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.

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MAIN MESSAGE

Therapeutic hypothermia is used to protect the brain after potentially damaging events and during surgery

It remains uncertain how best to implement therapeutic hypothermia to achieve neuroprotection after cardiac arrest and traumatic brain injury

Hypothermia permits prolonged aortic surgery to be performed without greater neurological sequelae than following brief procedures in normothermic patients

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 Præstø 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

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

First author	Diagnosis	Number	Temperature (°C)	Neuroprotection measure	Effect of hypothermia
Fakin (48)	Aortic dissection	60	32	P300 auditory evoked potentials	No difference
De Georgia (53)	Ischaemic stroke	40	33	Infarct size	No difference
Hemmen (54)	Ischaemic stroke	59	33	Modified Rankin scale, mortality	No difference
Nielsen (5)	Cardiac arrest	950	33	Mortality, Cerebral Performance Categories-scale	No difference
Castrén (44)	Cardiac arrest	200	34	Mortality, Cerebral Performance Categories-scale	No difference
Bernard (45)	Cardiac arrest	77	33	Mortality, disability	Positive
Hypothermia after Cardiac Arrest Study Group (24)	Cardiac arrest	275	32–34	Mortality, Cerebral Performance Categories-scale	Positive
Laurent (30)	Cardiac arrest	61	32	Mortality, Cerebral Performance Categories-scale	Positive
Hachimi-Idrissi (22)	Cardiac arrest	30	34	Mortality	No difference
Maekawa (6)	Traumatic brain injury	300	32–34	Glasgow Coma Scale, mortality	No difference

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

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 therapeutic hypothermia.

Furthermore, 73 % of patients in Nielsen and co-workers' study received cardiopulmonary resuscitation from 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 also 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 numbers of newborn neurons were found in rats that had undergone prolonged therapeutic hypothermia (94). 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

1. Remba SJ, Varon J, Rivera A et al. Dominique-Jean Larrey: the effects of therapeutic hypothermia and the first ambulance. Resuscitation 2010; 81: 268–71.
2. Williams GR, Spencer FC. The clinical use of hypothermia following cardiac arrest. Ann Surg 1958; 148: 462–8.
3. Karnatovskaia LV, Wartenberg KE, Freeman WD. Therapeutic hypothermia for neuroprotection: history, mechanisms, risks, and clinical applications. Neurohospitalist 2014; 4: 153–63.
4. Khaladj N, Shrestha M, Meck S et al. Hypothermic circulatory arrest with selective antegrade cerebral perfusion in ascending aortic and aortic arch surgery: a risk factor analysis for adverse outcome in 501 patients. J Thorac Cardiovasc Surg 2008; 135: 908–14.
5. Nielsen N, Wetterslev J, Cronberg T et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013; 369: 2197–206.
6. Maekawa T, Yamashita S, Nagao S et al. Prolonged mild therapeutic hypothermia versus fever control with tight hemodynamic monitoring and slow rewarming in patients with severe traumatic brain injury: a randomized controlled trial. J Neurotrauma 2015; 32: 422–9.
7. Gilbert M, Busund R, Skagseth A et al. Resuscitation from accidental hypothermia of 13.7 degrees C with circulatory arrest. Lancet 2000; 355: 375–6.
8. Mark E, Jacobsen O, Kjerstad A et al. Hypothermic cardiac arrest far away from the center providing rewarming with extracorporeal circulation. Int J Emerg Med 2012; 5: 7.
9. Wanscher M, Agersnap L, Ravn J et al. Outcome of accidental hypothermia with or without circulatory arrest: experience from the Danish Præstø Fjord boating accident. Resuscitation 2012; 83: 1078–84.
10. Thoresen M. Who should we cool after perinatal asphyxia? Semin Fetal Neonatal Med 2015; 20: 66–71.
11. Groysman LI, Emanuel BA, Kim-Tenser MA et al. Therapeutic hypothermia in acute ischemic stroke. Neurosurg Focus 2011; 30: E17.
12. Little NE, Feldman EL. Therapeutic hypothermia after cardiac arrest without return of consciousness: skating on thin ice. JAMA Neurol 2014; 71: 823–4.
13. Gutsche JT, Ghadimi K, Patel PA et al. New frontiers in aortic therapy: focus on deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 2014; 28: 1171–5.
14. Wu T-C, Grotta JC. Hypothermia for acute ischaemic stroke. Lancet Neurol 2013; 12: 275–84.
15. Sunde K, Søreide E. Therapeutic hypothermia after cardiac arrest: where are we now? Curr Opin Crit Care 2011; 17: 247–53.
16. Garrett JS, Studnek JR, Blackwell T et al. The association between intra-arrest therapeutic hypothermia and return of spontaneous circulation among individuals experiencing out of hospital cardiac arrest. Resuscitation 2011; 82: 21–5.
17. Aguila A, Funderburk M, Guler A et al. Clinical predictors of survival in patients treated with therapeutic hypothermia following cardiac arrest. Resuscitation 2010; 81: 1621–6.
18. Batista LM, Lima FO, Januzzi JL Jr et al. Feasibility and safety of combined percutaneous coronary intervention and therapeutic hypothermia following cardiac arrest. Resuscitation 2010; 81: 398–403.
19. Bruel C, Parienti J-J, Marie W et al. Mild hypothermia during advanced life support: a preliminary study in out-of-hospital cardiac arrest. Crit Care 2008; 12: R31.
20. Buntaine AJ, Dangerfield C, Pulikottil T et al. Putting class IIb recommendations to the test: the influence of unwitnessed and Non-VT/VF arrests on resource consumption and outcomes in therapeutic hypothermia and targeted temperature management. Crit Pathw Cardiol 2014; 13: 78–81.
21. Grossestreuer AV, Abella BS, Leary M et al. Time to awakening and neurologic outcome in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation 2013; 84: 1741–6.
22. Hachimi-Idrissi S, Corne L, Ebinger G et al. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation 2001; 51: 275–81.
23. Hinchey PR, Myers JB, Lewis R et al. Improved out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia: the Wake County experience. Ann Emerg Med 2010; 56: 348–57.
24. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346: 549–56.
25. Ikeda K, Ikeda T, Taniuchi H et al. Comparison of whole-body cooling and selective head cooling on changes in urinary 8-hydroxy-2-deoxyguanosine levels in patients with global brain ischemia undergoing mild hypothermia therapy. Med Sci Monit 2012; 18: CR409–14.
26. Kagawa E, Inoue I, Kawagoe T et al. Who benefits most from mild therapeutic hypothermia in coronary intervention era? A retrospective and propensity-matched study. Crit Care 2010; 14: R155.
27. Karnatovskaia LV, Festic E, Freeman WD et al. Effect of therapeutic hypothermia on gas exchange and respiratory mechanics: a retrospective cohort study. Ther Hypothermia Temp Manag 2014; 4: 88–95.
28. Kim JJ, Yang HJ, Lim YS et al. Effectiveness of each target body temperature during therapeutic hypothermia after cardiac arrest. Am J Emerg Med 2011; 29: 148–54.
29. Kulstad CE, Holt SC, Abrahamsen AA et al. Therapeutic hypothermia protocol in a community emergency department. West J Emerg Med 2010; 11: 367–72.
30. Laurent I, Adrie C, Vinsonneau C et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol 2005; 46: 432–7.
31. Leary M, Grossestreuer AV, Iannacone S et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation 2013; 84: 1056–61.
32. Lick CJ, Aufderheide TP, Niskanen RA et al. Take Heart America: A comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. Crit Care Med 2011; 39: 26–33.
33. May TL, Seder DB, Fraser GL et al. Moderate-dose sedation and analgesia during targeted temperature management after cardiac arrest. Neurocrit Care 2015; 22: 105–11.
34. Mooney MR, Unger BT, Boland LL et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. Circulation 2011; 124: 206–14.
35. Okada K, Ohde S, Otani N et al. Prediction protocol for neurological outcome for survivors of out-of-hospital cardiac arrest treated with targeted temperature management. Resuscitation 2012; 83: 734–9.
36. Prior J, Lawhon-Triano M, Fedor D et al. Community-based application of mild therapeutic hypothermia for survivors of cardiac arrest. South Med J 2010; 103: 295–300.

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37. Storm C, Nee J, Krueger A et al. 2-year survival of patients undergoing mild hypothermia treatment after ventricular fibrillation cardiac arrest is significantly improved compared to historical controls. Scand J Trauma Resusc Emerg Med 2010; 18: 2.
38. Stub D, Hengel C, Chan W et al. Usefulness of cooling and coronary catheterization to improve survival in out-of-hospital cardiac arrest. Am J Cardiol 2011; 107: 522–7.
39. Sunde K, Pytte M, Jacobsen D et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007; 73: 29–39.
40. van der Wal G, Brinkman S, Bisschops LLA et al. Influence of mild therapeutic hypothermia after cardiac arrest on hospital mortality. Crit Care Med 2011; 39: 84–8.
41. Walters EL, Morawski K, Dorotta I et al. Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and hemodynamic optimization in comatose patients with return of spontaneous circulation after out-of-hospital cardiac arrest: a feasibility study. Shock 2011; 35: 360–6.
42. Nielsen N, Hovdenes J, Nilsson F et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009; 53: 926–34.
43. Leary M, Cinousis MJ, Mikkelsen ME et al. The association of body mass index with time to target temperature and outcomes following post-arrest targeted temperature management. Resuscitation 2014; 85: 244–7.
44. Castrén M, Nordberg P, Svensson L et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation 2010; 122: 729–36.
45. Bernard SA, Gray TW, Buist MD et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346: 557–63.
46. Chau KH, Friedman T, Tranquilli M et al. Deep hypothermic circulatory arrest effectively preserves neurocognitive function. Ann Thorac Surg 2013; 96: 1553–9.
47. Ceriana P, Barzaghi N, Locatelli A et al. Aortic arch surgery: retrospective analysis of outcome and neuroprotective strategies. J Cardiovasc Surg (Torino) 1998; 39: 337–42.
48. Fakin R, Zimpfer D, Sodeck GH et al. Influence of temperature management on neurocognitive function in biological aortic valve replacement. A prospective randomized trial. J Cardiovasc Surg (Torino) 2012; 53: 107–12.
49. Kouchoukos NT, Masetti P, Murphy SF. Hypothermic cardiopulmonary bypass and circulatory arrest in the management of extensive thoracic and thoracoabdominal aortic aneurysms. Semin Thorac Cardiovasc Surg 2003; 15: 333–9.
50. Patel HJ, Nguyen C, Diener AC et al. Open arch reconstruction in the endovascular era: analysis of 721 patients over 17 years. J Thorac Cardiovasc Surg 2011; 141: 1417–23.
51. Percy A, Widman S, Rizzo JA et al. Deep hypothermic circulatory arrest in patients with high cognitive needs: full preservation of cognitive abilities. Ann Thorac Surg 2009; 87: 117–23.
52. Nathan HJ, Munson J, Wells G et al. The management of temperature during cardiopulmonary bypass: effect on neuropsychological outcome. J Card Surg 1995; 10 (suppl): 481–7.
53. De Georgia MA, Krieger DW, Abou-Chebl A et al. Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. Neurology 2004; 63: 312–7.
54. Hemmen TM, Raman R, Guluma KZ et al. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. Stroke 2010; 41: 2265–70.
55. Hong JM, Lee JS, Song H-J et al. Therapeutic hypothermia after recanalization in patients with acute ischemic stroke. Stroke 2014; 45: 134–40.
56. Krieger DW, De Georgia MA, Abou-Chebl A et al. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke 2001; 32: 1847–54.
57. Muroi C, Frei K, El Beltagy M et al. Combined therapeutic hypothermia and barbiturate coma reduces interleukin-6 in the cerebrospinal fluid after aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol 2008; 20: 193–8.
58. Karnatovskaia LV, Lee AS, Festic E et al. Effect of prolonged therapeutic hypothermia on intracranial pressure, organ function, and hospital outcomes among patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care 2014; 21: 451–61.
59. Mahaney KB, Todd MM, Bayman EO et al. Acute postoperative neurological deterioration associated with surgery for ruptured intracranial aneurysm: incidence, predictors, and outcomes. J Neurosurg 2012; 116: 1267–78.
60. Mack WJ, Ducruet AF, Angevine PD et al. Deep hypothermic circulatory arrest for complex cerebral aneurysms: lessons learned. Neurosurgery 2008; 62 (suppl 3): 1311–23.
61. Peberdy MA, Callaway CW, Neumar RW et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122 (suppl 3): S768–86.
62. Schmid-Elsaesser R, Hungerhuber E, Zausinger S et al. Combination drug therapy and mild hypothermia: a promising treatment strategy for reversible, focal cerebral ischemia. Stroke 1999; 30: 1891–9.
63. Oh JS, Kim SW, Cho HJ et al. Combination treatment with 17β-estradiol and therapeutic hypothermia for transient global cerebral ischemia in rats. Am J Emerg Med 2013; 31: 154–60.
64. Tirapelli DPDC, Carlotti CG Jr, Leite JP et al. Expression of HSP70 in cerebral ischemia and neuroprotetive action of hypothermia and ketoprofen. Arq Neuropsiquiatr 2010; 68: 592–6.
65. Wang CX, Yang T, Noor R et al. Delayed minocycline but not delayed mild hypothermia protects against embolic stroke. BMC Neurol 2002; 2: 2.
66. Dezena RA, Colli BO, Carlotti Junior CG et al. Pre, intra and post-ischemic hypothermic neuroprotection in temporary focal cerebral ischemia in rats: morphometric analysis. Arq Neuropsiquiatr 2012; 70: 609–16.
67. Zhao H, Shimohata T, Wang JQ et al. Akt contributes to neuroprotection by hypothermia against cerebral ischemia in rats. J Neurosci 2005; 25: 9794–806.
68. Yanamoto H, Nagata I, Nakahara I et al. Combination of intraischemic and postischemic hypothermia provides potent and persistent neuroprotection against temporary focal ischemia in rats. Stroke 1999; 30: 2720–6, discussion 2726.
69. Zhao H, Wang JQ, Shimohata T et al. Conditions of protection by hypothermia and effects on apoptotic pathways in a rat model of permanent middle cerebral artery occlusion. J Neurosurg 2007; 107: 636–41.
70. Berger C, Xia F, Köhrmann M et al. Hypothermia in acute stroke – slow versus fast rewarming. An experimental study in rats. Exp Neurol 2007; 204: 131–7.
71. Ding Y, Li J, Luan X et al. Local saline infusion into ischemic territory induces regional brain cooling and neuroprotection in rats with transient middle cerebral artery occlusion. Neurosurgery 2004; 54: 956–64.
72. Li J, Luan X, Lai Q et al. Long-term neuroprotection induced by regional brain cooling with saline infusion into ischemic territory in rats: a behavioral analysis. Neurol Res 2004; 26: 677–83.
73. Ji X, Luo Y, Ling F et al. Mild hypothermia diminishes oxidative DNA damage and pro-death signaling events after cerebral ischemia: a mechanism for neuroprotection. Front Biosci 2007; 12: 1737–47.
74. Zausinger S, Westermaier T, Plesnila N et al. Neuroprotection in transient focal cerebral ischemia by combination drug therapy and mild hypothermia: comparison with customary therapeutic regimen. Stroke 2003; 34: 1526–32.
75. Horiguchi T, Shimizu K, Ogino M et al. Neuroprotection role of adenosine under hypothermia in the rat global ischemia involves inhibition of not dopamine release but delayed postischemic hypoperfusion. Brain Res 2002; 952: 222–31.
76. Westermaier T, Zausinger S, Baethmann A et al. No additional neuroprotection provided by barbiturate-induced burst suppression under mild hypothermic conditions in rats subjected to reversible focal ischemia. J Neurosurg 2000; 93: 835–44.
77. Ji Y, Hu Y, Wu Y et al. Therapeutic time window of hypothermia is broader than cerebral artery flushing in carotid saline infusion after transient focal ischemic stroke in rats. Neurol Res 2012; 34: 657–63.
78. Ohta H, Terao Y, Shintani Y et al. Therapeutic time window of post-ischemic mild hypothermia and the gene expression associated with the neuroprotection in rat focal cerebral ischemia. Neurosci Res 2007; 57: 424–33.
79. Lee S-H, Kim Y-H, Kim Y-J et al. Atorvastatin enhances hypothermia-induced neuroprotection after stroke. J Neurol Sci 2008; 275: 64–8.
80. Barone FC, Feuerstein GZ, White RF. Brain cooling during transient focal ischemia provides complete neuroprotection. Neurosci Biobehav Rev 1997; 21: 31–44.
81. Huh PW, Belayev L, Zhao W et al. Comparative neuroprotective efficacy of prolonged moderate intraischemic and postischemic hypothermia in focal cerebral ischemia. J Neurosurg 2000; 92: 91–9.
82. Wang F, Luo Y, Ling F et al. Comparison of neuroprotective effects in ischemic rats with different hypothermia procedures. Neurol Res 2010; 32: 378–83.
83. Maier CM, Sun GH, Kunis D et al. Delayed induction and long-term effects of mild hypothermia in a focal model of transient cerebral ischemia: neurological outcome and infarct size. J Neurosurg 2001; 94: 90–6.
84. Wei G, Hartings JA, Yang X et al. Extraluminal cooling of bilateral common carotid arteries as a method to achieve selective brain cooling for neuroprotection. J Neurotrauma 2008; 25: 549–59.
85. Song W, Wu Y-M, Ji Z et al. Intra-carotid cold magnesium sulfate infusion induces selective cerebral hypothermia and neuroprotection in rats with transient middle cerebral artery occlusion. Neurol Sci 2013; 34: 479–86.
86. Inamasu J, Suga S, Sato S et al. Intra-ischemic hypothermia attenuates intercellular adhesion molecule-1 (ICAM-1) and migration of neutrophil. Neurol Res 2001; 23: 105–11.
87. Ceulemans A-G, Zgavc T, Kooijman R et al. Mild hypothermia causes differential, time-dependent changes in cytokine expression and gliosis following endothelin-1-induced transient focal cerebral ischemia. J Neuroinflammation 2011; 8: 60.
88. Zausinger S, Hungerhuber E, Baethmann A et al. Neurological impairment in rats after transient middle cerebral artery occlusion: a comparative study under various treatment paradigms. Brain Res 2000; 863: 94–105.
89. Maier CM, Ahern K, Cheng ML et al. Optimal depth and duration of mild hypothermia in a focal model of transient cerebral ischemia: effects on neurologic outcome, infarct size, apoptosis, and inflammation. Stroke 1998; 29: 2171–80.
90. Corbett D, Hamilton M, Colbourne F. Persistent neuroprotection with prolonged postischemic hypothermia in adult rats subjected to transient middle cerebral artery occlusion. Exp Neurol 2000; 163: 200–6.
91. Colbourne F, Corbett D, Zhao Z et al. Prolonged but delayed postischemic hypothermia: a long-term outcome study in the rat middle cerebral artery occlusion model. J Cereb Blood Flow Metab 2000; 20: 1702–8.
92. Lagina AT, Deogracias M, Reed K et al. The

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«Refrige-a-RAT-or»: an accurate, inexpensive, and clinically relevant small animal model of therapeutic hypothermia. Acad Emerg Med 2012; 19: 402–8.
93. Lee SM, Zhao H, Maier CM et al. The protective effect of early hypothermia on PTEN phosphorylation correlates with free radical inhibition in rat stroke. J Cereb Blood Flow Metab 2009; 29: 1589–600.
94. Silasi G, Colbourne F. Therapeutic hypothermia influences cell genesis and survival in the rat hippocampus following global ischemia. J Cereb Blood Flow Metab 2011; 31: 1725–35.
95. Lagina AT 3rd, Calo L, Deogracias M et al. Combination therapy with insulin-like growth factor-1 and hypothermia synergistically improves outcome after transient global brain ischemia in the rat. Acad Emerg Med 2013; 20: 344–51.
96. Theodorsson A, Holm L, Theodorsson E. Hypothermia-induced increase in galanin concentrations and ischemic neuroprotection in the rat brain. Neuropeptides 2008; 42: 79–87.
97. Ji Y-B, Wu Y-M, Ji Z et al. Interrupted intracarotid artery cold saline infusion as an alternative method for neuroprotection after ischemic stroke. Neurosurg Focus 2012; 33: E10.
98. Coimbra C, Drake M, Boris-Möller F et al. Long-lasting neuroprotective effect of postischemic hypothermia and treatment with an anti-inflammatory/antipyretic drug. Evidence for chronic encephalopathic processes following ischemia. Stroke 1996; 27: 1578–85.
99. Schwartz AE, Finck AD, Stone JG et al. Delayed selective cerebral hypothermia decreases infarct volume after reperfused stroke in baboons. J Neurosurg Anesthesiol 2011; 23: 124–30.
100. Cao Z, Balasubramanian A, Marrelli SP. Pharmacologically induced hypothermia via TRPV1 channel agonism provides neuroprotection following ischemic stroke when initiated 90 min after reperfusion. Am J Physiol Regul Integr Comp Physiol 2014; 306: R149–56.
101. Li J, Benashski S, McCullough LD. Post-stroke hypothermia provides neuroprotection through inhibition of AMP-activated protein kinase. J Neurotrauma 2011; 28: 1281–8.
102. Kawabori M, Hokari M, Zheng Z et al. Triggering Receptor Expressed on Myeloid Cells-2 Correlates to Hypothermic Neuroprotection in Ischemic Stroke. Ther Hypothermia Temp Manag 2013; 3: 189–98.
103. Colbourne F, Corbett D. Delayed and prolonged post-ischemic hypothermia is neuroprotective in the gerbil. Brain Res 1994; 654: 265–72.
104. De Bow SB, Colbourne F. Delayed transient ischemic attacks kill some CA1 neurons previously salvaged with postischemic hypothermia: neuroprotection undone. Brain Res 2003; 959: 50–7.
105. Corbett D, Larsen J, Langdon KD. Diazepam delays the death of hippocampal CA1 neurons following global ischemia. Exp Neurol 2008; 214: 309–14.
106. Corbett D, Nurse S, Colbourne F. Hypothermic neuroprotection. A global ischemia study using 18- to 20-month-old gerbils. Stroke 1997; 28: 2238–42, discussion 2243.
107. Ha K-Y, Kim Y-H. Neuroprotective effect of moderate epidural hypothermia after spinal cord injury in rats. Spine 2008; 33: 2059–65.
108. Ok J-H, Kim Y-H, Ha K-Y. Neuroprotective effects of hypothermia after spinal cord injury in rats: comparative study between epidural hypothermia and systemic hypothermia. Spine 2012; 37: E1551–9.
109. Török E, Klopotowski M, Trabold R et al. Mild hypothermia (33 degrees C) reduces intracranial hypertension and improves functional outcome after subarachnoid hemorrhage in rats. Neurosurgery 2009; 65: 352–9, discussion 359.
110. Wang LM, Yan Y, Zou LJ et al. Moderate hypothermia prevents neural cell apoptosis following spinal cord ischemia in rabbits. Cell Res 2005; 15: 387–93.
111. Maeda T, Mori K, Shiraishi Y et al. Selective occlusion of lumbar arteries as a spinal cord ischemia model in rabbits. Jpn J Physiol 2003; 53: 9–15.
112. Shin H-C, Tong S, Yamashita S et al. Quantitative EEG assessment of brain injury and hypothermic neuroprotection after cardiac arrest. Conf Proc IEEE Eng Med Biol Soc 2006; 1: 6229–32.
113. Che D, Li L, Kopil CM et al. Impact of therapeutic hypothermia onset and duration on survival, neurologic function, and neurodegeneration after cardiac arrest. Crit Care Med 2011; 39: 1423–30.
114. Gong P, Hua R, Zhang Y et al. Hypothermia-induced neuroprotection is associated with reduced mitochondrial membrane permeability in a swine model of cardiac arrest. J Cereb Blood Flow Metab 2013; 33: 928–34.
115. Tang Z-X, Chen G-X, Liang M-Y et al. Selective antegrade cerebral perfusion attenuating the TLR4/NF-κB pathway during deep hypothermia circulatory arrest in a pig model. Cardiology 2014; 128: 243–50.
116. Laptook AR, Corbett RJT, Sterett R et al. Quantitative relationship between brain temperature and energy utilization rate measured in vivo using 31P and 1H magnetic resonance spectroscopy. Pediatr Res 1995; 38: 919–25.
117. Urrea C, Danton GH, Bramlett HM et al. The beneficial effect of mild hypothermia in a rat model of repeated thromboembolic insults. Acta Neuropathol 2004; 107: 413–20.
118. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci 2012; 13: 267–78.
119. Ceulemans A-G, Zgavc T, Kooijman R et al. The dual role of the neuroinflammatory response after ischemic stroke: modulatory effects of hypothermia. J Neuroinflammation 2010; 7: 74.
120. Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in Mammalian central nervous system. J Cereb Blood Flow Metab 2003; 23: 513–30.
121. Dankiewicz J, Schmidbauer S, Nielsen N et al. Safety, feasibility, and outcomes of induced hypothermia therapy following in-hospital cardiac arrest-evaluation of a large prospective registry. Crit Care Med 2014; 42: 2537–45.
122. Nielsen N, Sunde K, Hovdenes J et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2011; 39: 57–64.
123. Tveita T. Pharmacodynamics in hypothermia. Update on therapeutic temperature management. Critical Care 2012; 6 (suppl 2): A6. http://ccforum.com/supplements/16/S2 (3.8.2015).
124. Pedersen TF, Thorbjørnsen ML, Klepstad P et al. Terapeutisk hypotermi – farmakologi og patofysiologi. Tidsskr Nor Lægeforen 2007; 127: 163–6.
125. Debaty G, Maignan M, Savary D et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. Intensive Care Med 2014; 40: 1832–42.
126. Cariou A, Sunde K. Cold fluids during cardiac arrest: faster cooling but not better outcome! Intensive Care Med 2014; 40: 1963–5.

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