Induced hypothermia and fever control for prevention and treatment of neurological injuries

Kees H Polderman

Increasing evidence suggests that induction of mild hypothermia (32–35°C) in the first hours after an ischaemic event can prevent or mitigate permanent injuries. This effect has been shown most clearly for postanoxic brain injury, but could also apply to other organs such as the heart and kidneys. Hypothermia has also been used as a treatment for traumatic brain injury, stroke, hepatic encephalopathy, myocardial infarction, and other indications. Hypothermia is a highly promising treatment in neurocritical care; thus, physicians caring for patients with neurological injuries, both in and outside the intensive care unit, are likely to be confronted with questions about temperature management more frequently. This Review discusses the available evidence for use of controlled hypothermia, and also deals with fever control. Besides discussing the evidence, the aim is to provide information to help guide treatments more effectively with regard to timing, depth, duration, and effective management of side-effects. In particular, the rate of rewarming seems to be an important factor in establishing successful use of hypothermia in the treatment of neurological injuries.

Lancet 2008; 371: 1955–69

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Introduction

From the 1940s onwards, various case reports and series, and uncontrolled studies have reported possible benefits of induced hypothermia on neurological outcome after cardiac arrest and traumatic brain injury (TBI).[1–3] However, these trials were severely hampered by the side-effects of hypothermia, which were difficult to manage because intensive care units (ICUs) were not yet available, and patients were treated in general wards without ventilatory or circulatory support. Additionally, physicians (erroneously) believed that body temperature needed to be lowered as much as possible to achieve benefits, because protective effects were presumed to be caused solely by decreases in brain metabolism and oxygen demand. The combination of severe side-effects and mixed study results prevented large-scale uptake of hypothermia as a medical method, although its use continued in the perioperative setting.

In the mid-1980s and early 1990s, animal studies provided a fresh impetus for clinical use of hypothermia and provided important insights into the mechanisms underlying hypothermia's protective effects (table 1).[4–6] Vitally, deep hypothermia (below 30°C) was clearly not needed to achieve benefits; protective effects could be achieved with mild-to-moderate hypothermia (32–35°C), with far fewer side-effects. Additionally, the advent of ICU and high-care facilities have made it possible to deal with side-effects more effectively, leading to a renewed interest in the clinical use of hypothermia.

Neurological injuries are an important cause of mortality and morbidity. TBI is a common cause of death and neurological disabilities in young people. The financial burden of these injuries is enormous, because of life-years lost, expensive rehabilitation, and often permanent disabilities.[8] Subarachnoidal haemorrhage and ischaemic stroke also frequently result in severe disabilities or death. The situation is worse for postanoxic encephalopathy after cardiac arrest, with mortality ranging from 65% to 95% for out-of-hospital cardiac arrest and from 40% to 50% for in-hospital witnessed arrests outside the ICU.[9–11] Even patients who survive can have permanent neurological injuries; only 10–20% are discharged alive without substantial neurological impairment.[10,12]

Over the past 15 years, hypothermia has been tested for many neurological emergencies (table 2). Some studies have provided clear evidence for protective effects; others have yielded mixed or conflicting results. Available evidence suggests that hypothermia will be more effective if it is applied soon after an injury, implying that, in the future, treatments would begin in the ambulance or emergency room. Moreover, increasing evidence suggests that fever (irrespective of its cause) can directly and adversely affect neurological outcome in various types of neurological injury. Therefore, symptomatic treatment of fever (cooling to normothermia or induction of mild hypothermia) could be used outside the ICU in high dependency units and in general wards. Further, some

Search strategy and selection criteria

An electronic search of Medline, EmBase, Current Contents, the Cochrane library, and a registry of ongoing clinical trials (www.clinicaltrials.gov) was done. The search was not restricted by language or type of publication. Corresponding authors of identified studies were contacted for additional information. The search terms used included "hypothermia" or "cooling" in various combinations with "cardiopulmonary resuscitation", "cardiac arrest", "cranio-cerebral trauma", "traumatic brain injury", "severe head injury", "ischemic stroke", "subarachnoid hemorrhage", "liver failure", "intra-cranial pressure", "myocardial injury", "heart attack", "bleeding", "side effects", "arrhythmias", and others. The author also used data from a personal archive with more than 1000 papers on the subject of hypothermia and fever management, including numerous studies published before 1966.

	Explanation	Time frame after injury
Prevention of apoptosis*	Ischaemia can induce apoptosis and calpain-mediated proteolysis. Hypothermia can prevent or reduce this process	Hours to many days or even weeks
Reduced mitochondrial dysfunction, improved energy homoeostasis†	Mitochondrial dysfunction is a frequent occurrence in the hours to days after an episode of ischaemia, and might be linked to apoptosis Hypothermia reduces metabolic demands and might improve mitochondrial function	Hours to days
Reduction of excessive free radical production†	Production of free radicals such as superoxide, peroxynitrite, hydrogen peroxide, and hydroxyl radicals is typical in ischaemia Mild-to-moderate hypothermia (30–35°) is able to reduce this event	Hours to days
Mitigation of reperfusion injury†	Cascade of reactions following reperfusion, partly mediated by free radicals but with distinctive and a range of features Suppressed by hypothermia	Hours to days
Reduced permeability of the blood–brain barrier and the vascular wall; reduced oedema formation*	Blood–brain barrier disruptions induced by trauma or ischaemia are moderated by hypothermia. The same effect occurs with vascular permeability and capillary leakage	Hours to days
Reduced permeability of cellular membranes (including membranes of the cell nucleus)†	Decreased leakage of cellular membranes, with associated improvements in cell function and cellular homoeostasis, including decrease of intracellular acidosis and mitigation of DNA injury	Hours to days
Improved ion homoeostasis†	Ischaemia induces accumulation of excitatory neurotransmitters such as glutamate and prolonged excessive influx of Ca^{2+} into the cell. This activates numerous enzyme systems (kinases) and induces a state of permanent hyperexcitability (exitotoxic cascade), which can be moderated by hypothermia	First minutes to 72 h
Reduction of metabolism*	Cellular oxygen and glucose requirements decrease by an average of 5–8% per degree Celsius decrease in temperature	Hours to days
Depression of the immune response and various potentially harmful proinflammatory reactions*	Sustained destructive inflammatory reactions and secretion of proinflammatory cytokines after ischaemia can be blocked or mitigated by hypothermia	First hour to 5 days
Reduction in cerebral thermopooling*	Some areas in the brain have significantly higher temperatures than the surrounding areas and measured core temperature. These differences can increase dramatically during injury, with up to 2–3°C higher temperatures in injured areas of the brain. Hyperthermia can increase the damage to injured brain cells; this is mitigated by hypothermia	Minutes to many days
Anticoagulant effects*	Microthrombus formation might add to brain injury after CPR. Anticoagulant effects of hypothermia might protect against thrombus formation. Thrombolytic therapy has been shown to improve outcome after CPR[7]	Minutes to days
Suppression of epileptic activity and seizures*	Many patients experience seizures after ischaemic episodes or trauma, or both, which might add to injury. Hypothermia has been shown to mitigate epileptic activity	Hours to days

On the basis of observations in animal studies, with some support from clinical observations (eg, reduction in inflammatory response and pro-inflammatory cytokine levels associated with hypothermia after traumatic brain injury and CPR; decrease in excitatory transmitters measured using microdialysis probes in human beings; decrease in local brain hyperthermia). CPR=cardiopulmonary resuscitation. *Some supporting clinical evidence. †Animal studies only.

***Table 1*: Possible mechanisms underlying protective effects of hypothermia**

evidence suggests that hypothermia can also prevent myocardial injury.[127,129,131,132] This Review discusses the evidence for symptomatic fever management (reduction of core temperature to 36·0–37·5°C) and for induction of mild hypothermia (lowering core temperature to 32·0–35·9°C) for several clinical conditions. Underlying mechanisms, practical aspects, and side-effects are also discussed briefly.

Pathophysiology

A complex cascade of processes ensues at the cellular level after a period of ischaemia (table 1) beginning from minutes to hours after injury and continuing for up to 72 h or longer.[4–6,140–143] These processes are temperature dependent—ie, strikingly increased by fever and inhibited by mild hypothermia. This chain of events is called secondary injury in patients with TBI and reperfusion injury or post-resuscitation disease in those with restored circulation after cardiopulmonary resuscitation.[4,8,142] A patient might develop additional injury in the hours and days after admission, which is triggered by new episodes of ischaemia, transient increases in intracranial pressure, or other mechanisms.

Neurological outcome is established to a substantial degree by mechanisms during the post-injury period. These mechanisms are more complex for TBI than for global ischaemic injury; however, ischaemia has a key role in all forms of brain injury and preventing ischaemic injury is central to all neuroprotective strategies. Interestingly, hypothermia affects all destructive mechanisms, instead of just one or two as was the case for previously studied potentially neuroprotective treatments.[4,140,141,143,144]

Theoretically, there exists a window of opportunity of several hours to perhaps even days during which injury can be mitigated by treatments such as hypothermia. Since the mechanisms shown in table 1 can be retriggered by new ischaemic episodes, rises in intracranial pressure,

	Effective	Level of evidence*	Evidence for efficacy or lack of efficacy of hypothermia
Cardiopulmonary resuscitation in patients with witnessed arrests and ROSC within 60 min			
Initial rhythm VT or VF	Yes	I	Two RCTs,[14,15] one additional RCT underpowered to reach statistical significance,[13] much supporting evidence[14–28]
Initial rhythm asystole or PEA	Probably	III	Data from several non-randomised trials, many animal studies[4–6,13,22]
Cardiopulmonary resuscitation in unwitnessed arrests	Unknown	IV	Animal studies and case reports only
Postanoxic encephalopathy in neonates	Yes	I	Three RCTs,[29–31] eight non-RCTs,[32–39] much supporting evidence
Traumatic brain injury in patients with intracranial hypertension (ICP ≥20 mm Hg), early cooling	Probably	Conflicting evidence	Many single-centre controlled trials and two meta-analyses with positive results.[40–57] One multicentre study with negative result,[58] three meta-analyses with non-significant trend for favourable effect[59–61]
Prevention of fever in patients with neurological injury	Probably	IIb	Many large observational studies;[62–75] some small intervention studies;[76,77] persuasive data from animal experiments[4–6,78–80]
Stroke (middle cerebral artery infarction)	Possibly	III	Seven small uncontrolled studies, basically initiated outside the treatment window but with some positive results[81–87]
Subarachnoid haemorrhage	Unknown	IV	Three case series[88–90]
Intraoperative hypothermia			
Intracerebral aneurysm surgery	No	IIa	Perioperative hypothermia with immediate postoperative rewarming did not significantly improve outcome in a large controlled study[91]
Thoracoabdominal aortic aneurysm repair (brain and spinal cord protection)	Probably	III	One small controlled study,[92] three uncontrolled studies,[93–95] persuasive data from animal experiments[96–99]
Cardiac surgery	Unknown	III	Conflicting results of studies.[100–103] Rapid warming strategies used in some of these studies might have influenced the outcome, since rapid rewarming after cooling is linked to adverse outcome in animal studies;[104–108] moreover, rapid warming with extracorporeal circulation can lead to cerebral hyperthermia,[109] with potentially harmful consequences
Control of intracranial pressure in liver failure	Probably	III	Three case series[110–112]
Refractory cardiogenic shock following cardiac surgery	Probably	III	Five case series, some fairly large[113–117]
Improved oxygenation in ARDS	Possibly	III	Case–control study and case series[118,119]
Reducing intracranial pressure in patients with cerebral oedema (irrespective of the cause)	Yes	I	Numerous clinical trials.[40–53,58,82–87,110–112,120–126] However, reduced ICP does not necessarily equal improved outcome
Reducing size of myocardial infarction	Possibly	IV	Positive preliminary study and subgroup data,[127,128] persuasive animal studies[129–132]
Preventing contrast nephropathy	Possibly	IV	Study is in progress, some positive data from pilot study[133]
Other indications: grand mal seizures, cardiac arrest caused by non-coronary causes, carotid artery transsection, late spinal ischaemia after aortic surgery, acute disseminated encephalomyelitis	Unknown	IV	Case reports, animal data[134–139]

*Level of evidence I=strong, supported by two or more sufficiently large well-designed RCTs or meta-analysis, or both. Level IIa=supported by at least one well-designed RCT and supporting evidence (eg, from animal studies). Level IIb=supported by one well-designed randomised trial without evidence from other sources. Level III=supported by at least one non-randomised trial (cohort study, case–control study). Level IV=supported by animal data, case reports, expert opinion. ARDS=acute respiratory distress syndrome. ICP=intracranial pressure. PEA=pulseless electrical activity. ROSC=return of spontaneous circulation. RCT=randomised controlled trial. VF=ventricular fibrillation. VT=ventricular tachycardia.

***Table 2*: Potential indications for neuroprotective effects of induced hypothermia**

or by rapid rewarming, the treatment duration cannot be too short. Additionally, prevention and management of side-effects are important since positive effects can be easily lost if complications are improperly managed.

Potential indications for use of hypothermia

Cardiac arrest and cardiopulmonary resuscitation

In the late 1950s, moderate hypothermia (26–32°C) was first used in patients who remained comatose after a cardiac arrest.[2,3] However, side-effects were difficult to manage and despite a trend towards improved outcome, results were inconclusive. In the 1980s, positive results from animal studies rekindled the interest. Six small clinical trials were done between 1997 and 2001 (figure 1; for details, see webtable 1)[16–21] and reported improved 21 outcomes compared with historical controls. Subsequently, three randomised controlled trials (RCTs) were done (figure 2; webtable 2).[13–15] The first trial enrolled 33 patients and reported improved neurological outcome in patients treated with hypothermia, but the study was underpowered to achieve statistical significance (favourable outcome of 19% in hypothermia group *vs* 0% in controls; p=0·15).[13]

See **Online** for webtable 1

See **Online** for webtable 2

The results of two larger, multicentred trials were reported in 2002.[14,15] Bernard and associates[14] enrolled 77 patients in whom cooling was initiated very early during transportation in an ambulance to the hospital after cardiopulmonary resuscitation; target temperature

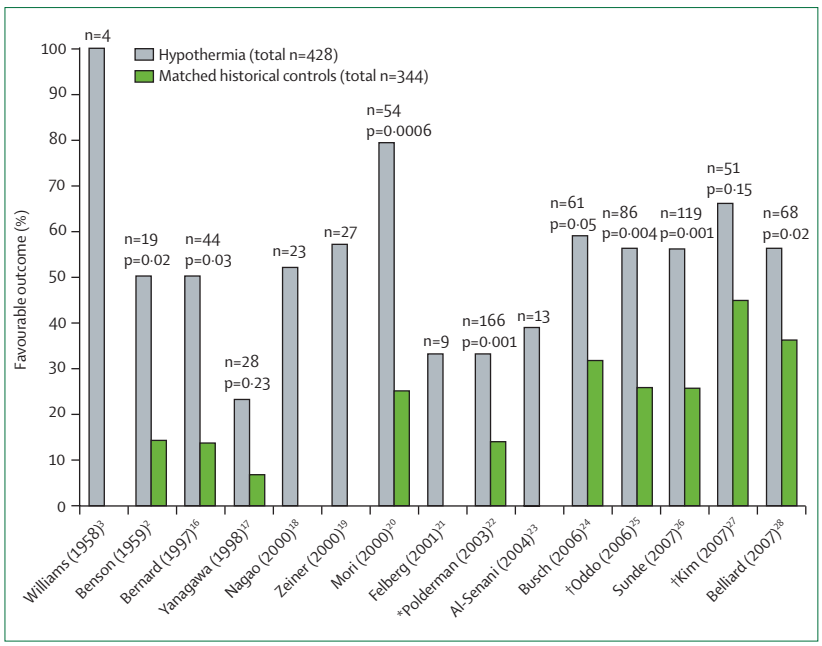

***Figure 1*: Hypothermia in cardiac arrest, non-randomised studies**
For full results of all studies and references see webtable 2. VF=ventricular fibrillation. VT=ventricular tachycardia. ns=not significant. *Patients with witnessed arrest and initial rhythm of asystole or pulseless electrical activity. †Studies enrolling several categories of patients, only patients with initial rhythm of VT/VF shown in graph.

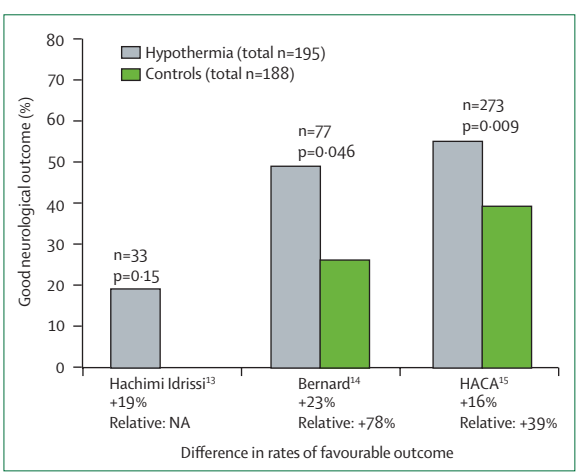

***Figure 2*: Randomised controlled trials assessing the effects of hypothermia in patients with witnessed cardiac arrest and an initial rhythm of ventricular fibrillation or ventricular tachycardia**
Absolute and relative differences (%) are shown at the bottom of the graph.

was 33°C for 12 h. The rate of favourable neurological outcome (no or moderate disability) was 49% (21/43 patients) in the hypothermia group versus 26% (29/34 patients) in controls (p=0·046). After adjusting for case mix, the odds ratio (OR) for good outcome was 5·25 (95% CI 1·47–18·76; p=0·011). More patients survived in the hypothermia group than in the control group, but this difference was not significant (21/43 *vs* 11/34; p=0·145).

The second, larger study was done in Europe and enrolled 273 patients.[15] Favourable neurological outcome was seen in 55% (75/136) of patients in the hypothermia group compared with 39% (54/137) of controls, with relative risk (RR) of 1·40 (95% CI 1·08–1·81). Mortality rates were 41% and 55% (RR 0·74, 95% CI 0·58–0·95) in the hypothermia group and in controls, respectively. In this study, cooling was initiated after a median time of 105 min and maintained for 24 h at 32–34°C. These results were achieved despite achieving target temperatures only after an average of 8 h after return of spontaneous circulation.

All the patients enrolled in these studies had by-stander witnessed cardiac arrests, with maximum intervals of 5–15 min from collapse to arrival of the ambulance and start of resuscitation. Additionally, the initial rhythm had to be ventricular fibrillation (VF) or ventricular tachycardia (VT), and the interval from collapse to return of spontaneous circulation could be no more than 60 min. Patients with persistent hypotension (mean arterial pressure <60 mm Hg[15] or systolic pressure <90 mm Hg[14]) or persistent hypoxia (oxygen saturation <85%) were excluded. Only about 10% of screened patients met these eligibility criteria. Thus, whether these findings apply to patients with other rhythms and especially to those with unwitnessed arrests need to be assessed. Some preliminary evidence suggests that hypothermia has protective effects in patients with witnessed arrests and asystole or pulseless electrical activity as the first recorded rhythm if they achieve return of spontaneous circulation.[13,22] Usually, these patients have a much poorer prognosis than do patients with VT or VF, because total absence of rhythm is associated with worse underlying causes and VT or VF is easier to reverse. However, in cases in whom return of spontaneous circulation is achieved, (on the basis of mechanisms underlying hypothermia's protective effects) efficacy could depend on the duration of oxygen deprivation and speed of reperfusion rather than the specific arrhythmia causing the disruption of brain perfusion.

Guidelines by the European Resuscitation Council and American Heart Association recommend the use of hypothermia after cardiac arrest if the initial rhythm is VT or VF, and to consider its use for other rhythms.[145] A meta-analysis concluded that the number needed to treat (NNT) to allow one additional patient meeting the study criteria to leave the hospital with good neurological recovery was 6, with a 95% CI of 4–14.[146] Subsequently, implementation studies in various settings (with matched historical controls) have provided additional support for the use of hypothermia to improve neurological outcome in clinical practice (figure 1).[23–28] Research questions for the future are whether very early cooling, or more extended cooling (eg, 72 h), or both can further improve outcome. Optimum target temperature also needs to be better defined. On the basis of available evidence, patients should be cooled to 32–34°C for 12–24 h, but this might change as more information becomes available.

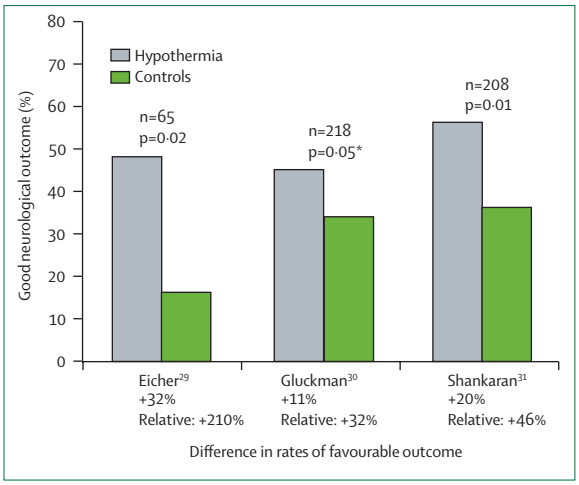

***Figure 3*: Randomised controlled trials assessing the effects of hypothermia in newborn children with perinatal asphyxia**
Absolute and relative differences (%) are shown at the bottom of the graph. *Large benefits in a predefined subgroup (p=0·009).

Perinatal asphyxia

The neuroprotective effects of hypothermia reported in studies in newborn animals are equal to or better than those in adult animals. In human beings, perinatal asphyxia is the occurrence of global anoxic injury to the brain in very young children. Eight small feasibility studies with 187 patients (118 cooled and 69 controls) assessed hypothermia as a treatment for neonatal asphyxia.[32–39] Most noted improvements in neurological outcome and none reported substantial adverse effects, but all were underpowered to reach significance. These data led to the initiation of several RCTs, three of which have been published (figure 3).[29–31] The inclusion criteria varied slightly, but all three studies enrolled newborn children with abnormal neurological signs and low Apgar scores, acidosis or low base deficit, or both, postnatal desaturation or bradycardia, or need for extended resuscitation. One study used electroencephalogram (EEG) abnormalities for a predefined subgroup analysis.[30]

The smallest trial was a multicentred pilot study with 65 infants of 35 weeks or more of gestation in seven centres.[29] 32 infants were cooled within 6 h of birth to a rectal temperature of 33°C for 48 h, whereas 33 were kept at normothermia. Neurodevelopmental assessment was done at 12 months. The number of patients with adverse outcome (death or severe motor disability) was significantly lower in the hypothermia group than in the control group (RR of death or severe neurological impairment 0·52 [95% CI 0·43–0·61] in hypothermia group *vs* 0·84 [95% CI 0·77–0·91] in control group; p=0·019).

The second study enrolled 234 infants in 25 centres; follow-up data at 18 months were available for 218 infants.[30] Patients were cooled to 34–35°C for 72 h within 5·5 h of their birth. The overall rate of adverse outcome (death or severe disability) was lower in cooled patients than in controls, although this difference was not significant (55% *vs* 66%, RR 0·61, 95% CI 0·34–1·09; p=0·1). After adjusting for initial severity of neurological injury (as shown by EEG changes), RR was 0·57 (95% CI 0·32–1·01; p=0·05). When the predefined subgroups were analysed, the effect in infants with less severe EEG changes—ie, less severely injured patients (n=172)—was much greater than in infants with greater severity of injury (adverse outcome 48% of hypothermia *vs* 66% of normothermia, RR 0·42, 95% CI 0·22–0·80; p=0·009; severe neuromotor disability 12% *vs* 28%; p=0.03).

The third study enrolled 208 patients with perinatal asphyxia in 15 centres in Europe and the USA. Infants were cooled to 33·5°C within 6 h of birth for 72 h.[31] The investigators reported significantly improved neurological outcome and reduced mortality in newborn infants treated with hypothermia (adverse outcome 44% *vs* 62%, RR 0·72, 95% CI 0·54–0·95; p=0·01; mortality 24% *vs* 37%, 0·68, 0·44–1·05; p=0·08). No increase in the rate of major disability in the survivors was noted (19% *vs* 30% for hypothermia *vs* controls, 0·68, 0·38–1·22; p=0·20).

These studies reported only minor side-effects, and benefits were seen in most participating centres. These studies showed an NNT of 6 to achieve one additional case with favourable outcome, which is similar to the number for cardiac arrests in adults.[146] Cooling was started fairly late in these trials (after 5–6 h), because of the need to acquire informed consent and various logistical issues. Benefits might increase if treatment can be initiated earlier, although this needs to be verified in future studies. The trials with lower target temperatures (33–33·5°C) reported greater benefits than the study with higher temperature (34–35°C), though the trial with higher temperature might have included more patients with very severe injuries. Three additional multicentred trials have been done in infants with neonatal asphyxia, which together have enrolled 830 infants. All three have stopped enrolment and are in the follow-up and evaluation phase; the results of these studies are expected in late 2008 or early 2009.

***Panel 1:* Mechanisms in secondary injury**

- Ischaemia and reperfusion (table 1)
- Local or generalised swelling of the brain, caused by a combination of postischaemic cytotoxic oedema, disruption of the blood–brain barrier, increased global brain perfusion (although injured areas can be hypoperfused), and obstruction of spinal fluid drainage. Brain oedema can lead to impaired venous drainage of and cerebral blood flow to injured areas, causing additional cerebral ischaemia and in extreme cases cerebral herniation and death
- Formation of local haematomas and contusion areas

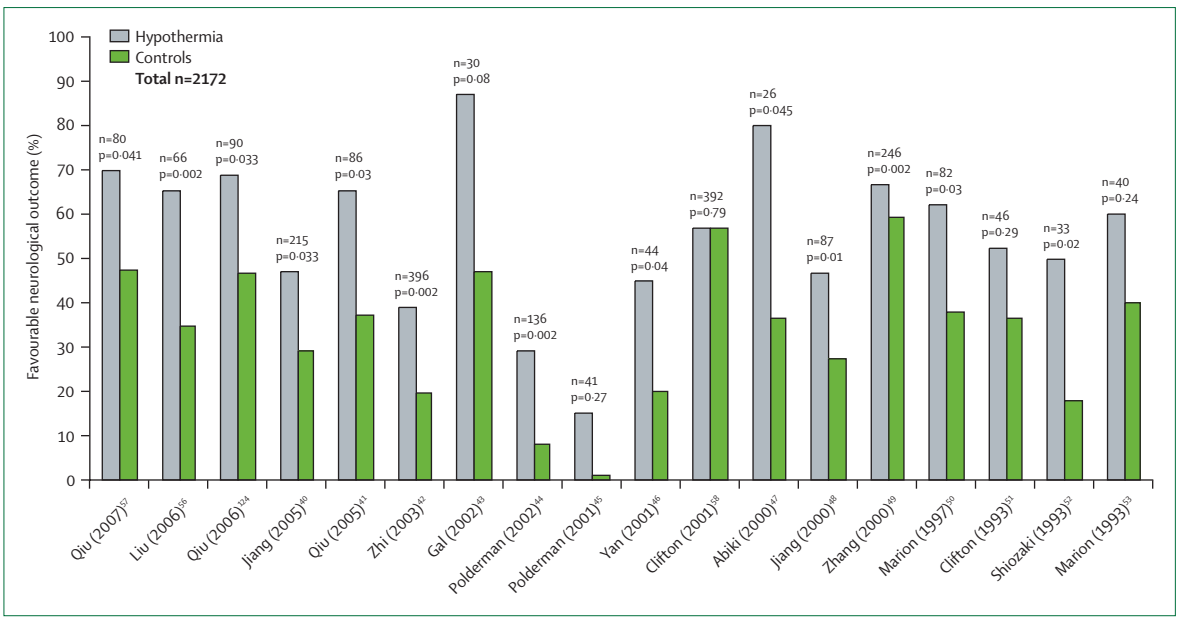

Figure 4: **Clinical trials assessing the effects of hypothermia on neurological outcome in patients with traumatic brain injury and intracranial hypertension**

Hypothermia should (at the very least) be strongly considered for newborn babies with perinatal asphyxia, especially those with mild-to-moderate injuries. Side-effects seem to be minor and an NNT of 6 is low. Target temperature should be 33–35°C, with some evidence suggesting that the lower range (33–33·5°C) is more effective; the duration should be 48–72 h. Research questions for the immediate future are similar to those in cardiac arrest, and concern optimum timing, duration, and target temperature.

Traumatic brain injury

TBI is a major source of death and severe disability worldwide. In the USA alone, this type of injury causes 290 000 hospital admissions and 51 000 deaths. 80 000 patients are left with permanent neurological disabilities.[8,137] Apart from the emotional effect, the financial burden of this is also enormous.

See Online for webtables 3–6

The final outcome is established to a substantial degree by secondary injury—ie, the destructive processes unfolding in the injured brain in the hours and days after initial trauma. These mechanisms can be divided into three components (panel 1). Traditionally, treatments in TBI focused on restoring and maintaining adequate brain perfusion, surgically evacuating large haematomas where necessary, and preventing or promptly treating oedema. Swelling of the brain can be monitored by measuring intracranial pressure, which is used to guide treatments and monitor success in most centres.

Many animal studies, in different species, have shown that hypothermia improves outcome after experimental induction of TBI, which has led to many clinical trials (figures 4 and 5).[60,61,120–124] Interpretation of these results is complicated, because different categories of patients were enrolled with differing types of injuries and widely diverging treatment protocols.[147] Most but not all have used high intracranial pressure as an inclusion criterion, while others used CT scan criteria. The duration of cooling varied from 24 h to more than 5 days, with some studies using intracranial pressure to guide depth (ie, temperature attained) and duration of treatment; rates of rewarming and responses to rebound intracranial hypertension also differed. Use of co-interventions, such as osmotic therapy, sedation, analgesia, paralysis, and targets for mean arterial pressure and cerebral perfusion pressure have also varied considerably. These factors are all important to establish outcome after TBI in general, and the potential efficacy of cooling in particular. Thus interpretation, comparison, and aggregation of results from these studies present complex challenges.

29 clinical studies have assessed the efficacy of hypothermia in TBI, with 27 in adult patients, of which 18 were controlled (webtables 3–6). Data from one pilot study was subsequently included in a larger trial, leaving 17 studies. Study protocols differed considerably, and not all studies were properly randomised. Two studies enrolled 131 patients with normal intracranial pressure. Only one reported outcome data (at 3 months); no significant differences were noted (good outcome in 21/45 [hypothermia] *vs* 27/46 patients [controls]; p=0·251).[148]

18 studies, with outcome data available for 2096 patients, used hypothermia in patients with high ICP that was refractory to conventional treatments (eg, sedation or analgesia, paralysis, osmotic therapy, and sometimes barbiturates) (figure 4; webtable 3).[40–53,56–58,124] All patients had decreased ICP during cooling. Of these 18 studies, four reported positive trends[43,45,51,53] and 13 reported significant improvements in outcome associated with

hypothermia treatment.[40–42,44,46–50,52,56,57,124] All of these were done in specialised neurotrauma centres, with experience in applying hypothermia and managing its side-effects. Ten were single centre studies[41,44,46,47,49,50,52,56,57,124] and three (all done in China)[40,42,48] were multicentre.

By contrast, one well designed multicentred RCT in 2001 did not show any effect on outcome in the overall patient group, although decreases in intracranial pressure were noted in the hypothermia group.[58] Benefits were seen only in a subgroup of patients: those in whom hypothermia was already present on admission and who were not rewarmed. Subsequent analysis showed that although this study was methodologically well designed, the way in which hypothermia was used had caused problems. This treatment was started fairly late and cooling was slow (average time to target temperature >8 h), and there were problems with hypotension, hypovolaemia, electrolytes, and hyperglycaemia.[147,149,150] Hypotensive episodes lasting for more than 2 h occurred three times more frequently in the hypothermia group than in the control group, with briefer episodes not being reported; bradycardia associated with hypotension took place four times more frequently.[58] Since even very brief episodes of hypotension or hypovolaemia can adversely affect outcome in TBI,[8,151–153] these and other problems might have greatly affected the results of this trial. These adverse events can occur as side-effects of cooling, but are quite easily preventable with proper intensive care, and thus should not be regarded as inevitable consequences of hypothermia treatment.[147,149]

Some of the participating centres had little or no previous experience of using hypothermia. The investigators subsequently reported substantial inter-centre variance in outcome between hospitals participating in their study, with apparently favourable results in large centres familiar with cooling being counterbalanced by negative results in smaller centres.[150] This experience does, however, underscore the potential difficulties of using hypothermia in TBI. Five meta-analyses dealing with this issue were reported between 2000 and 2007 (figure 5).[54,55,59–61] These analyses included varying number of clinical trials on the basis of differing assessments of the quality of randomisation and blinding procedures. All results noted a positive trend for hypothermia on neurological outcome, but was statistically significant in only two reviews (figure 5).[54,55] The study by Harris and co-workers[59] did not assess risk of death. All of these meta-analyses included studies done in patients with or without intracranial hypertension except for the analysis by the Brain Trauma Foundation.[55] Criteria for including studies in the respective meta-analyses differed slightly, partly explaining the differences in number of patients. Two meta-analyses[54,55] also assessed the effects of treatment duration and rate of rewarming, and observed that duration >48 h and slow rewarming were associated with improved outcome (data not shown but some details in webtable 6). All the meta-analyses found a reduced risk of unfavourable outcome and death associated with hypothermia treatment, but only two[54,55] were statistically significant.

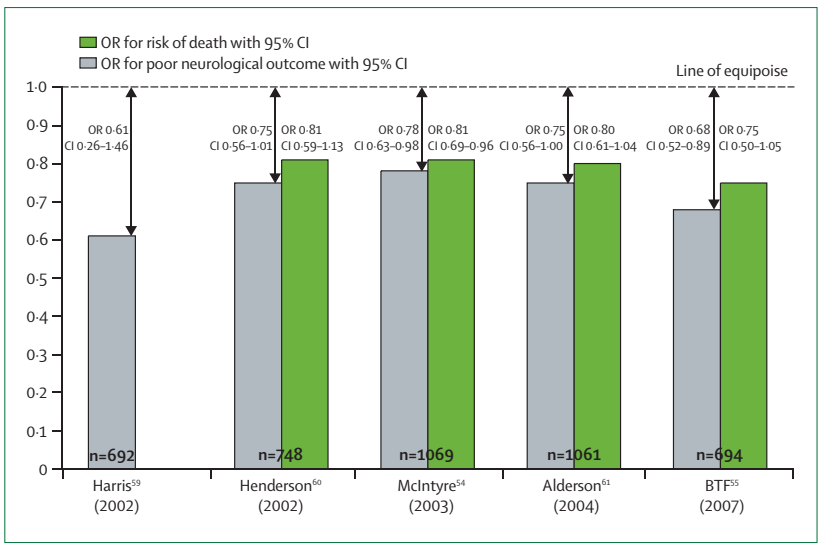

***Figure 5*: Meta-analyses looking at the effects of hypothermia on neurological outcome**
OR=odds ratio. BTF=Brain Trauma Foundation. Note: Mortality analysis was done in only 746 patients in Alderson (2004).

A problem with these analyses is that most did not take into account the differences in patient groups (eg, those with or without intracranial hypertension) and differences in treatment protocols, besides the use of hypothermia. Only one differentiated between studies enrolling patients with normal intracranial pressure and those with intracranial hypertension.[61] Only two assessed effects of treatment duration and speed of rewarming, concluding that cooling for 48 h or more and slow rewarming were both key factors in establishing the success of hypothermia treatment.[54,61] Thus, most evidence shows that cooling can be effective in patients with severe TBI and intracranial hypertension provided that treatment is initiated early, continued for long enough (2–5 days), and that patients are rewarmed slowly. One study that used hypothermia in patients with normal intracranial pressure did not find improvements in outcome associated with cooling.[148] Further studies will be needed to show whether better results might be achieved with lengthier (3–5 days) treatment; hence, routine clinical use cannot be recommended at present.

Hypothermia is clearly effective in controlling intracranial hypertension (class I evidence). However, lower intracranial pressure does not guarantee improved outcome, and positive effects on survival and neurological outcome have been achieved only in large referral centres with experience in hypothermia use, when treatment was applied within a few hours after an injury for more than 48 h in patients with raised intracranial pressure (class IIA evidence). Management of side-effects, such as hypotension or hypovolaemia, is of key importance. Rewarming should be done very slowly over a period of at least 24 h. TBI patients

with mild hypothermia (33–35°C) at admission, who are haemodynamically stable, should be allowed to remain in a hypothermic state (class IIA evidence). Although hypothermia can also be used to control intracranial pressure in the later stages after TBI, no evidence exists to show that neurological outcome is improved by such delayed application of hypothermia. This issue needs to be addressed in future studies. The most important research question for the immediate future is to definitively establish whether early and extended cooling (3–5 days, intracranial pressure guided) can improve neurological outcome.

Ischaemic stroke

Many animal studies have shown that mild hypothermia can significantly improve outcome in stroke models.[4–6,78,79,81,143,154–157] Some suggest that the available window of opportunity might be 1–2 h rather than the 2–6 h in global ischaemia and TBI,[154,155] but others have reported much longer time (up to 5 h) depending on the type of animal, whether full or only partial reperfusion was achieved, and other injury-related factors.[81,156,157] However, such data cannot be directly translated to the human brain, since its resilience to ischaemic injury and the role of secondary injury, which is amenable to therapeutic interventions, could be different.

The mechanism of injury in severe stroke differs from global anoxia: an extended period of ischaemia with necrosis occurs in the central area surrounded by a so-called penumbra zone, which is hypoperfused but not (yet) irreversibly damaged. In theory, this penumbra zone could be salvaged as long as it has not become necrotic. The salvageable zone could increase if reperfusion takes place—eg, after administration of clot-dissolving drugs.

Despite promising data from clinical trials in global anoxic injury and from the animal studies, no RCTs have assessed the use of hypothermia in ischaemic stroke. Seven small feasibility studies with 145 patients have used mild hypothermia in patients with ischaemic stroke.[82–84,86,87,158,159] Five of these were done in patients with middle cerebral artery infarction with brain oedema, a severe subtype of acute stroke.[82–84,86,87] In all cases, cooling was initiated many hours after admission to treat refractory intracranial hypertension. Use of hypothermia was noted to be feasible with limited and well controllable side-effects, although the incidence of non-fatal pneumonia was high in one study.[84] All investigators reported significant decreases in brain oedema and improved outcome compared with historical controls (mortality 38% *vs* 80% in the largest study).[84] Moreover, many deaths occurred during rewarming with rebound increases in ICP; a subsequent study showed that ICP increases were preventable when slow and controlled rewarming was done.[87]

However, none of these studies were properly controlled, and all had extended time intervals between onset of stroke and initiation of hypothermia (average 22 [9] h, range 4–75 h in the largest study with an additional 6·5 h before achieving target temperature).[84] Much of the injury is likely to have become permanent by that time. Only one study combined the use of hypothermia with thrombolysis,[86] which would seem to be a logical approach (ie, an attempt to restore blood flow combined with a treatment aimed at preventing reperfusion injury). This approach was found to be safe, but no firm conclusions can be drawn because of the small number of patients. Larger prospective studies to assess early hypothermia in severe and milder forms of ischaemic stroke are needed urgently. A clinical trial assessing efficacy of hypothermia to extend the therapeutic window of thrombolysis is underway.[160]

Hypothermia is mainly used in the ICU, which could present a logistical challenge since the cooling of stroke patients might require admission to intensive care and perhaps even mechanical ventilation. Although two small case series have suggested that induction of mild hypothermia in awake, non-ventilated patients could be feasible,[158,159] close monitoring and aggressive patient management remain vital to obtain good outcome; this might hamper future studies.

In summary, animal studies and some clinical data suggest that hypothermia could limit neurological injury in stroke, but insufficient evidence exists to recommend its use outside the context of clinical trials. Hypothermia can be used to control intracranial pressure in patients with severe middle cerebral artery infarction and cerebral oedema, and could improve their outcome (level III evidence).

Acute myocardial infarction

Mild hypothermia has been used in awake patients to reduce infarct size after acute myocardial infarction and coronary reperfusion. In these patients, the period of ischaemia before reperfusion is usually more extended than the period of cerebral ischaemia in patients with global brain anoxia after cardiac arrest. On the other hand, the occlusion might be incomplete with some perfusion remaining, and cardiac muscle might be more tolerant of ischaemia than brain tissue. Animal studies have shown promising results.[129–132]

Dixon and co-workers[127] did a small RCT in 42 patients with acute myocardial infarction who were undergoing emergency percutaneous transluminal coronary angioplasty (PTCA) intervention. 21 patients were cooled to 33°C for 3 h. Investigators noted a non-significant trend to smaller infarct sizes and lower risk of adverse cardiac events in the hypothermia group. This observation led to the initiation of two larger RCTs: COOL-MI (n=325 patients, target temperature 33°C for 3 h) and ICE-T (n=204 patients, target temperature 33°C for 6 h). Despite completion, results of the studies are yet to be reported. A problem in both the studies was the great difficulty in reaching target temperature quickly. The overall results were negative (infarct size as a percentage of total LV

function 14·1% *vs* 13·8%; p=0·86 in the COOL-MI study, and 10·2% *vs* 13·2%; p=0·14 in the ICE-T study for hypothermia patients *vs* controls, respectively).

Both studies reported apparent benefits in a subgroup of patients; those with anterior myocardial infarction in whom a core temperature less than 35°C was reached before reperfusion (COOL-MI infarct size 9·3% *vs* 18·2%; p=0·05 and ICE-T 12·9% *vs* 22·7%; p=0·09 for hypothermia patients *vs* controls, respectively). This observation led to a new RCT with plans to enrol 225 patients with anterior myocardial infarction, a two to one randomisation, and an attempt to reach a core temperature of less than 34°C before reperfusion, with more advanced cooling systems than available in previous studies.[128] However, this study has been halted because of funding difficulties, and its status is unclear.

In summary, no evidence shows that hypothermia is harmful to the injured heart, and rapid induction of hypothermia (before PTCA or reperfusion) might reduce infarct size in patients with anterior myocardial infarction. Another question is whether longer (12–24 h or more) application of hypothermia would have greater effects than the 3–6 h used in present studies. However, this would present substantial management difficulties in awake patients, so this question probably needs to be addressed in patients in intensive care who are sedated and mechanically ventilated.

Perioperative hypothermia

Hypothermia is often used to protect the brain, spinal cord, heart, or kidney during surgery to increase the time available for specific procedures. In cerebral aneurysm surgery, an additional goal is to prevent vasospasms. Since the timing of injury is known beforehand, hypothermia can be initiated before injury and, in theory, destructive processes could be prevented more easily. However, an important problem in this approach is that, after the surgery, patients are often very rapidly rewarmed. Persuasive evidence (albeit mostly from animal studies) leads us to believe that rapid rewarming can have harmful consequences.

Although initial studies showed promising results with intraoperative cooling in patients undergoing cerebral aneurysm surgery, a large prospective multicentre trial (Intraoperative Hypothermia for Aneurysm Surgery Trial [IHAST2]) did not confirm these findings.[91] Patients enrolled in the IHAST study were randomised to be cooled to 33°C just before aneurysm clipping and then rewarmed to 36·5°C immediately thereafter. Favourable outcome was seen in 329 (66%) of 499 hypothermia patients versus 314 (63%) controls (OR 1·14, 95% CI 0·88–1·48; p=0·32). Postoperative bacteraemia took place more frequently in the hypothermia group (5% *vs* 3%, p=0·05). In-depth neuropsychological evaluation done 3 months after surgery in 873 (93%) of surviving patients revealed higher composite neuropsychological scores (40·8 [10] *vs* 38·8 [11] points; p=0·003); fewer patients reported abnormalities in any of the five tests (68·2% *vs* 71·1%; p=0·023) in the hypothermia group than in controls.[161] Using the criteria of unimpaired, impaired, or dead for the composite score, 16·8% of hypothermia patients were classified as impaired versus 20·0% of controls (p=0·317).[162] Investigators also did a long-term follow-up in a smaller subgroup (n=163 patients) and noted no significant differences in composite scores at 9 months (46·3 [8·5] *vs* 45·4 [8·9] points) or at 15 months (46·3 [8·6] *vs* 47·1 [9·3]; p=ns).[163]

Although IHAST has been criticised for the very high rewarming rates in the intervention group (to allow blinding of the intensive care staff to the intervention), and for enrolling mostly patients at low risk of ischaemic injury in which high-risk patients could potentially have benefited more from hypothermia treatment, these results clearly suggest that the common practice of brief, intraoperative cooling after rapid rewarming has no or at best very minor effects on outcome in cerebral aneurysm surgery.

Hypothermia is frequently used to protect the spinal cord and prevent paraplegia during high aortic-cross surgery. Despite widespread use and general acceptance of hypothermia in this setting, few clinical data are available; only three studies with 123 patients have dealt with this issue. One case series (n=18 patients) reported favourable outcome compared with historical controls.[92] A small RCT in which the combined effects of intrathecal papaverine, spinal fluid drainage, and epidural hypothermia were compared with standard treatment reported spinal cord injury in two (12%) of 17 cooled patients versus seven (44%) of 16 controls (p=0·04).[93] Cambria and co-workers[94] reported a 3% rate of spinal cord injury in 61 patients treated with hypothermia (core temperature of 34°C plus continuous infusion of saline at 4°C into the epidural space), compared with 23% in 55 matched controls (p<0·001). In a follow-up study, these investigators noted injury in 27 of 150 (18%) patients undergoing high-risk thoracoabdominal aneurysm repair under hypothermia over a 10-year period compared with 44 of 152 (29%) in historical controls (p<0·01).[92] The results of these studies, coupled with positive data from animal studies,[96–99] make hypothermia a promising treatment for this category of patients. Properly designed RCTs are needed to confirm these results and show whether more extended cooling after surgical procedures might further improve outcome in such patients.

Hypothermia is also widely used in cardiac surgery, to reduce metabolism and increase available operating time. Four studies have assessed whether mild intraoperative hypothermia can prevent the development of cognitive deficits—a frequent problem after cardiac surgery in which ischaemia seems to have an important role.[164] Nathan and co-workers[100] did an RCT to compare intraoperative and brief postoperative cooling from 32°C to normothermia in patients undergoing cardiopulmonary bypass surgery. After 1 week, cognitive deficits

Panel 2: **Phases of hypothermia treatment**

1 Induction phase

Initiate cooling as quickly as possible, try to reach temperatures below 34°C and then achieve target temperature (usually 32 or 33°C) as rapidly as possible. One highly effective and safe method to jump-start cooling is through infusion of cold (4°C) fluids (1500–3000 mL of saline or Ringer's lactate solution).[175,176] This method can be combined with an invasive or surface cooling device to further increase cooling rates.[176] Intensive care should include careful monitoring of fluid balance with prevention of hypovolaemia or hypotension, tight control of glucose and electrolyte concentrations, prevention of infectious complications and bedsores, adjustment of doses of various drugs (including sedatives and opiates), prevention of shivering, and other interventions.[177] The presence of cardiac arrhythmias or cardiac shock should not be viewed as a contraindication, because hypothermia, contrary to popular belief, increases membrane stability and blood pressure provided core temperature remains more than 30°C.[4,6,177] Hypothermia has been used in animal studies and clinical studies to treat refractory arrhythmias[178–180] and refractory cardiac shock.[113–117] Although cardiac output usually decreases in conjunction with metabolism, an improvement in balance between oxygen supply and demand usually takes place.[177]

2 Maintenance phase

Tightly controlled core temperature, with no or minor fluctuations (maximum 0·2–0·5°C). Focus on prevention of long-term side-effects, such as pneumonia, wound infections, and bedsores.[177]

3 Rewarming phase

Slow and controlled rewarming (0·2–0·5°C/h in cardiac arrest patients, even slower in patients with traumatic brain injury). Studies using rapid rewarming in patients with traumatic brain injury[54,55,147] and in the perioperative setting[91] have had worse results than those using slow rewarming. Numerous animal studies have shown that rapid rewarming can adversely affect outcome and that slow rewarming preserves the benefits of cooling.[104–108] In clinical studies, rapid rewarming also increases the risk of hyperkalaemia and might cause transient regional or general imbalances between cerebral blood flow and oxygen consumption—ie, increased oxygen consumption relative to perfusion.[168,181]

were present in 45 of 94 (48%) of cooled patients versus 62 of 100 (62%) of controls (RR 0·77, 95% CI 0·59–1·00; p=0·048). Some differences were still present at 3 months, and on follow-up after 5 years in 131 patients, hypothermia patients had less neurological deficits although this difference did not attain statistical significance (RR=0·64; p=0·16).[165] A second RCT compared cooling to 28°C with maintaining at 35°C in 138 patients and confirmed this observation, with neurological deficits in none of 70 cooled patients versus seven of 68 controls (p=0·006).[101] By contrast, three other studies did not find conclusive benefits of intraoperative hypothermia on cognitive function.[102,103,166] However, Grigore and co-workers[103] reported that patients who developed postoperative hyperthermia developed significantly more cognitive deficits; similar observations were reported by Grocott and others.[167] Therefore, one should note that brain temperatures can exceed blood, rectal, oesophageal, and tympanic temperatures by as much as 1·2–1·9°C when patients are rapidly rewarmed after cardiopulmonary bypass.[109] As outlined previously, fever can be harmful to injured neurons and might be one of the mechanisms through which rapid rewarming can be detrimental. Further, rapid rewarming after cardiac surgery decreases jugular venous oxygen saturation, which does not occur with slow rewarming.[168] These issues are further complicated by differences in cardioplegic techniques—eg, warm versus cold, antegrade versus retrograde, different electrolyte concentrations in cardioplegic solutions, etc. Some evidence suggests that warm cardioplegia might provide myocardial protection while increasing the risk of adverse neurological events.[169,170] Taken together, the obvious conflicting observations could all potentially be explained by harmful effects of quick (re)-warming.

In summary, although intraoperative hypothermia is widely used, firm evidence from RCTs is often absent. Animal studies and initial clinical trials using hypothermia for spinal protection in major vascular surgery have shown highly promising results. By contrast, a large clinical study in patients undergoing cerebral aneurysm clipping noted no substantial effect of hypothermia, at least after quick rewarming.[91] Some evidence suggests that very rapid rewarming can be harmful, and might cancel out potential benefits of preceding hypothermia treatment or even make the (neurological) situation worse. This potential harm by rapid rewarming might apply especially to cognitive deficits after cardiopulmonary bypass surgery. Future studies that use intraoperative hypothermia should strive to use slower rewarming techniques, perhaps maintaining mild hypothermia for 12–24 h after surgery.

Other potential indications for mild hypothermia

Hypothermia has been used to treat encephalopathy and intracranial hypertension in various clinical situations. Three case series (n=36 patients) have shown that hypothermia can control intracranial pressure during orthotopic liver transplants in patients with liver failure with hepatic encephalopathy and can also serve as a bridge to transplant.[110–112] Case series and control studies have reported successful use of hypothermia for adult respiratory distress syndrome,[118,119] grand mal seizures,[134,135] late spinal ischaemia after aortic surgery,[135] and acute disseminated encephalomyelitis.[138,139] Three case series in paediatric patients (n=127)[113–115] and two small case series in adults (n=18 patients)[116,117] reported successful use of cooling to improve circulation and reverse refractory cardiac shock after cardiac surgery.

Three small case series (n=47) suggested that moderate hypothermia could be used to prevent and treat vasospasms in patients with subarachnoid haemorrhage.[88–90] Preliminary evidence suggests that hypothermia can also decrease ICP in patients with subarachnoid haemorrhage and intracranial hypertension.[126]

A multicentre trial (COOL-RCN) is assessing whether mild hypothermia could be used to prevent radiocontrast nephropathy in patients with pre-existing renal insufficiency undergoing diagnostic angiographies,

angioplasties, or stenting procedures.[171] Unfortunately, the study has been interrupted because of funding difficulties, and its current status is unclear. A pilot study in 30 patients reported a 10% incidence of contrast nephropathy (ie, a rise in serum creatinin concentrations ≥25% from baseline) compared with 40% in historical controls.[133]

Fever control

Fever is a common complication in patients with various types of neurological injury and is independently associated with an increased risk of adverse outcome.[62–75] This link persists after multivariate analysis (correcting for factors such as presence of infection), and applies to infectious and non-infectious causes. This issue has been studied most extensively in patients with ischaemic stroke.[62–67] One study reported an increase of 2·2% in the risk of adverse outcome (permanent disability or mortality) for every degree Celsius rise in temperature.[64] Similar correlations have been seen in patients with subarachnoid haemorrhage,[68,75] intracranial bleeding,[69,70] TBI,[71,72] and other neurological injuries including cardiac arrest.[73,74] One of these studies noted that the risk of unfavourable outcome increases by a factor of 2·3 per degree Celsius of temperature rise above 37°C.[74] Furthermore, in stroke patients the risks seems to be greater if fever develops in the first 24 h after injury.[62–64]

Whether this link is causal remains to be established; fever could simply be a marker of more severe injury. However, animal studies have shown that brain injury increases substantially when animals are externally warmed; this event is independent of initial severity of injury, and is especially pronounced if hyperthermia coincides with a period of ischaemia.[4–6,78–80] Conversely, fever control mitigates brain injury in these animals.

As mentioned, local brain temperatures frequently exceed core temperatures by as much as 2°C.[71,172–174] These differences increase in injured brains because of hyper-metabolism in injured areas caused by, among others, the exitotoxic cascade and inflammatory response (table 1) and so-called cerebral thermopooling—ie, problems in getting rid of the excess heat as a result of local oedema formation and vascular blockage.[4]

On the basis of observations discussed previously, to practise some form of fever control in patients with stroke and, probably, other types of neurological injury is prudent, which certainly applies to the ICU setting in which problems such as shivering can be more easily managed. Outside the ICU, so far only small studies assessing the feasibility of cooling awake, non-mechanically ventilated patients have been done.[158,159]

Treatment

A detailed discussion on practical issues and side-effects of hypothermia use is beyond the scope of this Review. Panel 2 shows that hypothermia treatment can be divided into three distinct phases each with specific management issues and side-effects.[177]

Conclusions

Use of mild hypothermia seems to be a major breakthrough in the treatment of neurological injuries. It is effective for postischaemic injury after global anoxia and for lowering of intracranial pressure in various types of brain injury, and needs to be rigorously tested for TBI, ischaemic stroke, and thoracoabdominal aneurysm repair in which initial data seem highly promising. Studies that establish optimum depth and duration of cooling are also needed. Increasing evidence suggests that fever is harmful to the injured brain, and it seems reasonable to maintain normothermia in most patients with neurological injuries who have decreased consciousness (especially in those previously treated with hypothermia) for at least 72 h after injury. Hypothermia remains widely underused in many countries, especially in the USA and (to a lesser extent) the UK and Germany; therefore, applying the existing evidence and working on implementation strategies should be a priority.

Conflict of interest statement

I have no conflict of interest to declare. I have given lectures at satellite symposia sponsored by the industry, who took care of all the arrangements including travel and accommodation.

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