Therapeutic hypothermia and controlled normothermia in the intensive care unit: Practical considerations, side effects, and cooling methods*

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Background: **Hypothermia is being used with increasing frequency to prevent or mitigate various types of neurologic injury. In addition, symptomatic fever control is becoming an increasingly accepted goal of therapy in patients with neurocritical illness. However, effectively controlling fever and inducing hypothermia poses special challenges to the intensive care unit team and others involved in the care of critically ill patients.**

Objective: **To discuss practical aspects and pitfalls of therapeutic temperature management in critically ill patients, and to review the currently available cooling methods.**

Design: **Review article.**

Interventions: **None.**

Main Results: **Cooling can be divided into three distinct phases: induction, maintenance, and rewarming. Each has its own risks and management problems. A number of cooling devices that have reached the market in recent years enable reliable maintenance and slow and controlled rewarming. In the induction phase, rapid cooling rates can be achieved by combining cold fluid infusion (1500–3000 mL 4°C saline or Ringer's lactate) with an invasive or surface cooling device. Rapid induction decreases the risks and consequences of short-term side effects, such as shivering and metabolic disorders. Cardiovascular effects include bradycardia and a rise in blood pressure. Hypothermia's effect on myocardial contractility is variable (depending on heart rate and filling pressure); in most patients myocardial contractility will increase, although mild diastolic dysfunction can develop in some patients. A risk of clinically significant arrhythmias occurs only if core temperature decreases below 30°C. The most important long-term side effects of hypothermia are infections (usually of the respiratory tract or wounds) and bedsores.**

Conclusions: **Temperature management and hypothermia induction are gaining importance in critical care medicine. Intensive care unit physicians, critical care nurses, and others (emergency physicians, neurologists, and cardiologists) should be familiar with the physiologic effects, current indications, techniques, complications and practical issues of temperature management, and induced hypothermia. In experienced hands the technique is safe and highly effective. (Crit Care Med 2009; 37:1101–1120)**

KEY WORDS: hypothermia; therapeutic; definitions; fever control; normothermia; side effects; neurologic injury; cardiac arrest; traumatic brain injury

Induced (therapeutic) hypothermia, defined here as an intentional reduction of a patients' core temperature to 32°C–35°C (Table 1), is being used with increasing frequency as a method to prevent or mitigate various types of neurologic injury (1). In recent years there has been a significant increase in our understanding of the cascade of destructive processes that unfold in the injured brain in the minutes to hours after an episode of ischemia or trauma. These processes, which have been collectively termed *postresuscitation disease* and *reperfusion injury* in the case of postanoxic injury and as "secondary brain injury" in the case of traumatic injury (TBI), can continue for hours to several days after the initial injury, and can be retriggered by new episodes of ischemia. The key point is that all of these processes are temperature dependent; they are all stimulated by fever, and can be blocked or mitigated by mild to moderate hypothermia. The wide-ranging effect of hypothermia on all of these mechanisms may explain why therapeutic hypothermia has proved to be clinically effective, whereas studies with pharmacologic agents that affect just one of the destructive processes have been much less successful (1).

The most recent guidelines from the American Heart Association and the European Resuscitation Council recommend the use of hypothermia for selected patients who remain comatose following a witnessed cardiac arrest (2). Under certain conditions, hypothermia is also used therapeutically in the treatment of severe traumatic brain injury, stroke, hepatic failure, spinal cord injury, myocardial infarction, and numerous others. The evidence for these and other potential indications has been discussed in various reviews (1, 3, 4).

Another important development in the field of neurocritical care is the increasing awareness that development of fever can adversely affect outcome in neurocritical patients. Various studies have shown that fever is independently associated with adverse outcome in patients with neurologic injury (including postanoxic injury following cardiac arrest), regardless of the cause of fever (1, 5–9).

All this means that the issue of temperature control and temperature manipulation is gaining importance in neurocritical care. However, inducing hypothermia and/or maintaining normothermia induces a large number of changes that can pose significant risks, and manipu-

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Table 1. Proposed terms and definitions surrounding therapeutic hypothermia

Therapeutic temperature management definitions	
Hypothermia	Core temperature <36.0°C regardless of the cause
Induced hypothermia	An intentional reduction of a patients' core temperature below 36.0°C
Therapeutic hypothermia	Controlled induced hypothermia: i.e., induced hypothermia with the potentially deleterious effects, such as shivering, being controlled or suppressed
Controlled normothermia/therapeutic normothermia	Bringing down core temperature in a patient with fever, and maintaining temperature within a range of 36.0°C–37.5°C, with the potentially deleterious effects, such as shivering, being controlled or suppressed
Temperature range definitions	
Mild therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 34.0°C–35.9°C
Moderate therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 32.0°C–33.9°C
Moderate/deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 30.0°C–31.9°C
Deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to <30.0°C
Mild hyperthermia	Core temperature 37.5°C–38.0°C
Moderate hyperthermia	Core temperature 38.1°C–38.5°C
Moderate/severe hyperthermia	Core temperature 38.6°C–38.9°C
Severe hyperthermia	Core temperature ≥39.0°C

lating body temperature in critically ill patients in a safe way can present considerable challenges to intensive care physicians.

This review will address the physiologic changes and potential side effects associated with hypothermia. Currently available methods for inducing hypothermia will also be discussed, and practical recommendations on how to deal with potentially harmful effects, as well as preventive measures, will be provided to help guide clinicians through this sometimes complex treatment.

One of the issues leading to misunderstandings in the field of therapeutic temperature management has been confusion over terminology. Terms such as *therapeutic hypothermia* and *induced hypothermia* have been used with different meanings, and expressions such as mild/moderate/severe hypothermia have been used to describe widely different temperature ranges. In addition, research findings from the field of accidental hypothermia have often (and sometimes inappropriately) been directly translated to the field of therapeutic hypothermia, without taking into account some major differences between these two clinical situations. For example, accidental hypothermia in the perioperative setting leads to an increase in heart rate, whereas controlled therapeutic hypothermia leads to a decrease in heart rate. These issues are discussed further below; a list of proposed definitions is provided in Table 1.

Literature Search Strategies

An electronic search of MEDLINE (OVID), EMBASE, Current Contents, and the Cochrane library was performed. The search terms used included "hypothermia" or "cooling" in various combinations with "methods," "devices," "induction," "arrhythmias," "hemodynamic," "bleeding," "side effects," "coagulopathy," "infection," "immune suppression," and various others. One of the authors has a personal archive with >1000 papers on the subject of hypothermia and temperature manipulation; data from this archive and from two reference books that have been published on the subject of induced hypothermia were also used (10, 11). A hand search of key journals was performed for studies published before 1966. The search was not restricted by language or type of publication. Studies from the field of perioperative hypothermia and accidental hypothermia were included in the search. Where no published studies were available the authors drew on their experience in >1000 patients. Where recommendations can be made based on published studies this is indicated by the appropriate references.

Induction of Hypothermia

Attempts to induce hypothermia will lead to the activation of counter-regulatory mechanisms to decrease heat loss. Under normal circumstances this will be accomplished by increasing the sympathetic tone and through vasoconstriction of vessels in the skin (12). This response complicates attempts to induce therapeutic hypothermia by surface cooling (see below). Under normal circumstances vasoconstriction begins at a core temperature of around 36.5°C (13); the reduction in heat loss resulting from cutaneous vasoconstriction is ±25% (14). In addition, heat production will be increased through shivering, with the shivering threshold being ~1°C below the vasoconstriction threshold (so at ±35.5°C) (13). Shivering has been linked to an increased risk of morbid cardiac events and adverse outcome if it occurs in the postoperative phase, where the patient who has become hypothermic and shivers will have a high rate of metabolism, increased oxygen consumption, excess work of breathing, higher heart rate, and a general stress-like response (15–18). In awake patients, this type of full counter-regulatory response can increase oxygen consumption by between 40% and 100% (19–24). This is an undesirable effect particularly in patients with neurologic and/or posthypoxic injury; indeed accidental perioperative hypothermia and the resulting stress response have been linked to an increased risk of morbid cardiac events, particularly in older patients with heart disease (15–17).

It should be noted that these adverse effects are linked to the hemodynamic and respiratory responses rather than to the shivering, *per se* (15). When an awake patient develops perioperative hypothermia, the average heart rate increases significantly (15–18); in contrast, inducing hypothermia intentionally in sedated patients has the opposite effect, with significant decreases in heart rate (12, discussed more extensively later). Shivering will increase oxygen consumption, but as the patient is on mechanical ventilation, there will be no increase in the work of breathing. The main problem of shivering during the induction phase is that it generates significant amounts of heat; sustained shivering can double the metabolic rate (12, 19), thereby significantly decreasing cooling rates. For this and other reasons, shivering should be aggressively treated especially in the induction phase of cooling (see later).

Shivering can be counteracted by administration of sedatives, anesthetics, opiates, magnesium, muscle paralyzers,

and various other drugs (discussed later and in Table 4). Skin counterwarming of the hands, feet, and face can also be used to reduce shivering (60, 99). In our experience, shivering can be managed without the use of paralytic agents in most patients in the setting of intensive care.

There are several reasons to reduce the use of paralytic agents during cooling. First, although muscular shivering activity will be blunted by paralysis, there will be no effect at the central level; in other words, the brain's attempts to generate a shivering response will not cease. Second, administration of paralytic agents may mask seizure activity. Seizures may occur in a substantial proportion of patients after postanoxic injury (25) or TBI (26), and unless patients are routinely monitored for seizure activity using continuous electroencephalographic monitoring paralysis can cause diagnostic problems. Third, using sedatives and analgesics to combat shivering has the advantage of inducing vasodilation, thereby increasing transfer of heat from the core to the periphery and further (1). This phenomenon occurs not only with volatile anesthetics but also with intravenous anesthetics and analgesics (32–38). Fourth, it is well recognized that prolonged paralysis significantly increases the risk of critical illness polyneuromyopathy (42); thus, in general, it makes sense to avoid prolonged administration of these agents if possible. Finally and perhaps most importantly, paralysis may mask insufficient sedation. Animal experiments have shown that the protective effects of hypothermia can be partially or even completely lost when animals are not sedated during hypothermia treatment. In one example, Thoresen et al (27) exposed newborn piglets to a period of global anoxia, after which some animals were treated with hypothermia. No sedation or analgesia was given to either hypothermic animals or controls. No protective effects on neurologic outcome were observed in this study (27). However, when the same research group performed the same experiment in the same animal model, with the same type and duration of injury but with sedation and analgesia used in both groups, there was a large improvement in neurologic outcome associated with hypothermia treatment (28). The loss of protective effects in the first study (27) was attributed by the authors to an aggravated stress response, which was prevented by appropriate sedation and analgesia in the second study (28).

Most clinical studies that have applied hypothermia successfully have used deep sedation and analgesia in their patients. However, some clinical studies have used mild hypothermia in awake, nonventilated patients with ischemic stroke (29–30) or acute myocardial infarction (31), and reported cooling awake patients appeared to be feasible and safe. However, even in these studies large doses of buspirone and meperidine were used to control shivering, and to allow patients to tolerate the treatment. Thus, overall, the available evidence suggests that proper sedation and analgesia are important for successful use of induced hypothermia.

Conversely, paralyzing agents have the advantage that they are highly effective and (in contrast to most sedatives and analgesics) do not cause hypotension, which can be an important advantage in some (hemodynamically unstable) patients. This is particularly important in the ambulance and emergency room setting where fewer options are available to maintain hemodynamic stability. In this setting, short-term paralysis should be considered more as a first-line option to control shivering. Thus, the advantages and disadvantages of the different shivering control methods should be carefully weighed in each individual patient. In our view, routine paralysis is usually unnecessary; it seems reasonable to use paralysis only when appropriate sedation/analgesia (and probably magnesium, see later) have failed to control shivering. Even in this situation, paralysis is rarely required in the maintenance phase, as the shivering response is markedly diminished and often ceases completely at temperatures below 33.5°C (39–41). The sedation strategy should entail administration of high bolus doses in the induction phase, and keeping maintenance doses given via continuous infusion pumps relatively low. The reason for this is that drug clearance changes, and in most cases is markedly reduced, during mild hypothermia (12, 43–58). Therefore, significant accumulation of drugs including opiates and sedatives (and muscle paralyzers, if these are used) is likely to occur when high continuous doses are given for prolonged periods during the maintenance phase of moderate hypothermia treatment.

Physiology of Cooling

Heat loss occurs via four basic mechanisms: convection, conduction, radiation, and evaporation (production of sweat). Under normal circumstances conduction (direct transfer of heat from one surface to an adjacent surface) is negligible, while convective heat loss (transfer of heat from a surface to the surrounding air) accounts for 20% to 30% of heat loss at room temperature in the absence of wind. Attempts to induce hypothermia all aim at increasing convective or conductive heat loss. A list of cooling methods and devices is shown in Table 2. 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. The rate of heat loss is higher with alcohol-based solutions because the rate of evaporation is higher (Table 2).

The effectiveness of the mechanisms controlling body temperature decrease with age; this is due to a decrease in sensitivity to small temperature changes (leading to a slower counter-regulatory response), a lower rate of metabolism, a less effective vascular response (i.e., less vasoconstriction), and frequently a lower lean body mass index (18, 59). Thus, in general, induction of hypothermia is easier in older patients than in younger ones. Doses of opiates and sedatives required to effectively suppress the body's warming mechanisms are usually much higher in younger patients. Similarly, achieving hypothermia in obese patients can take more time, because of the larger mass that needs to be cooled and due to the insulating properties of fat tissue.

When initiating hypothermia treatment, the treatment period can be divided into three phases. The first is the induction phase, where the aim is to get the temperature below 34°C and down to the target temperature as quickly as possible. In this phase a small overshoot ($\leq$1°C) should be regarded as acceptable provided temperature remains $>$30°C. In the maintenance phase the aim should be to tightly control core temperature, with minor or no fluctuations (maximum 0.2°C–0.5°C). Finally, the rewarming phase should be slow and controlled (warming rate 0.2°C–0.5°C/hr) (74).

Each of the three phases of hypothermia has specific management problems. In general, the risk of short-term side effects, such as hypovolemia, electrolyte disorders, and hyperglycemia, is greatest in the induction phase (1, 12, 61). This is the phase with the greatest patient "in-

Table 2. Currently available methods and devices for inducing and maintaining hypothermia

Method	Manufacturer	Efficacy of Induction, General and Specific Device-Related Advantages	General and Specific Device-Related Disadvantages
Surface cooling: air			
Exposure of skin	N/A	Easy, inexpensive, no procedural risk. Speed of induction low (~0.5°C/hr)	Relatively ineffective. Cannot be used for maintenance and rewarming phase
Skin exposure combined with water or alcohol sprays or sponge baths	—	Easy, inexpensive, relatively effective (alcohol sprays are more effective than water sprays). Speed of induction low to intermediate (~1.0°C/hr)	Labor intensive for nursing staff; patient remains wet for prolonged times. Cooling rate cannot be used for maintenance and rewarming phase
Fans	Various	Easily accomplished, inexpensive Speed of induction low to intermediate (~1.0°C/hr)	Additional risks of infection? Cannot be used for maintenance and rewarming phase
Air-circulating cooling blankets	Polar Air and Bair Hugger R, Arizant Healthcare, Eden Prairie, MN[c,d]	Relatively inexpensive; often already available due to use in ICU or operating room to warm patients. However, speed of induction is very low (~0.5°C/hr)	No more effective than skin exposure (~0.5°C/hr) in the intensive care unit
Specially designed beds	Deltatherm R, KCI, San Antonio, TX[d]	Cooling rates ~1°C/hr. May provide extra protection from bedsores. Targeted cooling of neck for quicker brain cooling. Highly reliable maintenance and controlled rewarming	Relatively large device, high noise levels during induction phase. Not marketed in the United States, device may be withdrawn from European market also, current status unclear
Surface cooling: fluids			
Ice packs	N/A	Easy, inexpensive cooling method. Speed of induction intermediate (~1°C/hr)	Risk of skin lesions and burns. Not reliable in maintenance and rewarming phase, labor-intensive if used for maintenance
Complete immersion in cold water	N/A	Speed of induction excellent (~8°C–10°C/hr); inexpensive	Unpractical, especially in the ICU setting and for maintaining a target temperature
Circulating cold water directly against skin of patient	LRS ThermoSuit system, Life Recovery Systems, Waldwick, NJ[c,d]	Only tested in animals, clinical trial ongoing. Very rapid induction rates (~10°C/hr) in animal study and in theory	Nonreusable; cannot be used for maintenance and rewarming phase
Prerefrigerated cooling pads	Laerdal Medi+Cool, Laerdal Medical AS, Stavanger, Norway[d]	Polyester and marino wool mesh filled with polymer crystals. Pads are immersed in cooled water, dried, and placed in a freezer for ±2 hrs before usage. Cooling activity ±2 hrs. Preliminary clinical trial ongoing. Low-tech approach, suitable for cooling in the field	No feedback system for temperature control. Theoretical risk of skin injury. Few data currently available. Cannot be used for rewarming, difficult to use in the maintenance phase
Prerefrigerated surface pads	Emcools AG, Vienna, Austria	Surface cooling elements, tested in animals, no clinical data yet available. Designed for use in prehospital setting	Cannot be used for maintenance and rewarming phase. Theoretical risk of skin injury. Few data currently available
Water-circulating cooling blankets	Blanketroll II hyper-hypothermia, Cincinnati Sub-Zero Company, Cincinnati, OH[c,d]	Reusable, significantly lower costs compared to most other devices. Cooling rate ~1.0°C–1.5°C/hr with two blankets	Labor intensive for nursing staff especially in induction phase. Two blankets required for quick induction if used as sole means of cooling
	Blanketroll III hyper-Hypothermia, Cincinnati Sub-Zero Company, Cincinnati, OH[c,d]	Some parts reusable, others disposable. Less labor-intensive than Blanketroll II. Targeted neck cooling possible. Cooling rate ~1.5°C/hr. Inexpensive compared to other disposable devices	Anecdotal evidence suggests some risk of overshoot in induction phase
Water-circulating cooling pads	CoolBlue Surface Pad System, Innercool Therapies, San Diego, CA[c]	Disposable vest and thigh wraps blankets. Less labor-intensive than Blanketroll II. Inexpensive compared with other disposable devices. Preliminary data appear promising	Few clinical data available so far; nonreusable materials

Table 2. —*Continued*

Method	Manufacturer	Efficacy of Induction, General and Specific Device-Related Advantages	General and Specific Device-Related Disadvantages
Hydrogel-coated water-circulating pads	Arctic Sun Temperature Management System, Medivance Inc., Louisville, CO[c,d]	User friendly, less labor intensive than water-circulating blankets; relatively high cooling rates (~1.5°C–2.0°C/hr), with lower percentage of patients' body that needs to be covered to achieve cooling. Reliable maintenance and rewarming phase	Slight risk of skin lesions (redness and mottling) if used at maximum setting for prolonged time (e.g., for prolonged fever control)[a]
Water-circulating wrapping garments	CritiCool and CureWrap systems, MTRE, Or-Akiva, Israel; Meditherm II and III systems, Gaymar, NY[c,d]	Wraps around the patient; skin contact better than with rubber blankets, material is nonadhesive. Cooling rates ~1.5°C/hr	Few clinical data available so far; nonreusable materials; causes reversible pressure tracks on the skin
Core cooling			
Intravascular catheters	CoolLine, Coolgard ↓ and Fortius, Alsius Corporation, Irvine, CA[c,d]	Uses intravascular balloons filled with cold saline. Relatively quick induction rates (~1.5°C–2.0°C/hr), highly reliable maintenance and rewarming rates. Provides venous access (two sideports apart from cooling sideports)	Requires invasive procedure, with some time loss and associated procedural risk; single use. Few data regarding prolonged usage, preliminary data suggest use up to 1 wk is safe. Some risk of catheter-related thrombosis
	Celsius Control System, Innercool therapies, San Diego, CA[c,d]	Uses metal catheter (10.7F or 14F) to accelerate heat loss. Quick induction rates (~2.0°C–4.5°C/hr depending on size and setting), highly reliable maintenance and rewarming rates. Venous access via single sideport on insertion sheath. Temperature sensor in catheter tip for blood temperature monitoring	Requires invasive procedure with some time loss and procedural risk. Only one sideport. Few data regarding prolonged usage. Some risk of catheter-related thrombosis
	SetPoint R and Reprieve Radiant Medical, Redwood City, CA[b]	Saline-filled balloons with helix system to improve heat extraction. Provides rapid cooling rates (~2.0°C–4.5°C/hr), reliable maintenance, and controlled rewarming	Requires invasive procedure with some time loss and procedural risk. No venous access provided by device (cooling system only). Some risk of catheter-related thrombosis
Infusion of ice-cold (4°C) fluids	N/A	Very rapid method to induce hypothermia (~2.5°C–3.5°C/hr); can easily be used in combination with other methods	Cannot be used to maintain temperature within narrow range; requires infusion of large volumes of fluid
Peritoneal lavage device	Velomedix, San Francisco, CA	Automates a cold peritoneal lavage	Tested in animals, preliminary clinical assessments ongoing, not yet commercially available.
Extracorporeal circulation	Various devices	Very quick and consistent cooling rates (~4.0°C–6.0°C/hr), reliable	Highly invasive, impractical in the ICU setting
Antipyretic agents	Various drugs (acetaminophen, aspirin, NSAIDs, others)	Low costs, little additional workload. Cooling rates average ~0.1°C–0.6°C	Efficacy is relatively low (temperature decrease ~0.1°C–0.6°C) especially in patients with "central" fever

ICU, intensive care unit; NSAIDS, nonsteroidal anti-inflammatory drugs.

[a]A (low) risk of skin lesions (usually redness and motteling) is probably inherent to all surface cooling devices, but has so far only been reported in one study (71); [b]manufacturer recently went bankrupt, future status of product currently unclear; [c]approved for clinical use in the United States; [d]approved for clinical use in Europe.

[†]The magnitude of this risk is still unclear. This may be similar to "regular" central venous lines, or lower (due to local effects of hypothermia on platelet function and coagulation), or higher (due to the greater size of these catheters compared to regular central venous catheter).

No randomized controlled trial assessing and comparing these devices and methods have been performed. Comments in the table are based on observational studies, method sections of papers reporting the results of hypothermia trials for various indications, data provided by the manufacturers, data obtained from the Food and Drug Administration website (www.fda.gov), and the experience of the authors.

stability," with numerous short-term changes required in ventilator settings, dosage of vasoactive drugs, insulin pumps, etc. The risks can be minimized by cooling patients as quickly as possible, i.e., by minimizing the duration of the induction phase and reaching the more stable maintenance phase as quickly as possible. This can be accomplished by using combinations of different cooling methods, for example, a combination of large-volume infusion of cold fluids and

surface cooling (62). In addition, preliminary results suggest that some of the new intravascular devices may have faster cooling rates than previously used methods. This also applies to rapid infusion of refrigerated fluids.

Once the core temperature decreases below ±33.5°C the patient tends to become more stable, with less risk for fluid loss or intracellular shifts, a cessation or significant diminishment of shivering, and a cessation of hypothermia-induced major changes in hemodynamic parameters. In this phase, attention should shift toward the prevention of longer-term side effects such as pneumonia, wound infections, and bedsores (see later).

Finally, the rewarming phase is associated with problems of its own, such as (again) electrolyte disorders caused by shifts from the intra-cellular to the extracellular compartment. This can be largely prevented by slow and controlled rewarming. In addition, there are numerous animal experiments showing that rapid rewarming after hypothermia treatment can adversely affect outcome (63–65). This is supported by some clinical observations. For example, Kawahara et al (66) reported that rapid rewarming following cardiac surgery leads to a decrease in jugular venous oxygen saturation, indicating hypoxia of the brain; significantly less jugular desaturations were observed when slower rates of rewarming were used. Lavinio et al (67) found that cerebrovascular reactivity was impaired during rapid rewarming following hypothermia treatment. In addition, patients who developed even mild hyperthermia had significantly more severe derangements of cerebrovascular reactivity, indicating the importance of maintaining controlled normothermia after hypothermia treatment (67). Bissonnette et al (68) observed that patients who were rapidly rewarmed often developed severe brain hyperthermia, even when core temperature measured at other sites remained normal. Thus, although no studies have been performed to determine the optimum rewarming rate in cardiac arrest patients following hypothermia treatment, based on the above it is highly plausible that slow rewarming will better preserve hypothermia's neuroprotective effects.

Cooling methods and devices are listed and described in Table 2. These can be broadly divided into (noninvasive) surface cooling devices, using adhesive pads, wrapping garments or rubber blankets, and (invasive) core cooling devices, using intravascular catheters (made of metal or with saline-filled balloons).

Most studies using intravascular devices have reported highly reliable maintenance of core temperature, and relatively rapid cooling rates once the catheter is in place (details in Table 2). A disadvantage is that an insertion procedure is required before cooling can be initiated, and this should be taken into account when calculating the "event-to-target-temperature" time, which is a more clinically relevant end point than the cooling rate *per se*. The time required for insertion strongly depends on the clinical setting (specifically, the rapid availability at all times of physicians capable of performing the insertion procedure) and other logistic factors.

A potential problem is the risk of catheter-related thrombosis. Some risk for thrombus formation is inherent to any indwelling central line (69); ultrasound studies have reported central venous catheter-related thrombus formation in 33% to 67% of patients when central venous catheter indwelling time was ≥1 week (69). Most of these thrombi remain asymptomatic, and resolve spontaneously when the central line is removed; the main problem is the associated risk of developing catheter-related infections (69). These issues have not been well studied for intravascular cooling devices, so the magnitude of this risk is unknown. Anecdotal evidence from centers using intravascular cooling devices on a regular basis suggests that the rate of symptomatic thrombosis is very low; this may increase when a device is left in place for prolonged periods of time. Only one small study has used ultrasound to detect thrombus formation associated with an intravascular cooling device, used to induce controlled normothermia in TBI patients with an average indwelling time of 5 days (70). Although none of these patients had a symptomatic thrombosis, the rate of asymptomatic thrombus formation was 50%, with a range of 33% to 75% depending on the indwelling time of the device. However, the value of this study is limited by its retrospective design and small number of patients (n = 11, of which one had to be excluded from analysis). Furthermore, the reported rate of asymptomatic catheter-related thrombosis is similar to what has been observed in studies with "regular" intravascular devices (69), although it should be pointed out that the catheter indwelling times were longer in these studies. Thus, it remains unclear whether the risk for catheter-related thrombosis differs between cooling catheters and "regular" catheters. Clearly, larger and prospective studies are needed to properly assess the risks (and efficacy) of these and other cooling devices.

A problem with surface cooling is that much of the patient's surface area needs to be covered, ranging from 40% to 90% in the induction phase depending on the efficacy of the cooling device and of the cooling pads/blanket. Prolonged and intense surface cooling carries a risk of skin lesions. This risk appears to be low, and is related to the temperature of the pads/blankets, duration of intense cooling, and the type of material (higher with rubber, lower with the newer materials). A major advantage of surface cooling is that it can be started immediately, in nurse-driven protocols without direct physician intervention.

The cooling rates reported in the literature for the older surface cooling technologies are significantly lower than for intravascular catheters and for the newer surface cooling devices (Table 2). There are no prospective studies that have compared currently available (surface and intravascular) cooling devices in a standardized way regarding efficacy of cooling, reliability of maintenance, and rewarming and side effects. Some studies have attempted to address this issue, but the results are difficult to interpret because of various methodologic issues. These include enrollment of small numbers and very different categories of patients; some studies were performed in the perioperative setting, making the results difficult to compare with studies enrolling intensive care unit patients. In the best comparative study published so far, Mayer et al (71) assessed the efficacy of two-surface cooling devices for fever management; however, there were problems in the way in which both methods were applied, in the sense that neither was used to maximum efficacy (72). Hoedemaekers et al (73) compared cooling rates for five invasive and noninvasive devices in small (n = 10) groups of patients. However, this study enrolled both patients requiring controlled hypothermia and controlled normothermia, making its results difficult to interpret; as explained above, achieving controlled normothermia is more difficult, and requires a different approach, than controlled hypothermia. Furthermore, some

aspects of the methods employed to calculate cooling rates were unclear in this study.

Significant increases in cooling rates can be achieved by using cold fluid infusion as an accessory cooling method (62). This implies that cooling devices should not only be judged solely or mainly on the basis of their cooling speed, but also (and perhaps especially) on their reliability to maintain target temperature within a narrow range and to slowly and safely rewarm the patient, as well the device-associated side effects and device-related physician and nursing workload (74).

Side Effects of Induced Hypothermia

Hypothermia induces physiologic changes in virtually every organ of the body. The kinetic properties of most enzyme systems are temperature-dependent; thus, the speed of various enzyme-mediated reactions is significantly influenced by hypothermia. This means, for example, that drug metabolism is significantly affected by induction of hypothermia (43). It should be realized that the distinction between physiologic ("normal") consequences and genuine side effects of hypothermia is to some extent artificial; some changes are physiologic, but are nevertheless undesirable in critically ill patients and therefore require preventive measures and/or proactive treatment. In contrast, other consequences of hypothermia can be regarded as side effects, but pose no great risk to the patient and thus usually do not require active treatment.

The most important side effects and changes are listed in Table 3. Details are discussed below.

Arrhythmias, Hemodynamic Changes, and Cardiovascular Effects. During mild-to-moderate hypothermia (32°C–34°C), cardiac output decreases by 25% to 40% mainly due to a decrease in heart rate (see later). In general, the decrease in metabolic rate is equal to or greater than the decrease in cardiac output. Temperature-corrected (mixed) venous saturation increases slightly or remains unchanged, reflecting an unchanged or improved circulatory state. Central venous pressure usually rises, and there is also an increase in arterial resistance (systemic vascular resistance) and a slight rise in blood pressure (by ±10 mm Hg) due to hypothermia-induced vasoconstriction of peripheral arteries and arterioles (75, 76). This vasoconstrictive effect is absent or less pronounced in cerebral arteries, where the balance between cerebral blood flow and cerebral metabolism is maintained or improved (77–81). In theory, an increase in SVR could increase the workload of the injured heart by increasing afterload. However, most patients who have had a circulatory collapse followed by reperfusion develop a systemic inflammatory response syndrome-like response with a pathologic decrease in vascular tone. In this situation an increase in systemic vascular resistance and vascular tone will be beneficial, and will also increase coronary perfusion. Furthermore, the hypothermia-induced decrease in heart rate (see later) will decrease myocardial oxygen demand.

The effect of hypothermia on myocardial contractility is strongly dependent on heart rate. If the heart rate is allowed to decrease along with the temperature, myocardial contractility as measured by systolic function usually increases, although there may be a mild degree of diastolic dysfunction (82–85). However, if the heart rate is artificially increased through administration of chronotropic drugs or a pacing wire, myocardial contractility decreases significantly. This phenomenon has been demonstrated in animal studies and also in patients undergoing cardiothoracic surgery (86). Thus, the effect of hypothermia on myocardial function strongly depends on whether the heart rate is allowed to decrease.

The fact that hypothermia can indeed improve circulatory parameters is shown by its successful usage in five small studies (three in pediatric patients and two in adults) to improve circulation and reverse refractory cardiac shock following cardiac surgery (87–91). Two small studies have reported that hypothermia can be used safely and effectively in hemodynamically unstable patients who remain comatose following cardiac arrest (166, 167). Whether hypothermia improves hemodynamic stability also depends on prevention of hypovolemia, which can develop because of hypothermia-induced "cold diuresis." If hemodynamic instability develops in the induction phase of cooling, hypovolemia is the most likely cause and a fluid challenge test is warranted.

Hypothermia also induces electrocardiographic changes and alterations in the heart rhythm. When hypothermic treatment is initiated and body temperature begins to drop, mild sinus tachycardia will initially develop. This is partly due to an increase in the venous return to the heart caused by a shift in circulatory volume from the peripheral compartment (especially the skin) to the core compartment, leading to a reflex increase in heart rate. Sinus bradycardia ensues as temperature drops below 35.5°C, with a progressive decrease in heart rate as temperature decreases further. At core temperatures of ±32°C the heart rate typically decreases to around 40–45 beats/min or even lower, although there is wide inter- and intraindividual variability and heart rate may remain at ±60 or even higher (1). This phenomenon is caused by a decrease in the rate of diastolic repolarization in the cells of the sinus node. Electrocardiographic changes include prolonged PR interval, widening of the QRS complex, increased QT interval, and sometimes so-called Osborne waves (Fig. 1). These changes usually do not require treatment; as explained above, at 32°C a heart rate of 40 is perfectly normal. If a stimulation of heart rate is deemed necessary, this can be accomplished by administering isoprenalin or dopamine, by rewarming the patient to slightly higher temperatures or (in extreme cases) by inserting a pacing wire. Atropine is ineffective in this situation. It should be kept in mind that excessive stimulation of heart rate during hypothermia is likely to decrease myocardial contractility (86), and that artificially increasing the heart rate by administration of chronotropic medication is rarely necessary. Conversely, if the heart rate does not decrease during hypothermia, care should be taken to rule out insufficient sedation as a cause of the (relative) tachycardia.

Whether or not the heart rate (or, more correctly, cardiac output) is sufficient in an individual patient can be determined by, for example, measuring the temperature-corrected (mixed) venous saturation and/or changes in metabolic parameters such as lactate levels. Regarding the latter parameter, it should be realized that lactate levels frequently increase during hypothermia (usually to around mmol/L with maximum of 5–6 mmol/L); however, once the target temperature has been reached these levels should remain stable. If lactate and metabolic acidosis increase further this may indicate insufficient circulation, requiring further diagnostic evaluation and perhaps therapeutic interventions such as fluid administration and/or administration of inotropic drugs.

Table 3. The most important physiological changes and potential side effects of hypothermia

Effect	Frequency	Treatment Required	Comment
Hypovolemia (due to cold diuresis); hypotension due to hypovolemia	Intermediate	Yes	More frequent in TBI than cardiac arrest, probably due to concomitant treatments such as mannitol administration
Cardiovascular changes: ↑ blood pressure, CVP, and mixed venous saturation; ↓ heart rate, ↓ Cardiac output	Frequent	Usually no	Mean arterial pressure increases slightly (±10 mm Hg) during mild hypothermia. Cardiac output decreases but at a rate equal to or less than decrease in metabolic rate. The net result is unchanged or improved balance between supply and demand
EKG changes: bradycardia, ↑ PR interval and QT interval, >QRS complex. Arrhythmias can develop at temp ≤28°C–30°C	Frequent	Usually no	There is no hypothermia-induced risk for severe arrhythmias unless core temperature decreases to <30°C. The risk increases significantly at temperature <28°C. Initial type of arrhythmia is usually artrial fibrillation; other arrhythmias including ventricular fibrillation may follow
Electrolyte disorders[a] (loss of K, Mg, P, Ca); in rewarming phase risk of hyperkalemia due to extracellular shift	Frequent	Yes	Far more frequent in TBI due to concomitant treatments such as mannitol administration. Maintain electrolyte levels in the high normal range (Mg ≥1.0 mmol/L, K ≥4.0, and PO ≥1.0 mmol/L, respectively) in all patients during hypothermia treatment. Rewarm slowly to avoid hyperkalemia in rewarming phase
Impaired coagulation cascade, risk of bleeding	Mild impairment of coagulation: frequent. Bleeding: Rare	Usually no	Platelet count and function and coagulation are impaired during hypothermia but bleeding problems are rare. No hypothermia study has reported significant problems with bleeding. Consider platelet administration before surgery/ invasive procedures. Administration of Desmopressin may improve platelet function during cooling (162)
Shivering	Frequent	Yes	Shivering leads to rewarming and should be controlled using intravenous magnesium, analgesia (bolus dose of meperidine or quick-acting opiates), sedation (propofol, benzodiazepines), and if necessary brief-acting paralytic drugs. Other drugs with antishivering effects: clonidine, ketanserin, tramadol, urapidil, and doxapram. The cardiovascular effects during shivering are different than in the post-operative setting. Shivering response is significantly blunted when temperature decreases below ±33.5°C
Increased infection risk, particularly airway and wound infections	Intermediate	Yes	Inflammatory response is suppressed by cooling. Prolonged (>24 hrs) cooling is associated with higher infection risk. Consider antibiotic prophylaxis
Insulin resistance, hyperglycemia	Frequent	Yes	Insulin doses required to maintain normoglycemia may increase during induction, and decrease during rewarming
Bedsores (due to vasoconstriction in the skin, immobilization, and immune suppression)	Intermediate	Yes	Extra attention required for bedsore prevention due to converging of risk factors
Lab changes: ↑ amylase, liver enzymes, lactate, ketonic acids, and glycerol; ↓ white blood cells and platelets; mild ↑ hematocrit; mild acidosis	Frequent	No	Usually no interventions required. Some lab values (coagulation parameters, blood gases, pH value) are influenced by temperature and should be temperature-corrected
Changes (usually decrease) in drug clearance (due to slowing of numerous liver enzymes)	Frequent	Yes	Adjust infusion rates; use bolus doses rather than increasing continuous infusion

CVP, central venous pressure; EKG, electrocardiogram; TBI, trumatic brain injury.

[a]The magnitude of this risk is still unclear. This may be similar to "regular" central venous lines, or lower (due to local effects of hypothermia on platelet function and coagulation), or higher (due to the greater size of these catheters compared to regular central venous catheters).

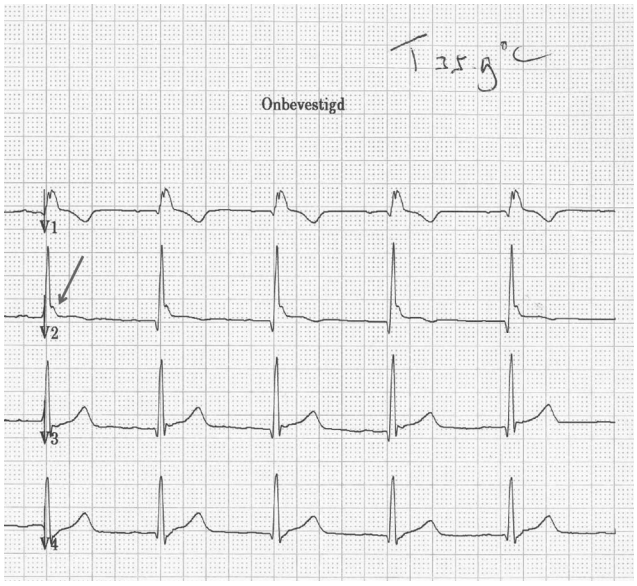

Figure 1. Electrocardiogram (EKG) changes during hypothermia treatment. In this patient, many of the EKG changes associated with hypothermia are apparent: Note the slightly prolonged PR interval, slight widening of the QRS complex and increased QT interval and Osborn wave (*arrow*). In this patient the changes developed during the induction phase of cooling persisted throughout the hypothermia treatment and disappeared at the end of the slow rewarming process. The EKG at a core temperature of 35.9°C.

The risk of developing clinically significant arrhythmias due to hypothermia is extremely low as long as the patients' core temperature remains higher than 30°C. In fact, experimental evidence suggests that mild hypothermia may increase membrane stability, thereby decreasing the risk of arrhythmias (175). Animal studies have shown that mild to moderate hypothermia significantly improves the likelihood of successful defibrillation and good resuscition outcomes (175–177). Various case reports describe successful use of hypothermia to treat arrhythmias (junctional ectopic tachycardia) in young infants (178–181), indicating that mild hypothermia indeed can improve membrane stability and decrease the likelihood of arrhythymias.

In contrast, more profound hypothermia (<28°C, in rare cases 30°C if electrolyte disorders and/or ischemia are present) can increase the risk of arrhythmias. This usually begins with atrial fibrillation, which can be followed by more severe arrhythmias including ventricular fibrillation (VF) and ventricular tachycardia, if temperature decreases further. It is important to realize that mechanical manipulations can trigger this transition from atrial fibrillation to VF, as the myocardium becomes highly sensitive to such manipulations during hypothermia (92). Thus, if a physician decides to perform chest compressions because of extreme bradycardia this can easily lead to a conversion of sinus rhythm to VF, or atrial fibrillation to VF. A major problem is that once arrhythmias do develop in deeply hypothermic patients these are far more difficult to treat than at mild hypothermia or normothermia. The reason for this is that the myocardium at deep hypothermia becomes less responsive to many anti-arrhythmic drugs (93–96). As these problems are rarely encountered at temperatures above 28°C–30°C, great care should be taken to keep core temperatures above this limit.

The increase in venous return induced by hypothermia can lead to activation of atrial natriuretic peptide and a decrease in the levels of anti-diuretic hormone. This (in combination with other mechanisms such as tubular dysfunction, see later) can lead to a marked increase in diuresis ("cold diuresis"), which if uncorrected can lead to hypovolemia, renal electrolyte loss, and hemoconcentration with increased blood viscosity (61, 97–98). The risk of hypovolemia is greater if the patient is simultaneously treated with agents that can increase diuresis, such as mannitol in TBI patients. The increase in blood viscosity (±2% per °C decrease in core temperature) can lead to problems in the microcirculation; the above-mentioned mechanisms combined with tubular dysfunction can lead to severe electrolyte disorders (see later), including a rise in serum sodium levels and osmolarity. Thus, careful attention should be paid to intravascular volume and fluid balance in patients treated with hypothermia, and hypovolemia should be avoided or promptly corrected.

Several studies have shown that mild hypothermia in awake patients leads to an increase in plasma levels of catecholamines (169, 170). However, studies in hypothermic patients under general anesthesia found no such difference in catecholamine levels. Indeed one study reported lower catecholamine levels in mildy hypothermic patients compared with controls (171). Conflicting observations have been reported from studies in children undergoing cardiac surgical procedures; one study reported increased catecholamine levels when patients were cooled to 26°C (172); however, another study reported no significant changes in catecolamine levels during surface cooling to 28°C, nor during circulatory arrest and cooling until 18°C (173). However, catecholamine levels did increase significantly during rewarming (172). Thus, catecholamine levels may increase during mild-to-moderate hypothermia, but this phenomenon may be linked to a shivering/stress response and to rewarming rather than to hypothermia *per se*. In addition, some animal studies suggest that hypothermia reduces ischemia-induced catecholamine release from hypoperfused tissues, while catecholamine secretion from noninjured tissues may increase (174). Thus, the relationship between hypothermia and catecholamine levels is a complicated one, which may be influenced by concomitant drug administration (especially sedatives) and other factors.

Coronary Perfusion and Ischemia. As explained above, perioperative hypothermia is associated with an increased risk of morbid cardiac events (15–17). Partly due to these observations, it is widely believed that hypothermia can cause coronary vasoconstriction and myocardial ischemia. However, the real situation is more complex. In healthy subjects, mild hypothermia (±35°C) actually increases coronary perfusion (100, 169). However, this is less clear in patients with coronary artery disease; hypothermia can induce vasoconstriction in severely atherosclerotic coronary arteries (100). Thus, which effect will occur may depend on the preexisting health of the patients' coronary arteries and on local factors.

On the basis of these observations one might reasonably expect hypothermia-induced coronary vasoconstriction to occur in patients who have been admitted following a cardiac arrest, based on the presence of coronary artery disease which has caused the cardiac arrest in the first place. However, as outlined above, various animal experiments (101–108) and preliminary clinical studies (109, 110) have shown that hypothermia may actually decrease myocardial injury following cardiac arrest, provided it is initiated early enough. Studies in patients undergoing cardiac surgical procedures have reported that under hypothermic conditions the reduction in cardiac work was greater than the reduction in coronary blood flow (111, 112). Thus, although the question whether hypothermia mitigates myocardial injury needs to be addressed in further (larger) studies, the available evidence certainly does not suggest that hypothermia increases such injury through hypothermia-induced vasoconstriction.

Drug Clearance. As outlined above, not only the serum levels and drug clearance but also the effects of various drugs may change (43–58). An example of the latter is the response to vasoactive drugs such as adrenalin and noradrenalin, which may be slightly blunted by hypothermia (52). Conversely, the half-life of vasopressors is increased, so higher concentrations will be achieved with the same dose. Apart from vasoactive pressor drugs, effects of hypothermia on drug levels and/or drug actions have been demonstrated for the following drugs: fentanyl, remifentanyl, and morphine; propofol, barbiturates, and midazolam; neuromuscular blocking agents such as vecuronium, rocuronium, and atracurium; phenytoin; nitrates; propanolol; and tissue/gas partition coefficients of volatile anesthetics (43–58). In most cases the effect of hypothermia is to increase drug levels and/or enhance the effect of the drug. The underlying mechanism is a reduction in the activity of many liver enzymes during hypothermia, combined with reduced perfusion of the liver and reduced production of bile leading to decreased excretion of some drugs. Changes in distribution volume and hypothermia-induced tubular dysfunction may also play a role. It seems likely that the metabolism of other drugs will be affected by temperature in a similar way, based on their excretion mechanism. These mechanisms should be taken into account when treating patients under hypothermic conditions. Sedation and analgesia should be a specific focus of attention; benzodiazepines and opiates, particularly morphine (58), can accumulate during hypothermia, complicating neurologic assessment after treatment. As explained above, adequate sedation is of key importance for effective cooling, but correct dosing can be difficult under hypothermic conditions.

Electrolyte Disorders. Electrolyte disorders may develop especially in the induction phase of cooling. Patients frequently develop low electrolyte levels during cooling; the reason is a combination of increased renal excretion (caused by a combination of cold diuresis and tubular dysfunction) and intracellular shift (61). Such electrolyte disorders can increase the risk of arrhythmias and have other adverse effects on outcome. Magnesium (Mg), in particular, may play an important role in mitigating brain injuries, myocardial injury, and arrhythmias (113–121). Mg depletion significantly increases brain injury in various animal models for TBI and stroke, and clinical studies have shown improved neurologic outcome with Mg supplementation in severe eclampsia and subarachnoid hemorrhage (114–116). Hypomagnesaemia is also associated with adverse outcome in patients with unstable angina or myocardial infarction (117, 118). The latter issue is particularly relevant if patients are treated with induced hypothermia following cardiac arrest. Several studies have linked hypomagnesemia to increased mortality in the intensive care unit (119, 120) and in the general ward (121).

All this implies that levels of Mg should be maintained in the high-normal [but perhaps not supranormal (122)] range in patients with neurologic injuries in general, and those treated with hypothermia, in particular. This also applies to other electrolytes such as potassium and phosphate. Potassium levels may rise during the rewarming phase, as potassium that was secreted into the cell in the induction phase is released. This is one of the reasons why rewarming should be done very slowly, giving the kidneys time to excrete the excess potassium. Hyperkalemia will not develop if rewarming is slow and if renal function is not grossly impaired (61).

Hyperglycemia. As explained above hypothermia can simultaneously decrease insulin sensitivity and reduce insulin secretion by pancreatic islet cells. Thus, patients treated with induced hypothermia will be at higher-than-average risk for developing hyperglycemia, and hyperglycemia may become more severe (or insulin requirements may increase) during cooling (1). This requires active management because hyperglycemia may adversely affect outcome in critically ill patients (123, 124). In addition, hyperglycemia may have specific negative effects on neurologic outcome, for example by increasing brain injury during episodes of ischemia (125–128). Thus, despite the fact that it is a physiologic consequence of hypothermia, hyperglycemia should be high on the list of potentially preventable side effects. What the appropriate target value for blood glucose should be is currently unclear, as there is conflicting evidence regarding the risks and benefits of very tight glucose control in some categories of patients (123, 124, 129–131); a major study addressing this issue is currently ongoing (132). However, it seems prudent to avoid at least severe hyperglycemia during cooling, with target values of 4–8 mmol/L.

Other Metabolic Effects and Blood Gas Management. Hypothermia leads to an increase in the synthesis of glycerol, free fatty acids, ketonic acids, and lactate, causing a mild metabolic acidosis, which in most patients does not require treatment. In contrast to the pH levels measured extracellularly, intracellular pH levels increase slightly during cooling.

The hypothermia-induced decrease in metabolic rate (±8% per °C drop in core temperature) also reduces oxygen consumption and CO_2 production. Ventilator settings should be adjusted during induction of hypothermia, and blood gases should be monitored frequently especially during the induction phase. It should also be realized that blood gas values are temperature dependent. Because blood gas analyzers warm blood samples to a temperature of 37°C before analysis, when the actual temperature differs significantly from 37°C these measurements will not be correct; in blood samples from hypothermic patients P_{O_2} and P_{CO_2} will be overestimated, and pH underestimated. For example, in a patient with a core temperature of 30°C and P_{CO_2} determined to be 40 mm Hg in an uncorrected measurement, the temperature-corrected P_{CO_2} value would be 29 mm Hg (133). In the same patient with an uncorrected P_{O_2} of 100 mm Hg, the temperature-corrected value would be 73 mm Hg. By the same token true pH is underestimated, with hypothermia leading to a

more alkalotic status compared with normothermia (pH increase ± 0.012 pH units/°C). In the example cited above (measured CO_2 40, corrected CO_2 29) the measured pH would be 7.40, whereas the temperature-corrected pH would be 7.50.

The concept of CO_2 management in which the Pco_2 obtained by measurement at 37°C is kept constant (for example, at 40 mm Hg) regardless of the actual body temperature is called *alpha-stat*. If the Pco_2 value is corrected for the actual body temperature, and is held constant at the same level as during normothermia, this implies that the "true" amount of CO_2 will increase during hypothermia. This concept of CO_2 management is called *pH-stat*. In other words, when alpha-stat CO2 management is applied, pH that is not corrected for current body temperature remains constant, while true pH increases because the actual $Paco_2$ has decreased. When pH-stat CO_2 management is used, true pH remains constant, while pH that is not corrected for temperature decreases. The effects of temperature on blood gas management have been studied most extensively in the context of hypothermic coronary and large vessel surgery, where the differences can be much more pronounced because the temperatures used are often lower than the 32°C–34°C range used in the intensive care unit (134–136).

The issue of which method is superior in the management of hypothermic patients has not been settled, and will not be extensively discussed here. Supporting evidence can be found for both methods (133–138). Supporters of the pH-stat method argue that application of alpha-stat management leads to hyperventilation, hypocapnia, and hypocapnia-induced cerebral vasoconstriction, while pH-stat management induces a degree of hypercapnia leading to cerebral vasodilation (provided cerebral autoregulation is intact); the latter would seem to be a more attractive option. However, hypercapnia can impair or abolish cerebral autoregulation, presumably because CO_2-induced vasodilatation limits the vessels' capacity to dilate further. This could imply that the body's capacity to divert blood to injured areas would be impaired. In addition, some animal studies suggest that respiratory alkalosis is physiologically appropriate during hypothermia to preserve normal physiologic conditions (135). In our clinic, we use a modified alpha-stat method where gases are temperature-corrected for CO_2 but slightly below-normal values (32–34 mm Hg, which is 42–44 mm Hg at 37°C) are maintained during hypothermia.

Regardless of which method of blood gas management is chosen, physicians using mild hypothermia in their patients should be aware of the effects of temperature on blood gas analysis (as well as on other laboratory measurements such as coagulation parameters). In addition, regardless of whether the alpha-stat or pH-stat method is used to guide pH/CO_2 values, the effect of temperature on Po_2 should always be taken into account, and Pao_2 should always be corrected for actual current body temperature in hypothermic patients. Thus, it would be a mistake to adapt inspired oxygen fraction to the apparently high uncorrected values of Pao_2 obtained during hypothermia. This also applies to measurements of mixed venous or venous saturation, which will be influenced by core temperature in the same way. If it is not possible to obtain blood gas results measured at the patient's true core temperature, values can be estimated using the following rule of thumb: for Po_2, subtract 5 mm Hg for every 1°C below 37°C; for Pco_2, subtract 2 mm Hg for every 1°C below 37°C; for pH, add 0.012 points for every 1°C below 37°C.

Coagulation Parameters. Hypothermia induces a mild bleeding diathesis, with increased bleeding time due to effects on platelet count, platelet function, the kinetics of clotting enzymes and plasminogen activator inhibitors, and other steps in the coagulation cascade (139–145). Standard coagulation tests will show no abnormalities unless they are performed at the patient's actual core temperature; as is the case with blood gas analyses usually the samples are warmed to 37°C before the clotting tests are performed. Despite the coagulation defects that can be caused by hypothermia, the risk of clinically significant bleeding induced by hypothermia in patients who are not already actively bleeding is very low. None of the large clinical trials in patients with TBI, subarachnoid hemorrhage, stroke, or postanoxic coma has reported significantly increased risks of bleeding associated with hypothermia. The situation may be different in patients who are already actively bleeding, for example in multitraumatized patients. In this situation the sites of bleeding should be controlled before hypothermic therapy is initiated. Of note, hypothermia does not begin to affect platelet function until temperature decreases below 35°C (139–145); clotting factors are affected only when temperature decreases below 33°C (140–142, 144). Thus, very mild hypothermia of 35°C does not affect clotting in any way, and this may be the temperature of choice for patients who have an indication for therapeutic hypothermia but are actively bleeding, or who are at very high risk for bleeding.

Infections. Hypothermia impairs immune functions and inhibits various inflammatory responses. Indeed, this side effect is inherent to the treatment because impairment of harmful inflammatory reactions in the brain may be one of the mechanisms through which hypothermia can exert protective effects (1, 3). Hypothermia inhibits the secretion of proinflammatory cytokines and suppression leukocyte migration and phagocytosis (1, 3, 146). Hypothermia-induced insulin resistance and hyperglycemia may further increase infection risks. Some of the clinical studies using induced hypothermia for various indications have reported a slightly, moderately and, in some cases, severely increased incidence of pneumonia when hypothermia was used for periods longer than 24 hours. However, most studies using hypothermia for 24 hours or less have reported no or only small increases in the infection rates. Antibiotic prophylaxis in the form of selective decontamination of the digestive tract can reduce Gram-negative infection rates and perhaps reduce mortality (147); there is some evidence that selective decontamination of the digestive tract can be used to prevent infections during prolonged use of hypothermia (98, 148), and depending on the setting this could be considered for patients undergoing hypothermia treatment.

Hypothermia also increases the risk of wound infections (149). This may be related both to diminished leukocyte function and to hypothermia-induced vasoconstriction in the skin. Thus extra care should be taken in cooled patients to prevent bedsores, which are more likely to show progression and/or impaired healing. In addition, extra attention should be paid to catheter insertion sites and to any surgical wounds which may be present.

Shivering. The problems and metabolic consequences of shivering in the induction phase have been discussed above. Shivering can be counteracted by administration of sedatives, anesthetics, opiates, and/or paralyzing drugs (Table 4). In most patients, shivering can be significantly attenuated by relatively small doses of opiates. When using para-

Table 4. Drugs that can be used to control shivering

Drug	Efficacy	Hypotensive Effect	Sedative Effect[a]	Additional Comments, Advantages, and Disadvantages
Magnesium (2–3 g)[b]	++	+	−	Advantages: some evidence for direct neuroprotective effects of Mg. "Pre-emptive" correction of hypothermia-induced Mg depletion
Propofol (20–150 mg)[b]	+++	+++	++++	Advantages: brief-acting. Anti-seizure effect. Disadvantage: more pronounced hypotension
Benzodiazepines (dose depending on type of drug; e.g. midazolam 2.5–10 mg)[b]	++	+	++++	Advantages: less hypotension. Disadvantages: Complicates neurological evaluation. Reduced metabolism during cooling can lead to drug accumulation with persistent sedative effect after rewarming
Meperidine 10–25 mg	++++	+	++	Advantages: rapid (1–5 mins) effect. Effect lasts longer than with quick-acting opioids. Effect more pronounced than other opioids because of activity at kappa receptors. Relatively mild hypotensive effect. Disadvantages: complicates neurological evaluation. Slower metabolism during cooling.
Quick-acting opiates: fentanyl 50–100 μg,[b] alfentanyl 100–250 μg	+++	+	++	Advantages: rapid (1–5 mins) effect. Relatively mild hypotensive effect. Disadvantages: complicates neurological evaluation. Decreased drug metabolism during cooling
Morphine 2.5–5 mg[b]	+++	+++	++	Advantage: low costs; additional sedative effect. Disadvantages: delayed (20 mins) effect. Greater hypotensive effect compared with fentanyl
Dexmedetomidine 50–100 μg[b]	++	+	++	Advantages: brief-acting; only mild hypotension. Disadvantages: only moderately effective; expensive. Currently not available in Europe
Clonidine 75–200 μg[b]	+++	++++	+	Effect in 4–7 mins. Disadvantages: Hypotension, additional bradycardia
Ketanserin 10 mg[b]	++	++	−	Effect in 4–7 mins. Advantages: increases cooling rate. Disadvantage: moderate hypotensive effect
Tramadol 50–100 mg	++	++	++	More rapid effect than morphine (±5 mins). Relatively mild hypotensive effect. Disadvantages: complicates neurological evaluation. Metabolism decreases during hypothermia. Can cause seizures
Urapidil 10–20 mg	+++?	+++	−	Conflicting results of studies on efficacy. Disadvantage: pronounced hypotensive effect
Doxapram 100 mg	+++	−	−	Advantages: rapid action (1–5 mins). Can increase heart rate and blood pressure. Disadvantages: can cause laryngeal spasms
Physostigmine 2 mg	++	++	−	Can cause additional bradycardia and hypotension
Flumazenil 0.25–0.5 mg	++	−	−	Few data available. Efficacy may be lower outside the perioperative setting
Nefopam 10–20 mg	+++	−	+	Can induce convulsions and anaphylactic reactions. Currently not available in the United States
Metamizol	+	−	−	Low efficacy
Ondansetron	+	−	±	Low efficacy
Other options: lidocaine, nalbuphine, pentazocine, methylphenidate	−/±	−	−	Questionable or no efficacy
Muscle paralyzers	+++++	−	−	Advantage: 100% effective. Disadvantages: does not affect neurological triggers for shivering; may mask insufficient sedation and/or seizure activity; long-term risks of critical illness neuropathy

For most drugs efficacy increases at higher doses. Efficacy scale: −, not effective; +, somewhat effective; ++, moderately effective; +++, effective; ++++, highly effective; +++++, 100% effective. Side effect scale: −, no risk; +, mild risk; ++, moderate risk; +++, clear risk; ++++, high risk.

[a]Having a sedative effect can be both advantageous (suppression of stress response, vasodilation with increased heat loss) and disadvantageous (complication of neurological evaluation, hypotension). Reduced metabolism during cooling can lead to drug accumulation with persistent sedative effect after rewarming; this applies especially to longer-acting drugs such as benzodiazepines and morphine, where a persistent sedative effect can complicate neurological evaluation; [b]can also be given as continuous infusion. General methods: there is some evidence that warm-air skin counterwarming can be used to combat shivering. Drugs such as acetamoinophen (paracetamol), buspirone, and/or nonsteroidal anti-inflammatory drugs can be used to lower the shivering threshold.

lyzing agents and/or when opiates are deemed undesirable, alternatives to treat shivering include administration of clonidine, neostigmine, and ketanserin. However, care should be taken to avoid adverse effects; for example, clonidine may worsen hypothermia-induced bradycardia. Warming of the hands, feet, and face ("skin counterwarming") may also reduce the shivering response (54, 60, 153–155); combination with sedation may be required to achieve this effect (99, 156).

Other Side Effects. Hypothermia is associated with impaired bowel function and may aggravate gastric emptying problems. In addition, a myriad of changes in laboratory measurements can occur; apart from hyperglycemia and electrolyte disorders, the most frequently occurring changes are a rise in liver enzymes and serum amylase, mild increase in serum lactate levels (average, 2.5–5 mmol/L; but may be higher in some cases) as well as ketonic acids and glycerol (leading to a mild metabolic acidosis), and a decrease in platelet count and sometimes white blood cell count (12).

Monitoring Temperature and Guiding Hypothermia Treatment

When applying induced hypothermia, it is of key importance that core temperature be measured accurately, and that the site chosen to measure core temperature reflect "true" core temperature. Although in most patients the goal of treatment is to lower brain temperature, side effects will be determined mainly by the temperatures in other organs. The generally accepted gold standard for "true" core temperature is the temperature of the blood, measured with a pulmonary artery catheter (151). All other sites for temperature measurement should be compared with this gold standard.

Most cooling devices now work with a controlled feedback system that continuously measures a patient's temperature and changes the temperature of the cooling element (catheters, pads, or blankets) accordingly.

In this regard, it should be realized that most of the devices and probes that are currently used to monitor core temperature in critically ill patients were not designed to detect rapid changes in temperature; rather, they were designed to reflect small temperature changes over prolonged periods of time as accurately as possible. The probes take some time to equilibrate, and monitoring devices to which the probes are connected usually have a low sampling frequency of temperature readings leading to further delays in registering temperature changes.

Many of the new cooling devices have relatively high cooling rates; especially when combined with cold fluid infusion, cooling rates of 4°C/hr or more can be achieved. Such rapid cooling will inevitably lead to a time lag between registered temperature and measured core temperature, unless blood temperature is measured directly. This applies to all of the most commonly used core temperature monitoring sites (bladder, rectum, esophagus, and tympanic membrane), although the lag times differ considerably. In the induction phase this time lag can lead to a significant "overshoot" of core temperature below the desired target, as the cooling device continues cooling (based on the measured temperature) while the target temperature has in fact already been reached. The faster the cooling rates, the greater will be the time lag between registered and actual core temperature. This problem can be avoided by using blood temperature to control cooling rates. A pulmonary artery catheter could be used for this purpose, and some cooling catheters have an inbuilt temperature sensor at the catheter tip to guide therapy.

The equilibration rate between the blood and the organ where temperature is measured is influenced by a number of factors including the type of organ, organ perfusion (which in turn is influenced by systemic factors such as presence of shock, hypotension, or hypovolemia—with slower equilibration when perfusion is decreased—and by preexisting disease such as atherosclerosis, again with slower equilibration if severe atherosclerosis is present), and by various local factors. The cooling method employed (especially surface vs. invasive cooling) can also affect temperature readings; invasive cooling methods cool the blood directly and therefore will affect temperature readings more rapidly.

Some technical issues may further compound this problem. For example, many of the bladder temperature probes (Foley catheters with temperature sensors) that are widely used (e.g., Covidien, Mansfield, MA) have a "floating" temperature sensor that is not welded to the interior of the catheter. The sensor can therefore move within the catheter, and if traction is applied to the catheter the tip of the temperature probe can move backward inside the saline-filled balloon that occludes the bladder. If the balloon has just been filled with room-temperature saline, this can significantly affect temperature readings.

For all these reasons, during the induction phase the registered temperature will constantly lag behind the actual core temperature. This means that the cooling device may continue to cool the patient even when target temperature has already been reached, because the temperature reading of the probe controlling the cooling device lags behind the actual core temperature. The device will continue cooling until the temperature input approaches the set target temperature; by this time the actual core temperature (as measured in the blood) may have dropped significantly below the target range.

All of the most commonly used temperature monitoring sites have specific advantages and problems. The average time lags between various core monitoring sites and the blood, as well as specific advantages and limitations of various core temperature monitoring sites, are summarized in Table 5.

Fever Control

Controlled normothermia represents a closely related but separate area of therapeutic temperature management. In many aspects inducing and maintaining normothermia is less problematic than inducing hypothermia, because the number of potential side effects is much lower. For example, side effects such as suppression of immune function and coagulation disorders do not occur during controlled normothermia (although the proinflammatory state associated with a fever response can be blunted by prevention of fever). In contrast, side effects such as shivering may be much more pronounced during controlled normothermia than in induced hypothermia. The reason for this is that the body's counter-regulatory mechanisms decrease significantly at lower temperatures, but work at maximum efficiency in the normal range. In patients with fever, the hypothalamic setpoint that regulates core temperature is temporarily "reset" to a higher value, and all mechanisms available to the body for heat conservation and heat generation are maximally activated to achieve this new "target value." For this reason, although there are fewer side effects, maintaining normothermia can be far more difficult (because of the

Table 5. Advantages, disadvantages, and time lag compared with gold standard of various temperature monitoring sites

Site	Level of Accuracy	Average Time Lag Between Site and Gold Standard	Specific Advantages, Problems, and Limitations
Pulmonary artery	High	N/A	+Highly precise and rapid temperature registration –Complex insertion procedure required –Needs to be removed after 72–96 hrs
Jugular bulb	High	N/A	+Highly precise temperature registration +Venous blood coming directly from the brain reflects brain temperature even more accurately than pulmonary artery catheter measurements –Complex insertion procedure required –Experimental form of neuromonitoring; used relatively rarely
Esophagus	High	5 mins (range, 3–10)	+Most rapid and accurate reflection of gold standard –Moderate risk of downward dislocation to stomach. This can lead to a longer time lag and a slight (1°C–3°C) drop in registered core temperature. As this deviation is relatively small, it may go unnoticed. Can be prevented by precise insertion to a depth of 32–38 cm –Potential interference of diagnostic/therapeutic procedures such as insertion of gastric feeding tubes, transesophageal echocardiography, gastroscopy, etc +Occasionally problematic probe insertion procedure
Bladder	Fair/high	20 mins (range, 10–60)[a]	+Fairly easy probe insertion procedure + +Low risk of dislocation +Combination with procedure (catheter insertion) that needs to take place anyway –Relatively long time lag –Readings affected by rate of diuresis (which may be low in some patients after cardiac arrest) –Sensor can move into saline-filled balloon at tip of some catheters, affecting temperature readings
Rectum	Fair/high	15 mins (range, 10–40)[b]	+Quick and easy probe insertion procedure –High risk of dislocation (however, dislocation is likely to be noticed immediately because of the magnitude of the difference with "true" core temperature) –Relatively long time lag
Nasopharynx	High	8 mins (range, 5–10)	+Relatively quick and easy probe placement procedure +Relatively short lag time +May reflect brain temperature better than more distant sites –Risk of probe misplacement + –Risk of nasal bleeding especially in patients receiving anticoagulants
Tympanic membrane	Moderate/fair	10 mins (range, 5–20)	+Very quick and easy probe placement procedure –May reflect brain temperature better than more distant sites –Readings may be inaccurate +Continuous measurement may be uncomfortable for awake patients
Forehead	Fair/high[c]	5 mins?[c]	+Good correlation (r^2 = .87) shown between temperature measured by device and temp at 18 mm depth from skin surface (i.e., in the frontal lobe of the brain) –Good correlation with blood and esophageal temperature –Not yet well studied under conditions of rapid hypothermia induction (i.e., rapid temperature change) or during prolonged hypothermic conditions –Requires ±15 mins of calibration time
Peripheral sites (axilla, groin, etc.)	Completely inaccurate	No correlation with gold standard	Peripheral measurements should never be used to guide hypothermia treatment. During hypothermia such readings are completely inaccurate

[a]In case of severe shock, oliguria, etc; [b]in case of severe shock; [c]several studies report good correlation of "deep forehead" temperature measured by Coretemp R device with blood and esophageal temperatures (183), but no studies have been performed during rapid induction of hypothermia or during hypothermia maintenance (only in the perioperative setting).

greater shivering response compared with the hypothermic state) than inducing hypothermia. Mayer et al (71) compared the efficacy of two surface cooling devices to maintain normothermia; they were able to maintain normothermia (defined as a core temperature ≤37.2°C) for 59% of the treatment time in one group and for 3% of the time in the other. Fever (temperature ≥38.3°C) occurred for 8% of the time in one group and for 42% of the time in the other. The frequency and severity of shivering was related to the efficacy of cooling (71). This underscores the difficulties that can be involved in

maintaining normothermia. This applies especially to cooling awake patients, where it is often more difficult to control shivering because high drug doses can lead to respiratory problems. Cooling can lead to a significant stress response if no anti-shivering treatment is given, or if the treatment is ineffective. Lenhardt et al (150) induced fever in nine healthy volunteers by infusing interleukin-2, and subsequently assessed the effects of surface cooling. They reported a 35% to 40% increase in oxygen consumption, an increase in catecholamine levels and significant patient discomfort associated with cooling.

In the clinical setting such responses can be counteracted with various antishivering drugs (Table 4). For the reasons outlined above, higher doses will usually be needed to control shivering during induction of normothermia than for hypothermia. This can be a problem especially when cooling awake and nonventilated patients. Two recent studies attempted to decrease myocardial injury in patients with myocardial infarction undergoing percutaneous coronary intervention, by inducing hypothermia before reperfusion; in both of these studies a majority of patients failed to reach target temperature before reperfusion. Interestingly, apparent benefits were observed in patients who did reach target temperature in these studies (1, 152).

Some studies have reported that shivering thresholds can be reduced by warming the hands, feet, and/or face of the patient, reducing the required doses of antishivering drugs (60, 153–155). However, others have reported no or only minor effects of hand/face warming on shivering thresholds (99, 156). There is some in unanethetized humans evidence that use of endovascular cooling methods to maintain normothermia reduces the shivering response (157), although no direct comparative studies have been performed to address this issue.

Apart from the cooling devices listed in Table 2, hyperthermia can also be treated with various antipyretic drugs such as acetaminophen. However, the effectiveness of these drugs is limited, especially in patients with neurologic (central) fever (158–164). In large studies the average decrease in temperature during treatment with high doses (4000–6000 mg/day) of acetaminophen is about 0.3°C–0.4°C (158–160). Similar results have been reported using high doses of aspirin (163), and in small studies with metamizol (161). Ibuprofen appears to be ineffective in reducing core temperature (164).

Despite the relatively minor effects, administration of fever-suppressing drugs is a helpful adjunctive treatment because it induces a drop in temperature without activating counter-regulatory mechanisms. The reasons for this and the precise mechanisms of action of antipyretics are beyond the scope of this review; this topic has been reviewed elsewhere (182). Thus, acetaminophen can be used as an accessory method to reduce hyperthermia in neurologic injury, but additional cooling methods will be required to achieve normothermia in most patients.

These observations lead to the following clinical scenario for the treatment of comatose survivors of witnessed cardiac arrest. Initiate infusion of cold (4°C) fluids using a pressure bag as soon as possible, preferably in the emergency room. A cooling device should be connected to the patient as soon as possible. The presence of arrhythmias or cardiogenic shock should not be regarded as counterindications for the use of mild hypothermia. percutaneous coronary intervention should be performed as rapidly as possible if acute myocardial infarction is suspected; cooling can be safely used in combination with it (168). A bolus dose of magnesium (2–3 g given over a period of 5–10 minutes) can be given to prevent shivering and cooling-associated hypomagnesemia. A (low) maintenance dose of sedation should be given. Maintenance doses of many drugs, especially sedatives, long-acting opiates, and muscle paralyzers, can and should be reduced in this phase to avoid cumulation caused by hypothermia-related reductions in drug clearance rates. If shivering occurs this can be controlled with bolus doses of magnesium (2–3 g given over 5–10 minutes) or fentanyl (50–100 μg rapid bolus dose), or one of the other drugs listed in Table 4. Lab samples should be drawn every 30 minutes in the induction phase and every 4–6 hours in the maintenance phase, with special attention to electrolyte and glucose levels and the blood gas analysis. Antibiotic prophylaxis should be considered to avoid infections; blood cul-

Table 6. Practical checklist of issues to address and to avoid during therapeutic temperature management

Checklist for induced hypothermia
Use cooling device with central feedback loop to control temperature. Use core temperature measurements to guide treatment. Add cold fluids in induction phase in most patients. Use pressure bag for administering cold fluids
Avoid hypovolemia and hypotension (cooling causes cold diuresis)
Avoid electrolyte disorders (cooling causes loss of K, Mg, P; rapid rewarming can cause hyperkalemia)
Avoid hyperglycemia (cooling causes insulin resistance and decreased insulin secretion)
Control shivering (options: magnesium; meperidine; quick-acting opiates; propofol; benzodiazepines. Alternatives: clonidine; ketanserin; tramadol; urapidil; doxapram)
Avoid skin damage/bedsores (prolonged direct exposure of the skin to ice or ice packs may cause burns. Cooling causes vasoconstriction in the skin)
Avoid/promptly treat infections (diagnosis can be difficult due to suppression of symptoms such as fever and leukocytosis. Consider antibiotic prophylaxis, perform frequent cultures of blood and other sites)
Use appropriate sedation and analgesia (animal data suggest loss of protective effects if sedation is insufficient; sedation also facilitates cooling by preventing shivering and causing vasodilation)
Adjust ventilator settings (cooling causes $\downarrow O_2$ consumption and $\downarrow CO_2$ production)
Adjust feeding rate (cooling decreases metabolism by 7% to 10% per °C decrease below 37°C)
Adjust drug dosage (drug clearance may change, including clearance of sedatives/opiates/paralyzers; use bolus doses during hypothermia induction phase, avoid high maintenance doses)
Don't let core temperature fall below 30°C (risk of arrhythmias arises at temp ≤28°C–30°C)
Don't "overtreat" (bradycardia, mild metabolic acidosis, slight rise in lactate levels, liver enzymes and amylase are normal consequences of hypothermia)
Long-term paralysis is usually unnecessary (paralysis will mask inadequate sedation, and can have adverse consequences such as increased risk of critical illness polyneuromyopathy). Paralysis can be considered in the induction phase to facilitate cooling and increase cooling speeds
Consider platelet administration before surgery or invasive procedures during cooling
Don't rewarm too quickly! (maximum 0.2°C–0.5°C/hr, slower in traumatic brain injury)
Be aware that insulin requirements may decrease during rewarming (risk of hypoglycemia).
General measures: provide good basic intensive care (many of the side effects of cooling can be prevented or controlled with proper care)

tures should be drawn once a day during hypothermia or controlled normothermia treatment. After 24 hours slow rewarming (±0.25°C/hr) should be initiated. Hypoglycemia may develop in this phase, and there is a risk for hyperkalemia if rewarming is too rapid (>0.5°C/hr), and/or if the patient has gross renal failure.

CONCLUSION

Induction of hypothermia has wide-ranging effects and will induce numerous physiologic changes in virtually every organ in the body. Physicians and nurses applying induced hypothermia in the intensive care unit need to be aware of the physiologic and pathophysiological changes and side effects associated with hypothermia, and should be familiar with the available cooling techniques. A "checklist" of the most important precautions and countermeasures is provided in Table 6.

The success of hypothermia treatments will be determined to a large extent by our ability to prevent or effectively deal with its side effects; this applies especially if hypothermia is used for prolonged periods. Devising comprehensive protocols with detailed recommendations on rates of cooling and rewarming, as well as on the proper management of side effects, will be the key to success. This will help us apply this highly promising treatment more effectively, and perhaps to expand its usage to other areas such as traumatic brain injury and stroke.

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