Mechanisms of action, physiological effects, and complications of hypothermia

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Background: **Mild to moderate hypothermia (32–35°C) is the first treatment with proven efficacy for postischemic neurological injury. In recent years important insights have been gained into the mechanisms underlying hypothermia's protective effects; in addition, physiological and pathophysiological changes associated with cooling have become better understood.**

Objective: **To discuss hypothermia's mechanisms of action, to review (patho)physiological changes associated with cooling, and to discuss potential side effects.**

Design: **Review article.**

Interventions: **None.**

Main Results: **A myriad of destructive processes unfold in injured tissue following ischemia–reperfusion. These include excitotoxicty, neuroinflammation, apoptosis, free radical production, seizure activity, blood–brain barrier disruption, blood vessel leakage, cerebral thermopooling, and numerous others. The severity of this destructive cascade determines whether injured cells will survive or die. Hypothermia can inhibit or mitigate all of these mechanisms, while stimulating protective systems such as early gene activation. Hypothermia is also effective in mitigating intracranial hypertension and reducing brain edema. Side effects include immunosuppression with increased infection risk, cold diuresis and hypovolemia, electrolyte disorders, insulin resistance, impaired drug clearance, and mild coagulopathy. Targeted interventions are required to effectively manage these side effects. Hypothermia does not decrease myocardial contractility or induce hypotension if hypovolemia is corrected, and preliminary evidence suggests that it can be safely used in patients with cardiac shock. Cardiac output will decrease due to hypothermia-induced bradycardia, but given that metabolic rate also decreases the balance between supply and demand, is usually maintained or improved. In contrast to deep hypothermia (≤30°C), moderate hypothermia does not induce arrhythmias; indeed, the evidence suggests that arrhythmias can be prevented and/or more easily treated under hypothermic conditions.**

Conclusions: **Therapeutic hypothermia is a highly promising treatment, but the potential side effects need to be properly managed particularly if prolonged treatment periods are required. Understanding the underlying mechanisms, awareness of physiological changes associated with cooling, and prevention of potential side effects are all key factors for its effective clinical usage. (Crit Care Med 2009; 37[Suppl.]:S186–S202)**

Key Words: hypothermia; normothermia; fever; mechanisms; neuroprotection; side effects; neurological injury; cardiac arrest; traumatic brain injury

When applying hypothermia in a clinical setting, it is important to be aware of the underlying mechanisms through which the treatment exerts its effects. Understanding these issues can help guide clinical decisions regarding the required depth and duration of the treatment, and help in understanding physiological changes and side effects occurring during mild (34°C–35.9°C), moderate (32°C–33.9°C), moderate-deep (30°C–31.9°C), and deep (<30°C) hypothermia (1). Insufficient understanding of these mechanisms is likely to decrease therapeutic efficacy, and can at worst lead to treatment failure. This is illustrated by early experiences with induced hypothermia in the treatment of cardiac arrest and traumatic brain injury (TBI), and other indications in the 1940s, 1950s, and 1960s (2–15). At that time, it was presumed that hypothermia exerted its effects exclusively through temperature-dependent reductions in metabolism, leading to decreased demand for oxygen and glucose in the brain. Patients were routinely treated with deep hypothermia (<30°C), based on the (erroneous) assumption that this was the sole mechanism of action, and that large reductions in temperature were required to achieve efficacy. In addition, core temperatures that were actually achieved varied considerably both between patients and within the same patient, because the available cooling and rewarming methods were not very reliable. The most frequently used cooling methods were placement of slabs of ice, ice pads, and refrigerated water on the patient's skin, and sometimes the opening of windows of the hospital wards during the winter months (to the disconcertment of some members of the medical and nursing staff) (11). Because intensive care facilities did not become widely available until the early 1960s, the treatment initially had to be applied in general wards (2–11). Duration of cooling varied considerably, ranging from 2 to 3 days to up to 10 days.

Despite this lack of well-controllable cooling methods and the use of temperatures <30°C (with a much greater risk for severe side effects compared with temperatures ≥30°C), many of these studies reported benefits compared with "expected outcome" or historical controls (2–11). However, these benefits were

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variable and uncertain, and as is to be expected there were significant problems in patient management. In the late 1960s, interest among clinicians in therapeutic usage of hypothermia seems to have simply fizzled out; there is a 38-yr gap between the publication of the first two case series describing use of hypothermia in cardiac arrest patients and the next study (8, 9, 16). These experiences illustrate the difficulties that can be encountered during use of controlled hypothermia.

Interest in cooling was rekindled in the early 1980s by the positive results from numerous animal experiments, some of which are discussed below. Many important insights regarding effective use of hypothermia and the mechanisms underlying its protective effects were gained at that time. An important breakthrough was the realization that neurological outcome could be improved by using mild to moderate hypothermia (31°C–35°C) rather than deep hypothermia (≤30°C), with far fewer and less severe side effects. The basis for this new insight was the observation that the protective effects of hypothermia were not (at least not exclusively or mainly) due to decreased oxygen and glucose consumption in the brain. Indeed, the mechanisms involved are far more complex.

A cascade of destructive events and processes begins at the cellular level in the minutes to hours following an initial injury. The injury can be ischemic or traumatic. Ischemia may be induced by obstruction of a blood vessel, by pressure/edema, or by other mechanisms. This destructive cascade is similar regardless of the cause, although there are differences in regard to how long the cascade is sustained. These processes—which have been collectively described in terms such as postresuscitation disease, reperfusion injury, and secondary brain injury—may continue for hours to many days after the initial injury and can be retriggered by new episodes of ischemia (17).

A key point is that all of these processes are *temperature dependent*; they are all stimulated by fever, and can all be mitigated or blocked by mild to moderate hypothermia. The wide-ranging effects of hypothermia may explain why it has proved to be clinically effective, whereas studies with agents that affect just one of the destructive processes have been far less successful (18–22).

The second important development was the advent of intensive care units (ICUs) to care for critically ill patients. The side effects of hypothermia can be far more easily managed in this setting, and the methods for inducing and maintaining hypothermia have improved significantly since the 1950s. These new insights and improvements in facilities have set the stage for a successful comeback of hypothermia as a clinical treatment.

Studies on mechanisms underlying hypothermia's protective effects point to four key factors determining success or failure of cooling treatment. These are:

- *Speed of induction* of hypothermia; outcomes in animal experiments are far better when cooling is initiated rapidly after injury.
- *Duration* of cooling (depending on the severity of the initial injury and the time interval until target temperature is reached).
- *Speed of rewarming* (this should be slow lest the destructive processes be reinitiated; this happens frequently if rewarming speeds are high).
- Proper management and *prevention of side effects*.

The equation is complicated by the fact that the relative contributions of different mechanisms to the ongoing injury may differ. There may be differences between various types of injury (e.g., traumatic vs. purely postischemic), between different patients (depending on genetic factors, comorbidities, gender, etc.), and even within the same patient over time. Thus, the available windows of opportunity for therapeutic interventions such as hypothermia may vary, and the same may apply to the required duration for the cooling treatment to be (fully) effective. For all these reasons, a better understanding of underlying mechanisms may help us to better target our treatments, and help improve outcome.

Many of the available data come from animal experiments; translating these results into clinical practice poses some limitations. Firstly, the relative importance of injury mechanisms may differ between humans and animals, and also between different animal species. Thus, if a specific treatment decreases the degree of histological brain damage in a specific area in rats, this treatment may have similar histological effects in humans but may not make a clinically significant difference in outcome (23, 24). Secondly, some treatments may target specific destructive mechanisms playing a central role in injury development in a particular animal model, whereas this particular mechanism is far less important in humans (25–27). Such a treatment would be highly effective in that animal model, but would prove far less effective in a clinical trial.

Such differences may result in overestimation of the potential positive effects of hypothermia; the brains of some animals, especially small animals such as rodents, appear to be more responsive to neuroprotection than the human brain (28, 29). On the other hand, protective effects may also be underestimated when looking at only one mechanism and/or only one animal model. For example, many animal studies have focused on the so-called *neuroexcitotoxic cascade*, which is central to the development of postischemic injury in many primitive mammalian animal models (mice, guinea pigs, rats, etc.). This mechanism plays out within relatively short time frames, [±2 hrs or less] (25–30). However, clinical studies in cardiac arrest patients have reported significant improvements in outcome even when induction of hypothermia was delayed for up to 8 hrs (17); this indicates that other, more protracted mechanisms must play a role in determining outcome in human brain injury. Thus, focusing exclusively on neuroexcitotoxicity would significantly underestimate the available time window for application of hypothermia.

Nevertheless, in spite of such limitations there is much that we can learn from animal experiments, in particular if a treatment has shown value in more than one animal model and/or in primates (orangutans, chimpanzees, etc.). What we have learned regarding ischemia–reperfusion and posttraumatic injuries, and the protective effects of hypothermia, is summarized in Figure 1 and are now discussed in more detail.

Underlying Mechanisms, Physiological Sequelae, and Consequences for Patient Management

Decrease in Cerebral Metabolism. When hypothermia was first used in a clinical setting it was presumed that its protective effects were due purely to a slowing of cerebral metabolism, leading to reduced glucose and oxygen consumption. Indeed this assumption is not completely incorrect: Cerebral metabolism decreases by 6% to 10% for each 1°C

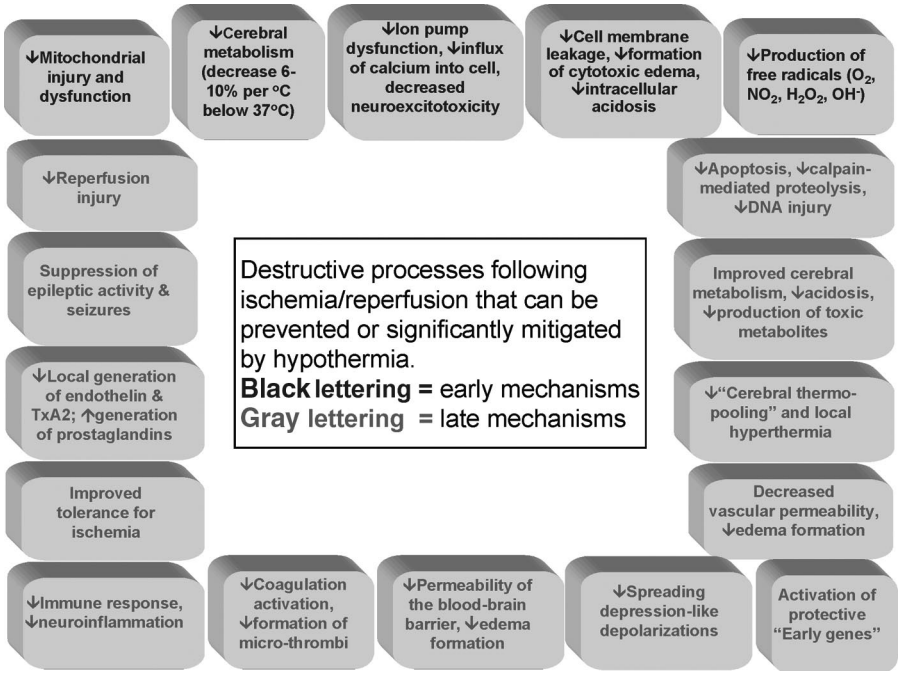

Figure 1. Schematic depiction of the mechanisms underlying the protective effects of mild to moderate hypothermia. *TxA2,* thromboxane A2.

reduction in body temperature during cooling (27, 29, 31–35). Early studies attempted to reduce metabolism as far as possible by using deep hypothermia (≤30°C). Our current understanding is that a reduction in metabolic rate is only one of many mechanisms underlying hypothermia's protective effects.

Physiological Consequences and Patient Management. When core temperature drops to 32°C, the metabolic rate decreases to 50% to 65% of normal; oxygen consumption and CO_2 production will decrease by the same percentage. If ventilator settings are left unchanged this will lead to hyperventilation, with potentially adverse consequences such as cerebral vasoconstriction (36, 37). The decrease in oxygen consumption will increase oxygen levels in the blood, posing a (theoretical) risk during reperfusion because high oxygen levels may increase reperfusion injury (38). Therefore, ventilator settings should be adjusted as temperature decreases, and frequent checks of blood gasses are necessary especially in the induction phase. During maintenance the feeding rate should also be adjusted to reflect lower metabolic demands.

Other metabolic changes include increased fat metabolism, leading to an increase in the levels of glycerol, free fatty acids, ketonic acids, and lactate. This in turn can cause mild metabolic acidosis. This phenomenon does not require treatment; pH rarely decreases below 7.25, and the drop in extracellular pH is not reflected in intracellular pH, which increases slightly under hypothermic conditions (33).

Another consequence of hypothermia is decreased insulin secretion and, in many patients, a moderate (and sometimes severe) insulin resistance. This can lead to hyperglycemia and/or a significant increase in doses of insulin required to maintain glucose levels within an acceptable range. This temperature-dependence of insulin requirements is particularly important in the rewarming phase, when insulin sensitivity may increase rapidly, leading to hypoglycemia if insulin doses are not decreased. Thus, glucose levels should be checked frequently particularly during rewarming and, to a lesser extent, the induction phase of hypothermia (1). For this and other reasons, rewarming rates following hypothermia treatment should be slow and controlled. In our unit the target rewarming rate is 0.25°C/hr for postcardiac arrest patients and 0.1°C/hr for patients following severe TBI.

Apoptosis, Calpain-Mediated Proteolysis and Mitochondrial Dysfunction. Following a period of ischemia and reperfusion, cells can become necrotic, fully or partially recover, or enter a path leading to so-called apoptosis or programmed cell death. Whether apoptosis will develop is determined by cellular processes such as mitochondrial dysfunction, other disorders in cellular energy metabolism, and release of so-called caspase enzymes. Numerous studies have shown that hypothermia can interrupt the apoptotic pathway, thereby preventing cellular injury from leading to apoptosis (39–43). Hypothermia seems to affect mainly the early stages of the apoptotic process and apoptosis initiation (40). Its effects include inhibition of caspase enzyme activation (39–41, 43, 44), prevention of mitochondrial dysfunction (42), decreased overload of excitatory neurotransmitters, and modification of intracellular ion concentrations. (The latter mechanisms are discussed in more detail below.)

Apoptosis begins relatively late in the postperfusion and/or posttrauma phase, while continuing for a period of 48 to 72 hrs or even longer (43–45). Thus, apoptosis is one of the mechanisms that can be mitigated (and perhaps even prevented) for some time after injury, providing (at least in theory) a wide window of opportunity for therapeutic interventions such as hypothermia. For this and other reasons, influencing apoptotic pathways could play an important role in providing neuroprotection and in mitigating postresuscitation injury in humans.

Ion Pumps and Neuroexcitotoxicity. A large body of evidence suggests that hypothermia inhibits harmful excitatory processes occurring in brain cells during ischemia–reperfusion. Levels of high-energy metabolites such as adenosine triphosphate and phosphocreatine decrease within seconds when oxygen supply to the brain is interrupted (27). The breakdown of adenosine triphosphate and the switch of intracellular metabolism to anaerobic glycolysis lead to an increase in intracellular levels of inorganic phosphate, lactate, and H^+, resulting in both intra- and extracellular acidosis and an influx of calcium (Ca^{2+}) into the cell. Loss of adenosine triphosphate and acidosis also inhibits the mechanisms that normally deal with excessive intracellular Ca^{2+} by sequestering Ca^{2+} from the cell, further aggravating intracellular Ca^{2+} overload. These problems are compounded by failure of adenosine triphosphate–dependent Na^+-K^+ pumps and K^+, Na^+, and Ca^{2+} channels, leading to an additional influx of Ca^{2+} (46). The excess Ca^{2+} induces mitochondrial dysfunction (increasing intracellular calcium influx yet further, in a vicious cycle) and

activates numerous intracellular enzyme systems (kinases and proteases). In addition, immediate early genes are activated and a depolarization of neuronal cell membranes occurs, with a release of large amounts of the excitatory neurotransmitter glutamate into the extracellular space (25). This leads to prolonged and excessive activation of membrane glutamate receptors, further stimulating Ca^{2+} influx through activation of Ca^{2+} channels in another vicious cycle. Under normal circumstances, neurons are exposed to only very brief pulses of glutamate; prolonged glutamate exposure induces a permanent state of hyperexcitability in the neurons (the *excitotoxic cascade*), which can lead to additional injury and cell death. Furthermore, high levels of glutamate can be neurotoxic, especially in energy-deprived cells. Glutamate receptor activation can persist for some time after reperfusion, even when glutamate levels have returned to normal; this may be another important mediator of brain cell death.

In summary, ischemia and reperfusion lead to an interruption of a delicate balance between calcium influx and sequestration at the cellular level. Numerous animal experiments have clearly demonstrated that key destructive processes of the neuroexcitatory cascade (such as calcium influx, accumulation of glutamate, and the release of its coagonist glycine) can be prevented, interrupted, or mitigated by hypothermia (23, 25, 45–53). Even a relatively small decrease in temperature can significantly improve ion homeostasis, whereas the occurrence of fever can trigger and stimulate these destructive processes.

It is unclear how long the window of opportunity to interrupt this cascade is. Disruptions in Ca^{2+} homeostasis begin in the minutes after injury but may continue for many hours (sometimes even days). Furthermore, the mechanism can be reinitiated by new episodes of ischemia. Thus, in theory this mechanism may be susceptible to therapeutic interventions provided these are initiated in the hours following injury. However, some animal experiments suggest that neuroexcitotoxicity can be blocked or reversed only if the treatment is initiated in the very early stages of the neuroexcitatory cascade (26–27, 30, 54). Other studies have reported somewhat wider time frames, ranging from 30 mins to up to 6 hrs (55–67). Thus, the period during which the neuroexcitatory cascade can be modified *in vivo* remains unclear; indeed, this may vary between different species and different types of injury. Some authors have suggested that the therapeutic window could be extended by combining hypothermia with other, more specific treatments such as caspase inhibitors or other experimental compounds (41, 68).

Immune Response and Inflammation. In most types of brain injury, a significant and protracted inflammatory response begins about 1 hr following a period of ischemia–reperfusion. Proinflammatory mediators such as tumor necrosis factor-α and interleukin-1 are released in large quantities by astrocytes, microglia, and endothelial cells; this rise begins ±1 hr after injury and they remain elevated for up to 5 days (27, 69). This stimulates the chemotaxis of activated leukocytes across the blood–brain barrier, leading to an accumulation of inflammatory cells in the injured brain, as well as the appearance of adhesion molecules on leukocytes and endothelial cells. Simultaneously, there is an activation of the complement system which begins in the very early stages after brain injury and further stimulates the passage of neutrophils and (in later stages) monocytes-macrophages (69). These inflammatory and immunologic responses occur especially during reperfusion and are accompanied by free radical production. This can cause significant (additional) injury through the phagocytic actions of macrophages, synthesis of toxic products, and further stimulation of immune reactions in a vicious cycle.

However, it should be realized that this inflammatory response is to some extent physiological, and may have a dual role in the sense that some inflammatory mediators have neuroprotective properties, whereas others are neurotoxic (69–72). Nevertheless, there is strong evidence suggesting that certainly a disproportionate and persistent production of cytokines and leukocyte infiltration can significantly increase the risk and extent of brain cell injury and infarction (68–74). Especially the interleukin-1 family appears to be important in this regard (74). Of note, this effect is to some extent time dependent, with the destructive aspects of inflammation outweighing the potential benefits especially in the later stages of injury (69–72). Thus, again, there may be a potential time window for therapeutic interventions to interrupt or mitigate this process before it becomes destructive.

Numerous animal experiments and some clinical studies have shown that hypothermia suppresses ischemia-induced inflammatory reactions and release of proinflammatory cytokines (75–78). Hypothermia also prevents or mitigates reperfusion-related DNA injury, lipid peroxidation, and leukotriene production (47–49), and it decreases the production of nitric oxide, which is a key agent in the development of postischemic brain injury (25). In addition, hypothermia can impair neutrophil and macrophage function, and (at temperatures <32°C–33°C) decrease white blood cell count.

In animal experiments, the extent of brain injury and infarct size can be significantly attenuated if any of these processes is mitigated or interrupted (25); given that hypothermia can affect all of these steps there is (at least in theory) a huge potential for improving outcome. Furthermore, given that the inflammatory response begins relatively late (>1 hr following ischemia–reperfusion), and given that the destructive processes take some time to develop fully and continue for prolonged periods of time, there appears to be a clear therapeutic window for use of hypothermia to favorably affect this specific mechanism.

Free Radical Production. A destructive process that is closely linked to but distinct from the mechanisms discussed above is the release of free oxygen radicals following ischemia–reperfusion. Mediators such as superoxide (O_2^-), peroxynitrite (NO_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) play an important role in determining whether injured cells will recover or die (47, 50, 79, 80). Free radicals can oxidize and damage numerous cellular components. Although brain cells have various enzymatic and nonenzymatic antioxidant mechanisms that prevent this type of injury under normal circumstances, free radical production following ischemia–reperfusion is so great that these defensive mechanisms are likely to be overwhelmed, leading to peroxidation of lipids, proteins, and nucleic acids.

Under hypothermic conditions the quantity of free radicals that is generated is significantly reduced, although free radical production is not completely prevented (47, 50, 79, 80). This allows the endogenous antioxidative (protective) mechanisms to better cope with free radicals that are being released, thereby preventing or significantly mitigating oxidative damage. This allows the cell to repair itself and recover, rather than suffering permanent damage and/or dying. The degree of inhibition of free radical produc-

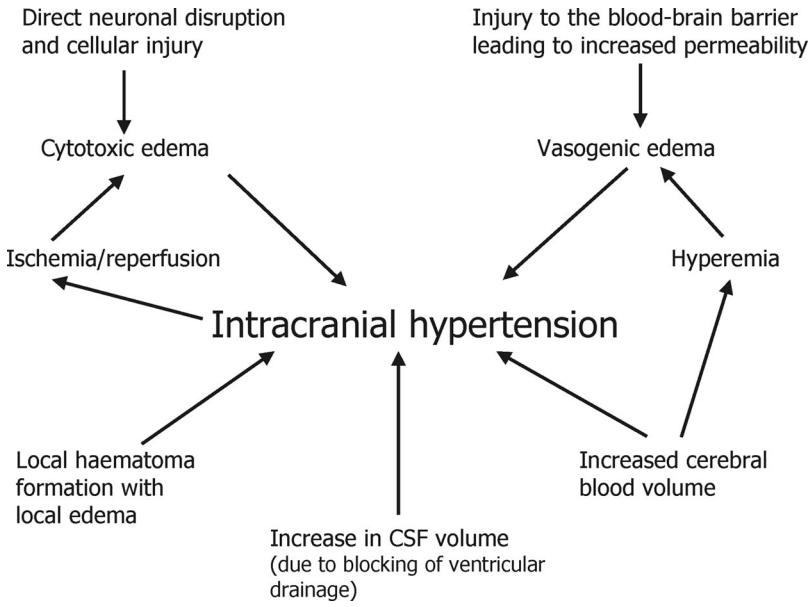

Figure 2. Schematic depiction of the potential role of intracranial pressure as both a marker of ongoing brain injury and a potential cause of additional injury, and of the factors that may contribute to a rise in intracranial pressure. *CSF*, cerebrospinal fluid.

tion appears to be more or less linearly linked to the temperature; i.e., the lower the temperature, the lower the amount of free radicals (79).

Vascular Permeability, Blood–Brain Barrier Disruption, and Edema Formation. Ischemia–reperfusion and/or traumatic injury can lead to significant disruptions in the blood–brain barrier, which can facilitate the subsequent development of brain edema (81–83). Therapeutic interventions such as mannitol administration in TBI or stroke can add to blood–brain barrier disruption (82). Mild hypothermia significantly reduces blood–brain barrier disruptions (81–83), and also decreases vascular permeability following ischemia–reperfusion, further decreasing edema formation (84). The concept of a membrane- and blood–brain barrier–stabilizing effect of hypothermia is supported by the observation that hypothermia decreases extravasation of hemoglobin following TBI (85). Ischemia–reperfusion affects blood–brain barrier integrity in other ways, including decreased fluidity and integrity of cell membranes and increased vascular permeability of microvascular endothelial cells in the brain, mediated by vascular endothelial growth factor *via* release of nitric oxide (86, 87).

These processes of membrane disintegration and hypoxia-induced leakage can be mitigated or reversed by hypothermia (87). Hypothermia also decreases cytotoxic edema *via* the mechanisms described above (dampening inflammatory responses and free radical production, improving ion homeostasis, etc.), and through other mechanisms, which are summarized in Figure 2. Brain edema can be monitored by measuring intracranial pressure (ICP), which can be regarded as a final common pathway for the destructive processes leading to brain edema (88) [Fig. 2].

The key role of brain edema and intracranial hypertension as a cause of (additional) neurological injury in severe TBI and ischemic stroke is well recognized (89, 90). Brain edema can also increase brain injury in acute encephalitis and meningitis (91), and some evidence suggests that edema-related injury can play a role in some patients with posthypoxic injury following cardiac arrest (92).

As intracranial hypertension appears to be both a marker for ongoing neurological injury and a cause of additional injury (88), it seems plausible that treatments that reduce ICP will also help improve neurological outcome. ICP is frequently used as a parameter to guide treatments and assess short-term therapeutic efficacy in patients with TBI (89, 93). Hypothermia has been used to treat brain edema and reduce ICP in a wide range of neurological injuries, including TBI, ischemic stroke, hepatic encephalopathy, meningitis, encephalitis, and subarachnoid hemorrhage (17, 28).

In theory, this mechanism of action would offer a relatively wide therapeutic window to mitigate neurological injuries. Brain edema may develop rapidly, but more typically arises several hours after injury, often peaking after 24 to 72 hrs (94). It should be noted that although hypothermia has been shown to decrease ICP in many clinical studies, the results in improving survival and neurological outcomes have been mixed (17, 88), with one large trial failing to show any benefits during hypothermia treatment in spite of hypothermia-induced decreases in ICP (95). These varying results may be (partly) linked to the management of hypothermia's side effects (17, 88); these issues are discussed more extensively below. As explained above, the speed of induction, duration and depth of hypothermia, and rewarming speeds all play important roles in determining whether or not lasting protective effects are achieved (1, 17, 88, 96, 97).

Intra- and Extracellular Acidosis and Cellular Metabolism. The diminished integrity of cell membranes, the failure of various ion pumps, development of mitochondrial dysfunction, inappropriate activation of numerous enzyme systems with cellular hyperactivity, and the disruption of various other intracellular processes all contribute to the development of *intracellular acidosis*, a factor that powerfully stimulates many of the abovementioned destructive processes (98, 99). Ischemia–reperfusion also leads to substantial rises in cerebral lactate levels (100–102). All of these factors can be significantly attenuated by hypothermia (98–103).

In addition, *brain glucose utilization* is affected by ischemia–reperfusion, and there is evidence suggesting that hypothermia can improve brain glucose metabolism; i.e., the ability of the brain to utilize glucose (104, 105). Similar observations have been made in severe TBI, for which animal experiments and some clinical studies suggest that an initial increase in cerebral glucose metabolism in the hours following trauma is followed by a deep and persistent decrease in metabolic rate, with a depression of mitochondrial oxidative phosphorylation and glucose utilization that can last for several weeks (106–108). Induced hypothermia applied during or after reperfusion increases the speed of metabolic recovery, with a better preservation of high-energy phosphates and reduced accumulation of toxic metabolites (106–108).

Brain Temperature and Cerebral Thermopooling. Even in healthy individ-

uals, the temperature of the brain is slightly higher than the measured core temperature (109–111). This difference can increase significantly in patients following neurological injury, with gradients ranging from 0.1°C to more than 2°C (112–118), although this phenomenon does not occur in all brain-injured patients (118). These differences may increase even further when a patient develops fever, a very frequent phenomenon in patients with neurological injuries (119–123). In addition, there may be small temperature differences between different areas of the brain even in healthy individuals, with active areas having a slightly higher temperature (124–127). These differences increase significantly when brain injury occurs, with injured areas becoming more hyperthermic than noninjured areas (128). The reason for this is that some of the destructive mechanisms discussed above lead to excessive generation of heat. These include excitotoxicity (which, as described above, induces "cellular hyperactivity" with extreme activation of enzyme systems, with concomitant generation of heat), the neuroinflammatory response, free radical production, and a process known as "cerebro thermopooling" (128, 129), meaning that excess heat generated in injured areas of the brain becomes more difficult to remove *via* the normal heat dissipation mechanisms (lymph and venous drainage) due to development of local brain edema. The heat thus becomes trapped in injured areas, further adding to hyperthermia-related injury.

Thus, a vicious cycle can arise: Brain injury leads to general overheating of the brain; more overheating occurs especially in injured areas; this leads to local and sometimes general brain edema, which then makes it more difficult to remove the excess heat. Due to this chain of events, brain temperatures in injured brain areas may exceed measured core temperatures by as much as 2°C to 4°C.

This is relevant because there is strong evidence from animal studies that (external) induction of hyperthermia significantly increases the risk and extent of neurological injury (17, 130–136). Hyperthermia increases the likelihood that ischemic areas become apoptotic or necrotic, even when fever develops (or is externally induced) some time after the initial injury. Baena et al (131) reported a 2.6-fold increase in neuronal injury in the rat hippocampus if mild warming (1°C–2°C above normal for 3 hrs) was induced 24 hrs after a brief episode of forebrain ischemia. This suggests that fever can be detrimental even when it is of short duration and occurs on the day after injury. Others have reported similar observations in different animal models (132–136). The effects of fever appear to be more pronounced when they coincide with an episode of cerebral ischemia, suggesting that ischemic brain cells become even more susceptible to the harmful effects of hyperthermia (135–136).

Numerous clinical studies have confirmed that fever is indeed an independent predictor of adverse outcome in stroke, TBI, and postanoxic injury following cardiac arrest (121–123, 137–142). Schwarz et al (121) found that even very mild hyperthermia (>37.5°C!) within the first 72 hrs was independently associated with poor outcome in patients with intracerebral hemorrhage, and that there was a linear relationship between the severity and duration of fever and the risk for adverse outcome. In patients with ischemic stroke, fever is associated with a 3.4-fold increase in risk for adverse outcome (140), a higher brain infarct volume (141), and increased mortality (142). Although it has not been conclusively proven that these relationships are causal (i.e., that fever increases injury rather than just being a marker), this is strongly suggested by the temporal relationship and the results from animal studies (130–136).

Coagulation Activation and Formation of Microthrombi. Cardiopulmonary arrest and resuscitation are accompanied by a marked activation of coagulation, which can lead to intravascular fibrin formation with blockage of the microcirculation in the brain and heart (143–146). Administration of anticoagulants such as heparin and recombinant tissue-type plasminogen activator improves microcirculatory reperfusion and survival in animal experiments (146, 147); in addition, thrombolysis can improve cerebral tolerance to ischemia (148). Initial clinical reports suggesting that administration of thrombolytic agents could improve neurological outcome and survival in cardiac arrest (149) have not been confirmed in larger studies (150). Nevertheless, activation of coagulation seems to play an important role in developing ischemia–reperfusion injury, and although reversing this mechanism by itself may not improve outcome, this may be different if additional mechanisms are targeted simultaneously.

Hypothermia has some anticoagulatory effects. Mild platelet dysfunction occurs at temperatures ≤35°C, and some inhibition of the coagulation cascade develops at temperatures ≤33°C; platelet count can also decrease during cooling (1, 151–154). In theory, this anticoagulation effect may constitute yet another neuroprotective mechanism. This remains speculative given that no studies directly addressing this issue have been performed.

Vasoactive Mediators. Several studies have shown that hypothermia affects the local secretion of vasoactive substances such as endothelin, thromboxane A_2 (TxA_2), and prostaglandin I_2 in the brain and at other sites. Endothelin and TxA_2 are powerful vasoconstrictive agents, whereas prostaglandin I_2 is a vasodilator. TxA_2 also stimulates platelet aggregation (155–157). TxA_2 and prostaglandin I_2 play an important role in regulating local cerebral blood flow, and a balance between the two is required to maintain homeostasis (155). This local homeostasis can be disrupted following an ischemic or traumatic event, with a relative increase in production of TxA_2 (158–161). This disruption in equilibrium can lead to vasoconstriction, hypoperfusion, and thrombogenesis in injured areas of the brain.

Animal experiments and small clinical studies suggest that this relative predominance of local vasoconstrictors can be corrected or modified by hypothermia (49, 162, 163). Aibiki et al (162) reported that moderate hypothermia (32°C–33°C) led to a reduction in prostanoid production and attenuation of the imbalance between TxA_2 and prostaglandin I_2 in patients with severe TBI. Chen et al (163) found decreased production of the vasoconstrictor endothelin-1 during induction of hypothermia.

This and other preliminary evidence suggests that hypothermia may favorably affect vasoactive mediator secretion in brain-injured patients. However, regulation of cerebral perfusion is a highly complex issue, especially in the injured brain; local circulation can be influenced by the presence or absence of cerebral autoregulation, ventilator settings and blood gas management, systemic blood pressure, fluid management including osmotic therapy, etc. Thus, the impact of hypothermia on this equation needs to be studied in greater detail.

Improved Tolerance for Ischemia. Hypothermia improves the tolerance for

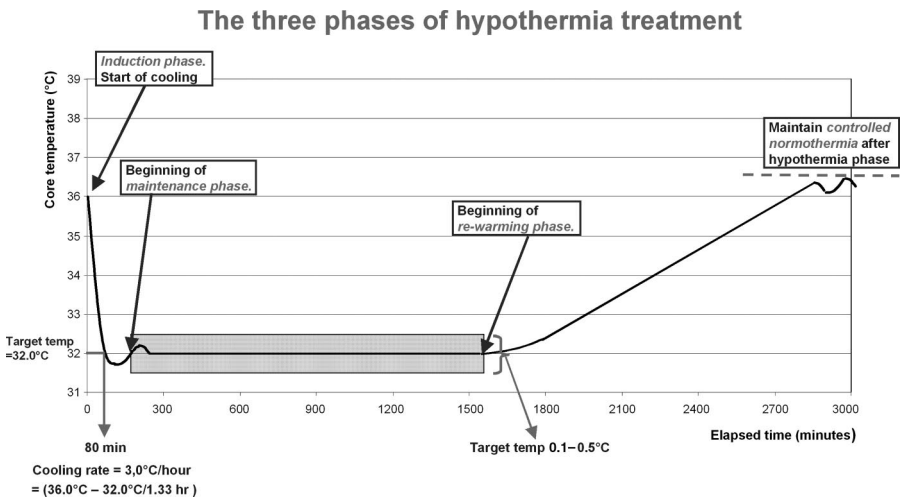

Figure 3. Graphic depiction of the three phases of hypothermia treatment. The induction phase should last between 30 and 120 mins; rapid cooling may lead to a small overshoot, which should be accepted provided it is no greater than 1°C. The maintenance phase usually lasts 24 hrs in cardiac arrest patients (may be longer for other indications) and should be characterized by no or minimal fluctuations in temperature. The rewarming phase should be slow and controlled, with rewarming rates of 0.2°C to 0.5°C in cardiac arrest patients and lower rewarming rates for other indications. Fever should be prevented after rewarming.

ischemia in various animal models (164–166). For this reason, it is widely used in the perioperative setting, especially in major vascular surgery, cardiothoracic surgery, and neurosurgical interventions (17). An ability to better withstand periods of ischemia would be an important protective mechanism, because many types of neurological injury can be complicated by ischemic events in the days following the initial insult.

For example, in patients with TBI a combination of biological factors (cytotoxic and vasogenic edema) and mechanical factors (blockage of spinal fluid drainage) can lead to cerebral edema and intracranial hypertension in the hours and days following initial injury (Fig. 2); cerebral edema can then cause additional ischemic injury. In patients with subarachnoid hemorrhage the development of vasospasms in the days and weeks following a bleeding episode can lead to significant ischemic injury. The risk for ischemic injury occurring in the postadmission period may also apply to postcardiac arrest patients, in whom cerebral ischemia may persist for several hours following successful resuscitation even when arterial oxygen levels are normal (167). Thus, a hypothermia-induced increase in tolerance for ischemia could be another powerful protective mechanism.

Suppression of Epileptic Activity. Nonconvulsive status epilepticus (i.e., epileptic activity without obvious clinical signs and symptoms) occurs frequently in patients with postanoxic encephalopathy, stroke, TBI, and subarachnoid hemorrhage (168–172). It remains uncertain whether nonconvulsive status is a direct cause of additional injury; however, mounting evidence suggests that brain injury can be significantly increased when nonconvulsive status occurs in the acute phase of brain injury; i.e., while the destructive processes outlined above are ongoing (168, 169). In other words, although the role of nonconvulsive status by itself has not been fully clarified, when it occurs in combination with ongoing brain injury the two are synergistically detrimental (168, 169).

Evidence from various sources shows that hypothermia can suppress epileptic activity. Small case series report successful use of cooling to treat grand mal seizures (173–175). Animal studies have shown that external warming increases the extent of epilepsy-induced brain injury, that prevention or prompt treatment of fever reduces these injuries, and that induction of hypothermia further decreases seizure-induced brain injury (176–179). This antiepileptic effect offers yet another pathway through which hypothermia could provide neuroprotection, and by which fever may increase neurological injury.

Spreading Depressionlike Depolarizations. Some animal studies have suggested that neuronal damage in various types of neurological injury can be significantly increased by so-called *spreading depressionlike depolarizations* (23, 179). This has been studied mainly in models for TBI and stroke; its potential role in the relatively brief global ischemic brain injury that characterizes cardiac arrest is unclear. Hypothermia can suppress spreading depressions in different types of neurological injury (23, 180–182), providing yet another mechanism by which hypothermia could improve outcome.

Influence on Genetic Expression. Hypothermia increases the expression of so-called *immediate early genes,* which are a part of the protective cellular stress response to injury, and stimulates the induction of *cold shock proteins*, which can protect the cell from ischemic and traumatic injury (97). This provides yet another mechanism through which hypothermia can provide neuroprotection.

Thus, hypothermia favorably affects a whole range of destructive mechanisms unfolding in the injured brain after ischemia or trauma. This wide range of effects probably explains its efficacy, in contrast to interventions that target just one or two of these mechanisms and have mostly proved unsuccessful in clinical trials. Different mechanisms may play a greater or smaller role in different types of brain injury, and/or during different phases of ongoing brain injury. A more detailed understanding of these processes will help us apply therapeutic hypothermia and controlled normothermia more effectively.

The other key element for successful use of therapeutic cooling is awareness and proper management of the physiological consequences and side effects. These issues are dealt with in the next section.

Physiological Aspects of Cooling

Phases of Cooling Treatment. A hypothermia treatment cycle can be divided into three distinct phases (Fig. 3):

- The induction phase, when the aim is to get the temperature below 34°C and then down to the target temperature as quickly as possible;
- The maintenance phase, when the aim is to tightly control core temperature, with minor or no fluctuations (maximum, 0.2°C–0.5°C);
- The rewarming phase, with slow and controlled warming (target rate, 0.2°C–0.5°C/hr for cardiac arrest patients and 0.1°C–0.2°C/hr for other

categories such as patients with severe TBI) (183).

Each of these phases has specific management problems. The risk for immediate side effects such as hypovolemia, electrolyte disorders, and hyperglycemia is greatest in the induction phase (17, 184, 185). This phase presents the greatest patient management problems, requiring frequent adjustments in ventilator settings; dosing of sedation, insulin, and vasoactive drugs; and fluid and electrolyte administration (185). The risks can be reduced by rapid induction of hypothermia; i.e., minimizing the duration of the induction phase and reaching the more stable maintenance phase as quickly as possible. Rapid cooling can be achieved by combining different cooling methods, for example, surface cooling with infusion of 1500–3000 mL of cold (4°C) fluids using a pressure bag (186). Furthermore, some of the new intravascular devices may have more rapid cooling rates than previously used methods (1).

The maintenance phase is characterized by increased stability of the patient, with a decreased shivering response and less risk for hypovolemia and electrolyte loss. In this phase, attention should shift toward prevention of longer-term side effects such as nosocomial infections and bedsores.

In the rewarming phase, the patient's temperature should be increased very slowly, for a number of reasons. Firstly, rapid rewarming can cause electrolyte disorders (in particular, hyperkalemia) caused by shifts from the intracellular to the extracellular compartment. This can be largely prevented by slow and controlled rewarming. Secondly, insulin sensitivity can increase during rewarming, and slow rewarming decreases the risk for hypoglycemia if the patient is being treated with insulin. Thirdly, some animal experiments and clinical observations suggest that rapid rewarming could lead to loss of some or even all of the protective effects of hypothermia (187–191). Significant decreases in jugular venous oxygen saturation have been reported during rapid rewarming of patients following cardiac surgery under hypothermic conditions, indicating hypoxia of the brain (190); more slow rewarming led to a decrease in the incidence and severity of jugular bulb desaturations (190). In another study, Bissonnette et al (191) reported that patients who were rapidly rewarmed following cardiopulmonary bypass surgery often developed severe brain hyperthermia, even when core temperature measured at other sites remained normal. Although none of these experiments directly addressed optimal rewarming rates for cardiac arrest patients treated with hypothermia, these and other findings indicate that rapid rewarming can increase ischemia and aggravate destructive processes in the injured brain (1).

Another important concept is the maintenance of strict normothermia following the rewarming phase. As discussed above, fever is independently linked to adverse outcome in all types of neurological injury, including postanoxic injury following cardiac arrest (17). In addition, cerebrovascular reactivity may be impaired following hypothermia treatment (192), increasing the potential harmful effects of fever.

Physiological Changes and Side Effects of Cooling

The induction of mild hypothermia induces numerous changes throughout the body. The most important physiological changes and side effects, and their consequences for patient management, are discussed below.

Shivering and Cutaneous Vasoconstriction. A separate article in this supplement is devoted to shivering (193); therefore, this topic is discussed only briefly here.

In awake patients, shivering induces unfavorable effects such as increased oxygen consumption and metabolic rate, excess work of breathing, and increased heart rate with increased myocardial oxygen consumption (1, 184, 194–197). In the perioperative setting, hypothermia has been linked to an increased risk for morbid cardiac events, particularly in older patients with heart disease (194–196). However, these adverse consequences are linked to the hemodynamic and respiratory responses rather than to shivering *per se*; these responses can be largely suppressed through administration of sedatives, anesthetics, opiates, or other drugs during therapeutic cooling (1). For example, in contrast to the tachycardia associated with perioperative (accidental) hypothermia, heart rates are markedly reduced during therapeutic cooling (1). Nevertheless, it is important to prevent or aggressively treat shivering because it significantly complicates hypothermia induction, and leads to an undesirable increase in metabolic rate and oxygen consumption (1). Appropriate sedation and analgesia will also cause vasodilation, which can facilitate heat loss through surface cooling.

Relatively effective and rapidly acting antishivering agents include fentanyl, alfentanyl, meperidine, dexmedetomidine, propofol, clonidine, and magnesium (1). Specific advantages and disadvantages of these and other agents are reviewed in more detail elsewhere (1). Brief-acting paralyzing agents can be useful in the induction phase, especially when hypothermia is initiated outside the ICU setting, but prolonged paralysis is usually unnecessary (1). The effectiveness of the shivering response decreases with age; therefore, the doses of drugs required to suppress shivering are usually lower in older patients. Warm-air skin counterwarming can be used as an accessory method to lower the shivering threshold, and to decrease drug doses required to prevent shivering (198, 199).

In our unit, the standard approach is to administer a loading dose of magnesium (30 mmol) and fentanyl (50–100 μg) when cooling is initiated, together with continuous infusion of either midazolam or propofol (the latter only in hemodynamically stable patients). If shivering occurs, another bolus of fentanyl (50–150 μg) is given, and more magnesium if serum Mg^{2+} is ≤2.0 mmol/L. In some patients, the dose of sedatives will be temporarily increased during induction and/or a bolus dose of midazolam (5–10 mg) will be given. If shivering persists, one of the following drugs is given, depending on the clinical circumstances: clonidine, meperidine, ketanserin, or (in rare cases) a brief-acting paralyzing agent. All patients should be carefully monitored for shivering during all phases of hypothermia treatment. Use of a recently developed shivering assessment scale (200) may be considered for this purpose.

The importance of adequate sedation and suppression of hypothermia-induced stress responses is underscored by observations from animal experiments suggesting that some or all of hypothermia's neuroprotective effects can be lost if cooling is used in nonsedated animals. One research group observed no protective effects when cooling was used after global anoxia in unsedated newborn piglets (201); when the experiment was repeated in the same model under adequate sedation, significant improvements in outcome were noted in hypothermia-treated animals (202). The authors concluded

that stress effects of cooling in unsedated animals could negate protective effects. Although this phenomenon has not been well studied in humans, it seems reasonable to avoid a cooling-related stress response.

Metabolism, Blood Gases, Glucose and Electrolytes. Hypothermia decreases the metabolic rate by ±8% per 1°C drop in core temperature, with a parallel decrease in oxygen consumption and production of carbon dioxide. This means that ventilator settings need to be adjusted frequently especially in the induction phase of hypothermia, to avoid accidental hyperventilation that can cause cerebral vasoconstriction. Blood gas values are temperature dependent, and if blood samples are warmed to 37°C before analysis (as is common in most laboratories), Po_2 and Pco_2 will be overestimated and pH underestimated in hypothermic patients (1). This topic has been reviewed elsewhere (203).

Blood gas management when CO_2 values measured at 37°C are kept constant (for example, at 40 mm Hg) regardless of the patient's actual core temperature is called *alpha-stat* management. The alternative is *pH-stat* management, in which Pco_2 is corrected for temperature and is maintained at a prespecified value. This implies that the temperature-corrected pH will remain constant during pH-stat management and will increase during alpha-stat management (1). Which of these two methods is superior remains to be determined, and may depend in part on whether or not cerebral autoregulation is preserved (1). Strictly applied alpha-stat management could lead to hyperventilation and cerebral vasoconstriction; strict pH-stat management could lead to hypercapnia, cerebral vasodilation, and increased ICP. Which option is preferable may depend on the precise nature of the neurological injury and the presence or absence of brain edema. Excessive hypocapnia can increase ischemia in injured areas of the brain, while excessive hypercapnia can increase brain edema; thus both can cause additional brain injury. These issues are more extensively addressed in a recently published review (1).

For accurate temperature correction, blood samples should be analyzed at the patient's real temperature; this can be most easily accomplished by performing on-site analysis in the ICU. If this is not possible, the blood gas values can be estimated in the following way.

In a sample assayed at 37°C:

- Subtract 5 mm Hg Po_2 per 1°C that the patient's temperature is <37°C;
- Subtract 2 mm Hg Pco_2 per 1°C that the patient's temperature is <37°C;
- Add 0.012 pH units per 1°C that the patient's temperature is <37°C.

Thus, a sample from a patient with a core temperature of 33°C analyzed in the lab at 37°C with the results pH 7.45, Pco_2 35 mm Hg, and Po_2 80 mm Hg would have the following temperature-corrected values: pH 7.50, Pco_2 27 mm Hg, and Po_2 60 mm Hg.

In our unit, we use temperature-corrected blood gas values but avoid severe hypercapnia. Target Pco_2 values at 32°C (our usual target temperature in cardiac arrest patients) are 32 to 36 mm Hg, which would be 42 to 46 mm Hg in an uncorrected sample.

Hypothermia can also decrease insulin sensitivity and the amounts of insulin secreted by the pancreas. This can lead to hyperglycemia and/or an increase in the doses of insulin required to maintain glucose levels within target range. Sustained hyperglycemia has been linked to adverse outcome in critically ill patients, and may pose additional risks in patients with neurological injuries (39), although the optimal targets for glucose control remain controversial (39). Prevention and/or prompt correction of severe hyperglycemia should be part of the therapeutic strategy during hypothermia treatment. Furthermore, it should be realized that doses of insulin required to maintain normoglycemia are likely to decrease when the patient is rewarmed; this means that hypoglycemia can easily develop in the rewarming phase as insulin sensitivity is restored, particularly if the patient is rewarmed (too) quickly.

Cooling can also affect *electrolyte levels*. A combination of hypothermia-induced intracellular shift and tubular dysfunction leading to an increase in renal excretion of electrolytes can lead to depletion of magnesium, potassium, and phosphate during cooling (185). These electrolyte disorders can increase the risk for arrhythmias and other potentially harmful complications (204, 205). There is evidence suggesting that magnesium could play a role in mitigating various types of brain injury (204, 205); hypophosphatemia has been linked to respiratory problems and increased infection risk (206). Thus, electrolyte levels should be kept in the high-normal range during and after hypothermia treatment.

Extra care should be taken during rewarming because hyperkalemia may develop during this phase, due to release of potassium sequestered to the intracellular compartment during hypothermia induction (1). Hyperkalemia can be prevented by slow and controlled rewarming, allowing the kidneys to excrete the excess potassium. Thus, the risk for rebound hyperkalemia in the rewarming phase should not be regarded as a reason to accept hypokalemia in the induction and maintenance phase. However, in patients with anuria or severe oliguria, renal replacement therapy should be started before the patient is rewarmed.

Cardiovascular and Hemodynamic Effects. Hypothermia has complex and opposing effects on the myocardium and myocardial contractility, depending on the patient's volume status and whether or not the patient is adequately sedated. Under normal circumstances, mild hypothermia will decrease heart rate and increase myocardial contractility in sedated and euvolemic patients (1, 207–211). Systolic function will improve but a mild degree of diastolic dysfunction may occur in some patients (1, 207–211). Blood pressure remains stable or increases slightly in most patients during mild hypothermia (1, 186, 211–213). Cardiac output decreases along with the heart rate; however, the hypothermia-induced decrease in metabolic rate usually equals or exceeds the decrease in cardiac output, so that the balance between supply and demand remains constant or improves (1).

The heart rate can be artificially increased by external pacing, or through administration of chronotropic drugs such as isoprenalin or dopamine. However, this is usually unnecessary; furthermore, myocardial contractility may be adversely affected (210, 211, 214). Two animal studies (210, 214) and one clinical study in patients undergoing cardiac surgery (211) reported that while increasing heart rate under normothermic conditions increased myocardial contractility and cardiac output, increasing the heart rate under hypothermic conditions significantly decreased myocardial contractility. When heart rates were not artificially increased, induction of mild hypothermia improved myocardial contractility (211).

Thus, in most patients the heart rate should be allowed to decrease along with the patient's core temperature; further-

more, it should be realized that normal values for heart rate change with temperature.

Despite these data, hypothermia is often still viewed as a (potential) cause of hypotension and (additional) myocardial dysfunction. There are several reasons for this:

Firstly, in contrast to mild hypothermia, deep hypothermia (<30°C) does decrease myocardial contractility (1, 215). Secondly, hypothermia can cause hypovolemia by inducing "cold diuresis" through a combination of increased venous return, activation of atrial natriuretic peptide, decreased levels of antidiuretic hormone and renal antidiuretic hormone receptor levels, and tubular dysfunction (185, 216–221). The increase in venous return is caused by constriction of peripheral vessels (particularly in the skin) due to hypothermia-induced increases in plasma norepinephrine levels and activation of the sympathetic nerve system. This leads to a shift of the blood from peripheral (small) veins to deeper veins and the core compartment of the body, increasing the venous return. In this way, hypothermia can induce hypovolemia, which if uncorrected can cause hypotension as well as electrolyte depletion and an increase in blood viscosity. The risk for hypovolemia increases significantly if the patient is simultaneously treated with diuretic agents such as mannitol. However, hypotension can be quite easily prevented by avoiding or promptly correcting hypovolemia, and by avoiding excessive stimulation of the heart rate.

Three studies in pediatric patients enrolling a total of 127 patients and two small studies in adult patients enrolling 18 patients have reported successful use of mild hypothermia (32°C–33°C) as rescue therapy to reverse refractory cardiac shock following cardiac surgery (222–226). Two additional studies have reported successful use of hypothermia in patients who remained comatose after a massive cardiac arrest leading to severe cardiac shock (227, 228). Rates of favorable outcome in patients with cardiac shock were 61% (14 of 23) in the first study and 39% (11 of 28) in the second study. Oddo et al (229) recently reported that the presence of cardiac shock on admission did not correlate with adverse outcome in a prospective series of 74 patients with witnessed cardiac arrest treated with hypothermia, regardless of initial rhythm or hemodynamic status. These observations suggest that cardiac shock should not be regarded as a counterindication for hypothermia treatment.

Hypothermia also causes changes in the heart rhythm and electrocardiogram. The hypothermia-induced increase in venous return discussed above initially leads to mild sinus tachycardia. Tachycardia can be much more pronounced if the patient is insufficiently sedated, and the shivering response with increased oxygen consumption and heat generation can lead to more marked tachycardia.

This is soon followed by sinus bradycardia when core temperature drops below 35.5°C. The heart rate decreases progressively as core temperature drops, and at 33°C the normal heart rate will be 45 to 55 bpm (although there is wide interpatient variability). The underlying mechanism is a decrease in the rate of spontaneous depolarization of cardiac pacemaker cells (including those of the sinus node), as well as prolongation of the duration of action potentials and a mild decrease in the speed of myocardial impulse conduction. The most common electrocardiogram changes are prolonged PR intervals, increased QT interval, and widening of the QRS complex. Sometimes so-called Osborne waves can be seen, although this is relatively rare during mild hypothermia.

These electrocardiogram changes usually do not require treatment. It is often assumed that mild hypothermia increases the risk for arrhythmias and decreases the chance of successful treatment of arrhythmias, because the hypothermic myocardium becomes less responsive to antiarrhythmic drugs and more difficult to defibrillate. However, in general this applies only to deep hypothermia (≤28°C); experimental evidence suggests that mild hypothermia can actually decrease the risk for arrhythmias, by stabilizing cell membranes and increasing the likelihood of successful defibrillation if arrhythmias do occur. Two studies have assessed the likelihood of successful defibrillation under hypothermic conditions compared with normothermia in a swine model. Both found higher rates of return of spontaneous circulation, increased likelihood of successful defibrillation, fewer shocks required to reach return of spontaneous circulation, and lower incidence of postdefibrillation asystole during mild hypothermia (230, 231). Similar observations have been reported in a rabbit model (232). Various case studies describe successful use of hypothermia to treat arrhythmias (junctional ectopic tachycardia) in young infants (233–235). All of this indicates that mild hypothermia decreases rather than increases the risk for arrhythmias, and facilitates rather than complicates the treatment of arrhythmias.

However, this changes if core temperature drops below 28°C (in rare cases, <30°C in patients with severe electrolyte disorders and/or severe myocardial ischemia). More profound hypothermia does increase the risk for arrhythmias, usually beginning with atrial fibrillation, which can progress to more severe arrhythmias including ventricular tachycardia and ventricular fibrillation if temperature decreases further. Thus, a *de novo* development of atrial fibrillation in a patient with a core temperature <30°C should be viewed as a warning sign, and the patient should be rewarmed to ≥30°C immediately. In general, a temperature drop below 30°C should be strenuously avoided during therapeutic cooling in the ICU, but cooling treatment should not be withheld because of the presence or risk for arrhythmias.

In addition, attending physicians and nurses should be aware that the myocardium becomes more sensitive to mechanical manipulations during deep hypothermia. For example, if a physician decides to perform chest compressions because of severe bradycardia at a core temperature <28°C, this manipulation can induce arrhythmias including ventricular fibrillation (1). An additional problem is that if arrhythmias do develop during deep hypothermia, they become significantly more difficult to treat, because the hypothermic myocardium can become less responsive to antiarrhythmic drugs (1). Furthermore, other treatments for atrial fibrillation, such as electric cardioversion, are frequently unsuccessful at low temperatures, and may actually trigger a conversion from atrial fibrillation to ventricular fibrillation. Cardioversion for nonlife-threatening arrhythmias should be avoided at core temperatures <34°C.

Coronary Perfusion and Ischemia. Hypothermia reduces metabolic rate and induces bradycardia, thereby providing protective effects for the ischemic myocardium. In addition, it has been shown that mild hypothermia (35°C) induces coronary vasodilation and increases myocardial perfusion in healthy volunteers (236, 237). In contrast, hypothermia can induce vasoconstriction in severely atherosclerotic coronary arteries (237). In addition, hypothermia can cause shiver-

ing, tachycardia, and increased myocardial oxygen consumption in insufficiently sedated patients. Indeed, accidental hypothermia in the perioperative setting increases the risk for morbid cardiac events (194, 195). Thus, preventing adverse effects depends on avoiding a stress response and effective suppression of shivering.

Some animal experiments and preliminary clinical studies have suggested that inducing mild hypothermia in the early stages following myocardial infarction could mitigate myocardial injury (17). This issue needs to be addressed in larger studies, but the available evidence certainly does not suggest that hypothermia increases myocardial injury.

Coagulation. Mild hypothermia can induce mild coagulopathy (1). Temperatures below 35°C can cause platelet dysfunction and a mild decrease in platelet count; at temperatures <33°C, other steps in the coagulation cascade, such as the synthesis and kinetics of clotting enzymes and plasminogen activator inhibitors, may also be affected (1). These effects have been studied mostly *in vitro*. Clinical observations suggest that the risk for severe bleeding associated with therapeutic cooling is relatively small; none of the studies in patients with cardiac arrest, severe TBI, or stroke have reported significant bleeding problems, although it should be emphasized that actively bleeding patients were excluded from all of these studies (1, 17). Schefold and coworkers (238) recently assessed the risk and severity of bleeding during simultaneous use of mild hypothermia and thrombolysis. They found that bleeding risks were similar to historical controls treated with thrombolytics alone, although there was a trend toward more red blood cell units being required to reach target hematocrit in hypothermic patients who developed bleeding complications and needed transfusions. However, neurological outcomes were significantly better in patients treated with both thrombolytics and hypothermia, even in those who developed bleeding complications (238). The authors conclude that bleeding risks should not be viewed as a reason to withhold hypothermia treatment.

These factors should be taken into account when deciding whether or not to use hypothermia in patients who are actively bleeding, or who have a high bleeding risk. If possible the (potential) source of bleeding should be (surgically) controlled before cooling is initiated. If this is not possible, the risks of bleeding should be weighed against the benefits of cooling, and careful consideration should be given to the appropriate depth of hypothermia for that patient. Very mild hypothermia (35°C) does not affect coagulation, and can be safely used even if bleeding risks are high. Temperatures of 33°C to 35°C affect platelet function only; if surgical procedures are performed under hypothermic conditions, platelet transfusion may be considered. Coagulation factors other than platelet function are affected only when temperatures decrease below 33°C.

Drug Clearance. The speed of most enzyme-mediated reactions is temperature-dependent; therefore, the speed of these reactions is significantly slowed by hypothermia. One of the consequences is a decrease in the rates of drug metabolism by the liver (17, 239). Hypothermia-induced reductions in clearance have been demonstrated for a number of commonly used ICU medications, including vasoactive drugs such as epinephrine and norepinephrine; opiates such as morphine, fentanyl, and remifentanil; sedatives such as propofol, volatile anesthetics, barbiturates, and midazolam; neuromuscular blocking agents such as rocuronium, atracurium, and vecuronium; and other drugs such as phenytoin, nitrates, and some beta-blockers (1, 239). Other drugs metabolized by the liver are likely to be affected in similar ways.

The net effects of hypothermia on drug action may be more complex than simply increasing the concentration of active metabolites. Temperature can also directly affect the body's response to specific drugs. For example, the effects of vasoactive drugs, such as epinephrine and norepinephrine, on blood pressure can be slightly blunted by hypothermia. Hypothermia-induced changes in the volume of distribution and renal function may also influence how drugs work under hypothermic conditions.

However, in most cases the effect of hypothermia will be to increase drug levels, thereby enhancing drug potency and effect duration. From a practical perspective, it seems reasonable to make empirical dose adjustments in drugs with relatively short half-lives that are metabolized by the liver (e.g., midazolam). When an increase in depth of sedation is required, or an episode of shivering needs to be treated, it is preferable to use bolus doses rather than to increase maintenance dose.

Drugs with long half-lives (e.g., amiodarone) are far less affected by these mechanisms, because the amounts eliminated in 24 hrs are low regardless of temperature; therefore, effects of amiodarone are less temperature-dependent, and clearance is only slightly decreased under hypothermic conditions.

Risk for Infections. Hypothermia inhibits the proinflammatory response through inhibition of leukocyte migration and phagocytosis and decreased synthesis of proinflammatory cytokines (1). Indeed, suppression of harmful neuroinflammation is one of the mechanisms through which hypothermia may exert its protective effects; the downside of this protective mechanism is an increased risk for infections. Development of (accidental) hypothermia in the perioperative setting has been linked to increased risk for infections of the respiratory tract and (surgical) wounds (1, 240–242). Some evidence suggests that this may even apply to controlled normothermia; i.e., suppression of a febrile response. For therapeutic cooling (i.e., cooling of sedated and mechanically ventilated patients) the risk for nosocomial infections appears to be closely linked to treatment duration (higher risk if treatment is continued for >24 hrs) and to the category of patients (lowest risk in cardiac arrest patients, highest risk in patients with severe stroke). Most of the studies reporting increased risks of infection during therapeutic cooling also observed that final outcomes did not appear to be adversely affected, even when infections occurred (17). The suppression of inflammatory responses in the lung has also been used therapeutically to improve oxygenation in patients with severe acute respiratory distress syndrome (17).

Strategies to deal with increased infection risks include considering antibiotic prophylaxis. Recent publications suggest that the use of selective decontamination of the digestive tract can significantly reduce the risk for nosocomial infections and decrease mortality in ICU patients (243, 244). Clinical studies with therapeutic cooling in settings in which selective decontamination of the digestive tract was used have reported low infection rates (186, 216), even when hypothermia was used for prolonged periods (216).

Patients should be carefully monitored for signs of infection during therapeutic temperature management. Some normal signs of infection are absent or

suppressed during hypothermia; this obviously applies to development of fever but may also apply to increased C-reactive protein level and elevated white blood cell count. One telltale sign of developing infection can be a sudden increase in the "workload" of the cooling device; i.e., a decrease in water temperature and increase in noise levels of the device that is being used to cool the patient. Such increases in cooling power may indicate either shivering or an attempt by the body to generate fever, and thus the presence of an infection.

Many treatment protocols (including in our ICU) include daily blood surveillance cultures to screen for bacteremia. The threshold for antibiotic treatment should be low. In patients developing infections after hypothermia treatment, fever should be treated symptomatically, to prevent new or additional neurological injuries (17).

The risk for wound infections may be further increased by hypothermia-induced cutaneous vasoconstriction. The same applies to the development of bedsores, which once formed will be more likely to progress and become infected because of the immune-suppressed state and complete immobilization of the patient. Nurses and physicians should be aware of these additional risks and take extra precautionary measures. Extra attention should also be paid to catheter and central line insertion sites, as local infections also are more likely to develop here.

Other Effects. Hypothermia is associated with impaired bowel function and delayed gastric emptying. There is no specific strategy to deal with this issue; routine measures such as insertion of duodenal probes and/or administration of metoclopramide or low-dose erythromycin may be considered, taking care that the combination of hypothermia with these drugs does not cause QT prolongation (1). Hypothermia often causes a mild rise in serum amylase; however, the risk for clinically significant pancreatitis is extremely low (1).

Many other changes in laboratory measurements can develop during hypothermia. Apart from those already mentioned (hyperglycemia; low electrolyte levels; decreased platelet and white blood cell counts; increased levels of glycerol, free fatty acids, ketonic acids, lactate, and amylase), these may include a rise in liver enzymes (serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase) and increased levels of cortisol, norepinephrine, and epinephrine (184).

CONCLUSION

Hypothermia is the first treatment with a proven ability to reverse postischemic injury in the clinical setting. As such, it represents a major breakthrough, the importance of which is only just beginning to be fully appreciated. However, there are numerous pitfalls in using therapeutic cooling to maximum efficacy, particularly if prolonged treatments are required to improve outcome, as seems to be the case for stroke and severe TBI. Understanding the mechanisms that underlie hypothermia's protective effects, awareness of the physiology of cooling, and knowing and understanding the potential side effects are all key factors in effectively using this therapeutic strategy. There are still many misconceptions surrounding therapeutic cooling; some risks are imagined or overestimated, whereas others are not fully appreciated.

Temperature management strategies are likely to play an increasingly important role in the care of (neuro)critically ill patients. In view of the numerous potential applications for induced hypothermia or controlled normothermia, it is increasingly important that physicians and nurses caring for critically ill patients, particularly those with neurological injuries, be aware of these issues, to help them avoid the pitfalls and risks of this treatment.

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