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REVIEW

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Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence

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Abstract *Objective:* Hypothermia has been used for medicinal purposes since ancient times. This paper reviews the current potential clinical applications for mild hypothermia (32–35°C). *Design and setting:* Induced hypothermia is used mostly to prevent or attenuate neurological injury, and has been used to provide neuroprotection in traumatic brain injury, cardiopulmonary resuscitation, stroke, and various other disorders. The evidence for each of these applications is discussed, and the mechanisms underlying potential neuroprotective effects are reviewed. Some of this evidence comes from animal models, and a brief overview of these models and their limitations is included in this review. *Results:* The duration of cooling and speed of re-warming appear to be key factors in determining whether hypothermia will be effective in preventing or mitigating neurological injury. Some other potential usages of hypothermia, such as its use in the perioperative setting and its application to mitigate cardiac injury following ischemia and reperfusion, are also discussed. *Conclusions:* Although induced hypothermia appears to be a highly promising treatment, it should be emphasized that it is associated with a number of potentially serious side effects, which may negate some or all of its potential benefits. Prevention and/or early treatment of these complications are the key to successful use of hypothermia in clinical practice. These side effects, as well as various physiological changes induced by cooling, are discussed in a separate review.

Keywords Therapeutic hypothermia · Induced hypothermia · Neurological injury · Resuscitation · Severe head injury · Artificial cooling · Review · Stroke · Ischemic injury · Reperfusion injury · Intracranial pressure

Introduction

Aim and scope of this review

When considering hypothermia (defined as a core temperature $\leq$35°C) in the intensive care unit (ICU) one should distinguish between uncontrolled (i.e., spontaneous, accidental) and controlled hypothermia induced by artificial cooling, which is used to prevent or attenuate various forms of neurological injury. There is growing evidence that induced hypothermia can have neuroprotective effects in some patients with neurological injury. The clinical use of hypothermia is therefore likely to increase in the near future; thus, physicians working in the ICU should have some knowledge regarding the evidence supporting its clinical applications, and of the physiological consequences and side effects that may develop when a patient is treated with hypothermia. This review firstly discusses potential mechanisms for hypothermia's neuroprotective effects, followed by potential clinical applications with evidence graded from I–IV according to the criteria outlined in Table 1. Physiological changes and

Table 1 Criteria for levels of evidence

Level I:	Supported by at least two sufficiently large randomized controlled clinical trials (RCCTs) of good quality[a], and/or supported by a meta-analysis of RCCTs
Level IIa:	Supported by at least one RCCT meeting the abovementioned criteria, supported by data from other sources (animal experiments, case control studies, etc.)
Level IIb:	Supported by one RCCT without supporting evidence from other sources
Level III:	Supported by at least one clinical non-randomized trial (cohort studies, case control studies, etc.)
Level IV:	Recommendations and opinions by experts and guideline committees, based on clinical experience, descriptive studies, case reports, etc.

[a] Correct randomization procedure, inclusion of all consecutive patients that meet inclusion criteria, double-blinded protocol, comparable baseline characteristics between study groups, same treatment for both groups apart from studied intervention, well-defined end points and targets, good description of results, end points, and clinical characteristics

side effects induced by cooling, as well as various cooling techniques, will be discussed in a separate review.

Historical perspective

The use of hypothermia for clinical purposes has ancient roots, beginning with its usage by the ancient Egyptians, Greeks, and Romans [1, 2, 3]. For example, Hippocrates advocated packing wounded patients in snow and ice to reduce hemorrhage [1]. In the early nineteenth century, Napoleon's Surgeon General Baron Larrey observed that injured soldiers who became hypothermic and were put closer to a fire died more rapidly than those who remained hypothermic [4]. The concept of neuroprotection also dates back to ancient times, with the observation that infants abandoned and exposed to cold often remained viable for prolonged periods. Clinical interest in hypothermia began in the 1930s and 1940s with observations and case reports describing successful resuscitation of drowning victims who were hypothermic, even after prolonged periods of asphyxia. The first scientific report describing clinical application of hypothermia, a case series in patients with severe head injury, was published in 1945 [5]. Hypothermia was subsequently used in the 1950s during intracerebral aneurysm surgery [6, 7] and for cerebral protection during complete circulatory arrest, to enable intracardiac operations in a bloodless field [8, 9]. Also in the 1950s, Rosomoff demonstrated benefit in dogs treated with moderate hypothermia during or after focal brain ischemia and experimental traumatic brain injury (TBI) [10, 11]. Clinical trials with hypothermia in a small number of patients were first carried out in the 1960s by Rosomoff and Safar [12] and by Lazorthes and Campan [13]. It should be noted that relatively deep hypothermia (30°C or lower) was used in most of these studies. These experiments were discontinued because of side effects, uncertain benefit, and management problems [12, 14].

However, interest in therapeutic hypothermia was rekindled in the early 1980s when animal studies showed that benefits could be obtained also with mild (32–35°C) rather than moderate or deep hypothermia, with fewer and less severe side effects. Moreover, with improvements in intensive care capabilities and the increased abilities to control or prevent side effects of artificial cooling, larger clinical trials for various clinical situations had become feasible.

Underlying mechanisms

Usefulness and limitations of animal models

Much evidence underlying hypothermia's clinical use and understanding of its neuroprotective mechanisms comes from animal models, which can largely be divided into two basic categories. In global ischemia models (most closely representing the clinical situation of cardiac arrest or near drowning) a transient (5–30 min) complete or nearly complete (<5% of normal in cortex) global lack of blood flow is induced. If flow is not restored within 30 min, widespread necrosis ensues, and functional recovery of the tissue is not possible. If reperfusion occurs within 30 min, there is selective neuronal death, showing that there are differences in sensitivity to ischemia between different types of neurons and different brain regions. The time course of cell death also differs: after a severe ischemic insult, CA1 pyramidal neurons of the hippocampus (which are more sensitive to ischemia than striatal neurons) remain viable for 2–3 days before succumbing to the insult, whereas the more resistant striatal neurons begin to die just 3–12 h after reperfusion.

Focal models are a closer representation of the clinical situation of stroke, with a localized, more prolonged (60–90 min in experimental models) ischemic period resulting from the occlusion of a single cerebral blood vessel. Blood flow patterns in this model are more complex and usually less severe than in global ischemia. Pan-necrosis will ensue in a central core region closest to the occluded vessel if reperfusion is not re-established within 60 min. Surrounding the edge of this core is a region referred to as the penumbra, which is hypoperfused and at risk of dying but can be salvaged with increased perfusion and/or other interventions. If no intervention occurs, the tissue at risk will begin to die within 3–4 h of reperfusion. Cell loss is

restricted to neurons; glial cells are far more resistant to ischemia. If the occlusion lasts 6 h the penumbra evolves to become core, and spreads outward with time. In animal models the development of injury caused by focal ischemia is significantly more rapid than in global ischemia. At normothermia, infarction is essentially complete by 24 h. Ischemic edema has a more protracted time course, peaking at approximately 48 h after injury.

Virtually all animal experiments studying effects of hypothermia on global or focal neurological injury have reported clear and unmistakable protective effects provided that hypothermia was applied quickly enough; however, reproducing these results in clinical trials has proved more difficult. One problem is that the brains of some animals, especially small animals such as rodents, appear to be more responsive to neuroprotection than human brains. The small, lissencephalic rodent brain has different rheological and metabolic properties than the complex, comparatively enormous gyrencephalic human brain; thus, if a specific treatment decreases the degree of histological brain damage in rats, this treatment may be effective in humans also but the effect may be too small to be clinically significant [15, 16]. In addition, specific treatments may influence a single destructive mechanism that plays a central role in animals but is less important in humans [15, 16]. Despite these limitations and differences between animal experiments and clinical trials, animal models can provide valuable clues on how hypothermia works and especially in what way it should be used. Many of the mechanisms underlying hypothermia's effects have been derived from animal experiments, although many were subsequently confirmed in clinical studies.

Underlying mechanisms

Traditionally, it has been assumed that protective effects of hypothermia were due to slowing of cerebral metabolism leading to decreased glucose and oxygen consumption. Indeed, cerebral metabolism is reduced by between 5 and 7% for each degree Centigrade reduction in body temperature during induction of hypothermia [17, 18]; however, protective effects of cooling appear to be much greater than can be explained by changes in metabolism alone [17]. Thus, although decreases in metabolism probably do play a role, other mechanisms may be much more important. In recent years the destructive processes taking place in neurons and other brain cells during ischemia and reperfusion have been partly elucidated. Effects of hypothermia on these processes, which occur over a period of minutes to many days after injury, have also been extensively studied. Some of these data are briefly discussed herein (for more information see [18, 19, 20, 21].

Apoptosis, calpain-mediated proteolysis and mitochondrial injury

Cells exposed to ischemia can either become necrotic, recover (fully or partially), or enter a path leading to programmed cell death, so-called apoptosis. Whether apoptosis will develop is determined by a number of distinct processes; these include mitochondrial dysfunction with disturbed energy metabolism and release of so-called caspase enzymes [22, 23, 24, 25]. Many studies have shown that hypothermia can prevent cell injury from leading to apoptosis, probably at an early stage of the process [23]. This effect appears to be mediated by inhibition of caspase activation [22, 23, 24] and prevention of mitochondrial dysfunction [25]. Other mechanisms include decreased overload of excitatory neurotransmitters and modification of intracellular ion concentrations. These processes take place over a period of up to 48 h, which may (partly) explain why hypothermia can be neuroprotective even if initiated some time after injury.

Ion pumps and neuroexcitatory cascade

There is a large body of evidence suggesting that hypothermia improves ion homeostasis and inhibits deleterious neuroexcitatory processes occurring in brain cells during ischemia and reperfusion. Hypothermia influences many different steps in this cascade, the central feature of which is influx of Ca^{2+} into the cell. When blood flow and/or oxygen supply to the brain are interrupted levels of high-energy metabolites, such as adenosine triphosphate (ATP) and phosphocreatine, decrease within seconds [18]. The ATP breakdown and compensatory activation of anaerobic glycolysis leads to increased levels of inorganic phosphate, lactate, and H^+, all of which result in intra- and extracellular acidosis. Cellular homeostasis is further disturbed by failure of ATP-dependent Na^+–K^+ pumps and K^+, Na^+, and Ca^{2+} channels, leading to loss of cellular Na^+ gradients and an influx of Ca^{2+}. Loss of ATP and acidosis prevent sequestration of Ca^{2+} from the cell, further aggravating intracellular Ca^{2+} overload [21].

The excess Ca^2 leads to mitochondrial dysfunction, activation of various intracellular enzymes (kinases and proteases), and induction of immediate early genes. Another important consequence is the depolarisation of neuronal cell membranes and the release of large amounts of the excitatory neurotransmitter glutamate into the extracellular space [21]. Under normal circumstances neurons are exposed to only very brief pulses of glutamate. Excess production is immediately absorbed by presynaptic terminals and glial cells in an energy-dependent process. This re-uptake is impaired during ischemia, leading to huge increases in extracellular glutamate levels. This leads to prolonged and excessive activation of membrane glutamate receptors, further stimulating

Ca^{2+} influx through activation of Ca^{2+} channels in a vicious cycle. This "excitotoxic cascade," where neurons remain in a permanent state of hyperexcitability, can culminate in additional injury and cell death. High levels of glutamate can be neurotoxic especially in energy-deprived cells. Even after glutamate levels return to normal shortly after reperfusion, glutamate receptor activation can persist and is considered to be an important mediator of brain cell death.

Various animal experiments have shown that hypothermia improves ion homeostasis and blocks or slows many of these destructive neuroexitatory processes [21, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37]. Key destructive processes, such as calcium influx, accumulation of glutamate, and release of its co-agonist glycine, are blocked by hypothermia [28, 29, 30].

The cascade initiated by the disruption in Ca^{2+} homeostasis continues in the hours to days (!) after ischemia. Potentially, this would provide a significant time window (48–72 h following ischemia) for therapeutic interventions such as hypothermia.

Immune response and inflammation

Various inflammatory and immunological responses occur following ischemia-induced cell injury, especially during reperfusion. Pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNFα) and interleukin-1 (IL-1), are released in large quantities by astrocytes, microglia, and endothelial cells following reperfusion. Levels begin to rise ±1 h after reperfusion and remain elevated for up to 5 days [21]. They stimulate accumulation of inflammatory cells in the injured brain, as well as the appearance of adhesion molecules on leukocytes and endothelial cells. Excessive leukocyte infiltration may increase the risk and extent of cell damage and infarction through their phagocytic actions, synthesis of toxic products, and further stimulation of immune reactions.

Hypothermia suppresses ischemia-induced inflammatory reactions and release of pro-inflammatory cytokines in animal and clinical studies [38, 39]. Other anti-inflammatory mechanisms include prevention or mitigation of reperfusion-related DNA injury, lipid peroxidation, and leukotriene production [31, 32], as well as decreasing the production of nitric oxide, a key agent in the development of post-ischemic brain injury [21]. All this is important because in animal experiments infarct size can be significantly decreased if some or all of the these mechanisms are inhibited [21].

Free-radical production

Oxygen radicals, such as superoxide (O_2^-), peroxynitrite (NO_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-), are important mediators in the transition from cell injury to cell death [29, 35]. Excessive free-radical production causes peroxidation of lipids, proteins, and nucleic acids. Neurons have various enzymatic and non-enzymatic protective mechanisms to avert this type of damage, but production of free radicals during ischemia and reperfusion may be so great that these antioxidant systems are overwhelmed. Induction of hypothermia slows these destructive process by decreasing the amounts of free radicals that are produced, allowing endogenous protective mechanisms to perform their task without being inundated [29, 35].

Vascular permeability and edema formation

Ischemia induces disruptions in the blood-brain barrier, facilitating subsequent development of edema [40, 41]. These disruptions may be further increased by therapeutic interventions such as mannitol administration [41]. Hypothermia appears to reduce disruptions in the blood-brain barrier [40, 41] as well vascular permeability following ischemia-reperfusion injury [42], thereby decreasing edema formation. Induction of hypothermia also decreases extravasation of hemoglobin following TBI [43]. This observation supports the concept of a membrane- and blood-brain barrier-stabilizing effect. The importance of brain edema in the development of (additional) neurological injury in patients with TBI is well recognized [44, 45]; however, edema formation may also play a role other kinds of neurological injury, including post-hypoxic injury following CPR [46].

Altered membrane permeability and intracellular acidosis

Ischemia and reperfusion directly impair the fluidity and integrity of cell membranes [47]. This process of membrane disintegration can be modified or reversed by hypothermia [47]. Secondary events, such as the development of intracellular acidosis, a factor which powerfully stimulates many of the abovementioned destructive processes [48], appear to be reduced by hypothermia [48, 49].

Cerebral thermo-pooling

Cerebral thermo-pooling signifies the presence of areas in the brain with significantly higher temperatures (differences of up to 2–3°C!) than the measured core temperature, a phenomenon that can develop in the brain following neurological injury [50, 51, 52, 53]. There is strong evidence that hyperthermia significantly increases the risk and extent of neurological injury (see "Fever in patients with neurological injury"); therefore, isolated

brain areas with higher temperatures may be more severely injured than areas with lower temperatures. Induced hypothermia can be used to prevent or mitigate cerebral thermo-pooling. Fever is a frequently occurring and important problem in patients with neurological injury [54], and regional differences in temperature appear to increase in patients with hyperthermia [51, 52, 53].

Cerebral metabolism

Evidence from animal experiments and some clinical observations suggest that TBI can directly influence the metabolic rate of brain cells [15, 55, 56, 57]. In animal experiments, an initial increase in cerebral glucose metabolism lasting for several hours is followed by a persistent decease in metabolic rates, with depression of mitochondrial oxidative phosphorylation and glucose utilization lasting for several weeks. Induction of hypothermia increases the speed of metabolic recovery during and after reperfusion and is associated with better preservation of high-energy phosphates and reduced accumulation of toxic metabolites [55, 56, 57].

Thus, in contrast to various pharmacological agents that each affect only one of the abovementioned steps, hypothermia can influence many key destructive mechanisms that occur during ischemia, reperfusion, and cerebral edema.

Potential clinical applications of hypothermia

Cardiopulmonary resuscitation

Cardiac arrest is a major cause of death in most western countries. Mortality ranges from 65 to 95% for out-of-hospital cardiac arrest [58, 59] and from 40 to 50% for in-hospital witnessed arrests outside the ICU [60, 61]; however, even in this latter category many surviving patients will suffer neurological injury, and just 10–20% are discharged alive without significant neurological deficits [60, 61]. The rationale for the use of hypothermia in these patients is that cerebral damage in CPR occurs not only during the period of cardiac arrest and resuscitation, but is due in large part to the generation of free radicals and other mediators during reperfusion [36]. In addition, there is evidence suggesting that cerebral ischemia may persist for several hours following successful resuscitation, even when saturation and arterial oxygen levels are normal [62]. In animal experiments hypothermia improves outcome in rats [63, 64, 65], dogs [66, 67, 68, 69, 70], and monkeys [71] even when initiated several hours after ischemia [63, 64, 65]. Protective effects are greater if cooling is initiated sooner [70, 72].

Moderate hypothermia (28–32°C) was used in patients following CPR in clinical trials as early as the late 1950s [73, 74]. Although there was a trend to improved outcome the results were inconclusive, and efforts were abandoned because of side effects and problems associated with the use of hypothermia. However, based on the consistently positive results of animal studies as described above, a number of small uncontrolled clinical trials involving a total of ±150 patients were carried out in the late 1980s and 1990s, reporting improved outcomes compared to historical controls [75, 76, 77, 78, 79, 80, 81]. These studies, demonstrating that moderate hypothermia could be safely used and might be effective following CPR, led to the initiation of two randomized controlled clinical trials, the results of which were published early in 2002 [82, 83]. The first study, by Bernard and coworkers [82], was carried out in Australia and included 77 patients (43 in the hypothermia group and 34 controls). In this study cooling was started very early, in the ambulance carrying the patients to the hospital following CPR. Target temperature was 33°C for a period of 12 h. The authors reported significant improvements in good neurological outcome (defined as no or moderate disability) in the hypothermia group: 21 of 43 vs 9 of 34 patients, or 49% vs 26% (p=0.046). There were no significant differences in survival (21 of 43 vs 11 of 34, p=n.s.). The second, larger study was carried out in Europe by the therapeutic hypothermia after cardiac arrest group and included 273 patients [83]. Rates of good neurological outcome were 55% (75 of 136 patients) vs 39% (54 of 137 patients; RR 1.40, 95% CI 1.08–1.81) and mortality rates 41 vs 55% (RR 0.74, 95% CI 0.58–0.95) for hypothermia patients vs controls, respectively. In this study cooling was initiated after a median of 105 min and maintained for 24 h, with a target temperature of 32–34°C. These results were achieved despite the fact that target temperatures were reached only after an average period of 8 h after restoration of spontaneous circulation (ROSC).

Inclusion criteria for both of these studies were fairly strict; both included only patients who had experienced witnessed arrests, with estimated intervals of no more than 5–15 min from collapse to arrival of ambulance and start of resuscitation by emergency medical personnel, initial rhythm of ventricular fibrillation or ventricular tachycardia, and an interval of no more than 60 min from collapse to ROSC. Patients with persistent hypotension (MAP<60 mmHg [83] or systolic pressure <90 mmHg [82]) or hypoxia (oxygen saturation <85%) were excluded, and there were various other exclusion criteria. This is illustrated by the fact that in the European study, of a total of 3551 patients assessed for eligibility, 3276 were excluded for various reasons [83].

Thus, it remains a matter for debate to what extent the findings of these studies can be applied to other categories of CPR patients, such as those with asystole upon arrival of the ambulance. Such patients have a poorer prognosis

than patients with initial electrical activity such as VT of VF, which is easier to reverse than asystole; however, on the basis of the mechanisms that probably underlie hypothermia's protective effects (see "Underlying mechanisms") there is no reason to assume that the effects would be limited to specific categories of patients with specific types of arrhythmia following CPR. It could be argued that because the prognosis of other categories of CPR patients is poorer, protective effects of hypothermia are likely to be smaller; on the other hand, the argument that protective effects could be even greater in these "sicker" categories of patients is equally valid. Animal experiments have demonstrated neuroprotective effects of a similar magnitude in asystole compared with VF/VT. Preliminary results from non-randomized studies from our own center and others in patients with asystole and pulseless electrical activity, with otherwise similar inclusion criteria as the studies described above, suggest that induced hypothermia can also be effective in these categories of patients [84, 85]. Further studies are required to address this issue.

Summary, levels of evidence, and recommendations

Class-I evidence (from animal experiments, two RCTs and various non-randomized trials) supports the use of hypothermia in selected categories of patients following CPR [witnessed arrest, brief interval (15 min) until arrival of ambulance, VF, or VT upon arrival of ambulance, ROSC within 60 min, no refractory cardiac shock or persistent hypoxia, not responsive to verbal commands]. Cooling should be initiated as soon as possible but should not be withheld even if delays of up to 8 h occur. Treatment should be continued for 12–24 h, with target temperatures of 32–33°C. Patients should be slowly rewarmed, as there is evidence suggesting that quick rewarming may have deleterious effects (discussed below). Much less data are available for other categories of patients, such as those meeting the abovementioned criteria but with asystole upon arrival of the ambulance. Although their overall prognosis is poorer, their basic neurological injuries are the same, and there is class-III evidence supporting use of hypothermia in these patients. Attending physicians should use their clinical judgment and interpretation of the available literature. In our center we use hypothermia in all patients following CPR with witnessed arrests who meet the abovementioned criteria, regardless of initial rhythm provided that there are no significant counter-indications (such as ongoing hemorrhage) and that the prognosis does not appear hopeless for other reasons (presence of malignancies, severe chronic diseases, etc.)

Traumatic brain injury

Traumatic brain injury (TBI) is the most common cause of death and disability in young people in Western countries. In the United States TBI is responsible for approximately 270,000 hospital admissions, 52,000 deaths, and 80,000 patients with permanent neurological disabilities [86]. The financial burden of this is enormous, due to the large number of life years lost and the varying degrees of severe disabilities. An important facet in the treatment of TBI is the realization that a substantial part of the neurological damage does not occur immediately (at the moment of impact) but develops at later stages, during hospital admission [44, 45]. While neurological damage occurring at the moment of injury is probably irreversible, the subsequent (secondary) injury is not, and thus therapy for TBI has focused on prevention or mitigation of this secondary injury [44].

One of the causes of secondary injury is swelling of the brain. In TBI, accumulation of vasogenic fluid can cause cerebral edema within hours, which can lead to a rise in intracranial pressure (ICP) and additional damage to injured area's of the brain. This in turn can lead to reductions in cerebral blood flow, ischemia, and cerebral herniation, further increasing the extent of brain damage, morbidity, and risk of death. Other mechanisms are also involved; these include reperfusion injury of injured area's, release of excitatory glutamids, and other deleterious processes discussed in "Underlying mechanisms". These developments can be exacerbated by brain edema and increased ICP, leading to a vicious cycle of ever increasing brain injury. An additional problem is the presence of local hyperthermic areas in the brain, where temperatures are substantially higher (up to 2°C!) than the measured core temperature [51, 52, 53]. Hyperthermia has harmful effects especially during periods of ischemia or reperfusion (see "Fever in patients with neurological injury"); therefore, averting this phenomenon may also improve outcome.

In theory, all of the abovementioned processes can be moderated by hypothermia. Indeed, TBI was the first clinical condition for which hypothermia was used in a clinical trial [5]. A number of subsequent trials [13, 87, 88, 89, 90], all uncontrolled with varying treatment protocols and variable duration of hypothermia, failed to conclusively demonstrate benefit. Because of this and the difficulties involved in caring for hypothermic patients in the absence of intensive care facilities and adequate monitoring equipment, these efforts were abandoned; however, in subsequent years animal experiments demonstrated clear benefits of mild to moderate hypothermia on outcome in experimental brain injury [91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101]. It is noteworthy that some of these studies reported that protective effects of hypothermia were enhanced by magnesium supplementation [97, 98, 99, 100, 101]. These results, as well as new insights

into the pathophysiology of neurological damage following TBI and improvements in facilities to care for these patients, have led to the instigation of several clinical trials. Since the early 1990s the results of 13 clinical studies, involving a total number of 1321 patients, have been published [102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114]. The end points of these studies were intracranial pressure [102 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113], neurological outcome [105, 106, 107, 108, 109, 110, 111, 112, 113, 114], and survival [105, 106, 107, 108, 109, 110, 111, 112, 113, 114]. All except one of these studies were performed in patients with high ICP. One study in 91 patients with normal ICP, of whom 45 were treated with hypothermia, observed no benefits in survival or neurological outcome [114]. In all the other studies intracranial hypertension (ICP >20 or >25 mmHg; normal value <15 mmHg) was used as inclusion criterion, and decreases in ICP were used as one of the measures of effectiveness. All authors reported that hypothermia was able to reduce ICP in patients with intracranial hypertension [105, 106, 107, 108, 109, 110, 111, 112, 113]; however, unfortunately the results regarding effects on survival and neurological outcome have been conflicting.

Eight studies were published between1993 and 2001 [102, 103, 104, 105, 106, 107, 110]. These were all single-center studies carried out in specialized neurotrauma centers, with experience in the use of induced hypothermia. Most of these studies observed favorable effects of cooling on neurological outcome [102, 103, 104, 105, 106, 107], mainly in patients with a Glasgow coma scale (GCS) of 4–7 on admission [107]; however, with one exception [107] these studies were relatively small, and benefits were not statistically significant except on subgroup analysis [107].

In 2001 the results of a large multi-center trial by Clifton and coworkers were published. This study included 392 patients in 11 centers, and observed no benefits in survival or neurological outcome, although, as in previous studies, hypothermia was able to decrease ICP [112]. Indeed, there were more "days with complications" in patients treated with hypothermia. The only subgroup that appeared to benefit from hypothermia were patients with hypothermia already present at admission [112]. An accompanying editorial stated that hypothermia for TBI should now be considered "a good idea proved ineffective." These findings, contradicting the results of all previous single-center trials, led to the discontinuation of use of hypothermia in most neurotrauma centers worldwide. The debate regarding use of hypothermia in TBI had apparently been settled by this study; however, in the past year the results of two large new clinical trials have been published, both of which reported significant improvements in neurological outcome and survival in TBI patients treated with hypothermia [111, 113]. One of these studies was carried out in our own hospital [111]. We observed statistically significant benefits of hypothermia in neurological outcome and survival in a group of 136 patients, despite the fact that hypothermia was used only as an option of last resort, in patients in whom all other forms of therapy had failed. Similarly to previous observations [107] the largest effects were seen in patients with GCS of 5 or 6 at admission. In this subgroup good neurological outcome was 29%, vs 8% in controls; mortality was 52% vs 76%. The other recently published study, by Zhi et al., was performed in China and included 396 patients, making it the largest study published thus far [113]. In that study rates of good neurological outcome were 38.8 vs 19.7%; for moderate disability, 22.7 vs 18.2%; and death, 25.7 vs 36.4% for hypothermia patients vs controls, respectively. In these studies hypothermia was maintained for longer periods of time (on average 115.2 h [111] and 62.4 h [113], respectively) and speed of re-warming was much slower compared with the Clifton et al. study [112].

In our study we used ICP to guide timing and speed of re-warming. Cooling was continued as long as ICP rose when re-warming was initiated [111]. These differences in protocol may be crucial. In a meta-analysis recently published (which did not yet include these last studies [111, 113]), McIntyre et al. concluded that induced hypothermia can be effective in reducing rates of mortality and poor outcome in TBI, but that depth and duration of hypothermia as well as rates of re-warming are crucial in achieving these improvements [115].

Other factors that may have affected the Clifton et al. [112] study are the speed of cooling, which was relatively slow, and the fact that some of the participating centers had little previous experience in the use of therapeutic hypothermia. Indeed, there was significant inter-center variance between hospitals participating in this study, with results of hypothermia appearing to be more favorable in larger centers with more experience in its application [116]. As outlined above and described in more detail in part 2 of this review, treatment of TBI is a complex undertaking, and often supportive treatments and therapeutic interventions vary substantially even between similar hospitals in the same country. Side effects of cooling may, if left untreated, negate any potential benefits [117]. For example, artificial cooling may induce hypovolemia, severe electrolyte disorders, arrhythmias, and hypotensive episodes [111, 117, 118, 119, 120]. Indeed, hypotensive episodes (defined as MAP $\leq$70 mmHg lasting for more than 2 h) were somewhat more common in the hypothermia group compared with controls (10 vs 3%, respectively) in the Clifton et al. study [112].

Bradycardia associated with hypotension for two or more consecutive hours occurred in 16% of the patients in the hypothermia group vs 4% in the normothermia group. No sub-analysis was performed excluding these patients. Importantly, no information was provided regarding

episodes of hypotension with a duration of less than 2 h. As even brief episodes of hypotension or hypovolemia may adversely affect outcome in TBI [44, 121, 122, 123], these and similar issues may have affected the results of this trial.

Another issue is the risk of hypothermia-induced electrolyte disorders, especially in patients with TBI [118, 119]. Magnesium may be particularly important in this regard, as both clinical and animal studies have linked hypomagnesemia to adverse outcome in neurological injury [97, 99, 124]. Moreover, serum levels of Mg and other electrolytes are frequently low in patients with TBI at admission [125], a problem that can be significantly compounded by the induction of hypothermia [118, 119]. If hypomagnesemia adversely affects neurological outcome, and if magnesium depletion is aggravated by hypothermia, hypothermia can adversely affect outcome through this mechanism (again negating possible benefits) unless hypomagnesemia is prevented.

Yet another side effect of hypothermia is insulin resistance and a decrease in insulin levels; if untreated, this will lead to hyperglycemia. This again is a potential confounder, as hyperglycemia may be associated with increased mortality while strict regulation of glucose levels has been found to decrease mortality and length of stay in the ICU [126, 127]. No data regarding glucose levels and/or occurrence of hyperglycemia are provided in the paper by Clifton et al. [112].

All in all, if these and other risks were indeed insufficiently taken into account, they may have had a significant impact on the results of the multi-center trial. Smaller hospitals with less experience in using therapeutic hypothermia may have been less adept at controlling side effects. These issues are discussed in more detail elsewhere [117]. Nevertheless, despite these potential problems, the fact that consistent benefits could not be demonstrated in this trial highlights the difficulties involved in using therapeutic hypothermia in patients with TBI, where treatment is often much more complex than in CPR patients, and where side effects of hypothermia are likely to have a much greater impact, potentially negating any positive effects. Another problem is the fact that patients with TBI often have other injuries, which in some situations may be a counter-indication for using hypothermia. This issue is discussed in part 2 of this review.

Summary, levels of evidence, and recommendations

Results from animal experiments overwhelmingly support the concept of a protective role for hypothermia in TBI; however, clinical trials have provided conflicting results. Hypothermia is clearly effective in controlling intracranial hypertension (level of evidence: class I); however, lower ICP does not equal improved outcome, and positive effects on survival and neurological outcome have been achieved only in tertiary referral centers with experience in use of hypothermia, using ICP to guide depth and duration of cooling and applying strict protocols for overall treatment of TBI. Routine usage of hypothermia in TBI can currently not be recommended; however, studies where patients were cooled for >48 h followed by slow rewarming have all reported favorable effects, and a recently published meta-analysis supports its usage in experienced centers in research settings. If hypothermia is used, it should be of sufficiently long duration (48 h or longer, preferably guided by ICP measurements). Rewarming should be slow, over a period of at least 24 h (level of evidence: class IIa). Centers should have experience in using hypothermia and managing side effects, and therapy should be guided by ICP measurements (level of evidence: class IIa). Fever should be prevented in all TBI patients in the first 24–48 h (level of evidence: class IIa, discussed in "Fever in patients with neurological injury"). The TBI patients with mild hypothermia (33–36°C) at admission who are hemodynamically stable should be allowed to remain hypothermic (level of evidence: class IIa). In our own hospital we now use hypothermia as the primary non-surgical option, based on the findings of the study carried out in our own center [111].

Stroke

As is the case for CPR and TBI there is overwhelming evidence from animal studies showing benefits of therapeutic hypothermia in stroke [15, 16 28, 29, 30, 31, 32, 33, 34]. As explained in "Usefulness and limitations of animal models" and "Underlying mechanisms", ischemic injury develops more rapidly in animal models of focal ischemia than in models of global ischemia. This could imply that the time window for applying hypothermia in stroke may be more limited than in post-hypoxic injury and/or TBI. In animal models of focal ischemia hypothermia is effective if delayed for up to 1 h, compared with approximately 2 h in global ischemia models, and the mitigating effects of hypothermia on neurological injury decrease if the delay is longer; however, as explained in **"**Usefulness and limitations of animal models" results from animal models cannot be directly translated to the human brain. The time window may be longer or shorter, depending on the resilience of the human brain compared with the animal brain, and on the role of secondary injury which is more amenable to treatment. As explained in **"**Usefulness and limitations of animal models" the penumbra zone, which is not yet irreversibly damaged, increases outward with time, and in theory this zone can be salvaged as long it has not become necrotic; thus, in theory some benefit could still be

derived from cooling even in later stages, although earlier intervention would be preferable.

Several uncontrolled clinical trials have assessed the feasibility of induced hypothermia in patients with stroke [128, 129, 130, 131, 132, 133], mostly in patients with middle cerebral artery (MCA) infarction (approximately 10% of patients presenting with acute stroke). These trials were relatively small, with the largest including 50 patients [130]. Use of hypothermia was reported to be feasible with limited side effects, although the incidence of non-fatal pneumonia was high in one study [130]. Hypothermia decreased ICP in all of these studies, and Schwab et al. reported increased survival in hypothermic patients compared with historical controls [129, 130]. Mortality rates of MCA infarction can increase to approximately 80% in cases complicated by cerebral edema and intracranial hypertension [132]. In contrast, mortality in the largest study by Schwab et al. was 38% [130]. Many of the deaths occurred during re-warming after rebound increases in ICP. A subsequent study by the same group demonstrated that these increases in ICP could be prevented by slower and controlled re-warming [134]. Regarding bleeding complications, one small study reported that hypothermia could be safely used even after thrombolysis [133]; however, all these studies included small numbers of patients and were not designed to detect differences in outcome. In addition, time intervals between onset of ischemic stroke and initiation of hypothermia were relatively long, 22±9 h with a range of 4–75 h in the largest study [130]. Average time required to achieve temperatures $\leq$33°C was 6.5 h, ranging from 3.5 to 11 h [130]. Clearly these intervals need to be significantly reduced for hypothermia to have optimum effects, as most of the permanent neurological damage in focal ischemia (in contrast to global ischemia) occurs in the first few hours. The optimum duration of cooling is also unknown. In most published studies this period ranged from 24 to 72 h, averaging 55 h in the largest study [130], followed by passive or active re-warming irrespective of ICP or other factors; however, as rapid re-warming may induce rebound effects on intracranial pressure, rates of re-warming are probably a key factor in preserving any beneficial effects of hypothermia; thus, it remains to be determined how therapeutic hypothermia should be used in stroke, and how its effects should be monitored.

Summary, levels of evidence, and recommendations

Animal experiments and preliminary clinical studies suggest that hypothermia may help limit neurological damage in stroke patients with middle cerebral artery infarction. No controlled clinical trials are available, and required duration and timing of hypothermia are unknown (albeit that animal experiments suggest that the therapeutic window may be smaller than in CPR or TBI). No studies applying hypothermia in the immediate aftermath of stroke have yet been published. Overall, there is class-III evidence for effectiveness of hypothermia in stroke with severe middle cerebral artery infarction. No clinical studies have been performed in other categories of stroke patients. Use of hypothermia in stroke should be viewed as experimental and should only be used in the context of clinical trials, in centers with extensive experience in the use of hypothermia.

Fever in patients with neurological injury

Fever is very common in neurological patients in the ICU, affecting 30–60% of patients with ischemic stroke [135, 136] and the majority of patients with head injury, intracerebral hemorrhage, and subarachnoid hemorrhage [137, 138]. There are several mechanisms through which fever might adversely affect neurological outcome; these include increasing cerebral metabolism, glutamate release, edema formation, and inducing disruption of the blood-brain barrier. Castillo and Dávalos demonstrated that hyperthermia is associated with early neurological deterioration and increases in glutamate concentrations in cerebrospinal fluid, thus linking excitoxicity with hyperthermia in human stroke [139]. Several studies have reported worse neurological outcome and higher mortality in patients who develop fever from non-infectious causes after various types of ischemic brain injury (review in [140]). This link has been studied mostly in patients with stroke [139, 141, 142, 143, 144, 145, 146, 147, 148], but also in patients with subarachnoid hemorrhage [149, 150], intracerebral hemorrhage [151], and TBI [53]. One chart review study also documented worse outcome in febrile adults after cardiac arrest [152]. The relationship between high temperature and adverse outcome in stroke is most clear if fever develops within the first 24 h [146, 148].

From these descriptive studies, it cannot be determined with certainty whether fever itself exacerbates neurological injury, or whether it is simply a co-marker of severity of injury; however, in animal experiments induction of even moderate hyperthermia significantly increases the extent of neurological damage and leads to greater morbidity and mortality, independent of initial severity of injury [27,153, 154, 155, 156, 157, 158, 159, 160]. Hyperthermia facilitates the transformation of ischemic penumbra to infarction and ischemic necrosis [27, 154, 155, 156, 157]. This applies not only to hyperthermia occurring shortly after injury, but also to later periods [153, 154]. For example, Baena et al. demonstrated that moderate, transient whole-body hyperthermia (39–40°C for 3 h), induced 24 h after a brief episode of forebrain ischemia in rats, increased neuronal injury in the hippocampus 2.6-fold [153]. Similar observations were reported by others [154, 160]. These findings suggest that fever can be detrimental even when it is of short duration and

occurs on the day after injury. The extent of injury appears to increase especially when hyperthermia coincides with the onset of cerebral ischemia [27, 155, 157]. In this regard an important physiological phenomenon is that local brain temperatures may exceed core temperatures by between 0.1 and 2.0°C [51, 52, 53]. These differences increase even further when core temperatures are higher than 38.0°C.

Physicians treating patients with neurological injury should be aware that intraventricular catheterization itself is a risk factor for unexplained (non-infectious, i.e., "central") fever [161]; therefore, temperature may decrease following removal of an intracranial probe even in the absence of infection. In animal experiments the natural occurrence of postischemic fever and fever-induced additional brain injury can be prevented, and neurological outcome improved, by combinations of cooling and/or administration of antipyretic/anti-inflammatory drugs [24, 154]; however, in a large study in 220 awake patients, Mayer et al. were unable to effectively control temperature with acetaminophen alone or in combination with air-blanket cooling [162]. Half of their patients remained febrile despite interventions. Air cooling only marginally improved control of fever, in part because 12% of their (awake) patients did not tolerate this intervention. These results suggest that more invasive measures will be required to achieve strict temperature control in patients with "central" fever. Following a small feasibility study published in 2000 [163], a trial is currently underway in Scandinavian countries using an intravascular device to control temperature in awake patients with stroke. No data from this trial are available yet.

Summary, levels of evidence, and recommendations

Fever is an independent predictor of adverse outcome, mortality, and more severe neurological impairment in patients with neurological injuries. This difference persists when patients are matched for other factors and if potential confounders, such as infection, are excluded. A causal nature for this relationship has been demonstrated in animal experiments, although it has not been conclusively proven in clinical studies. In animal experiments the clearest association between fever and increased neurological injury exists in the first 24 h, although adverse effects have also been demonstrated when fever was induced at later stages. This temporal relationship is clearer in stroke than in other forms of neurological injury; therefore, we recommend that fever be prevented or immediately treated in all ventilated patients with neurological injury in the ICU if it occurs within the first 24–48 h (level of evidence: class IIb). These patient should be cooled to normothermia (or lower, in patients meeting criteria for use of therapeutic hypothermia). An exact temperature limit beyond which cooling should be initiated cannot be given, although most studies used upper limits of 37.5–38.0°C. We recommend 37.5°C in view of the fact that brain temperatures often exceed measured core temperatures. This recommendation assumes that the patient is already intubated. The equation may be different in awake, non-ventilated patients, because cooling is likely to require sedation and perhaps ICU admission and intubation. This may be undesirable for clinical reasons and/or impractical for logistical reasons. A rigorous search for infectious causes should be undertaken in all patients with hyperthermia (not forgetting sinusitis, an often overlooked focus of infection in the ICU; level of evidence: class IV); however, hyperthermia should be treated symptomatically even in the presence of infection. Intraventricular drains should be removed as soon as possible as their presence can induce "central" fever.

Hypothermia in subarachnoid hemorrhage

No large clinical studies in patients with subarachnoid hemorrhage (SAH) have yet been carried out. Two animal studies have reported that induction of mild hypothermia (32°C), both immediate and delayed for 60 min, reversed experimentally induced vasospasms in rats [164, 165]. Three small case series including a total of 47 patients have suggested that moderate hypothermia can indeed be used to prevent vasospasms in patients with SAH, and/or to reduce such vasospasms if they have already developed [166, 167, 168]. These patients were treated with hypothermia when they failed to respond to conventional therapy, including intravascular angioplasty. Symptoms of vasospasms improved or disappeared in all patients based on clinical and neurological assessment. The occurrence of vasospasms after initial hemorrhage is a major complication and an important cause of morbidity and mortality in patients with SAH; thus, prevention of these vasospasms is a prime goal of therapy in these patients. Some corroborating evidence for hypothermia's effect on vasospasms comes from intraoperative use of hypothermia during cerebral aneurysm clipping (see "Intraoperative hypothermia"). An additional protective mechanism could be a hypothermia-induced decrease in ICP, which has been demonstrated in various other categories of patients (see "Traumatic brain injury" and "Fever in patients with neurological injury") and in one study in 21 patients with SAH [169]; however, although the abovementioned studies [166, 167, 168] reported better than expected neurological outcomes compared with historical controls, these findings are still very preliminary, and at this stage no firm conclusions regarding outcome can be drawn from these studies.

Summary, levels of evidence, and recommendations

There is class-IV evidence for the use of hypothermia to prevent vasospasms in patients with SAH. Initial results appear promising, but hypothermia for this purpose should be used only in experienced centers and in the context of clinical trials. As discussed in "Fever in patients with neurological injury", fever in patients with SAH is associated with vasospasms and poor outcome and should be treated symptomatically.

Intraoperative hypothermia

Intraoperative hypothermia was first used clinically in the 1950s by Bigelow et al. to enable intracardiac operations in a bloodless field [8, 9]. It is currently used in neurosurgical procedures [170, 171, 172, 173], cardiac surgery [174, 175], and major vascular surgery [176, 177, 178, 179, 180]. Usually, the aim of intraoperative hypothermia is to increase time available for specific surgical procedures, by reducing metabolism and providing protection for the brain and/or the spinal cord during local vascular occlusion or complete circulatory arrest. In neurosurgical procedures, such as aneurysm clipping, an additional goal is prevention of perioperative and postoperative vasospasms.

An important difference between intraoperative hypothermia and other therapeutic applications is that treatment can be initiated *before* and *during* the insult. This may be important because protective effects of hypothermia particularly in focal ischemia may be much greater if hypothermia is initiated quickly. The same animal experiments showing protective effects of hypothermia in focal ischemia also support its use in certain types of surgery, during periods of interrupted blood flow to specific areas of the brain [24, 154, 155, 156, 181].

Neurosurgery

A number of clinical studies have been carried out to assess effectiveness of intraoperative hypothermia in neurosurgical procedures. Karibe et al. [171] measured cerebral blood flow (CBF) in 24 patients undergoing cerebral aneurysm surgery, who were randomized for intraoperative normothermia or hypothermia. They observed improved CBF in the frontal cortex ipsilateral to the aneurysm on day 4 following surgery in the hypothermia group, and concluded that intraoperative hypothermia can reduce severity of ischemia induced by temporary cerebral vessel occlusion. Hindman et al. [170] used hypothermia in 114 patients with and without SAH during intracranial aneurysm surgery in a randomized pilot study. They observed a lower frequency of neurological deterioration at 24–72 h after surgery, greater frequency of discharge to home, and a greater incidence of long-term good outcomes in the hypothermia group; however, the number of patients was too small to achieve statistical significance [170]. This pilot study has led to the development of a large prospective multi-center trial, the IHAST2 (Intraoperative Hypothermia for Aneurysm Surgery Trial, part 2), which plans to enroll a total of 1000 patients [182]. The results of this trial are expected in early 2004.

Vascular surgery and spinal cord protection

Hypothermia is also used intraoperatively to protect the spinal cord and prevent paraplegia during high aortic cross surgery. The risk for paraplegia during this procedure ranges from 5 to 40%, depending on duration of cross clamp time and on whether the aorta is dissecting. Animal studies have shown a two- to threefold duration in the aortic clamp time required to induce paraplegia under mild hypothermic conditions [183, 184]; however, despite the widespread use of hypothermia in aortic arch surgery, relatively few clinical data are available. In an uncontrolled study in 20 patients cooled to 30°C during thoracoabdominal aortic aneurysm repair, Frank et al. reported no neurological deficits in any of their patients [178]. Similar results were reported by Cambria et al. [179] who observed lower rates of neurological deficits in a group of 70 patients compared with historical controls (2.9 vs 23%, respectively). A small controlled trial comparing the effect of spinal fluid drainage, papaverin, and epidural hypothermia to controls also concluded that hypothermia conferred added protection against neurological injury [180].

Cardiac surgery

Transient cognitive deficits develop in 30–80% of patients undergoing cardiac surgery during the first postoperative month, with deficits persisting in 0–30% of patients depending on the definition and type of cognitive function test used [185, 186]. The cause is presumed to be ischemic brain injury occurring during the procedure. In a randomized controlled trial Nathan et al. assessed the effect of intraoperative and brief postoperative cooling on cognitive function in patients undergoing cardiopulmonary bypass surgery [174]. The authors reported a 48% (cooled patients) vs 62% (controls) incidence of cognitive deficits 1 week after cardiac surgery, with some differences still present after 3 months. Other authors have published similar observations [175]; however, some authors failed to demonstrate conclusive benefits of intra- and postoperative hypothermia on cognitive function in elective bypass surgery [187, 188]. It has been hypothesized that these differences may be due to duration of

cooling and speed of re-warming [174]. In addition, it has been shown that brain temperatures can exceed rectal-, esophageal-, and tympanic temperatures by between 1.2 and 1.9°C following re-warming after cardiopulmonary bypass [190]. In view of the potentially harmful effects of fever in injured neurons (see "Fever in patients with neurological injury") this may be one of the mechanisms through which rapid re-warming might be detrimental. In addition, differences in cardioplegia techniques (warm vs cold, antegrade vs retrograde) may play a role. There is some evidence suggesting that warm cardioplegia may afford myocardial protection but increase adverse neurological events [189, 191].

Summary, levels of evidence, and recommendations

Although intraoperative hypothermia is widely used, firm evidence from randomized controlled trials is lacking or is (in the case of cardiac surgery) conflicting. The use of hypothermia in cerebral aneurysm clipping is supported by animal experiments, some case-control series, and one well-designed clinical trial [170], which showed a trend for improved outcome but failed to achieve statistical significance. A larger trial is currently underway. No harmful effects have been observed in any of the studies. At this moment the evidence supporting use of intraoperative hypothermia for intracerebral aneurysm surgery is class-IIb evidence. For cerebral- and spinal cord protection during thoraco-abdominal aortic aneurysm repair the evidence rates as class-III evidence. The use of mild hypothermia for neuroprotection during cardiac surgery is supported by class-III evidence.

Studies in children and neonates

In animal experiments, neuroprotective effects of hypothermia in newborn and young animals are comparable to, or even better than, those observed in adult animals. Clinical data regarding use of therapeutic hypothermia in children and neonates are still limited. Eight small feasibility studies have been performed in patients with neonatal asphyxia, including a total of 187 patients (of whom 118 were cooled and 69 used as controls) [192, 193, 194, 195, 196, 197, 198, 199]. No serious adverse effects of hypothermia were reported; side effects were similar to those seen in adults (discussed in a separate review) and were reversible with re-warming. One study in 9 infants reported induction of reversible pulmonary hypertension, requiring an increase in inspired oxygen fraction during application of hypothermia [198]. This could present difficulties in patients in whom oxygenation is already problematic. Some of these authors reported improved outcome compared with small control groups [192, 193, 194, 195] or historical controls [196]; however, the differences in outcome did not reach statistical significance [192, 193, 194, 195, 196].

One study applied hypothermia in 21 pediatric patients with severe traumatic brain injury [200]. The authors reported a decrease in intracranial hypertension during 48-h treatment with hypothermia compared with controls with similar severity of injury, without significant adverse events.

Surface cooling of the trunk or cap cooling with water have been used to induce hypothermia in neonates and infants, which is easier in newborns and young children because of the large skin surface relative to weight and the as yet underdeveloped counter-regulatory mechanisms.

Summary, levels of evidence, and recommendations

Animal data and preliminary results from a number of small clinical studies in patients with neonatal asphyxia appear promising. Some corroborative evidence comes from studies in adults (see "Cardiopulmonary resuscitation" and "Traumatic brain injury"). Nevertheless, the use of hypothermia in neonates and infants has not been sufficiently well studied to warrant its use outside clinical trials (level of evidence: class III). Larger, properly randomized and controlled studies are urgently needed to clarify these issues.

Other potential indications for therapeutic hypothermia

Based on observations that hypothermia lowers ICP in TBI and stroke, cooling has been used to treat intracranial hypertension in other situations; one of these is liver failure with hepatic encephalopathy. Preliminary evidence from animal models [201] and two small case series suggest that hypothermia can be highly effective in these situations, serving as a bridge to transplant [202] or as a tool to prevent acute ICP rises during orthotopic liver transplants [203]. Case series and case reports have also described successful use of hypothermia for the following indications: grand mal seizures [204, 205]; cardiac arrest due to non-coronary causes [206; K.J. Hartemink, unpublished data]; carotid artery transsection due to stab wounds (K.J. Hartemink, unpublished data); late spinal ischemia following aortic surgery (K.J. Hartemink, unpublished data); and acute disseminated encephalomyelitis [207, 208, 209].

Hypothermia has also been applied clinically for purposes other than neuroprotection. Two small studies in 57 pediatric [210] and 10 adult patients [211] have reported successful use of cooling to improve circulation and reverse refractory cardiogenic shock following cardiac surgery. Three case reports and one small case-controlled trial [212] have reported improvements in

oxygenation in patients with ARDS after induction of hypothermia. One study suggested that hypothermia can decrease infarct size in patients with acute myocardial infarction following emergency percutaneous coronary intervention [222].

Finally, there are some potential applications of hypothermia that thus far have been studied only in animals. Two studies have reported favorable effects of cooling in bacterial meningitis in a rat model [213, 214]. Hypothermia has also been shown to provide protection in spinal cord contusion in rats [215]. A number of studies have demonstrated that reduction in myocardial temperature attenuates injury and necrosis after prolonged ischemia [216, 217, 218, 219], whereas fever increases the extent of myocardial injury during ischemia and reperfusion [220]. Studies in various animal models also suggest that rapid induction of hypothermia (mild, moderate, or deep) could be used to prevent or delay cardiac arrest in hypovolemic shock due to severe bleeding and exsanguination, to bridge the time until surgical intervention can be performed [for review see 221]. These studies show that infusion of ice-cold fluids could provide cerebral and perhaps also myocardial protection [221]; however, some caution in the interpretation of these results and their extrapolation to humans is warranted, especially in view of the side effects associated with deep hypothermia (<30°C).

Summary and conclusion

It is clear that the equation for neuroprotection is complicated, and in many instances physicians have to make difficult decisions based on partly conflicting data. However, the following seems clear:

1. Hypothermia can be an effective mode of neuroprotection in postischemic injury following CPR, at least in selected categories of patients. Protective effects improve if hypothermia is initiated early, although success has been achieved even when target temperatures were only reached many hours after injury. Indeed, in theory protective effects could be achieved for a period up to 48–72 h as this is the period of time during which secondary injury develops.
2. There is direct and circumstantial evidence for potential benefits in other categories of patients such as TBI, SAH, and stroke; however, the negative results of one large study in TBI patients underscore the difficulties involved in successfully applying hypothermia. This requires strict protocols, vigilance, and attention to the prevention of side effects, and sufficient experience in using induced hypothermia. It is important to prevent side effects through prevention of arrhythmias, hypovolemia and hypotension, hyperglycemia, electrolyte disorders (especially hypomagnesemia), and infections (see part 2 of this review).
3. The duration of hypothermia is critical, since cells may die if hypothermia is discontinued prematurely. In addition, too rapid re-warming may have adverse effects that may negate any benefits derived from cooling; therefore, re-warming should be done slowly, over a period of 24 h, or guided by ICP if an intracranial probe is present.

All this means that successful use of hypothermia requires first-rate intensive care treatment and a concerted effort by the whole ICU team. Although the difficulties should not be underestimated, the evidence clearly suggests that these efforts will be worthwhile.

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