Neuroprotective effects of hypothermia

BACKGROUND The neuroprotective effects of hypothermia have been shown in case reports and animal studies. Therapeutic hypothermia is used to provide neuroprotection during certain types of surgery and after serious events that pose a threat to the brain. The aim of this review is to describe the efficacy of such treatment in adults.

METHOD All articles retrieved from five searches in PubMed were examined. Studies were included if they had a hypothermia protocol and a measurement of neuroprotection. The list of randomised studies was completed using studies identified from five international review articles. In all, 103 of 678 studies fulfilled the inclusion criteria, of which 48 were clinical trials. Ten of the clinical trials were randomised, using a normothermic control group.

RESULTS Several randomised clinical trials have suggested that avoidance of hyperthermia provides the same neuroprotection as therapeutic hypothermia after cardiac arrest and traumatic brain injury, but prognostic factors and inclusion criteria vary markedly between the patient populations, including time to target temperature. Two studies found that cognitive function after prolonged aortic surgery under deep hypothermia was equivalent to that after brief normothermic interventions. Animal studies show a neuroprotective effect of hypothermia, but this is dependent on the extent of anoxic damage as well as the rate of cooling.

INTERPRETATION It remains uncertain how best to implement therapeutic hypothermia to achieve neuroprotection after acute events that pose a threat to the brain. Hypothermia during aortic surgery seems to provide adequate neuroprotection for prolonged interventions.

The modern use of therapeutic hypothermia can trace its roots back to the early 1800s, when the French surgeon Dominique Jean Larrey realised that cooled body tissue had greater hypoxia tolerance (1). Nevertheless, clinical use of hypothermia for neuroprotection did not become common until the latter half of the twentieth century, and the first reported use of hypothermia after cardiac arrest was published in 1958 (2).

Today, therapeutic hypothermia is widely used in the treatment of cardiac arrest survivors who remain comatose after cardiopulmonary resuscitation (3), and also in surgical procedures, such as aortic arch surgery (4). In recent years, large randomised trials have suggested that avoidance of hyperthermia provides the same neuroprotection as induction of moderate (30–34°C) hypothermia after cardiac arrest (5) and traumatic brain injury (6).

Neuroprotective effects of hypothermia have nevertheless been demonstrated in several reported cases of accidental hypothermic cardiac arrest. At the University Hospital of North Norway, successful rewarming has been achieved for patients with body temperatures as low as 13.7 °C (7) and up to seven hours after hypothermic cardiac arrest (8). The Praesto Fjord accident of 2011 further illustrates the neuroprotective effects of hypothermia – seven Danish adolescents were rewarmed after several hours of hypothermic cardiac arrest. All survived, and six emerged from the accident without serious neurological sequelae (9).

In this context, we will provide an overview of the use of hypothermia in various therapeutic procedures and discuss the neuroprotective efficacy of such treatment in adults. Therapeutic hypothermia to counter hypoxic-ischaemic encephalopathy in neonates is better documented and will not be discussed further in this article (10).

Method A literature search was conducted on 26 August 2014 in the electronic database PubMed. All articles retrieved for the following five searches were examined: #1 «Therapeutic hypothermia» AND neuroprotection, #2 stroke AND hypothermia AND neuroprotection, #3 «cardiac arrest» AND hypothermia AND neuroprotection, #4 surgery AND hypothermia AND neuroprotection, and #5 «therapeutic targeted temperature management». Any randomised clinical trials that were not captured by our search, but found in other review articles, were also included (11–15).

A total of 678 publications were identified. The main criterion for inclusion of articles was that they had a hypothermia protocol and a measure of neuroprotection. All case reports, studies in children and neonates, studies in which hypothermia was induced with drugs or local injection of cold fluids, and animal studies without a normothermic control group were excluded.

Hypothermia was defined as temperatures below 35 °C, but studies with protocols...
involving lower temperatures were also included. To obtain an overview of published studies that fulfilled the above criteria, a wide range of measures of neurological damage and neuroprotection were included: neuronal damage in the hippocampus, inflammation of brain tissue, standardised neurological tests, EEG, mortality, cerebral oedema, infarct size, serum markers of brain injury, morphometric analysis of brain tissue, auditory evoked potentials as well as excitatory transmitter release.

Studies were considered for inclusion on the basis of the abstract. If this was inadequate or absent, the full text was accessed in order to assess whether the study met the inclusion criteria. A total of 103 studies were included, of which 48 were clinical studies. The remainder were experimental studies in the following species: rat (n = 42), gerbil (n = 4), pig (n = 3), mouse (n = 3), rabbit (n = 2), baboon (n = 1). Extra weight has been assigned to those clinical studies that were randomised (n = 10). Based on these studies, we provide an overview of the use of hypothermia as a neuroprotective intervention in adults, and relate the observed treatment effects to knowledge derived from experimental studies which directly examine the cerebral physiological effects of hypothermia.

**Clinical trials**

The 48 clinical studies included spanned a wide range of topics. In total, there were 31 studies (5, 16–45) that examined the effects of hypothermia after cardiac arrest, eight on hypothermia in cardiac or aortic surgery (4, 46–52), four on ischaemic stroke (53–56), two on subarachnoid haemorrhage (57, 58), two on neurosurgery (59, 60) and one on traumatic brain injury (6).

Of the clinical studies, ten were randomised with a normothermic control group (5, 6, 22, 24, 30, 44, 45, 48, 53, 54) (Table 1). Of these, three reported positive effects of hypothermia (24, 30, 45), while the other seven found no differences between patients who underwent therapeutic hypothermia and their normothermic counterparts (5, 6, 22, 44, 48, 53, 54).

**Cardiac arrest**

Therapeutic hypothermia in patients who remained comatose after resuscitation from cardiac arrest was by far the most common intervention in the 48 clinical trials that met the inclusion criteria. In the 1990s, hypothermia was increasingly tested as a neuroprotective therapy (3). This led to the publication in 2002 of two randomised studies in the *New England Journal of Medicine*. These showed positive effects of therapeutic hypothermia after cardiac arrest, and included 77 (45) and 275 (24) patients respectively. These studies laid the foundations for the inclusion of therapeutic hypothermia in the guidelines for the treatment of cardiac arrest (61).

In 2013, however, a large randomised trial (950 patients) examined the effects of prevention of hyperthermia versus therapeutic induction of hypothermia after cardiac arrest (5). In this study there was no difference in neuroprotection between those patients treated with moderate hypothermia (33 °C) and those who received preventive treatment against hyperthermia (36 °C). It is therefore unclear whether moderate hypothermia after cardiac arrest has a neuroprotective effect over and above that achieved via prevention of hyperthermia alone. On the other hand, patients were randomised to one of the two treatment groups up to four hours after restoration of spontaneous circulation. It is thus possible that assigning patients to the cooling protocol as late as four hours after cardiac arrest may make it difficult to detect any neuroprotective effect of hypothermia in randomised studies (5).

**Ischaemic stroke**

All four clinical studies on the treatment of ischaemic stroke are small and prospective. Hong and co-workers (55) found that hypothermia had a beneficial effect on degree of disability (modified Rankin Scale) after three months, compared with a normothermic group. This study was admittedly not randomised, but includes patient data from two hospitals, one of which cooled patients, while the second kept them normothermic.

However, the COOL AID study (53), which also examined the use of hypothermia in the treatment of ischaemic stroke, was randomised. In this study there was no difference in infarct size on MRI between the two groups, but patients were selected for treatment up to 12 hours after symptom onset. The number of patients was small (40 patients), however, and it is therefore difficult to draw conclusions from this study.

In the ICTuS-L study, a limit of six hours was set for inclusion in the hypothermia protocol. But once again, no differences were

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**Table 1** Overview of randomised clinical trials with a normothermic control group, which examined the neuroprotective effects of hypothermia

<table>
<thead>
<tr>
<th>First author</th>
<th>Diagnosis</th>
<th>Number</th>
<th>Temperature (°C)</th>
<th>Neuroprotection measure</th>
<th>Effect of hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fakin [48]</td>
<td>Aortic dissection</td>
<td>60</td>
<td>32</td>
<td>P300 auditory evoked potentials</td>
<td>No difference</td>
</tr>
<tr>
<td>De Georgia [53]</td>
<td>Ischaemic stroke</td>
<td>40</td>
<td>33</td>
<td>Infarct size</td>
<td>No difference</td>
</tr>
<tr>
<td>Hemmen [54]</td>
<td>Ischaemic stroke</td>
<td>59</td>
<td>33</td>
<td>Modified Rankin scale, mortality</td>
<td>No difference</td>
</tr>
<tr>
<td>Nielsen [5]</td>
<td>Cardiac arrest</td>
<td>950</td>
<td>33</td>
<td>Mortality, Cerebral Performance Categories-scale</td>
<td>No difference</td>
</tr>
<tr>
<td>Castrén [44]</td>
<td>Cardiac arrest</td>
<td>200</td>
<td>34</td>
<td>Mortality, Cerebral Performance Categories-scale</td>
<td>No difference</td>
</tr>
<tr>
<td>Bernard [45]</td>
<td>Cardiac arrest</td>
<td>77</td>
<td>33</td>
<td>Mortality, disability</td>
<td>Positive</td>
</tr>
<tr>
<td>Hypothermia after Cardiac Arrest Study Group [24]</td>
<td>Cardiac arrest</td>
<td>275</td>
<td>32–34</td>
<td>Mortality, Cerebral Performance Categories-scale</td>
<td>Positive</td>
</tr>
<tr>
<td>Laurent [30]</td>
<td>Cardiac arrest</td>
<td>61</td>
<td>32</td>
<td>Mortality, Cerebral Performance Categories-scale</td>
<td>Positive</td>
</tr>
<tr>
<td>Hachimi-Idrissi [22]</td>
<td>Cardiac arrest</td>
<td>30</td>
<td>34</td>
<td>Mortality</td>
<td>No difference</td>
</tr>
</tbody>
</table>
found between hypothermic and normothermic treatment of patients (54).

**Aortic surgery**

Two studies with normothermic control groups examined the use of deep hypothermia (core temperature < 30 °C) during aortic surgery (46, 51). In both studies, patients were cooled to below 20 °C. No differences in cognitive function were seen between patients who underwent a lengthy procedure under deep hypothermia and those who underwent a shorter procedure under normothermic conditions.

In both studies, the authors interpret their results as positive with respect to neuroprotection, as they demonstrate that hypothermia can safely be used during surgical procedures that require prolonged cardiac arrest. This use of deep hypothermia to prevent neurological damage thus differs from the use of moderate hypothermia as an interventional treatment following cardiac arrest or ischaemic stroke.

**Experimental animal studies**

Most of the experimental studies focus on cerebral ischaemia – fully 37 of the 42 studies in rats (62–98) as well as all eight studies (99–106) in mouse, gerbil or baboon. Other studies looked at the protective effects of hypothermia after spinal cord injury, aortic surgery or subarachnoid haemorrhage (107–111). In all, 47 (62–64, 67–94, 98–104, 106–114) of the 55 experimental animal studies reported a neuroprotective effect of hypothermia.

Only four of the experimental animal studies were performed in models of cardiac arrest, two in rats (112, 113) and two in pigs (114, 115). Three of these supported the use of therapeutic hypothermia in cardiac arrest patients (112–114). One study indicated the importance of rapid cooling after restoration of spontaneous circulation (113). In this rat study, the neuroprotective efficacy of hypothermia declined rapidly. Cooling was not effective after four hours, indicating that the protective effect of hypothermia is dependent on the degree and duration of anoxic injury prior to treatment. The same effect was also seen in animal studies that used therapeutic hypothermia after cerebral ischaemia (66, 78, 93, 102, 103, 106).

**Physiological mechanisms**

A reduction in cerebral metabolism at low temperatures may explain why hypothermia can protect brain cells against ischaemia. It has been shown empirically that brain glucose turnover decreases by about 5% for every degree the temperature is reduced (116). Assuming a direct correlation between metabolism and neuroprotection, cooling to 33 °C, for example, should give a 20% reduction in damage. Laboratory experiments have shown that the neuroprotective effect may be even stronger (117, 118).

Neuroprotective effects of hypothermia can also be seen without a significant reduction in metabolism, suggesting that other factors are important too (33). Cooling can affect a number of the mechanisms that cause ischaemic brain injury (14, 118). The accumulation and release of excitotoxic amino acids such as glutamate are reduced, while effects on glutamate receptors can limit harmful calcium influx into cells. Hypothermia can inhibit inflammatory responses to ischaemia, such that formation of oxygen free radicals, reactive nitrogen compounds, cytokines and matrix metalloproteases, and proinflammatory mediators is greatly reduced (14, 119).

In the event of ischaemic brain injury, brain cells can either undergo necrotic cell death or apoptosis. Hypothermia can inhibit apoptosis through effects on both caspase-dependent and caspase-independent cellular mechanisms. Moreover, certain cold shock proteins can increase cell survival by inhibiting apoptosis specifically during cooling (118).

Ischaemic lesions can also damage the blood-brain barrier, creating a risk of cerebral oedema. Mild hypothermia protects against both blood-brain barrier damage and oedema. It is also likely that cooling inhibits activation of water channels in ischaemia, through reduced expression of aquaporin 4 (118). Another important point is that hypothermia reduces the hyperperfusion that normally follows ischaemia (120). Hyperperfusion can exacerbate brain damage by triggering oedema and by creating a risk of haemorrhage in the damaged tissue.

**Discussion**

The neuroprotective effects of cooling appear clear from experimental studies and cases of accidental hypothermia. Nevertheless, clinical data are still insufficient to permit an evidence-based evaluation of therapeutic hypothermia in some of the areas considered in this article. The use of deep hypothermia during aortic surgery does appear justified, however, as it allows longer interventions to be performed during circulatory arrest.

With respect to patients who remain comatose after cardiac arrest, both the time to initiation of cardiopulmonary resuscitation and time to effective hypothermia vary between studies. It therefore remains to be determined whether moderate hypothermia is more effective than simple avoidance of hyperthermia. Further randomised studies where therapeutic hypothermia is initiated soon after cardiac arrest are needed to clarify this point.

In ischaemic stroke, there is currently little evidence to support the use of therapeutic hypothermia. None of the controlled clinical trials showed a protective effect of hypothermia, and cooling increases the risk of complications such as cardiac arrhythmia and pneumonia. Moreover, the drugs used for intravenous thrombolytic treatment of ischaemic stroke are less effective at low temperatures.

Variation in control conditions makes it difficult to compare the neuroprotective effect of therapeutic hypothermia directly between studies. While few randomised studies have shown a neuroprotective effect of cooling, such an effect has been demonstrated in several reported cases of prolonged cardiac arrest after accidental hypothermia without significant neurological sequelae (7–9). This suggests a robust neuroprotective effect of lowering the body temperature before the heart stops.

Hypoxic normothermic cardiac arrest differs from cardiac arrest associated with accidental hypothermia in that cerebral metabolic requirements are not reduced prior to cardiac arrest. Around 40% of cardiac arrest patients treated with hypothermia are discharged from hospital without severe neurological sequelae (121). Pneumonia is the most common complication during such treatment, along with arrhythmias, metabolic disorders and epileptic seizures (122). Pharmaceutical treatment of these complications of hypothermia thus has the potential to increase survival in this patient group, but is challenging due to hypothermia-induced changes in the drugs’ pharmacological properties (123, 124).

For patients treated with hypothermia to limit brain damage after an ischaemic event, it appears necessary to initiate treatment as early as possible to allow them to gain maximal benefit from the neuroprotective mechanisms demonstrated in experimental animal studies. In the baboon, selective cooling of the brain to 25°C, initiated 2.5 hours after occlusion of the left internal carotid artery and anterior cerebral artery, reduced infarct size to 0.5% of the left hemisphere, compared with 35% in normothermic animals (99).

Such rapid cooling is distinct from what happens in randomised clinical trials. In one study, patients were recruited up to 12 hours after symptom onset (53). In the key study by Nielsen and co-workers, in which avoidance of hyperthermia was found to be as effective as hypothermia, it also took up to 12 hours for the target temperature of 33 °C to be reached in the hypothermia patients (5). Bernard and co-workers, who showed a neuroprotective effect of hypo-
thermia against anoxic brain damage, rapidly cooled patients to a core temperature of 33.5 °C within two hours of restoration of spontaneous circulation (45). Rapid cooling therefore seems to be very important to optimise the neuroprotective effect of therapeutical hypothermia.

Furthermore, 73% of patients in Nielsen and co-workers’ study received cardiopulmonary resuscitation by bystanders compared to only 49% of those in Bernard and co-workers’ study, which may have contributed to a shorter anoxic period in the first group of patients. It is therefore possible that patients in Bernard and co-workers’ study were at greater risk of brain injury and so benefitted more from neuroprotective treatment than those studied by Nielsen et al. (5).

The beneficial effect of selective cerebral cooling in the baboon must also be considered in light of the fact that the animals were cooled to 25 °C, compared to the 32—34 °C typical in clinical trials. This may have helped to reduce infarct size by reducing metabolism further (116). However, a study published after we conducted our literature search failed to confirm the efficacy of rapid therapeutic hypothermia following cardiac arrest (125). The results of this study are admittedly subject to debate with respect to whether cardiopulmonary resuscitation was started early enough and whether the patients might therefore have been too severely injured to benefit from any neuroprotective effect of hypothermia (126).

It is still not clear whether therapeutic hypothermia only delays cell damage or whether it can have longer-lasting effects. A number of plastic changes occur in the brain after ischaemic injury, including regeneration of brain cells and extensive synaptic remodelling. In a study that examined post-ischaemic healing and cellular regeneration in the hippocampus, the largest number of newborn neurons were found in rats that had undergone prolonged therapeutic hypothermia (118). Reduced apoptosis may result in increased survival of newborn neurons and/or hypothermia may stimulate neurogenesis.

Gliogenesis also seems to increase after therapeutic hypothermia, as does angiogenesis (118). Whether the latter is an advantage or a disadvantage is unclear. Nevertheless, it appears that, on the whole, cooling has beneficial long-term effects on the repair process (118).

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**References**


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Ohta H, Terao Y, Shinlani Y et al. Therapeutic time window for local hypothermia is wider than the gene expression associated with the neuroprotection in rat focal cerebral ischemia. Neurol Res 2011; 33: 107–12.


Lagina AT, Deogracias M, Reed K et al. The expression of HSP70 in cerebral ischemia and neuroprotective action of hypothermia and ketoprofen. Arq Neuropsiquiatr 2010; 68: 592–6.

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