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REVIEW

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Application of therapeutic hypothermia in the intensive care unit

Opportunities and pitfalls of a promising treatment modality—Part 2: Practical aspects and side effects

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Abstract Induced hypothermia can be used to protect the brain from post-ischemic and traumatic neurological injury. Potential clinical applications and the available evidence are discussed in a separate paper. This review focuses on the practical aspects of cooling and physiological changes induced by hypothermia, as well as the potential side effects that may develop. These side effects can be serious and, if not properly dealt with, may negate some or all of hypothermia's potential benefits. However, many of these side effects can be prevented or modified by high-quality intensive care treatment, which should include careful monitoring of fluid balance, tight control of metabolic aspects such as glucose and electrolyte levels, prevention of infectious complications and various other interventions. The speed and duration of cooling and rate of rewarming are key factors in determining whether hypothermia will be effective; however, the risk of side effects also increases with longer duration. Realizing hypothermia's full therapeutic potential will therefore require meticulous attention to the prevention and/or early treatment of side effects, as well as a basic knowledge and understanding of the underlying physiological and pathophysiological mechanisms. These and other, related issues are dealt with in this review.

Keywords Review · Induced hypothermia · Neurological injury · Neuroprotection · Side effects · Physiological changes · Cardiopulmonary resuscitation (CPR) · Arrhythmias · Coagulation · Shivering · Electrolyte disorders · Intracranial pressure · Ischemic brain injury · Reperfusion injury

Introduction

Induced hypothermia is being used with increasing frequency to provide protection for the brain, spinal cord and perhaps other organs, such as the heart, against post-ischemic and post-traumatic injury. A large body of evidence from animal experiments suggests that hypothermia may be effective in various clinical situations if applied appropriately and quickly enough. These observations have been confirmed by an increasing number of clinical studies showing that hypothermia can be successfully used clinically for indications such as post-hypoxic injury following cardiopulmonary resuscitation (CPR). These issues and the evidence supporting various clinical applications of induced hypothermia are discussed in a separate review.

The expanding use of hypothermia in medicine means that most intensivists and others working in the ICU are likely to be confronted with patients who are treated with artificial cooling. Therefore, it is important that those employing hypothermia as a medical tool obtain a basic understanding of the underlying mechanisms, the physiology of temperature regulation and the many physiological changes taking place when a patient is cooled. Moreover, hypothermia can be a two-edged sword; although significant benefits can be achieved, there are

many potential side effects that, if left untreated, can diminish or even negate the potential benefits. These side effects, as well as physiological changes associated with cooling and various practical aspects in inducing hypothermia, are the topic of this review.

Physiology and mechanisms

Physiology of temperature regulation and induction of hypothermia

The human body can be roughly divided into two thermal compartments: a "core" compartment, consisting of the trunk and head, excluding the skin, and a "peripheral" compartment, consisting of the skin and extremities. Under normal circumstances core body temperature is strictly regulated around a set point of 36.60±0.38°C. Slight variations in this set point occur in the course of a day; usually body temperature is highest at ±18:00 h. The temperature of the peripheral compartment is less strictly controlled and, under normal circumstances, is 2–4°C lower than the core temperature. This difference increases in cold environments and decreases in warm environments. The core temperature is regulated by limiting or increasing heat transfer to the periphery through vasodilation or vasoconstriction; in turn; heat loss from the peripheral compartment is regulated through changes in skin perfusion (again through vasodilation or vasoconstriction) and by increasing or decreasing the production of sweat. When warm blood flows from the core to the periphery, heat is transferred from the blood to the surrounding tissues and to the cooler tissue near the skin. The rate of conduction from peripheral blood vessels to the outside depends on the *diffusion coefficient*, which is determined by tissue characteristics. For example, fat insulates about three times as well as muscle, so that obese patients will lose heat more slowly than those who are lean [1, 2]. In experiments in healthy volunteers, the increase in metabolic rate due to shivering is attenuated by the square root of percent body fat [2]. In addition, there are differences between different muscle groups in regard to the intensity of shivering and the amount of heat that can be generated. Muscles of the trunk region began to shiver sooner, and at a higher intensity, than those of the limbs [2].

Apart from sweat production *(evaporation),* heat loss can occur via *convection*, *conduction* and *radiation* (Table 1). The amount of heat loss depends on the temperature gradient, exposed surface and thermal conductivity. At rest and under normal circumstances 50–70% of the heat loss in awake patients occurs through radiation [1, 3]. In sedated patients in the ICU most heat loss will occur via radiation and convection. When patients are actively cooled this is often accomplished by facilitating convection and/or conduction, as well as by facilitating the transfer of heat from the core to the peripheral compartment (see below).

Induction of hypothermia

If hypothermia develops (either accidentally or intentionally induced), the body will immediately try to counteract this disturbance in homeostasis. The initial response will be to decrease heat loss, mainly through increasing sympathetic tone and through vasoconstriction in the skin. This response complicates attempts to induce therapeutic hypothermia by external cooling (see below). In addition, heat production will be increased through shivering and, in later phases, through the increased metabolism of fats, carbohydrates and proteins. Shivering can lead to increases in oxygen consumption of between 40% and 100% [4, 5, 6], an undesirable effect particularly in patients with neurological and/or posthypoxic injury. These responses can be counteracted by the administration of sedatives, anesthetics, opiates and/or paralyzing drugs (see below). Sedation and anesthesia also increase

Table 1 Mechanisms of heat loss

Mechanism	Definition	Influencing factors
Radiation	Transfer of heat between the separated surfaces of two objects with different temperatures via electromagnetic (infrared) radiation, without direct contact between the objects and without a heat transfer medium. Accounts for 50–70% of heat loss in awake patients	Independent of temperature of surrounding air; depends on temperature and emissivity of surrounding objects
Conduction	Direct transfer of heat from one surface to a second, adjacent surface. Amount of heat loss is closely related to contact surface; in standing patients heat loss through conduction is negligible, but this increases in the sitting or lying position	Difference in surface temperatures; insulation between these surfaces
Convection	Transfer of heat from a surface to the surrounding air. Accounts for 20–30% of heat loss at room temperature in the absence of wind	Difference in temperature between surface and air; (speed of) movement of air ("wind chill factor")
Evaporation	Heat loss derived from the evaporation of water from skin & lungs. Accounts for ±15% of heat loss (5% from the skin, 10% from the lungs) under non-sweating circumstances	Influenced by saturated vapor pressure at skin, temperature & the air

peripheral blood flow, thereby increasing the transfer of heat from the core to the periphery. As explained above, the rate of heat loss is determined by the temperature gradient, body composition and the conductive properties of the environment. For example, water is a much better conductor of heat than air and, thus, wet skin will transfer heat much more easily than dry skin. Heat loss is further increased by the use of alcohol-based, rather than water-based, solutions.

It should be noted that the capacity and effectiveness of the mechanisms to control body temperature decrease with age. Younger patients will therefore react earlier and with greater intensity and effectiveness to changes in body temperature than older patients. In addition, older patients have a lower rate of metabolism, often a lower body mass index (BMI) and less effective vascular response (i.e., less vasoconstriction). Thus, in general, the induction of hypothermia in younger patients will be significantly more difficult than in older patients. Induction of hypothermia in younger patients often requires high doses of sedatives to counteract the above-mentioned counter-regulatory mechanisms. Similarly, achieving hypothermia through surface cooling in obese patients will take more time due to the insulating properties of fat. This implies that the surface cooling of obese patients will be more difficult and require significantly more time to achieve target temperatures.

Metabolic and cellular effects of hypothermia

Hypothermia affects many intracellular processes. Some of these are directly related to its protective effects; these aspects are discussed in more detail in Part 1 of this review. Here we will focus on those features that are relevant to physiological and pathophysiological changes induced by cooling. These changes are listed in Tables 2, 3 and 4.

Hypothermia leads to a lowering of the metabolic rate. Indeed, in the past it was assumed that the protective effects of hypothermia were due solely to the slowing of cerebral metabolism, with associated decreases in consumption of glucose and oxygen. It has since become clear that other mechanisms are involved, which probably play a much greater role than the changes in metabolic rate. These issues are discussed in Part 1 of this review. Nevertheless, the effects on metabolism are significant and probably do play a part in providing neuroprotection.

Table 2 Physiologic effects of mild to moderate hypothermia. These effects occur, to varying degrees, in most or all patients when hypothermia is induced. The temperature limits below which these effects occur are estimates and are influenced by age and co-morbidity (especially cardiovascular disease)

System	Temperature	Effect
Physiological 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 ↓ Carbon dioxide 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 adrenaline and noradrenaline
	≤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	ECG changes: increased PR-interval, widening of QRS-complex, increased QT interval
	≤28–30°C	↑↑ Risk of tachyarrhythmias, beginning with atrial fibrillation
	≤35°C	↑ central venous pressure and ↓ cardiac output
	≤35°C	↑ or = mixed venous saturation
Renal	≤35°C	↑ Diuresis, tubular dysfunction, electrolyte loss & electrolyte disorders
Hematological	≤35°C	↓ Platelet count, impaired platelet function, impaired coagulation cascade
	≤33°C	↓ White blood cell count, impaired leukocyte function
Gastrointestinal	≤35°C	Impaired bowel function/impaired intestinal motility/ileus, 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, propanol and volatile anesthetics (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

Table 3 Frequently occurring changes in laboratory measurements induced by hypothermia. The extent of these changes depends on the degree of hypothermia; the lower body temperature, the more pronounced the changes in laboratory values will be

Frequency	Effect
Almost always	Mild to moderate increase in serum amylase levels (300–600 μ/l)
	Mild thrombocytopenia (platelet count 100–150x10^{12})
	Increase in serum lactate levels (2.5–5 mmol/l)
Frequent	Moderate to severe thrombocytopenia (platelet count 30–100x10^{12})
	Rise in serum glucose levels (due to decreased insulin sensitivity and decreased insulin secretion)
	High serum amylase levels (600–1200 μ/l)
	High serum lactate levels (5–7 mmol/l)
	Decrease in levels of potassium (K), magnesium (Mg), phosphate (P), calcium (Ca)
	Leukocytopenia (WBC (2–3x10^{9}/l)
Occurring regularly	Mild increase in liver enzymes (particularly SGOT and SGPT)
	Metabolic acidosis (due to increase in lactate levels and increased production of free fatty acids, ketones and glycerol)
	Slightly increased APTT and APTT
Occurring occasionally	Manifest acidosis, lactate levels $\geq$7 mmol/l
	Severe leukocytopenia (WBC <2x10^{9})
	Increase in serum amylase $\geq$1200 μ/l
	Severe thrombocytopenia (platelet count $\leq$30x10^{12})
	Manifest coagulation disorders with marked increase in APTT and PTT

Table 4 Potential side effects of hypothermia. These are effects that occur relatively frequently during induction of hypothermia and that are often unwelcome. Many of these effects can be prevented or counteracted, or the effects mitigated. Physicians applying therapeutic hypothermia should be aware of these potential side effects

Frequency/ degree of risk	Effect
High risk	Coagulopathy: increased bleeding time, increased APTT/CT, thrombocytopenia, thrombocytopathia
	Impaired coagulation cascade
	Electrolyte disorders[a] (loss of K, Mg, P, Ca)
	Hypovolemia (due to increased diuresis/hypothermia-induced diuresis)[b]
	Rise in serum amylase
	Changes in drug effects & drug metabolism
	Insulin resistance
Low risk	Manifest bleeding, severe coagulation disorders (possibly higher risk in trauma patients and/or patients who already have bleeding problems for other reasons; hypothermia-induced coagulopathy may increase extent and severity of bleeding in these cases. See discussion in "Practical aspects and side effects")
	Airway infections
	Wound infections and healing
	Myocardial ischemia
Rare	Manifest pancreatitis
	Intracerebral bleeding

[a] Depends on category of patients; higher risk in TBI and SAH, lower risk in post-anoxia/CPR
[b] Risk appears to be significantly higher in patients with TBI than in patients following CPR

In addition, these changes in metabolism occur in all organ systems; this means, for example, that there will be a decrease in oxygen consumption and carbon dioxide production (which implies that ventilator settings should be adjusted), a reduction in feeding requirements, etc. Metabolism is reduced by between 5% and 7% per Celsius degree reduction in body temperature [7, 8, 9]. Cerebral blood flow is also decreased, but, when corrected for the decrease in metabolism, the net result is a relative increase.

Many hypothermia-induced metabolic changes occur relatively quickly, within the first few hours. These include changes in energy metabolism and decreases in adenosine tri-phosphate (ATP) demand. Other changes, such as a rise in lactate levels, occur over a longer period of time (>3 h). Induction of hypothermia also leads to an increase in membrane stability, with decreased permeability of cellular membranes, the blood-brain barrier and blood vessel walls [10, 11, 12, 13, 14]. One of the consequences of this is a decrease in edema formation, that appears to be one of the ways in which hypothermia can protect against neurological injury. In addition, hypothermia can prevent or mitigate the excessive influx of Ca^{2+} into the cell, as well as decrease accumulation of the excitatory neurotransmitter glutamate in the extracellular space [15]. Calcium influx and glutamate accumulation are key elements in the destructive cascade that can follow a period of ischemia; calcium influx into the cell can lead to mitochondrial dysfunction and the activation of various enzymes which can cause additional cell injury and death [15]. Hypothermia also leads to a decrease in intracellular acidosis (although the extracellular pH usu-

ally decreases slightly during cooling, due to increased levels of lactic acid, glycerol, free fatty acids and ketonic acids; see below).

Hypothermia also influences the immune system, with an inhibition of neutrophil and macrophage function, suppression of inflammatory reactions and inhibition of the release of pro-inflammatory cytokines [16, 17, 18]. This effect on immune response may contribute to hypothermia's neuroprotective effects, but, of course, increases the risk of infections (see below). Other anti-inflammatory mechanisms include the prevention or mitigation of reperfusion-related DNA injury, lipid peroxidation and leukotriene production as well as a decrease in the production of nitric oxide [19, 20]. In addition, hypothermia decreases reperfusion injury and free radical production [19].

Practical aspects and side effects

Induction of hypothermia causes a large number of physiological changes in the circulatory and respiratory systems, coagulation system, drug metabolism, etc. (listed in Table 2). For the successful use of hypothermia, awareness of these physiological effects and pathophysiological mechanisms is of key importance. The failure to demonstrate positive effects of hypothermia in some clinical trials may be partly due to insufficient regard for side effects causing the (partial) negation of protective effects. In addition, unawareness of hypothermia's physiological consequences may lead to over-treatment. For example, even mild hypothermia induces decreases in cardiac output, mild acidosis, a rise in lactate levels and a moderate increase in levels of amylase. These changes are normal, do not signify any deterioration in the patients' condition and do not require treatment. Naturally, such changes can sometimes be unwanted, such as shivering with its associated rise in oxygen consumption and patient discomfort. Many of these physiological effects can be counteracted by appropriate medication, such as sedatives, analgesics or paralyzers. The use of therapeutic hypothermia will usually require ICU admission and monitoring and often (but not always) sedation and intubation.

The physiological and pathophysiological effects of cooling largely depend on the degree of hypothermia. For example, a significant risk for severe arrhythmias occurs only at temperatures below 28–30°C. Such low temperatures are now rarely employed in induced hypothermia, although they are used more frequently in specific surgical procedures, such as major vascular surgery. This review will focus on the effects of mild to moderate hypothermia (31–35°C).

The physiological adaptations to hypothermia, changes in laboratory values and potential side effects are listed in Tables 2, 3 and 4. These changes depend to varying degrees on the patients' age, underlying disease, co-morbidity etc. Some of these changes can be suppressed or prevented by medication, appropriate sedation or other factors.

Cardiovascular and hemodynamic effects

Hypothermia is initially associated with sinus tachycardia, after which bradycardia develops. This is partly due to decreases in metabolism and partly to the direct effects of hypothermia on the heart. Various ECG changes may occur (listed in Table 2). The risk of arrhythmias during mild or moderate hypothermia is very low, but increases significantly when the temperature drops below 30°C. The initial arrhythmia is usually atrial fibrillation, which can be followed (at temperatures $\leq$28°C) by the risk of ventricular flutter or fibrillation. An additional problem is that arrhythmias in deeply hypothermic patients are difficult to treat, as the myocardium becomes less responsive to defibrillation and anti-arrhythmic drugs. When therapeutic hypothermia is applied, therefore, great care should be taken to keep temperatures at 30°C or more, as the risk of clinically significant arrhythmias increases exponentially below this temperature level.

Initially, the induction of mild hypothermia increases myocardial oxygen demand relative to supply; the mechanism is probably a hypothermia-induced increase in plasma levels of adrenaline and noradrenaline leading to an increase in cardiac output and oxygen demand [21]. With further reductions in temperature, decreases in heart rate and the slowing of metabolism will reduce cardiac afterload and oxygen demand. Mild hypothermia decreases cardiac output by about 25% and leads to increased vascular resistance and a rise in central venous pressure. During severe hypothermia ($\leq$30°C) left ventricular contractility itself may decrease, inducing systolic and diastolic dysfunction. In healthy subjects mild hypothermia (35.5°C) has been shown to increase coronary perfusion [21, 22]. However, one study reported that, in patients with pre-existent coronary artery disease, coronary vasoconstriction may occur during hypothermia [22]. This difference is presumed to be caused by endothelial dysfunction associated with atherosclerosis [21]. This would imply that there is a theoretical risk of myocardial injury during the induction of mild hypothermia in patients with cardiovascular disease, especially in the phase when cooling is initiated and the heart rate temporarily increases.

On the other hand, there is strong evidence from animal studies that the induction of hypothermia during or following myocardial infarction can decrease the infarct size [23, 24, 25, 26, 27, 28, 29, 30]. Hypothermia has been used in one clinical study in 42 patients with acute myocardial infarction undergoing emergency percutaneous coronary intervention [31]. Twenty-one patients were

treated with hypothermia for 3 h after reperfusion, the other patients served as controls. The hypothermia group had a trend to smaller infarct sizes and fewer major adverse cardiac events, though these differences did not reach statistical significance in this small number of patients. Although firm conclusions regarding the benefits for cases of myocardial infarctions cannot yet be drawn, these data do at least suggest that hypothermia did not adversely effect outcome in these patients with coronary artery disease.

Coagulation

Hypothermia induces a mild bleeding diathesis, with increased bleeding time due to its effect on platelet count [32, 33], platelet function [32, 33, 34], the kinetics of clotting enzymes and plasminogen activator inhibitors [35, 36] and other steps in the coagulation cascade [36, 37, 38]. It should be pointed out that the laboratory results of standard coagulation tests such as prothrombin time and partial thromboplastin times will remain normal, because these tests are usually performed at 37°C in the lab. Tests will be prolonged only if they are performed at the patient's actual core temperature [39]. However, in spite of the above-mentioned abnormalities, the risk of significant bleeding is very low, even in patients with traumatic brain injury (TBI) [40]. None of the clinical trials in patients with TBI, subarachnoid hemorrhage, stroke or post-anoxic coma have reported increased intracranial bleeding associated with cooling. These observations are confirmed by data from animal experiments showing decreased extravasation of hemoglobin during hypothermia [12]. Overall, few bleeding complications were seen in any of the major clinical trials using hypothermia, and risks of bleeding should therefore not preclude the use of hypothermia if deemed appropriate. Platelets and/or fresh frozen plasma can be administered to improve coagulation if necessary.

Coagulation disorders may be a greater problem in trauma patients. Here the use of therapeutic hypothermia is somewhat controversial and a potential conflict between 'protecting the brain and protecting the body' may arise. Various studies have reported an association between hypothermia and adverse outcome in trauma patients [41, 42, 43]; this link has given hypothermia an ominous reputation among trauma surgeons and has led to recommendations of the aggressive re-warming of trauma patients. However, its should be pointed out that most of these studies were uncontrolled and retrospective, and in most cases no multivariate analysis was performed to correct for potential confounders [review of this issue: 44]. One study that did perform multivariate analysis, correcting for factors such as presence of shock (associated with both hypothermia and adverse outcome, and therefore a potential confounder) concluded that hypothermia is a marker, but not a cause, of adverse outcome [45]. Thus, although hypothermia does induce a degree of coagulopathy, its reputation in trauma patients may be partly undeserved; the use of therapeutic hypothermia in trauma patients should, therefore, not be automatically excluded. This view is underscored by observations that active re-warming of hypothermic patents with TBI may adversely affect outcome [46]. We therefore recommend that the use of hypothermia be considered in trauma patients who meet inclusion criteria as set out in Part 1 of this review (for example, patients who have undergone CPR with unclear neurological outcome) provided they do not have active bleeding and are hemodynamically stable.

Infection

Evidence from clinical and in vitro studies shows that hypothermia can impair immune function. Indeed, (as discussed above) inhibition of inflammatory responses may be one of the mechanisms through which hypothermia exerts neuroprotective effects. Hypothermia inhibits the release of various pro-inflammatory cytokines [16, 17] and suppresses chemotactic migration of leukocytes and phagocytosis [47]. Hypothermia-induced insulin resistance and hyperglycemia may further increase infection risks (see below). Thus, there are plausible mechanisms for an immunosuppressive effect of hypothermia.

A number of studies, mostly in patients with stroke or TBI, have indeed reported higher risks of pneumonia when therapeutic hypothermia is used over longer periods of time ($\geq$48–72 h) [48, 49]. However, other studies using hypothermia for prolonged periods in patients with TBI reported no increase in infection rates [50, 51]. This may be attributable to antibiotic prophylaxis or selective decontamination of the digestive tract (SDD), which were used in some of these studies [51]. Short-term cooling ($\leq$24 h) does not appear to increase the risk of infection [50, 52, 53]. Overall, the risk of respiratory tract infections appears to increase when patients are cooled for 48 h or more; this problem appears manageable with rigorous surveillance and, perhaps, prophylactic measures.

Some studies have also reported a higher risk of wound infections associated with hypothermia [54, 55]. This may be related to both diminished leukocyte function and hypothermia-induced vasoconstriction. Animal studies have shown that the establishment of infection probably occurs within the first 3 h of bacterial inoculation [55, 56, 57] and is facilitated by local vasoconstriction and hypoperfusion. This may be important in patients requiring surgery during treatment with hypothermia. Moreover, other wounds, including bed sores and catheter insertion sites, are more likely to show progression and/or impaired healing during cooling.

Hypovolemia, fluid balance and electrolytes

The induction of hypothermia can lead to the loss of significant amounts of fluids, due to so-called hypothermia-induced diuresis [58, 59, 60, 61]. This may be especially pronounced in patients with TBI, in whom diabetes insipidus, induced by cranial trauma, and administration of medication such as mannitol may exacerbate fluid losses [51, 59, 60]. The impact of this may be significant, especially in patients with TBI or subarachnoidal hemorrhage (SAH) where even very brief episodes of hypovolemia or hypotension can significantly, and adversely, affect outcome [62, 63, 64]. Indeed, any beneficial effects of hypothermia may be lost due to side effects if these are not treated proactively and vigorously [58]. Therefore, close attention should be paid to the patients' diuresis and fluid balance especially during *induction* of hypothermia (i.e., the phase when the patients' body temperature is decreasing, which is the phase when excessive diuresis and hypovolemia are most likely to occur [51, 58, 59]). In our center we infuse 500–1000 ml of saline and electrolytes (see below) in TBI patients upon initiation of cooling (provided the patients are young and have no significant counter-indications) and supplement fluid losses that occur during cooling [51, 58, 59]. However, these problems are much less evident in other categories of patients, such as those with post-anoxic coma following CPR [52, 53, 65]. The reason for this difference is probably that the risk of excessive fluid loss in TBI patients is caused by a combination of hypothermia and other factors, such as the administration of mannitol to decrease intracranial pressure.

Another important problem is induction of electrolyte disorders. We and others have observed severe electrolyte disorders (i.e., low levels of Mg, K, P and Ca) during cooling of patients with TBI [59, 66]. Such electrolyte disorders can cause cardiac arrhythmias as well as hypotensive episodes with decreases in cerebral blood flow. Magnesium may be especially important in this regard, because of its specific role in mitigating neurological injuries [67, 68, 69, 70, 71]. Intracellular free magnesium in the brain declines by up to 60% following moderate traumatic brain injury in rats [72]. Numerous animal studies have shown that magnesium depletion leads to significantly worse outcomes in experimental TBI; administration of magnesium before or even after trauma substantially mitigates secondary injury and reduces the loss of cortical cells [67, 68, 69, 73, 74, 75, 76]. Magnesium may also play a role in the prevention of reperfusion injury, which is one of the key mechanisms underlying secondary neurological injury [76]. In addition, loss of magnesium is associated with vasoconstriction of cerebral and coronary arteries [77, 78, 79].

Clinical studies in ICU patients have shown that hypomagnesemia is associated with adverse outcome [80]. Severe head injury itself is associated with significant loss of electrolytes including magnesium [71]; thus many patients with TBI have hypomagnesemia at admission [71], which subsequently can be significantly exacerbated by the induction of hypothermia [59]. Electrolyte disorders are easily treated or prevented; physicians utilizing induced hypothermia should be aware of these risks. It should be noted that serum levels do not always accurately reflect magnesium status [79], and in our opinion magnesium levels should be maintained in the high or high-normal range in all patients with neurological injury [70]. Other electrolytes, such as phosphorus and potassium, should also be monitored closely and maintained in the high-normal range [70].

Other metabolic effects

Hypothermia decreases insulin sensitivity and insulin secretion, which can lead to hyperglycemia. Hyperglycemia is associated with increased infection rates, increased incidence of renal failure and critical illness neuropathy and various other complications, while prevention of hyperglycemia and tight control of glucose levels may decrease morbidity and mortality in ICU patients [81]. These protective effects are due to the prevention of hyperglycemia *per se* rather than to the direct effects of insulin [82, 83]. This underscores the importance of tight glucose regulation, especially in patients treated with hypothermia in whom hyperglycemia is more likely to develop. The amounts of insulin required to maintain glucose levels within the normal range are likely to increase during the induction of hypothermia, and physicians applying hypothermia should be aware of this phenomenon.

Hypothermia also induces mild acidosis through various mechanisms including increased synthesis of glycerol, free fatty acids, ketonic acids and lactate. These changes are normal metabolic consequences of hypothermia and should not be attributed to complications such as bowel ischemia.

Shivering

As discussed in "Physiology and mechanisms", the body will employ various mechanisms to generate heat, including shivering which may increase oxygen consumption and patient discomfort. In ventilated patients this can be counteracted by the administration of sedatives and analgesics or, if deemed appropriate, the administration of muscle paralyzers. Shivering can be attenuated by relatively small doses of opiates; meperidine (pethidine) appears to be somewhat more effective in this regard due to a higher activity at the kappa receptor [15]. This means that lower doses (12.5–25 mg) can be used, which may be especially important if hypothermia is used in awake

patients. When using paralyzers and/or opiates is deemed undesirable, alternatives with which to treat shivering include the administration of clonidine, neostigmine and ketanserine. However, care should be taken to avoid adverse effects; for example, clonidine may aggravate hypothermia-induced bradycardia.

Miscellaneous

Another important issue is the effect of hypothermia on drug metabolism and pharmacokinetics. The enzymes that metabolize most drugs are highly temperature-sensitive and, thus, drug metabolism is significantly affected by hypothermia. Clearance of various drugs is decreased and in most patients doses should be lowered during hypothermia. Unfortunately, few data are available regarding the effects of hypothermia on the metabolism of specific drugs. However, the studies that have been carried out confirm the expectation that plasma levels increase and the effects of drugs are prolonged. For example, plasma levels of propofol increase by approximately 30% and of fentanyl by 15% when individuals are 3°C hypothermic [55]. A number of the medications for which data are available are listed in Table 2.

Cooling methods and practical guidelines

Methods to induce hypothermia

There are numerous strategies to cool patients, based on the four basic mechanisms for heat loss: convection, conduction, evaporation and radiation. In addition, heat generation in patients with hyperthermia can sometimes be reduced by antipyretic agents. However, in patients with elevated temperature caused by impaired thermoregulation (such as central fever or heat stroke) these agents are often ineffective. Various cooling techniques have been used in in vitro and clinical studies, including ice-water circulating blankets, ice bags, air mattresses, cooling catheters, intravenous infusion of cooled fluids (4°C) followed by cooling through other methods, the infusion of extracorporeally cooled blood via the carotid artery, helmets and cooling caps with cold fluids or chemical cooling capabilities, ice-water nasal lavage, cold peritoneal lavage and cardiopulmonary bypass [31, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93]. The methods most commonly employed in the clinical setting are summarized in Table 5. Cooling caps and coils wrapped around the head have been used mainly in infants and neonates, but have also been tried in adults.

Most large clinical trials published so far have used either water-cooling or air-cooling blankets. Air-cooling blankets have also been used in general wards in awake patients [94, 95]. Water-cooling blankets are much more efficient for cooling than for warming patients, because

Table 5 Methods for inducing hypothermia

Method	Basic mechanism	Manufacturer
Peripheral cooling		
Fans[a]	Convection	-
Air-circulating cooling blankets	Convection	"Polar Air" and "Bair Hugger", Augustine Medical, Eden Prairie, USA
Ice packs	Conduction	-
Water-circulating cooling blankets	Conduction	"Blanketrol II hyper-hypothermia", Cincinnati Sub-Zero, Cincinnati, USA
Immersion	Conduction	-
Specially designed beds	Conduction	"TriaDyne", Kinetic Concepts International, San Antonio, USA
Cooling caps	Conduction	"Frigicap"
Water and alcohol sprays	Evaporation	-
Sponge baths	Evaporation	-
Exposure of skin	Radiation	-
Core cooling		
Intravascular catheters	Conduction	"Celcius Control", Innercool therapies, San Diego, USA "CoolLine" and "Coolgard", Alsius, Irvine, USA "SetPoint" and "Reprieve", Radiant medical, Redwood City, USA
Infusion of ice-cold (4°C) fluids	Conduction	-
Extracorporeal circulation	Conduction	Various devices
Antipyretic agents	Effect on CNS	Various drugs

[a] Use of fans to cool patients may be associated with increased infection risks

the temperature difference can be set much higher; during warming a set temperature above 40–42°C can cause burns, whereas the skin is much more tolerant of lower temperatures. As explained in "Physiology and mechanisms", the speed of inducing hypothermia may be important in achieving optimum effects. The times required to achieve target temperatures have varied considerably in the clinical trials published so far, ranging from approximately 2 h [51, 52] to around 8 h [46, 53] or even longer [49]. These time periods depend on patient factors (nature of the underlying disease or injury, age, sex, BMI), countermeasures to prevent shivering and heat generation, and on technical aspects such as the cooled surface, temperature of the blankets or air, cooling capacity, etc. In a recently published study in patients with TBI we were able to induce temperatures of 34°C or below in 95% of our patients within 2 h, by using two cooling blankets (above and below the patient) with the water temperature set at 4°C until the core temperature was 33°C or less (the target temperature being 32°C), and by using water and alcohol sprays and exposing the areas of skin that were not directly cooled [51]. Heat transfer from core to periphery may also be facilitated by the use of vasodilatory medication.

An even quicker method was described in a preliminary report by Bernard et al. [96], who used large volumes (30 ml/kg) of ice-cold (4°C) intravenous fluid (lactated Ringer's solution) to cool 22 comatose survivors of out-of-hospital cardiac arrest quickly. These authors were able to decrease core temperature from 35.5 to 33.8°C within 30 min with no adverse consequences, and concluded that this was an inexpensive and effective method of initially inducing mild hypothermia. We have used this method in selected cases in our own clinic with good results and no adverse effects.

A new development is the availability of intravascular cooling catheters such as the CoolLine, SetPoint and others (Table 5). These are central lines with two or three balloons filled with temperature-controlled saline, allowing direct intravascular (and, therefore, core) cooling via the subclavian, superior caval or femoral vein. Experience with these catheters has been relatively limited so far, although they are rapidly gaining in popularity. Initially, two small feasibility trials in six [90] and eight patients [91] reported that it was an effective, relatively quick method to induce and maintain hypothermia, and that it was less labor-intensive than the 'conventional methods' listed above. Of note, no thrombus formation on these catheters was observed upon removal in these studies. Endovascular cooling has also been used to induce brief periods of hypothermia in 20 non-sedated patients undergoing percutaneous coronary intervention with the aim of reducing infarct size [31]. A larger trial using this device to cool 51 patients with hyperthermia in a neurosurgical ICU has recently been published; the authors reported that the device was safe and effective in inducing hypothermia [92]. However, no studies have yet been published in which these devices have been used for longer-term (>24 h) cooling.

Yet more novel approaches include the use of selective brain cooling [86], peritoneal cooling [88] and ice-water nose cooling [93]. Experience with these methods is limited to animal studies and/or small case series [93]. Treatment with paracetamol or acetaminophen may serve as an accessory method to lower temperature, especially in patients with hyperthermia, although their effectiveness in patients with neurological injury is limited [94].

Practical guidelines

Therapeutic hypothermia can be used in various types of neurological injury and perhaps for other indications, such as the prevention of reperfusion injury. The use of hypothermia will often require intubation, mechanical ventilation, sedation and, at times, pharmacologic paralysis to prevent shivering. A major problem induced by these measures is that they may significantly hamper neurological assessment of the patient; thus patients should be carefully monitored for, for example, the development of seizures, which may present much less clearly. As outlined in "Practical aspects and side effects", the induction of hypothermia can cause a number of side effects; however, many of these can be prevented or attenuated. Fluid balance should be carefully monitored and hypovolemia and hypotension avoided, especially in patients with TBI or SAH. Electrolyte disorders (especially hypomagnesemia) and arrhythmias should be prevented, if necessary by the early or prophylactic administration of anti-arrhythmic agents. This also applies to hyperglycemia, which should be combated through intensive insulin therapy and frequent monitoring.

Infections should be prevented by early or even prophylactic treatment with antibiotics. Bleeding complications can be avoided by the timely administration of platelets or fresh frozen plasma, particularly if surgical interventions or invasive procedures are performed. From this perspective, realizing hypothermia's full therapeutic potential presents a great challenge to ICU physicians, requiring first-rate quality in many aspects of intensive care. This applies not only to intensivists but, in equal measure, to ICU nurses and others caring for critically ill patients in the ICU. Hypothermia-induced vasoconstriction of the skin and increased risk of wound infections will increase the risk of bed sores, as will the sedation and paralysis often required in these patients. The risk of respiratory tract infections may increase, requiring extra vigilance and interventions by the nursing staff, physiotherapist and others. Infections should be treated promptly and aggressively. The use of selective decontamination of the digestive tract should be considered in these patients.

The insertion sites of central venous catheters will require close monitoring and extra care. The patient may become relatively unstable, especially in the cooling phase while the core temperature is decreasing. Polyuresis, electrolyte disorders and hypotension may develop, especially in patients with TBI; ventilator settings will need to be changed as oxygen demand and production of carbon dioxide decrease due to the slowing of metabolism. Blood samples must be frequently drawn and analyzed on site or sent for analysis; the patient must be closely monitored for any signs of shivering, seizures etc. All this will, at least temporarily, increase the nursing work load. This is something to keep in mind as various studies have demonstrated that shortages of nursing and medical staff due to increased workload can adversely affect outcome [97].

The successful application of hypothermia thus requires a concerted team effort and the difficulties involved, as well as potential side effects and risks, should not be underestimated. Using this therapy requires vigilance, attentiveness and experience. ICUs considering the use of therapeutic hypothermia should adopt strict guidelines and protocols, and provide training for ICU physicians, nursing staff and other members of the ICU team. When hypothermia has been used it is important that patients should not be re-warmed too quickly, as this may have adverse effects especially in patients with TBI.

Summary and conclusions

A large body of evidence suggests that hypothermia can be used to prevent or limit damage to the injured brain and spinal cord, and perhaps the heart, in selected categories of patients. It is important to induce hypothermia as quickly as possible, as protection appears to be greater when cooling is initiated early (although benefits have been reported even when cooling was initiated many hours after injury). As shown in this review, the induction of hypothermia will affect every organ in the body and it is important that ICU staff members are aware of this and are able to distinguish physiological changes from pathophysiological side effects.

The successful application of hypothermia requires the use of strict protocols, vigilance by the medical and nursing staff, and close attention to the prevention of side effects. The volume status of patients treated with cooling should be monitored carefully, to prevent hypovolemia and hypotension. Other measures should include the frequent monitoring of electrolyte levels to avoid electrolyte disorders (especially hypomagnesemia) and prevention or early treatment of arrhythmias, if necessary by early or prophylactic administration of anti-arrhythmic agents. In addition, hyperglycemia should be avoided through intensive insulin therapy and frequent monitoring of glucose levels, and infections should be prevented by early or prophylactic treatment. Bleeding complications can be avoided by the administration of platelets or plasma if surgical interventions or invasive procedures are required. Patients should be re-warmed slowly, as too rapid re-warming can adversely affect outcome.

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