</em></td>
<td>↑ with cooling → hyperglycaemia or ↓ insulin required.</td>
<td>Induction and rewarming/frequent BGL checks and insulin adjustments, slow rewarming.</td>
</tr>
<tr>
<td><em>Cardiovascular/haemodynamic effects</em></td>
<td>Mild hypothermia: In euvoalaemic, adequately sedated pts</td>
<td>Sedate adequately. Allow ↑ HR 45–55 at 33°C (artificial ↑ ↑ HR → contractility) Avoid and correct hypovolaemia. Avoid stimulating HR.</td>
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<td>↓ HR, ↓ myocardial contractility, → or slightly ↑ BP, ↓ CO.</td>
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<td></td>
<td>↓ metabolic rate matches or exceeds ↓ CO → balance maintained.</td>
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<td></td>
<td>Initial transient ↑ HR due to ↓ venous return (↑ if sedation inadequate, shivering untreated)</td>
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<td></td>
<td>Stabilises cell membranes → risk of arrhythmias, ↑ successful defibrillation.</td>
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<tr>
<td></td>
<td>Deep hypothermia: (&lt; 30°C) ↓ contractility, ↑ risk for arrhythmias, ↓ successful defibrillation, ↓ response to antiarrhythmics</td>
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<td>Cold diuresis: the result of ↓ venous return (due to peripheral vessel constriction), atrial natriuretic peptide activation, ↓ ADH and renal ADH receptor levels, and tubular dysfunction → hypovolaemia. Risk ↓ if diuretic agents used e.g. mannitol.</td>
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<tr>
<td><em>Coronary perfusion</em></td>
<td>↓ metabolic rate and HR protects ischaemic myocardium, ↑ coronary vasodilatation and perfusion. But in severely atherosclerotic coronary vessels constrict, shivering can occur → may affect result of hypothermia. Shivering can ↑ myocardial O2 consumption.</td>
<td>Sedate adequately-prevent shivering. Modify doses of certain drugs.</td>
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<tr>
<td></td>
<td>Sedate adequately.</td>
<td></td>
</tr>
<tr>
<td><em>Drug clearance</em></td>
<td>Most enzyme-based reactions slowed → ↓ drug clearance by liver. Tubular dysfunction may also affect clearance, and response to some drugs alters e.g. ↑ effect of adrenaline and noradrenaline. BUT most drug levels → ↓ strength and duration of effect</td>
<td>Modify doses of certain drugs.</td>
</tr>
<tr>
<td><em>Infection</em></td>
<td>↓ leucocyte migration and phagocytosis, ↓ proinflammatory cytokine synthesis → ↓ proinflammatory response → may protect against damaging neuroinflammation, but ↑ risk for infection (↑ risk with ↓ duration).</td>
<td>Low threshold for antibiotic treatment may be advisable.</td>
</tr>
<tr>
<td></td>
<td>↑ risk for wound infection due to cutaneous vasocostriction</td>
<td></td>
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<tr>
<td></td>
<td>Signs of infection: e.g. fever and possibly CRP and WCC ↓.</td>
<td>in 'cooling power' required may indicate fever and infection.</td>
</tr>
<tr>
<td><em>Gut</em></td>
<td>↓ gut function and gastric emptying, ↓ metabolic rate.</td>
<td>Reduce feeding target in maintenance phase.</td>
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</table>


**Inflammation:** In most brain injury, an inflammatory response begins about 1 h after ischaemia–reperfusion and persists for up to 5 days.²⁴,³⁵ Large amounts of proinflammatory mediators are released inducing inflammatory and immune responses which can cause additional injury.³⁵ This response if controlled is adaptive and can be neuroprotective, but if continued and excessive, injury increases.³⁵–³⁸ Hypothermia has been shown to suppress these reactions.³⁹–⁴¹ Moreover, there again appears to be a defined time window during which hypothermia could provide a therapeutic effect on these mechanisms.

**Free radicals:** Following ischaemia–reperfusion injury, the production of free radicals that can oxidise and damage cell components is increased, and the cell defence mechanisms to prevent such injury are likely to be overwhelmed.²⁹,⁴² With hypothermia, the release of free radicals is considerably decreased, allowing endogenous antioxidative mechanisms to prevent or attenuate oxidative damage to cells.²⁵,⁴²

**Blood brain barrier/vascular permeability:** Traumatic or ischaemia–reperfusion injury may disrupt the blood–brain barrier which can result in brain oedema.³¹,³³,³⁴ Mild hypothermia reduces such disruptions and also reduces vascular permeability after ischaemia–reperfusion injury and this may decrease brain oedema.³³–³⁴,³⁵ These findings have prompted studies investigating the use of hypothermia to attenuate secondary brain injury and therefore the development of cerebral oedema (prophylactic hypothermia) and also of ‘rescue’ hypothermia as a specific treatment of raised intra-cranial pressure (Eurotherm3235 Trial ISRCTN34555414). It is possible that therapies that reduce intra-cranial pressure such as hypothermia also improve neurological outcome, however the association between controlled intra-cranial pressure and improvement in neurological outcome is uncertain.¹⁶,¹⁷,⁴⁶,⁴⁷

**Intra-/extra-cellular acidosis and cellular metabolism:** The reduction in cell membrane integrity, ion-pump failure, mitochondrial dysfunction, and cellular hyperactivity all contribute to the development of intracellular acidosis which stimulates many of these harmful processes.³⁸,⁴⁰ These potentially harmful processes can be attenuated by hypothermia.⁴⁸,⁴⁹

**Elevated brain temperature:** The temperature of the brain is normally slightly higher than the core temperature³⁶,⁵¹ and this difference can increase between 0.1 and 2.0 °C following brain injury and further still with fever.⁵²–⁵⁴ Animal studies indicate that hyperthermia increases the risk and degree of brain injury⁵⁵–⁵⁷ and clinical studies confirm fever as an independent predictor of adverse outcomes after stroke and traumatic brain injury.⁵⁸–⁶⁰ Therefore, the use of hypothermia in brain-injured patients may prevent or ameliorate potential hyperthermia-related adverse effects.

**Coagulation:** Activation of coagulation appears to play a role in the development of ischaemia–reperfusion injury.¹⁷,⁶¹ Reversal of this mechanism, combined with targeting of other mechanisms, could improve outcomes.¹⁷ Hypothermia induces some anticoagulatory effects which could in theory provide neurological protection.¹⁷ The effect of hypothermia on coagulation is summarised in Table 1. Whilst there have been no significant bleeding problems in many studies of patients with severe TBI, stroke or cardiac arrest, patients with active bleeding were generally excluded from these studies.¹⁴,¹⁶ However, as the effect on clotting factors only

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becomes significant below 33 °C, it may be that cooling to 35 °C can be safely undertaken in patients with active bleeding.17 Once bleeding is controlled in such patients, further cooling to 33 °C may be reasonable.17

**Vasoactive mediators:** A number of studies indicate that the secretion of vasoactive substances (endothelin and thromboxane A2 [vasoconstrictors], prostaglandin I2 [vasodilator]) at sites including the brain is affected by hypothermia. Thromboxane A2 and prostaglandin I2 are key regulators of cerebral blood and balanced production is required to maintain homeostasis.62,63 Disruption to such production by ischaemia/truma can cause damaging results to perfusion.54,65 Evidence suggests that hypothermia attenuates such imbalances67,68; however, the regulation of cerebral perfusion after neurological injury is complex and influenced by cerebral autoregulation and patient management factors.17 Therefore, the influence of hypothermia on the secretion of vasoactive mediators in brain-injured patients requires further investigation taking this contextual complexity into account.

**Improved tolerance of ischaemia:** In several animal models, ‘preconditioning’ with hypothermia improves the subsequent tolerance for ischaemia.67,68 Considering that brain injury is frequently complicated by ischaemic events occurring after the initial insult, this may also be a valuable neuroprotective mechanism.

**Reduction of epileptic activity:** Epileptic activity without clinical signs and symptoms (non-convulsive) occurs frequently in brain-injured patients. When non-convulsive epileptic activity occurs in the setting of acute brain injury the combined effect is injurious.69,70 Evidence indicates that hypothermia suppresses epileptic activity71,72 and this is an additional mechanism through which hypothermia could provide neuroprotection.

**Early gene activation:** Hypothermia stimulates early gene activation which is part of the protective cellular stress response to injury and promotes production of cold shock proteins that can be cytoprotective in the presence of ischaemic and traumatic injury.17

**Shivering:** The unfavourable effects of shivering can generally be suppressed by administering adequate sedation and paralytic agents during induction of cooling. In addition, sedation may lead to vasodilatation which promotes heat loss by surface cooling. The neuroprotective effect of hypothermia may be lost if adequate sedation is not administered.73

**Cardiovascular/haemodynamic effects:** The effects of hypothermia on the myocardium and its contractility partly depend on the patient’s volume status and adequacy of sedation.17 **Table 1** summarises the changes to heart function related to hypothermia. The decrease in metabolic rate usually matches or exceeds the decrease in cardiac output thus maintaining or improving the equilibrium between supply and demand.14 The heart rate decreases with a lower temperature (40–50 at 33 °C) and it is generally advisable to allow this decrease.17 Myocardial contractility improves when heart rate decreases with hypothermia, and artificially increasing heart rate during hypothermia markedly decreases myocardial contractility.74,75 Hypothermia can also produce ‘cold diuresis’ causing hypovolaemia.17 Prompt correction of hypovolaemia may prevent hypotension.

**Coronary perfusion:** Hypothermia could provide protection for ischaemic myocardium, however this may be affected by coronary artery disease.76,77 There is preliminary evidence that suggests that early induction of hypothermia after myocardial infarction may ameliorate subsequent myocardial injury.16

**Drug clearance:** Clearance of drugs by the liver and the kidneys is decreased during hypothermia.14,16,78 Therefore, the levels of most drugs increase with hypothermia and it may be reasonable to modify doses of certain drugs.17

**Infection:** Hypothermia suppresses the pro-inflammatory response. Whilst this may protect against damaging neurological injury, the risk for infection is potentially increased.14

**Other:** Hypothermia is linked with reduced gut function.14 In addition, fat metabolism increases with hypothermia leading to higher levels of free fatty acids, ketones and lactate, which may reduce pH. Liver enzymes may also become elevated.17

In summary, hypothermia may attenuate secondary injury and provide protection in the presence of many injurious processes after ischaemic or traumatic injury. The large range of mechanisms of action through which hypothermia may confer its protective effects is a key to its efficacy compared with treatments that target only one or two mechanisms.17 A better understanding of the destructive mechanisms and side effects involved in different types and phases of injury will potentially enable the application of hypothermia more effectively in the future.

**What is the clinical evidence?**

Hypothermia is the first treatment shown to be potentially efficacious in clinical trials for postischaemic injury. We will examine the evidence for the use of TH for neurological injury, ischaemic cardiac injury and the early evidence of benefit in acute kidney injury.

**Neurological injury**

**Out-of-hospital cardiac arrest:** After positive results from animal studies13,79,80 small clinical trials in patients who remained comatose following cardiac arrest showed improved outcomes compared to historical controls.81–85 Subsequently, randomised controlled trials showed positive neurological results for cooling after cardiac arrest.1,2 The initial cardiac rhythm in these studies was ventricular fibrillation or pulseless ventricular tachycardia. Bernard et al.1 recruited 77 patients and cooling was initiated during CPR at the scene or early during transport to hospital with a target temperature of 33 °C for 12 h. The rate of favourable neurological outcomes was 49% (21/43) in the hypothermia group, and 26% (9/34) in the control group (p = 0.046). The adjusted odds ratio for good outcome in the hypothermia versus normothermia group in multivariate analysis was 5.25 (1.47–18.76, p = 0.011). Similarly, in the European study2 (n = 273) favourable neurological outcome rate was 55% (75/136) in the hypothermia group and 39% in controls. Cooling was started after a median time of 105 min and maintained for 24 h at 32–34 °C (target temperature was reached at an average of 8 h after return of circulation). American Heart Association86 and European Resuscitation Council guidelines87 now recommend using TH after cardiac arrest with an initial rhythm of ventricular tachycardia or pulseless ventricular fibrillation (VF) and consideration of its use for other rhythms.

Recently a further trial by Bernard et al. of TH for out-of-hospital VF cardiac arrest patients found that paramedic cooling with a rapid infusion of cold fluid decreased core temperature at hospital arrival.58 However, it was not shown to improve outcome at hospital discharge compared with cooling commenced in the hospital. The difference in patient temperature between the groups was modest (0.8 °C) and of relatively short duration, possibly due to the short transport times in a large metropolitan network of hospitals. Such a brief difference in core temperature may have been insufficient to significantly affect neurological outcomes at hospital discharge. The RINSE trial (NCT01172678) which is currently recruiting in Australia, may help to clarify the benefit that immediate induction of hypothermia provides for any patient with an out-of-hospital cardiac arrest receiving cardiopulmonary resuscitation. This RCT aims to determine whether immediate cooling during cardiopulmonary resuscitation by paramedics...
using a rapid infusion of cold saline, improves outcome at hospital discharge, compared with standard care.

Peri-natal hypoxic ischaemic encephalopathy: Early studies indicated that prolonged mild hypothermia after perinatal hypoxic-ischaemic encephalopathy reduced brain injury and improved neurological outcome. However, the results of several clinical trials of hypothermia in such patients were inconclusive. When neurological outcome at >18 months was assessed, a composite outcome of death or disability was used making interpretation difficult, and estimates for therapeutic benefit rarely reached statistical significance. A recent meta-analysis including more recent studies has helped to clarify this issue, finding that moderate hypothermia is associated with a reduction in mortality and neurological dysfunction at 18 months in infants with hypoxic-ischaemic encephalopathy. Cumulative findings are gradually leading to a practice change and increasing adoption of hypothermia in treatment of this group.

Traumatic brain injury: Experimental models of TBI indicate that hypothermia induced pre-injury reduces neurological damage and mortality, and improves neurological outcomes. Animal studies also suggest that if hypothermia is induced within a few hours of the primary injury, it may also improve neurological outcomes.

Over the last 20 years, numerous clinical studies have investigated hypothermia in TBI patients and many studies support a likely benefit, however they vary in study design in a number of key factors such as rate of induction, duration of hypothermia, and rate of re-warming. There is still considerable uncertainty surrounding the use of hypothermia to treat TBI. Six adult patient meta-analyses have been performed with different inclusion criteria. The most recent meta-analyses found an increase in favourable long-term neurological outcomes and/or mortality in patients receiving hypothermia versus normothermia. This resulted in the first grade III recommendation for the use of hypothermia in adult patients with severe TBI.

Although most single centre studies found hypothermia to be effective, the Clifton study found no improvement in outcomes for adults and the Hutchison study found no improvement in children instead there was a trend towards higher mortality in children receiving hypothermia (p = 0.06). However, these two trials had significant methodological limitations which may have prevented detection of benefit and in the hypothermia groups may have caused harm.

In these two studies, induction of hypothermia only commenced on hospital arrival and was further delayed by the lack of rapid cooling methods. In the Clifton study, the time to target temperature was 8.4 h and in the Hutchison study it was 10.2 h. Animal models suggest that the ‘therapeutic window’ may have been missed due to these delays, decreasing the likelihood that these trials would show a beneficial effect of hypothermia. In the Clifton trial a subgroup of patients from the hypothermia group who were hypothermic on arrival to hospital had significantly better long-term neurological outcome compared to normothermic patients, which may support the proposed beneficial effect of early hypothermia. In order to test whether earlier hypothermia is beneficial, paramedic initiated hypothermia at the location of injury would be ideally tested in future trials.

The duration of hypothermia in the 2 multi-centre trials was 24 h in the Hutchison trial and 48 h in the Clifton trial and this may not be sufficient given that cerebral oedema is often most marked at this time. Brain tissue swelling in severe TBI often lasts 3–5 days and in recent adult meta-analyses hypothermia applied for >48 h was associated with reductions in mortality and more favourable neurological outcomes. Future trials should therefore maintain therapeutic hypothermia for >48 h.

In the Hutchison and Clifton multicentre studies, re-warming was performed at a pre-set time, regardless of the patients’ intracranial pressure (ICP). Initiation of re-warming in TBI patients with high ICP may account for the increased use of vasopressors and hyperventilation in the hypothermic group of children. On the other hand, recent meta-analyses found that re-warming rate was not an independent risk factor for survival. Nevertheless in future trials, re-warming may be better guided by a clinically relevant physiological trigger such as ICP and re-warming occur over a prolonged period (≤0.25 °C/h) to prevent rebound and uncontrolled intracranial hypertension.

Another consideration in the Hutchison trial was that neurological outcomes were better than expected in normothermic patients. This may have been due to prevention of hyperpyrexia and it may be that the benefit of hypothermia in previous studies is attributable to the prevention of hyperpyrexia rather than a therapeutic effect of hypothermia. Future trials should therefore include strict temperature control and prevention of hyperpyrexia in the control group. Another criticism of the Clifton trial was the variance in hypothermia between centres which may have decreased the ability to detect an overall beneficial effect of hypothermia.

Clifton and colleagues have recently completed a further trial of prophylactic hypothermia in patients with severe TBI which was prematurely terminated, likely as a result of methodological issues. TBI patients were enrolled within 2.5 h of injury addressing the question of whether prophylactic hypothermia had been commenced too late in the past; however a 48 h duration of hypothermia may not be sufficient, and re-warming at 48 h without allowance for individualized management of ICP in relation to cooling is problematic. In addition, the protocol allowed for large volumes of IV fluid administration which could lead to intracranial hypertension. These and other concerns make this trial’s findings inconclusive and the question still remains as to whether prophylactic hypothermia for severe TBI improves neurological outcomes. Further investigation is required.

Peri-operative hypothermia: Intraoperative hypothermia is widely used during cardiac and neurological surgery but without strong evidence from randomised controlled trials. As the ischaemic injury is predictable, hypothermia can commence pre-injury and theoretically prevent damaging processes.

In cardiac surgery, results of clinical studies to assess the benefit of hypothermia are inconclusive. A meta-analysis by Rees et al. examining the effect of hypothermia during cardiopulmonary bypass on neurological outcomes found a trend towards a reduced incidence of non fatal strokes in the hypothermic group (OR 0.68, 95%CI 0.43–1.05). On the other hand, there was a trend for a higher number of non-stroke related perioperative deaths in the hypothermic group (OR1.46, 0.59–2.37). Nathan et al. found that patients taken off cardiopulmonary bypass at a lower temperature (34 °C versus 37 °C) showed better neurocognitive performance 1 week and 3 months after cardiac bypass surgery. However, this benefit was not sustained at 5 year follow-up. Inconsistencies in study designs may explain some of this variation in results: patient population; site and method for temperature determination; cardiopulmonary bypass techniques; temperature regime; myocardial protection; surgical techniques; re-warming rates and postoperative management of hypothermia may all differ between patients and hospitals which can affect outcome. Cognitive deficits post cardiopulmonary bypass surgery could potentially be linked to rapid re-warming which decreases venous oxygen saturation. Stronger evidence supports the avoidance of fast re-warming and hypothermia during or after cardiopulmonary bypass surgery.

In aortic surgery, animal studies and early clinical trials using cooling to protect the spinal cord showed promising
results. On the other hand, hypothermia showed no difference in outcome in a large clinical study of patients undergoing cerebral aneurysm clipping. However, these patients received rapid rewarming and there is evidence that re-warming rapidly can decrease the benefits of hypothermia or even worsen outcomes.

Importantly, postoperative hyperthermia may be associated with more cognitive deficits. Conflicting results in some studies of peri-operative therapeutic hypothermia may be due to the harmful effects of rapid re-warming. Therefore, slower re-warming should be adopted in future studies using intraoperative hypothermia.

Ischaemic stroke: Animal models suggest hypothermia could limit neurological injury in stroke. However, the clinical studies have been relatively small with late initiation of hypothermia when much of the injury may have become irreversible. Some recent studies have combined hypothermia with thrombolysis to simultaneously restore blood flow and prevent reperfusion injury. Whilst this approach appears to be safe, larger prospective studies are needed to assess benefit. However, the requirement for close monitoring and management of temperature in non-sedated patients may require ICU admission and this presents a challenge for future studies.

Cardiac injury

Animal studies and preliminary human studies suggest a protective effect of hypothermia on the ischaemic heart and several studies have shown that mild hypothermia is feasible and safe to apply in the setting of acute myocardial infarction. However, mild hypothermia has not been shown in prospective randomised trials to significantly reduce infarct size or mortality rate. Based on current evidence, the use of hypothermia to reduce infarct size or improve heart function cannot be recommended but if patients are rapidly cooled to target temperature quickly after cardiac arrest, and this is maintained at 32–34°C for the recommended period, then their myocardial function and neurological outcome may both be improved. However, further studies are required before recommendations regarding the induction of hypothermia following cardiac injury could be made.

Kidney injury

Whilst some of the mechanisms of action of hypothermia previously mentioned are more applicable to brain injury, many of these protective mechanisms could potentially provide benefit if hypothermia was used prophylactically for the kidneys after injury or in patients at high risk for kidney injury undergoing procedures recognised as injurious for the kidneys.

In a renal ischemia-reperfusion injury model of hypothermia, the temperature of the rats during the ischemia phase significantly affected the severity of injury. Rats kept hyperthermic at around 40°C developed more severe and unrecoverable renal injury (measured by creatinine), rats kept at ~37°C developed recoverable renal injury, whereas those at ~33°C had reduced renal injury. Furthermore, Zager et al. found that hypothermia was very effective during ischemia in rats, and also effective but to a lesser extent when applied during early reflow post-ischemia, and that these benefits were additive. However, there has been little clinical investigation of the renal effects of TH. A pilot study of 30 patients undergoing angiographic procedures to assess whether mild hypothermia reduces the incidence of contrast-induced nephropathy in patients with pre-existing renal injury (serum creatinine rise from baseline >25%) found the incidence to be 10% in those who received hypothermia compared to 40% in historical controls.

In the European multi-centre trial which evaluated the neurological effects of 24 h of mild hypothermia (32–34°C) after cardiac arrest, the effect on renal function was also evaluated. There was no difference between groups in the incidence of acute kidney injury or the need for renal replacement therapy. There was a delayed improvement in renal function in the cooled group indicated by creatinine clearance (but not in serum creatinine) that occurred within 4 weeks.

Two randomised trials have been conducted to evaluate mild hypothermia for 24 h and rewarming on kidney function after coronary artery bypass graft surgery. In one trial, 223 patients were cooled to 32°C during cardiopulmonary bypass and randomised to rewarm to 37°C or 34°C. In this trial, patients rewarmed to 37°C had a higher incidence of renal injury (25% increase in serum creatinine or a 25% decrease in creatinine clearance) than those rewarmed to 34°C (17% versus 9%, p = 0.07). In a second trial, 267 patients were randomised to mild hypothermia at 34°C or normothermia (37°C). In this trial, mild hypothermia provided no benefit in serum creatinine levels or reduction in incidence of renal injury compared to normothermia (20%: 34°C versus 15%: 37°C, p = 0.28). Rewarming on cardiopulmonary bypass in this study was an independent risk factor for renal injury. Given the association of cardiopulmonary bypass technique with increased risk for kidney injury, the use of this method of re-warming to assess the effect of hypothermia on renal function may not be optimal. Instead, continuation of cooling postoperatively using advanced techniques followed by slow rewarming might be considered in this setting.

Overall, there is some experimental evidence and a plausible rationale to suggest a potential benefit of prophylactic hypothermia for kidney injury, however clinical evidence is inconclusive. Further investigation in this area is warranted, particularly considering the largely unsuccessful attempts to find effective therapies for acute kidney injury (AKI).

Hypothermia and AKI

AKI is common in the ICU and occurs in approximately 36% of critically ill patients, and is independently associated with increased mortality and with prolonged length of stay. It increases both the human and financial costs of care. Therefore, it is important to investigate treatments with potential to ameliorate or prevent AKI.

The most extensively used and validated consensus definition and method of classifying AKI is the RIFLE classification system. The serum creatinine cutoffs of the RIFLE criteria are most commonly used to classify the severity of AKI: no AKI: <50% increase in SCR, risk of AKI: 50–200% increase, kidney injury: >200–300% increase, failure of kidney function: >300% increase or SCR >4 mg/dl with a rise ≥0.5 mg/dl.

Some injury pathways for AKI in the critically ill include exposure to endogenous and exogenous toxins, metabolic factors, ischaemia and reperfusion insults, neurohumoral activation, inflammation, and oxidative stress. Of these, ischaemia–reperfusion may be the most common. Hypothermia may prevent or reduce injury and assist renal recovery through a reduction in metabolic demand, decreased production of free radicals, promotion of cellular integrity, limitation of apoptosis and through anti-inflammatory effects.

Investigations of potential treatments for AKI have had limited success to date, however, from the results of animal and human studies, further investigation of hypothermia as a prophylactic therapy for kidney injury appears warranted for patients at high risk for AKI. The POLAR trial which has commenced recruitment in Australia and New Zealand with the primary aim to assess the effect of prophylactic hypothermia on neurological effects.
outcome, is doing just this, by also investigating the effect of hypothermia on renal function in its renal substudy.

**Prophylactic hypothermia: POLAR and POLAR-acute kidney injury**

POLAR (Prophylactic Hypothermia to Lessen trAumatic brain injury), is a randomised, blinded, controlled trial of hypothermia in ICU patients with severe traumatic brain injury (TBI). The trial is being conducted at 6 sites in Australia and New Zealand and recruitment has commenced (ACTRN12609001064235). POLAR is endorsed by the Australian and New Zealand Clinical Trials Group (ANZICS CTG) and has NHMRC and Victorian Neurotrauma Initiative funding. The trial has a planned cohort of 500 patients and is one of the largest TBI trials currently being conducted. Participants will be intubated, severe TBI patients (GCS ≤ 8), aged between 18 and 60 years who are able to be randomised within 3 h of injury. Patients will be randomised to receive either early and sustained hypothermia (33 °C) for ≥72 h (maximum 7 days) using state of the art cooling systems, followed by slow controlled rewarming (0.17 °C/h or 4 °C/h); or normothermia (36.5–37.5 °C). Hypothermia will be induced as quickly and early as possible and rewarming will proceed after 72 h of cooling if the ICP is controlled and the patient has achieved a degree of stability. Pre-hospital randomisation at the scene of injury and cooling with cold fluid (0.9% saline at 4 °C) will be performed by paramedics. In addition, early emergency department recruitment will occur.

Previous Australian experience with pre-hospital cooling of cardiac arrest patients will be applied.88 Guidelines for standard care of TBI patients to reduce the effect of variance in patient care. Previous Australian experience with pre-hospital cooling of cardiac arrest patients will be applied.88 Guidelines for standard care applicable to both groups have been provided and a run-in phase is underway. Patient recruitment is being undertaken at sites that receive larger volumes of major trauma and have experience in the care of TBI patients to reduce the effect of variance in patient care. The primary outcome measure is the proportion of favourable neurological outcomes at 6 months post-injury (Glasgow outcome scale, extended (GOSE) 5–8). This is considered the most appropriate primary outcome given the large human and financial benefit that may result from an increase in favourable neurological outcomes in TBI.

‘POLAR-AKI’ and ‘POLAR-Biomarkers’ comprise the Intensive Care Foundation-funded renal substudy of the POLAR trial to assess the effect of prophylactic TH on the development of AKI and the response to this treatment using multiple renal biomarkers with different time profiles. This cohort of patients is ideal for a study of hypothermia for renal injury since there is a moderate incidence of AKI in this group.148,153 and all patients have recently sustained a timed physical injury. AKI will be classified using methods based on the RIFLE criteria; a classification system used extensively and validated to classify renal function in several populations with studies cumulatively involving over 250,000 subjects.152 With a cohort of 500 patients (all POLAR trial participants), this will be the largest study of hypothermia to protect against AKI yet performed, increasing the probability of detecting a treatment effect of TH. The POLAR trial provides a unique opportunity to clarify the potential benefit of hypothermia as a brain protective and kidney protective therapy. This trial when completed may also provide insight into the mechanisms of action of therapeutic hypothermia in AKI.

### Conflict of interest statement

Alistair Nichol and Stephen Bernard are investigators of the POLAR trial, a National Health and Medical Research Council/ Victorian Neurotrauma Initiative funded clinical trial of Hypothermia in Traumatic Brain Injury (NCT00987688). Elizabeth Moore, Alistair Nichol and Rinaldo Bellomo are investigators of the Renal Substudy of the POLAR trial.

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