Induced hypothermia to treat post-ischemic and post-traumatic injury.

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ABSTRACT:

Although the concept that low temperatures can protect cells from various types of injury is not new (indeed this has been recognised since ancient times), effective clinical usage of induced hypothermia has only recently become feasible, with the advent of high-quality intensive care facilities and new insights into the mechanisms underlying hypothermia's protective effects. These insights have led to the realisation that benefits can be achieved using mild (32-35°C) rather than moderate or deep hypothermia, with easier induction and less severe side effects. Clinical use of hypothermia received a significant boost when two recently published clinical trials showed that neurological outcome after CPR can be improved by relatively brief periods of cooling, at least in some situations. Nevertheless, appropriate and effective use of induced hypothermia presents a challenge to clinicians working in the ICU and ER, and realising the potential benefits of hypothermia is far from easy. This paper reviews several potential clinical applications of induced hypothermia, and discusses physiological and practical aspects as well as side effects of artificial cooling. The concepts underlying hypothermia-associated neuroprotection and cardioprotection are discussed, as well as possible reasons why clinical trials for some indications such as severe head injury have produced conflicting results.

Introduction

The concept of hypothermia as a protective method in specific types of injury is an ancient one. Medicinal use of hypothermia was described by the ancient Egyptians in the so-called Ebers Papyrus, and by Hippocrates, Celsus and Galaenus (1-3) . In the 1930s and 1940s various case reports described successful resuscitation of drowning victims who were hypothermic, even after prolonged periods of asphyxia. Hypothermia was subsequently used on a case-by-case basis in various categories of patients. These included patients with cancer, cardiopulmonary resuscitation (CPR) and traumatic brain injury (TBI). In 1945 Fay and colleagues published a case series describing their experience in patients with severe TBI (4). This publication was followed by various other uncontrolled studies in patients with TBI and CPR (5-11). At this time it was assumed that hypothermia exerted its effects exclusively through a decrease in metabolism, leading to a reduction in oxygen demand and glucose consumption in the brain. Therefore, patients were generally treated with deep hypothermia (usually <30°C) for variable periods of time. This was in a time without intensive care facilities, so patients were usually cooled using ice and cold water on the general ward. Some of these studies appeared to show benefits (compared to "expected outcome" or historical controls), but these benefits were variable and uncertain. This uncertainty regarding efficacy, as well as management problems and the severe side effects associated with hypothermia, led to the discontinuation of this form of treatment.

These experiences illustrate that it can be difficult to obtain benefits from induced hypothermia. Apart from the risk of side effects, an additional problem is that benefits on neurological outcome may become apparent only after prolonged periods of time, long after the patient leaves the ICU. Nevertheless, interest in hypothermia was rekindled in the early 1980s by the positive results of a large number of animal experiments, which showed that outcome after neurological injury could be improved using mild hypothermia (32-34°C) rather than moderate or deep hypothermia, with fewer and less severe side effects. Moreover, these side effects could be far more easily managed with the advent of intensive care units to care for these patients.

Dr. Poldermann (right) together with the present Chairman, dr. Peter Andrews (middle), and former Chairman, dr. M Piek (left), of the Trauma and Emergency Sub-committee of the European Society of Intensive Care Medicine.

Photo: E. Søreide

Since the early 1990 a number of new clinical trials with hypothermia have been carried out in various categories of patients, mostly following CPR or TBI. Two randomized controlled trials and four studies using historical controls were performed in selected patients following CPR (see below). These studies reported clear improvements in neurological outcome in patients treated with hypothermia (12-13). However, trials performed in patients with TBI have produced conflicting results (14-26). Possible reasons for this are discussed below.

These and other potential indications of induced hypothermia with the available levels of evidence are listed in Table 1.

The goal of therapy is usually to protect the injured brain ("neuroprotection"). However, hypothermia has also been used in animal experiments and one small clinical trial to limit injury and reduce infarct size following acute myocardial infarction ("cardioprotection") (27-35). This and some other indications are discussed in more detail in §3.

To understand how hypothermia exerts its protective effects, a basic understanding of the underlying mechanisms may be helpful. These will be briefly discussed in the next paragraph, and are summarized in Table 2.

Table 1. Potential applications of induced hypothermia and levels of evidence according to the following system:

Level I: supported by at least two sufficiently large randomized controlled clinical trials (RCCTs) of good quality*, and/or supported by a meta-analysis of RCCTs.

*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 & targets, good description of results, endpoints and clinical characteristics.

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 trials (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.

I. Neuroprotection			
Potential indication		**Level of evidence**	**Evidence & comments***
Cardiopulmonary resuscitation in	Initial rhythm VT or VF	I	2 RCTs, much supporting evidence.
patients with witnessed arrests	Initial rhythm asystole or PEA:	III	Two non-randomized trials, many animal experiments.
and ROSC within 60 minutes:			
Cardiopulmonary resuscitation in unwitnessed arrests		IV	Animal experiments only
Traumatic brain injury		IIa	Various controlled trials and one meta-analysis; however, one large study with negative result
Prevention of fever in patients with neurological injury		IIb	Many observational studies; some small intervention studies; persuasive data from animal experiments
Stroke (middle cerebral artery infarction)		III	5 Small uncontrolled studies
Subarachnoid hemorrhage		IV	Three case series
Intra-operative hypothermia	Intracerebral aneurysm surgery	IIb	One controlled pilot study, one small uncontrolled study. Large trial currently in progress.
	Thoraco-abdominal aortic aneurysm repair (brain and spinal cord protection)	III	One small controlled study, two uncontrolled studies
	Cardiac surgery	III	Conflicting results of studies
Control of intracranial pressure in liver failure		IV	Case series
Refractory cardiogenic shock following cardiac surgery		IV	Large case series
Improve oxygenation in ARDS		III	Case control study and case series
Other indications: grand mal seizures, cardiac arrest due to non coronary causes, carotid artery transsection, late spinal ischemia following aortic surgery, acute disseminated encephalomyelitis.		IV	Case reports
II. Cardioprotection			
Decreasing infarct size after myocardial infarction		III	Animal data and one small RCT (non-significant difference observed)

*All indications supported by animal experiments

Table 2. Possible mechanisms underlying protective effects of hypothermia.

Mechanism	Explanation	Time frame after injury
Prevention of apoptosis	Ischemia can induce apoptosis (i.e., programmed cell death.) Hypothermia can prevent this.	Hours-many days or even weeks
Reduction in production of free radicals	Production of free radicals such as superoxide, peroxynitrite, hydrogen peroxide and hydroxyl radicals is a hallmark of ischemia. Moderate hypothermia is able to block these events.	Hours-days
Mitigation of reperfusion injury		Hours-days
Reduced permeability of the blood-brain barrier and the vascular wall; reduced oedema formation.	Blood-brain barrier disruptions induced by trauma or ischemia are moderated by hypothermia. The same effect occurs with vascular permeability and capillary leakage.	Hours-days
Reduced permeability of cellular membranes.	Decreased leakage of cellular membranes with associated improvements in cell function and cellular homeostasis, including decrease of intracellular acidosis	Hours-days
Improved ion homeostasis	Ischemia induces accumulation of excitatory neurotransmitters such as glutamate and prolonged excessive influx of Ca^{2+} into the cell. This induces a state of permanent excitability "exitotoxic cascade" that can be moderated by hypothermia.	First minutes-72 hours
Reduction of metabolism	Reduced oxygen and glucose requirements	Hours-days
Reduction of pro-inflammatory reactions and depression of the immune response and inflammation.	Sustained destructive inflammatory reactions and secretion of pro-inflammatory cytokines following ischemia can be blocked or mitigated by hypothermia	First hour-5 days
Reduction in cerebral thermo-pooling.	There are area's in the brain with 2-3°C higher temperatures than the surrounding areas and measured core temperature. These differences increase dramatically in injured brains. Hyperthermia can increase damage to injured brain cells; this is mitigated by hypothermia.	Minutes-many days

Mechanisms

Although the view that protective effects of hypothermia were exclusively or mainly due to slowing of cerebral metabolism and decrease in oxygen and glucose consumption has now been abandoned, this does appears to be one of the underlying mechanisms (though probably not the primary one). Overall metabolism (including metabolism of brain and heart cells) is reduced by 5-7% for each °C reduction in body temperature during moderate hypothermia (36-37). However, animal experiments have shown that the degree of neuroprotection that can be achieved with mild hypothermia is similar to the results obtained with deeper hypothermia. These effects are much greater than can be explained by reduced metabolism alone. Moreover, hypothermia appears to be effective even if initiated several hours after injury, something that is difficult to explain by reductions in metabolic rate alone.

In recent years it has been shown that hypothermia can influence and mitigate many of the destructive processes that take place in cells following ischemic injury. These mechanisms are listed in Table 2. For a more extensive discussion of these mechanisms and of the available evidence the reader is referred to reference 38.

Based on the time frame during which these destructive processes occur it becomes evident that, at least in theory, secondary cell injury and death can be influenced and perhaps prevented for a substantial period of time. This period could (again in theory) be as long as 48-72 hours following ischemia. In addition, a crucial element in the development and progression of neurological injury is that it occurs not just at the moment of the destructive event (which can be global ischamia following cardiac arrest, traumatic injury, focal ischemia during stroke, or another event), but may develop only at later stages following injury. This additional injury, caused by mechanisms such as reperfusion, (local or general) swelling of the brain with secondary ischemic episodes, increases in intracranial pressure and other mechanisms, may be extensive. In fact, it may become the main cause of adverse neurological outcome. The concept of this so-called secondary

injury is well recognized in the treatment of traumatic head injury (39-40); however, similar events may occur following other types of neurological injury, including global ischemia following cardiac arrest.

Clinical indications for induced hypothermia.

Potential applications and the available level of evidence are listed in Table 1. The most common indications, post-anoxic injury following cardiac arrest and severe traumatic brain injury, will be discussed in more detail. Some other indications will be briefly dealt with, or are only listed in Table 1. The interested reader who wishes to obtain more extensive information on the other applications is referred to reference 38.

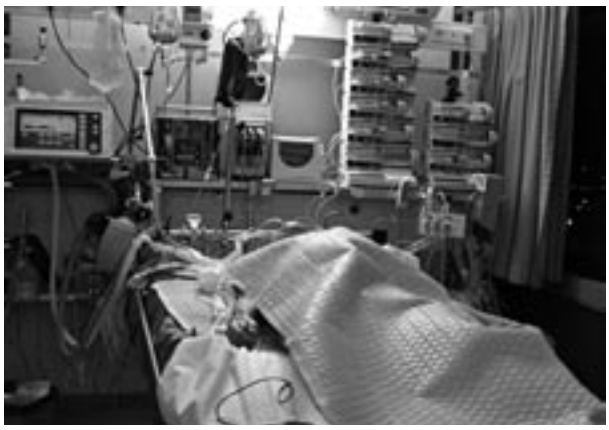

Fig.1. Hypothermia is being induced in a patient using water-circulating blankets placed above and below the patient, set at maximum cooling capacity during induction of hypothermia (water temperature 4°C). In addition cold fluids are being infused intravenously to speed up the cooling process.

Hypothermia following cardiopulmonary resuscitation.

In spite of many and intense efforts to improve outcome following CPR, mortality and morbidity associated with cardiac arrest remain extremely high. Mortality following cardiac arrest outside the hospital ranges from 65%-95%; this figure is approximately 40-50% for in-hospital witnessed arrests (41-44). Many of the surviving patients suffer severe neurological impairment; only 10-20% of patients reaching the hospital are discharged alive without significant neurological deficits.

As discussed above, moderate hypothermia (28-32°C) was first used in patients with CPR in clinical trials in the late 1950's (5-6). Efforts were then abandoned because of side effects, problems in the clinical management in patients treated with hypothermia, and because effects on outcome were uncertain. When animal studies consistently showed favorable effects of hypothermia on neurological outcome and survival, and because of the persistently dismal prognosis of patients who remained comatose after CPR, hypothermia was again used in a number of small uncontrolled studies. In vitro studies had by then shown that favourable results could be achieved using somewhat higher temperatures (between 31 and 35°C) than had been used in the 1950s studies. At these temperatures the risk and severity of side effects is much lower. In addition, with the advent of intensive care unit's (with invasive hemodynamic monitoring, mechanical ventilation and improved antibiotic treatments) the possibilities to care for these patients had improved substantially.

Four clinical studies involving a total of ±150 patients were carried out in the middle and late 1990's (44-47). These studies all reported improved outcomes compared to historical controls; this showed that mild-to moderate hypothermia could at least be safely used in these patients, and might be effective. This led to the initiation of two randomized controlled clinical trials, the results of which were published early in 2002 (12-13). These two studies included comatose CPR patients who had had witnessed arrests, and ventricular fibrillation or ventricular tachycardia without output upon arrival of the ambulance. Patients were treated with mild hypothermia (32-33°C) for either 12 hours (12) or 24 hours (13). The first study was carried out in Australia and included 77 patients (12); the other study was performed in several European countries and included 273 patients (13).

Both studies reported significant improvements in neurological outcome (defined as no or moderate disability) in patients who were cooled. In the first study rates of favourable neurological outcome were 49% vs. 26% ($p=0.046$), in the second study 55% vs. 39% (RR 1.40, 95% CI 1.08-1.81) for cooled patient vs. controls, respectively.

The second study also reported a significant difference in mortality: 41% vs. 55% (RR 0.74; 95% CI 0.58-0.95) for patients treated with hypothermia vs. controls, respectively. These results were achieved in spite of the fact that target temperatures were reached only eight hours after restoration of spontaneous circulation (ROSC). Target temperatures were reached much more quickly (core temperature <35°C within 30 minutes and <33.5°C within 120 minutes) in the second study. Here significant differences were observed in spite of the fact that the number of patients was smaller. Taken together, these studies show that benefits of cooling can be achieved even after substantial periods of time; however, although the two studies are difficult to compare directly, the fact that the difference in outcome was somewhat more pronounced in the smaller study (23% vs. 16%) suggests that effects may be greater if cooling is initiated quickly.

A problem in translating the results of these studies into clinical practice is that inclusion and exclusion criteria were relatively strict. As partly outlined above, patients had to have witnessed arrests, brief interval (5-15 minutes) until arrival of the ambulance, presence of ventricular fibrillation (VF) or ventricular tachycardia (VT) upon arrival of the ambulance, ROSC within 60 minutes, no refractory cardiogenic shock (MAP<60) or persistent hypoxia, and had to be unresponsive to verbal commands. Application of these criteria led to the exclusion of 3276/3551 (92.3%) of eligible patients in the

largest of the two studies (13). Thus it remains to be determined whether these findings can be applied to other categories of CPR patients, such as those with asystole upon arrival of the ambulance.

Data from animal studies suggest that hypothermia would be effective irrespective of the initial rhythm. This makes physiological sense; one would expect the time to ROSC, that is the duration of the cardiac arrest and the time that the brain has been deprived of oxygen, to be the key factor determining the extent of neurological injury and the chances of neurological recovery (The initial rhythm is important, of course, for the cardiac prognosis; VT and VF have a much greater likelihood of reverting to normal sinus rhythm, and asystole and PEA often signify more severe cardiac injury).
Few clinical data are yet available in this category of patients. One study describing the use of ice-cold water infusion to induce hypothermia also included patients with asystole and PEA (49). No outcomes were reported in that study. We recently completed a non-randomized study in 166 patients specifically to assess outcome in patients with asystole and PEA (50). Apart from the initial rhythm, inclusion criteria were similar to those used in the above-mentioned studies (12-13). Four hospitals participated in this study. Overall incidence of good neurological outcome was 41% in patients treated with hypothermia, vs. 20% in controls ($p<0.01$). These data have as yet been published only in abstract form. Further studies will be required to address this and other issues.

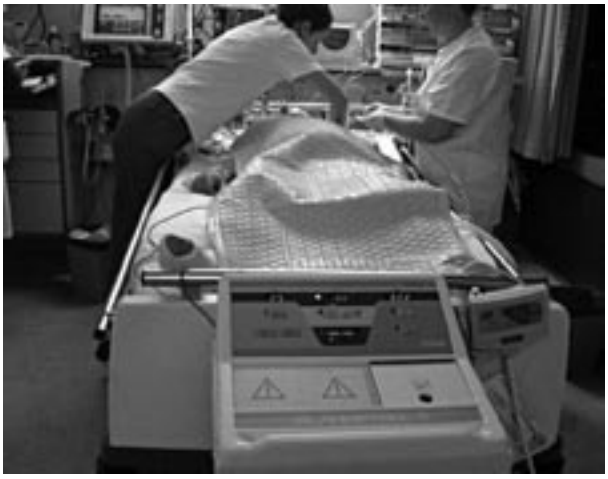

Fig. 2. The target temperature has been reached. Target temperature is now set at 32 or 33°C, with water temperatures usually varying between 20 and 34°C. One cooling blanket can now be removed as less cooling capacity is needed to maintain hypothermia than to induce it.

Hypothermia in traumatic brain injury.

A large body of animal experiments strongly suggests that hypothermia can also exert protective effects in traumatic brain injury. This has led to a total of thirteen clinical studies to assess effects of induced hypothermia on neurological outcome in TBI (14-26). End points of these studies were intracranial pressure (14-25), neurological outcome (15-26), and survival (15-26). Variable treatment protocols, variable duration of cooling and different rates of re-warming were used in these studies. Unfortunately, the results have been conflicting.

Most studies have used ICP to guide therapy; only one was carried out in patients with normal ICP. This study reported no benefits in survival or neurological outcome (26). In all the other studies, intracranial hypertension (ICP >20 or 25 mmHg; normal value <15 mmHg) was used as inclusion criterion; decreases in ICP were used as one of the measures of effectiveness. High ICP is thought to be associated with adverse outcome, and it is assumed that oedema formation with intracranial hypertension is one of the mechanisms through which secondary neurological injury occurs. Thus using ICP to monitor short-term therapeutic efficacy makes patho-physiological sense. All the studies in patients with intracranial hypertension reported that induced hypothermia significantly reduced intracranial pressure (14-15). The first studies that were published also reported favourable effects on neurological outcome and survival (14-22), mainly in patients with a Glasgow coma score between 4 and 7 on admission (19). These studies were all carried out in specialized and experienced neurotrauma centers. With one exception (19) these trials were relatively small, and benefits were not statistically significant except on subgroup analysis.

These findings led to the initiation of a multi-centred study, the results of which were published in 2001. This study, including 392 patients in 11 centers, reported no benefits in survival or neurological outcome (23); this in spite of the fact that, as in previous studies, hypothermia was able to reduce ICP (23). On subgroup analysis, one group of patients that did appear to benefit from cooling were those who already had spontaneous hypothermia on admission. In this category of patients maintaining hypothermia rather than re-warming appeared to improve outcome (23). Nevertheless, outcome in the overall group was not improved by cooling, and the authors reported more “days with complications” in cooled patients. An accompanying editorial stated that hypothermia for TBI should now be considered ‘a good idea proved ineffective’ (51). These findings, contradicting the results of all previous single-centre trials, led to the discontinuation of the use of hypothermia in most neurotrauma centers worldwide.

However, the favorable results achieved with cooling in patients following cardiac arrest have rekindled interest in application of hypothermia in TBI also. In addition, in the past year the results of two new large clinical trials have been published, both of which reported significant benefits in TBI patients treated with hypothermia (24-25).

One of these studies, by Zhi et al., was carried out in China and included 396 patients, making it the largest study published so far (25). In this study patients were cooled for a time period averaging 62.4 hours (range 1-7 days). The authors reported significantly improved outcomes in the hypothermia group; the percentage of patients with good neurological outcome

was 38.8% vs. 19.7%, and mortality was 25.7% vs. 36.4% for hypothermia patients vs. controls, respectively (25).

The other trial was carried out in our own centre in the Netherlands (24). In this study hypothermia was used as an option of last resort, to treat refractory intracranial hypertension in patients in whom all other forms of therapy had failed. Outcome was compared to patients in whom the last step in our protocol prior to induced hypothermia had succeeded in lowering ICP to levels below 20 mm Hg.

We included 136 patients in our study, and observed statistically significant benefits in neurological outcome and survival in patients treated with hypothermia. The largest difference was seen in patients with a GCS of 5 or 6 at admission. In this group of patients the rate of good neurological outcome was 29%, vs. 8% in controls ($p<0.02$). Mortality was 52% vs. 76% ($p<0.01$), respectively. The observation that the greatest benefits occurred in this particular subgroup was in keeping with findings from the largest single-centre study published before ours (19). This study included 82 patients and reported benefits in the subgroup with GCS of 5-7 on admission. However, in contrast to this study, we also observed statistically significant benefits in the overall group and not just in one subgroup.

Similar to the study by Zhi et al, we maintained hypothermia for prolonged periods of time (average duration 4.8 days, range 2-14 days). We re-warmed our patients very slowly (1°C/12 hours), with discontinuation of cooling being guided by ICP. Cooling was re-initiated if ICP rose above 20 mmHg when body temperature increased. In addition core temperatures below 34°C were achieved relatively quickly, with an average time interval of 3.1 hours between injury and achievement of target temperatures.

How can the contradictory findings between all these single-centre studies and the multi-centre trial by Clifton et al. be explained?

The explanation may lie in a combination of factors, including the speed and duration of cooling, speed of re-warming, and the occurrence of harmful side effects. In the multi-centre study hypothermia was applied for an arbitrary period of time (48 hours) after which patients were re-warmed, regardless of rises in intracranial pressure. Time to induction of hypothermia was relatively long (average 8.4 ± 3.0 hours). In addition, a number of the centres participating in the study had little previous experience in the use of hypothermia. Subsequent analyses have shown a significant inter-centre variance between hospitals participating in this study, with more favourable results of hypothermia being obtained in larger centres with more experience in cooling (52). This is important because both cooling patients and the treatment of TBI can be complex undertakings. There are huge differences in the treatment of patients with severe TBI between various treatment centres. These differences can be found even between similar hospitals

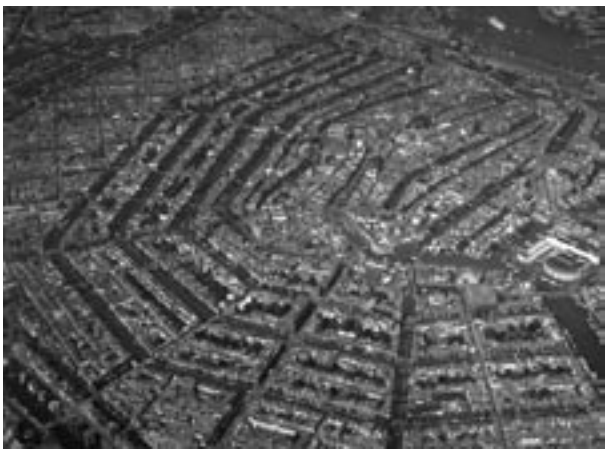

Fig. 3. Aerial photo of the city of Amsterdam. The VU university medical center is located at the periphery of the city, near the bottom of the picture.

Fig. 4. Aerial photo of the VU university medical center.

in the same region or country. Induced hypothermia can lead to side effects such as hypovolemia and hypotension which, if left untreated, can negate the potential benefits of this treatment (53). This risk is especially pronounced in patients with TBI, in whom even brief episodes of hypovolemia or hypotension can have greater and more harmful effects than in other categories of patients (39-40,54-55). Moreover, the risk of developing these side effects is much greater in TBI patients due to various other treatments that increase the risk and degree of these side effects (see below). Indeed, in the Clifton study hypotensive episodes (defined as MAP ≤70 mmHg lasting for more than 2 hours) as well as a number of other side effects occurred more frequently in the hypothermia group than in controls (23).

A meta-analysis reviewing a number of the studies on induced hypothermia in patients with TBI (those that had been published before the winter of 2002) was published in 2003 by the Journal of the American Medical Association (56). This meta-analysis assessed mortality and neurological outcome corrected for the duration of cooling and rate of re-warming. The authors concluded that hypothermia could be effective if used for prolonged periods, and that its effectiveness may be influenced by the rate of re-warming. This conclusion was reached in spite of the fact that the two favourable studies described above (24-25) were not included in the analysis.

Fig. 5. Hypothermia can also be applied in patients in the prone position.

Nevertheless, the fact that consistent benefits could not be demonstrated in the multi-centred Clifton study illustrates the difficulties associated with the medical application of hypothermia, especially in patients with TBI. Side effects of hypothermia such as hypovolemia and hypotension can have a much greater impact in patients with TBI; in addition, other treatments frequently used in TBI patients, such as administration of noradrenalin, dopamine, mannitol or barbiturates, can increase these side effects (38,57).

Hypothermia has been used in small numbers of patients in many other clinical situations (Table 1). These will not be discussed in detail. The reader who wishes to learn more about these indications is referred to reference 38.

Mostly the aim has been to protect the injured brain from (additional) damage. Attempts have also been made to use hypothermia to provide cardioprotection. Data from animal studies suggests that induction of hypothermia during or following myocardial infarction can decrease infarct size (27-34). Hypothermia has been used in one clinical study including 42 patients with acute myocardial infarction undergoing emergency percutaneous coronary intervention (35). Half of the patients were cooled for 3 hours after intervention; these patients had a trend to smaller infarct sizes and less major adverse cardiac events. However, these differences did not reach statistical significance in this small study. Further studies will be required to address this issue.

Physiology of hypothermia induction and temperature regulation

Under normal circumstances core body temperature in humans is strictly regulated around a setpoint of 36.6 ± 0.4°C. This

Tab. 3. Physiologic effects of induced hypothermia which may develop (to varying degrees) in most patients during induction of hypothermia. Temperatures below which these effects occur are influenced by age and co-morbidity, such as the presence of cardiovascular disease. (Adapted, with permission, from reference 57; http://dx.doi.org/10.1007/s00134-003-2151-y).

System	Temp	Effect
Physiologic attempts to increase temperature	30-35°C	In awake patients: generation of heat: shivering, peripheral vasoconstriction, increased muscle activity, increased oxygen consumption, increased rate of metabolism
	≤30°C	'Hibernation': shivering ceases, marked decrease in rate of metabolism.
Metabolic	30-35°C	↓ Oxygen consumption
		↓ CO_2 production
		↓ Metabolism
		↑ Fat metabolism: ⇒ ↑ Glycerol, free fatty acids, ketonic acids, lactate; metabolic acidosis
	≤35°C	↓ Insulin sensitivity ↓ insulin secretion
Endocrine	≤35.5°C	↑ Levels of adrenalin and noradrenalin
	≤33°C	↑ Levels of cortisol
Cardiovascular	£36->35°C	Tachycardia
	≤35°C	Bradycardia
	≤34°C	Slight increase in blood pressure (average 10 mmHg)
	≤32°C	Mild arrhythmias in some patients
	≤33°C	EKG changes: increased PR-interval, widening of QRS-complex, increased QT interval.
	≤28-30°C	↑↑ Risk of tachyarrhythmia's, beginning with atrial fibrillation
	≤35°C	↑ CVP and ↓ CO
	≤35°C	↑ or = mixed venous saturation
Renal	≤35°C	↑ Diuresis, tubular dysfunction, electrolyte loss & electrolyte disorders
Haematological	≤35°C	↓ Platelet count, impaired platelet function, impaired coagulation cascade
	≤33°C	↓ White blood cell count, impaired leucocyte function
Gastro-intestinal	≤35°C	Impaired bowel function/subileus, mild pancreatitis (occurs very frequently!) ↑ liver enzymes
Immune suppression	≤35°C	Impaired neutrophil and macrophage function; suppression of pro-inflammatory mediator release; ⇒ increased risk of infection (mainly pneumonia & wound infections)
Neurological	≤30-31°C	↓ Consciousness, lethargy, coma.
Pharmacokinetics	≤35°C	Altered clearance of various medications (data available for muscle paralyzers, propofol, fentanyl, phenytoin, pentobarbital, verapamil, propanolol and volatile anaesthetics (reduced clearance), but in all likelihood applies to many other types of medication)
		No effect on gentamycin clearance in animal experiment
		No effect on neostigmine effect or clearance in healthy volunteers

setpoint can be adjusted, and slight variations occur in the course of each day. Core temperature is regulated by limiting or increasing heat transfer to the peripheral body compartment through vasodilation or vasoconstriction. Subsequent heat loss from the peripheral compartment varies through changes in skin perfusion (again through vasodilation or vasoconstriction) and by adjustments in the production of sweat (evaporation). Apart from by evaporation, subsequent heat loss can occur through convection, conduction and radiation. The amount of heat loss is influenced by the temperature gradient, exposed surface, and thermal conductivities. For example, heat loss occurs more slowly in obese patients due to the insulating properties of fat and the greater diffusion coefficient.

At rest and under normal circumstances, 50-70% of heat loss in awake patients occurs through radiation (57). In sedated patients in the supine position most heat loss will occur through radiation and convection. Active cooling of sedated patients often entails facilitating convection and/or conduction and by facilitating transfer of heat from the core to the peripheral compartment (see below).

Cooling of patients will lead to immediate counter-responses to counteract the disturbance in homeostasis. The first step will be to limit heat loss through vasoconstriction in the skin and by increasing sympathetic tone. This will complicate attempts to induce therapeutic hypothermia by external cooling (see below). In awake or mildly sedated patients heat production will be increased through shivering. This can lead to increases in oxygen consumption of between 40% and 100% (58-59), an undesirable effect particularly in patients with neurological injury. Shivering can be counteracted by administration of sedatives, anaesthetics, opiates and/or paralyzing drugs (see below). Sedation and anaesthesia also increase peripheral blood flow, which facilitates and increases transfer of heat from the core to the periphery. The capacity and effectiveness to control body temperature decrease with age; therefore, counter-regulatory responses to hypothermia will occur more quickly, and be more intense and effective, in younger than in older patients. This difference is amplified because rates of metabolism decrease with age, and older patients often have a lower body mass index (with decreased capacity for heat generation and less effective insulation) and a less effective vascular response. This means that induction of hypothermia will be more difficult, and take more time, in younger patients than in older patients. Often, higher doses of sedatives or opiates will be required to counteract the counter-regulatory mechanisms. Similarly, achieving hypothermia through surface cooling in obese patients will take more time due to the insulating properties of fat.

Side effects of induced hypothermia

Hypothermia induces physiological changes in virtually every organ in the body. This includes changes in the circulatory, respiratory and coagulation systems, drug metabolism, etc. Awareness of these physiological effects and of the potential side effects is of key importance for successful use of hypothermia in clinical practice, especially in patients with TBI. A number of these changes are described in more detail below. Various others are listed in Table 3.

Cardiovascular and hemodynamic effects.

Mild hypothermia decreases cardiac output by about 25%, and leads to an increase in vascular resistance and CVP.

Induction of hypothermia may induce changes in heart rhythm and the electrocardiogram. When body temperatures begin to decrease patients will initially develop sinus tachycardia. As temperature decreases further (below 35.5°C) this is followed by sinus bradycardia. While temperature remains higher than 30°C the risk of developing clinically significant arrhythmias is very low. However, these risks increase significantly if core temperature decreases below 28-30°C, and may be increased further if electrolyte disorders develop. Usually the first observed form of arrhythmia is atrial fibrillation, which can be followed by more severe arrhythmia's including VT and VF if temperature decreases further. A problem is that once arrhythmia's do develop these are much more difficult to treat, because the myocardium becomes less responsive to defibrillation and cardiac drugs during hypothermia. Thus great care should be taken to keep temperatures above 30°C.
In healthy subjects mild hypothermia (35.5°C) increases coronary perfusion (60-61). However, this is less clear in patients with coronary disease; indeed in these patients coronary vasoconstriction may occur (61). On the other hand, as outlined above there is evidence that hypothermia can help reduce infarct size after myocardial infarction (35). This suggests that hypothermia does not adversely effect cardiac outcome in patients with coronary artery disease. All in all this issue appears complex, and perhaps conflicting forces are at work here. Further studies will be required to settle these issues.

Hypovolemia and fluid balance.

Cooling can cause an increase in diuresis ("hypothermia-induced diuresis") which occurs especially in the phase where body temperature is decreasing. This occurs especially in patients with TBI, who are often treated with various other agents that can increase diuresis. Although this usually does not present major problems in other categories of patients, its impact may be much greater in patients with TBI where even brief periods of hypovolemia and hypotension can have significant detrimental effects on neurological outcome (54-55).

Electrolyte disorders. Various studies have observed the development of electrolyte disorders associated with hypothermia (53,62). This again may occur more frequently, and be more pronounced, in patients with TBI (57). This is important because electrolyte disorders, especially hypomagnesaemia, can cause cardiac arrhythmias, vascular

spasms (including spasms of cerebral and coronary arteries, hypotensive episodes and decreased cerebral blood flow (63-66). In animal studies depletion of magnesium (Mg) leads to significantly worse outcomes in experimental TBI, while administration of Mg even some time after trauma substantially mitigates secondary injury and reduces the loss of cortical cells (63-66). Magnesium may also play a role in the prevention of reperfusion injury (38) (Table 2). Hypomagnesaemia is associated with adverse outcome in clinical studies (67).

In view of the risks associated with electrolyte depletion it is noteworthy that animal and clinical studies show that TBI itself can induce electrolyte disorders (57,68). This means that many patients with TBI already have hypomagnesaemia at admission, which can be worsened by induction of hypothermia (53). Serum levels of Mg do not always accurately reflect Mg status; therefore Mg levels should be maintained in the high or high-normal range in patients with neurological injury.
As is the case with hypovolemia, electrolyte disorders can be quite easily prevented. Fluid homeostasis, intravascular volume and electrolyte levels should be carefully monitored in all patients treated with induced hypothermia, especially those with TBI.

Other metabolic effects.

Hypothermia can decrease insulin sensitivity and reduce insulin secretion, which can lead to hyperglycemia. Hyperglycemia is associated with adverse events such as increased infection rates, critical illness neuropathy and renal failure. Strict control of glucose levels using intensive insulin therapy has been shown to decrease morbidity and mortality in the ICU (69-70), at least in surgical patients (69). Thus tight glucose regulation may be important in critically ill patients. Physicians applying induced hypothermia should be aware that hyperglycemia is more likely to develop, and that the amounts of insulin required to maintain glucose levels in the normal range will increase during induction of hypothermia (57).

Hypothermia also leads to increased synthesis of glycerol, free fatty acids, ketonic acids and lactate, which will lead to the development of mild metabolic acidosis. This mild acidosis is a normal consequence of hypothermia. In contrast, intracellular pH levels increase slightly during hypothermia.

The lowering of metabolic rate also decreases oxygen requirements and the synthesis of carbon dioxide (CO_2). Fluctuations in CO_2 levels can affect the vascular tone of cerebral arteries; this implies that blood gasses should be monitored frequently, and ventilator settings adjusted, during induction of hypothermia.

Coagulation.

Hypothermia induces a mild bleeding diathesis, with increased bleeding time due to effects on platelet count, platelet function, the kinetics of clotting enzymes and plasminogen activator inhibitors, and other steps in the coagulation cascade (57). Standard coagulation tests will show no abnormalities, as these are usually performed at 37°C. These tests will be prolonged only if they are performed at the patient's actual core temperature. Nevertheless, the risk of clinically significant hypothermia-associated bleeding is very low, even in patients with traumatic injuries (57). Indeed no clinical trial in patients with TBI, SAH, stroke or post-anoxic coma has reported increased risk of intracranial bleeding associated with hypothermia.

Infection.

Hypothermia can impair immune function and inhibit various inflammatory responses. Indeed, dampening harmful inflammatory reactions in the brain following ischemic or traumatic injury is one of the mechanisms through which hypothermia exerts its protective effect (38). Underlying mechanisms include inhibition of pro-inflammatory cytokine secretion and suppression of leucocyte migration and phagocytosis. Hypothermia-induced insulin resistance and hyperglycemia may also increase infection risks. Some studies have reported increased risks of pneumonia (26, 71) and of wound infections (72-73) in patients kept hypothermic for prolonged periods. In our experience careful monitoring of patients and use of antibiotic prophylaxis (SDD) can prevent respiratory tract infections.

The risk of wound infections may be related both to diminished leukocyte function and to hypothermia-induced vasoconstriction in the skin (57, 74-75). Thus extra care should be taken in cooled patients to prevent bed sores, which are more likely to show progression and/or impaired healing.

Miscellaneous.

Most patients treated with hypothermia are sedated, sometimes paralysed, intubated and mechanically ventilated, although hypothermia has been used in awake patients (38). A major problem is that sedatives hamper the neurological assessment of these patients. This has a number of consequences. One is that neurological deterioration may not be immediately apparent; in addition, if a patient develops sub-clinical seizures (which occur frequently in patients with TBI or following CPR) the risk of missing the diagnosis is increased. This implies that these patients should be carefully monitored clinically, and that EEG monitoring should be considered. If possible, brief-acting sedatives and/or opiates should be used, and should be intermittently discontinued to allow neurological assessment. It should also be remembered that hypothermia can strongly affect drug metabolism and pharmacokinetics, because the enzymes that metabolize most drugs are highly temperature-sensitive. Metabolism and clearance of most drugs has not been studied at hypothermic temperatures, but it is likely that metabolism of many types of drugs is significantly slowed. Information on some types of medication is available; these include propofol, fentanyl, muscle paralysers and barbiturates. Clearance of these drugs is significantly decreased at lower

temperatures (57).

Methods to induce hypothermia.

Strategies to cool patients can be roughly divided into core and peripheral cooling, and are usually based on increasing heat loss through convection or conduction. Basic measures usually include sedation and prevention of heat generation through shivering. Heat generation can sometimes be reduced by antipyretic agents, but these are relatively ineffective in patients with neurological injury and impaired thermoregulation. The most commonly used cooling methods are ice-water circulating blankets, ice bags, air mattresses, cooling catheters, and intravenous infusion of cooled fluids (4°C). Currently, there is no method which is has been shown to be clearly superior over the others. The speed of cooling appears to be important, and the efficacy of air cooling may be lower in this regard. In addition, there are substantial differences in costs, as well in the accuracy of maintaining a specific temperature. For a more detailed discussion of these issues the reader is referred to reference 57.

Conclusion.

There is increasing evidence that hypothermia can be used to protect injured cells from (additional) injury. Cooling has been used to provide neuroprotection and (less frequently) cardioprotection following ischemic and traumatic injury. Successful application of hypothermia requires attention to the prevention of side effects and thus implementation of strict protocols. Treatment should be initiated as soon as possible following injury. However, based on the mechanisms underlying hypothermia's protective effects, treatment can be successful even if initiated some time after injury, and in some studies success has been achieved when target temperatures were reached >8 hours after injury.

The optimum period of cooling for most indications is still unknown; in traumatic brain injury, the evidence suggests that neurological outcome can be improved if hypothermia is maintained for prolonged periods of time (>48 hours, preferably guided by ICP) and if patients are not too quickly re-warmed.

Overall, it appears that after many decades of failed or only partly successful attempts, we are now in a position to finally realize hypothermia's therapeutic potential in various types of injury, provided the proper precautions are taken and provided that our supportive treatments will be first-class.

References

1. Hippocrates (460-375 BC). De Vetere Medicina. Translation: Jones WHS, Withington ET. Hippocrates. Loeb Classical Library.
2. Celcus AC (1ST century AD) De Medicina. Translation: Spencer WG: DE Medicina. Loeb Classical Library.
3. Galaenus C (129-199 AD) Opera Omnia (Medicorum Graecorum Opera). Translation: Brock AJ. Galaenus: On the natural faculties.
4. Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. *Assoc Res Nerv Ment Dis Proc* 1945; **24**: 611-619
5. Benson DW, Williams GR, Spencer FC. The use of hypothermia after cardiac arrest. *Anesth Analg* 1958; **38**: 423-428
6. Williams GR Jr, Spencer FC. The clinical use of hypothermia following cardiac arrest. *Ann Surg* 1958; **148**: 462-468
7. Woringer E, Schneider J, Baumgartner J, Thomalske G. Essai critique sur l'effet de l'hibernation artificielle sur 19 cas de souffrance du tronc cérébral après traumatisme sélectionnés pour leur gravité parmi 270 comas postcommotionels. *Anesth Analg* (Paris) 1954; **11**: 34-45
8. Sedzimir CB. Therapeutic hypothermia in cases of head injury. *J Neurosurg* 1959; **16**: 407-414
9. Lazorthes G, Campan L. Hypothermia in the treatment of craniocerebral traumatism. *J Neurosurg* 1958; **15**: 162-167
10. Hendrick EB. The use of hypothermia in severe head injuries in childhood. *Ann Surg* 1959; **79**: 362-364
11. Bohn DJ, Biggar WD, Smith CR, Conn AW, Barker GA. Influence of hypothermia, barbiturate therapy, and intracranial pressure monitoring on morbidity and mortality after near-drowning. *Crit Care Med* 1986; **14**: 529-534
12. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346**: 557-563
13. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; **346**: 549-556
14. Bernard OS. Induced hypothermia in intensive care medicine. *Anaesth Intensive Care* 1996; **24**: 382-388
15. Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *J Neurosurg* 1993; **79**: 363-386
16. Tateishi A, Soejima Y, Taira Y Nakashima K, Fujisawa H, Tsuchida E, Maekawa T, Ito H. Feasibility of the titration method of mild hypothermia in severely head-injured patients with intracranial hypertension. *Neurosurgery* 1998; **42**: 1065-1069
17. Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes RL, Choi SC. A phase II study of moderate hypothermia in severe brain injury. *Journal of Neurotrauma* 1993; **10**: 263-271
18. Jiang J-Y, Yu M-K, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *J Neurosurg* 2000; **93**: 546-549
19. Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997; **336**: 540-546
20. Hayashi S, Inao S, Takayasu M, Kajita Y, Ishiyama J, Harada T, Yoshida J. Effect of early induction of hypothermia on severe head injury. *Acta Neurochir Suppl* 2002; **81**: 83-84
21. Tokutomi T, Morimoto K, Miyagi T, Yamaguchi S, Ishikawa K, Shigemori M. Optimal temperature for the management of severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. *Neurosurgery* 2003; **52**: 102-111
22. Metz C, Holzschuh M, Bein T, Woertgen C, Frey A, Frey I, Taeger K, Brawanski A. Moderate hypothermia in patients with severe head injury: cerebral and extracerebral effects. *J Neurosurg* 1996; **85**: 533-541
23. Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar JP, Wagner FC, Marion DW, Luerssen TG, Chesnut RM, Schwartz M . Lack of Effect of Induction of Hypothermia after Acute Brain Injury. *N Engl J Med* 2001; **344**: 556-563
24. Polderman KH, Tjong Tjin Joe R, Peerdeman SM, Vandertop

WP, Girbes ARJ. Effects of artificially induced hypothermia on intracranial pressure and outcome in patients with severe traumatic head injury. *Intensive Care Med* 2002; **28**: 1563-1567
25. Zhi D, Zhang S, Lin X. Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surg Neurol* 2003; **59**: 381-385
26. Shiozaki T, Hayakata T, Taneda M, Nakajima Y, Hashiguchi N, Fujimi S, Nakamori Y, Tanaka H, Shimazu T, Sugimoto H. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. Mild Hypothermia Study Group in Japan. *J Neurosurg* 2001; **94**: 50-54
27. Hale SL, Dae MW, Kloner RA. Marked reduction in no-reflow with late initiation of hypothermia in a rabbit myocardial infarct model. *J Am Coll Cardiol* 2003; **41**(6 Suppl B): 381-382
28. Hale SL, Dae MW, Kloner RA. Hypothermia during reperfusion limits 'no-reflow' injury in a rabbit model of acute myocardial infarction. Cardiovasc Res 2003; 59: 715-722
29. Hale SL, Kloner RA. Elevated body temperature during myocardial ischemia/reperfusion exacerbates necrosis and worsens no-reflow. *Coron Artery Dis* 2002; **13**: 177-181
30. Hale SL, Kloner RA. Myocardial temperature reduction attenuates necrosis after prolonged ischemia in rabbits. *Cardiovasc Res* 1998; **40**: 502-507
31. Miki T, Liu GS, Cohen MV, Downey JM. Mild hypothermia reduces infarct size in the beating rabbit heart: a practical intervention for acute myocardial infarction? *Basic Res Cardiol* 1998; **93**:372-383
32. Hale SL, Dave RH, Kloner RA. Regional hypothermia reduces myocardial necrosis even when instituted after the onset of ischemia. *Basic Res Cardiol* 1997; **92**: 351-357
33. Hale SL, Kloner RA. Myocardial temperature in acute myocardial infarction: protection with mild regional hypothermia. *Am J Physiol* 1997; **273**(1 Pt 2): H220-227
34. Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *Am J Physiol Heart Circ Physiol* 2002; **282**: H1584-591
35. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, Jenkins JS, Baim DS, Gibbons RJ, Kuntz RE, Popma JJ, Nguyen TT, O'Neill WW. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol* 2002; **40**: 1928-1934
36. Milde LN. Clinical use of mild hypothermia for brain protection: a dream revisited. *J Neurosurgical Anesthesiology* 1992; **4**: 211-215
37. Small DL, Morley P, Buchan AM. Biology of ischemic cerebral cell death. *Prog Cardiovasc Dis* 1999; **42**: 185-207
38. Polderman KH. Therapeutic hypothermia in the Intensive Care unit: problems, pitfalls and opportunities (review). Part 1: indications and evidence. *Intensive Care Medicine* 2004 (in press; http://dx.doi.org/10.1007/s00134-003-2152-x).
39. Ghajar J. Traumatic brain injury. *Lancet* 2000; **356**: 923-929
40. Reinert MM, Bullock R. Clinical trials in head injury. *Neurol Res* 1999; **21**: 330-338
41. Eisenberg MS, Horwood BT, Cummins RO, Reynolds-Haertle R, Hearne TR (1990) Cardiac arrest and resuscitation: a tale of 29 cities. *Ann Emerg Med* 1990; **19**: 179-186
42. Bernard SA. Outcome from prehospital cardiac arrest in Melbourne, Australia. *Emerg Med* 1998; **10**: 25-29
43. Berger R, Kelley M. Survival after in-hospital cardiopulmonary arrest of non critically ill patients - a prospective study. *Chest* 1994; **106**: 872-879
44. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. *Lancet* 1994; **343**: 1055-1059
45. Sterz F, Zeiner A, Kurkciyan I, Janata K, Mullner M, Domanovits H, Safar P. Mild resuscitative hypothermia and outcome after cardiopulmonary resuscitation. *J Neurosurg Anesthesiol* 1996; **8**: 88-96
46. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med* 1997; **30**: 146-153
47. Yanagawa Y, Ishihara S, Norio H, Takino M, Kawakami M, Takasu A, Okamoto K, Kaneko N, Terai C, Okada Y. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation* 1998; **39**: 61-66
48. Nagao K, Hayashi N, Kanmatsuse K, Arima K, Ohtsuki J, Kikushima K, Watanabe I. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. *J Am Coll Cardiol* 2000; **36**: 776-783
49. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003; **56**: 9-13
50. Polderman KH, Sterz F, van Zanten ARH, Uray T, Losert H, de Waal R, Girbes ARJ, Holzer M. Induced hypothermia improves neurological outcome in asystolic patients with out-of hospital cardiac arrest. *Circulation* 2003; **108**: IV-581 (abstract 2646)
51. Narayan RK. Hypothermia for traumatic brain injury--a good idea proved ineffective. *N Engl J Med* 2001; **344**: 602-603.
52. Clifton GL, Choi SC, Miller ER, Levin HS, Smith jr KR, Muizelaar JP, Wagner FC, Marion DW, Luerssen TG. Intercenter variance in clinical trials of head trauma – experience of the national acute brain injury study: hypothermia. *J Neurosurg* 2001; **95**: 751-55
53. Polderman KH, Peerdeman SM, Girbes ARJ. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. *Journal of Neurosurgery* 2001; **94**: 697-705
54. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Guidelines for cerebral perfusion pressure. *J Neurotrauma* 2000; **17**: 507-511
55. Fearnside MR, Cook RJ, McDougall P, McNeil RJ. The Westmead Head Injury Project outcome in severe head injury. A comparative analysis of pre-hospital, clinical and CT variables. *Br J Neurosurg* 1993; **7**: 267-279
56. McIntyre LA, Fergusson DA, Hebert PC, Moher D, Hutchison JS. Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. *JAMA* 2003; **289**: 2992-2999 (Review)
57. Polderman KH. Therapeutic hypothermia in the Intensive Care unit: problems, pitfalls and opportunities (review). Part 2: practical aspects and side effects. *Intensive Care Medicine* 2004 (in press; http://dx.doi.org/10.1007/s00134-003-2151-y)
58. Frank SM, Fleisher LA, Olson KF, Gorman RB, Higgins MS, Breslow MJ, Sitzmann JV, Beattie C. Multivariate determinates of early postoperative oxygen consumption: the effects of shivering, core temperature, and gender. *Anesthesiology* 1995; **83**: 241-249
59. Horvath SM, Spurr GB, Hutt BK, Hamilton LH. Metabolic cost of shivering. *J Appl Physiol* 1956; **8**: 595-602
60. Frank SM, Satitpunwaycha P, Bruce SR, Herscovitch P, Goldstein DS. Increased myocardial perfusion and sympathoadrenal activation during mild core hypothermia in awake humans. *Clin Sci* (Lond) 2003; **104**: 503-508
61. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. *Circulation* 1998; **77**: 43-52
62. Aibiki M, Kawaguchi S, Maekawa N. Reversible hypophosphatemia during moderate hypothermia therapy for brain-injured patients.

Crit Care Med 2001; **29**: 1726-1730
63. McIntosh TK Vink R, Yamakami I, Faden AI. Magnesium protects against neurological deficit after brain injury. *Brain Res* 1989; **482**: 252-260
64. Vink R. Decline in intracellular free Mg^{2+} is associated with irreversible tissue injury after brain trauma. *J Biol Chem* 1988; **263**: 757-761
65. Vink R, Cernak I. Regulation of intracellular free magnesium in central nervous system injury. *Front Bioscience* 2000; **5**: 656-665
66. Polderman KH, Zanten ARH van, Girbes ARJ. The importance of magnesium in critically ill patients: a role in mitigating neurological injury and in the prevention of vasospasms. *Intensive Care Med* 2003; **29**: 1202-1203
67. Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW. Association of hypomagnesemia and mortality in acutely ill medical patients. *Crit Care Med* 1993; **21**: 203-209
68. Polderman KH, Bloemers F, Peerdeman SM, Girbes ARJ. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Critical Care Medicine* 2000; **28**: 2022-2025
69. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *New Engl J Med* 2001; **345**: 1359-1367
70. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA* 2003; **290**: 2041-2047
71. Schwab S, Georgiadis D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke* 2001; **32**: 2033-2035
72. Kurz A, Sessler DI, Lenhardt R, and the Study of Wound Infection and Temperature Group. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *New Engl J Med* 1996; **334**: 1209-1215
73. Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology* 2001; **95**: 531-543
74. Sheffield CW, Sessler DI, Hunt TK. Mild hypothermia during isoflurane anesthesia decreases resistance to E. Coli dermal infection in guinea pigs. *Acta Anesthesiol Scand* 1994; **38**: 201-205
75. Sheffield CW, Sessler DI, Hunt TK, Scheuenstuhl H. Mild hypothermia during halothane anesthesia decreases resistance to S. Aureus dermal infection in guinea pigs. *Wound Rep Reg* 1994; **2**: 48-56