Methods of cooling: Practical aspects of therapeutic temperature management

David B. Seder, MD; Thomas E. Van der Kloot, MD

Objectives: **To review traditional and newer means of inducing, maintaining, and withdrawing therapeutic hypothermia and normothermia. To suggest treatment algorithms for temperature modulation and review neuromonitoring options.**

Design: **A review of current literature describing methods of performing therapeutic temperature management and neuromonitoring during the cooling, maintenance, and decooling periods. Algorithms for performing therapeutic temperature management are suggested.**

Results: **Temperature management can be safely and effectively performed using traditional or newer modalities. Although traditional means of cooling are feasible and efficacious, modern devices utilizing feedback loops to maintain steady body temperature and prevent overcooling have advantages in ease of application, patient safety, maintenance of target temperature, and control of decooling. Neuromonitoring options should be adapted to an individual patient and situation.**

Conclusions: **Intensivists should be familiar with techniques to induce, maintain, and withdraw therapeutic temperature management, and select the most appropriate method for a given patient and situation. (Crit Care Med 2009; 37[Suppl.]:S211–S222)**

Key Words: therapeutic hypothermia; therapeutic temperature management; cooling; brain injury; cardiac arrest; intravascular cooling; surface cooling; intracranial pressure; fever; shivering

Therapeutic temperature management (TTM), elegant in conception, can be simple to perform, such as when a hemodynamically stable cardiac arrest survivor is uneventfully cooled and rewarmed with a commercial hypothermia device, or can be complex, such as when a spontaneously breathing patient with traumatic brain injury develops persistent neurogenic fever and shivers uncontrollably when normothermia with ice packs and cold fluid is initiated. TTM can be performed using conventional modalities, readily available in most hospitals, or with one of several newer devices now commercially available. These techniques are better described as being complimentary rather than competing; temperature management is complex, and the circumstances and patients highly varied, so that routine administration of TTM favors facility in a variety of modalities.

From the Division of Pulmonary and Critical Care Medicine and Neuroscience Institute, Maine Medical Center, and Tufts University School of Medicine, Portland, ME (DBS); and University of Vermont College of Medicine, Burlington, VT (TEVdK).

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: sederd@mmc.org

DOI: 10.1097/CCM.0b013e3181aa5bad

Overview of Cooling

Mechanisms. Induction and maintenance of hypothermia or normothermia requires interruption of the body's normal thermoregulation mechanisms, as well as active heat exchange. Commonly employed techniques for preventing heat production through shivering are summarized in Appendix 1. Removal of heat is achieved *via* four mechanisms: conduction, convection, radiation, and evaporation (1).

Heat *conduction* involves thermal energy transfer between molecules within a material, or between materials in direct contact with one another, and is an intrinsic property of a material. Water and metal conduct heat well, whereas neoprene and ceramic materials conduct poorly and are therefore used as insulators. *Convection* relates to thermal energy transferred by molecular movement within a fluid or gas. Convective heat transfer may be driven by motion caused by heat itself (such as heat rising into the air) or by an external force driving the motion of the medium (such as a fan blowing air onto a patient). *Radiation* is heat transfer *via* electromagnetic radiation, and is therefore independent of matter. *Evaporation*, the heat transfer of liquid to gas phase change (e.g., sweating), plays a small role in human heat transfer under normal circumstances (2), but is sometimes used in conjunction with convection (for example, spraying patients who are then cooled by evaporation under the stimulus of fans).

Therapeutic hypothermia (TH) can be induced by each of these mechanisms of heat transfer or by mechanisms in combination. Heat transfer is frequently necessary to cool patients when elimination of heat production alone is inefficient in achieving a therapeutic core temperature in the clinical setting.

Phases of Temperature Modulation in Therapeutic Hypothermia

Temperature modulation during therapeutic hypothermia may be broken down into four phases: induction, maintenance, decooling, and normothermia. Each of these phases requires active control of heat transfer and management of physiological compensatory mechanisms, as well as monitoring for and prevention of associated complications.

In the setting of cardiac arrest, animal and human data support initiation of cooling as soon as possible after return of spontaneous circulation (ROSC) (3–8). Conversely, although it is clear that in animal models the induction of hypothermia before arrest or at the time of arrest is neuroprotective (4, 9), no human study has shown that time from initiation of therapy to therapeutic temperature is a significant predictor of outcome, and the

optimal rate of cooling is unknown. The optimal duration of TH is also unknown, although in the setting of cardiac arrest, improved outcomes have been demonstrated with 12 (10) and 24 (11) hrs of TH at 32°C to 34°C, whereas hypothermia for neonatal asphyxia is commonly performed for 72 hrs (12, 13) and hypothermia for the cerebral edema associated with liver failure may be performed for as long as 5 days (14, 15). After 5 days of TTM, the risk for developing ventilator associated pneumonia in intubated patients may rise precipitously (16).

Decooling is increasingly understood to be safest when performed with active temperature modulation, resulting in a controlled return to normothermia over 12 to 24 hrs (17), as opposed to a passive approach in which the patient's intrinsic thermoregulatory mechanisms are restored, and in which the rate of decooling may be very rapid and frequently associated with "rebound" fever. Fever in the first 72 hrs after ROSC is associated with poor outcome (18, 19). Although unproven, an increasing body of evidence (20–23) supports the cautious prevention and treatment of fever in the setting of critical neurological illness, and many clinicians attempt to maintain a core temperature of 36°C to 37.5°C until at least 72 hrs after ROSC (24). Decooling is associated with electrolyte shifts (25), vasodilation, and the "postresuscitation" syndrome (26–28), and may be the most challenging period of postarrest care, in terms of hemodynamic instability and complications (29). Therefore, devices and methods used for therapeutic hypothermia must provide the ability to rapidly and accurately control heat exchange and maintain the goal temperature in a steady range.

When hypothermia is employed for the management of elevated intracranial pressure (ICP) (30–32) or for hepatic encephalopathy and cerebral edema, slow decooling is particularly important, as rapidly rising brain temperature may result in ICP crisis, brain herniation, and death (17). Under these circumstances, invasive continuous ICP monitoring should be utilized to maintain cerebral perfusion pressure (CPP) and ICP goals during decooling.

Therapeutic Hypothermia

At experienced centers, therapeutic hypothermia in adults is routinely performed after cardiac arrest, in patients awaiting liver transplant with cerebral edema from acute liver failure, and for the control of refractory elevated ICP. These indications are reviewed elsewhere in this supplement. Among cardiac arrest survivors, it is standard to perform therapeutic hypothermia in all patients, independent of the initial heart rhythm or location of the arrest (33, 34), unless one or more of the following conditions exist:

1. The patient can follow verbal commands;
2. More than 8 hrs have elapsed since ROSC;
3. There is life-threatening bleeding or infection;
4. Cardiopulmonary collapse is imminent, despite vasopressor or mechanical hemodynamic support;
5. An underlying terminal condition exists.

Prehospital initiation of hypothermia typically relies upon rapid bolus administration of 30 to 40 mL/kg cold (4°C) isotonic resuscitation fluid (35, 36) by emergency medical service providers, targeting a core temperature of 32°C to 34°C. This prehospital approach is effective at decreasing the time to therapeutic temperature—an endpoint supported by animal data—and one large (insufficiently powered) randomized trial demonstrated a trend toward better neurological outcomes (36). The initiation of hypothermia in the field, however, puts the decision to cool—a complex question with significant management repercussions—into the hands of emergency medical service providers, preventing physicians from performing a precooling neurological assessment and potentially leading to some patients being cooled unnecessarily. Furthermore, arrest patients are often hypothermic on presentation, and accurate core temperature is not typically measured in the field, so there is potential for accidental overcooling. Finally, induction of hypothermia rapidly drives down the serum potassium (20), and the lack of baseline potassium measurement and rapid correction could lead to repeat cardiac arrest on the basis of hypokalemia. Despite these concerns, prehospital TH appears to be safe (36), and remains a promising approach that not only decreases the time to therapeutic temperature (35), but if applied by emergency management service protocols, may increase the overall utilization of TH (37–39), resulting in important epidemiological gains (40).

Simultaneous evaluation and treatment of cardiac and neurological injuries of the cardiac arrest survivor may require that TH be initiated during cardiac catheterization and revascularization. Induction can be performed with sedation, paralysis, and cold fluid infusion, or with sedation, paralysis, and a commercial surface or intravascular cooling device. This aggressive multidisciplinary approach (41), often in patients with shock or even requiring aortic counterpulsation, has been reported in several studies, and despite a greater reported incidence of periprocedural bleeding, seems to result in excellent overall neurological and mortality outcomes (42–46).

Baseline neurological assessment of the cardiac arrest survivor, performed before sedation and neuromuscular blockade, should include an assessment of the Glasgow Coma Scale, cranial nerves, reflexes, general motor tone, convulsive or nonconvulsive seizure activity (47, 48), and myoclonus (49). Rarely, catastrophic hemorrhagic or ischemic stroke may present as cardiac arrest, and if the circumstances of the arrest are unclear, noncontrast computed tomography scan of the head should be obtained at the time of initial evaluation. Figure 1 outlines the initial 72 hrs of management after ROSC.

The *maintenance phase* typically occurs in an intensive care unit and is a period in which metabolic and hemodynamic homeostasis is paramount. It may include adequate but not excessive mean arterial pressure to maintain brain perfusion despite a state of cerebral autoregulatory failure (50); volume-cycled mechanical ventilation targeted to normal pH (hypercarbia should be avoided) and otherwise in accord with the principles of lung-protective ventilation; a perfusing heart rhythm and treatment of the underlying ischemic state if necessary; antibiotic prophylaxis if pulmonary infiltrates are present (51, 52); maintenance of a blood glucose level of 120 to 160 mg/dL (53, 54, 55); normal electrolyte levels with special attention to potassium, magnesium, and phosphate (20, 56); cautious medication dosing taking into account the radical reduction in drug metabolism and duration of action caused by hypothermia (57–59); and the aggressive treatment of shivering, with neuromuscular blockade if necessary (Appendices 1

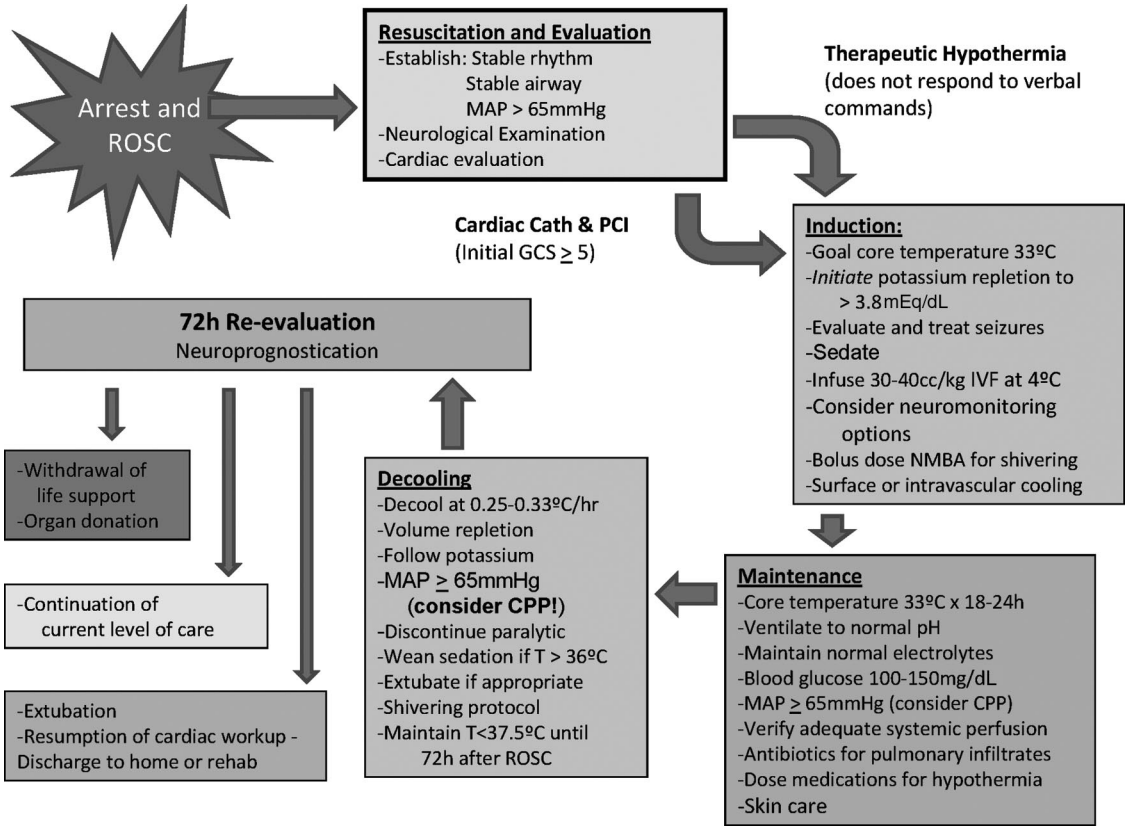


Figure 1. Treatment of the cardiac arrest survivor. *ROSC*, return of spontaneous circulation; *MAP*, mean arterial pressure; *Cath*, catheter; *PCI*, percutaneous coronary intervention; *GCS*, Glasgow Coma Scale; *IVF*, intravenous fluid: normal saline or lactated Ringer's solution; *NMBA*, neuromuscular blockade agents; *CPP*, cerebral perfusion pressure; *T*, temperature.

and 2). The decooling phase is when hemodynamic instability is most common.

A "postresuscitation" syndrome—characterized by increased inflammatory cytokine levels, vasodilation, and hypotension (22)—has been described, frequently exacerbating the cutaneous vasodilation routinely associated with decooling, and myocardial dysfunction related to acute myocardial infarction, defibrillation injury (60), or cardiomyopathy (61). Even episodic hypotension after cardiac arrest is associated with higher mortality (33, 62), and decooling is the period in which elevated ICP and low CPP are most likely to develop. Slow decooling avoids violent hemodynamic fluctuations, with a goal rate of 0.2°C to 0.33°C per hour until the patient is at 36.5°C or 37°C, but physiological fluctuations may be seen if shivering occurs. Fluid boluses, inotropes, and vasopressors may be necessary to maintain CPP during decooling, and if significant hemodynamic instability or signs of elevated ICP occur, it is sometimes necessary to slow or stop the temperature decooling process. We discontinue neuromuscular blockade when the patient temperature reaches 35°C, and wean sedation when the body temperature reaches 36°C.

Control of Postcooling Fever and Therapeutic Normothermia

Because "rebound" fever is common and harmful (18, 19, 21, 23, 63, 64), and because brain injury may be attenuated by fever control (65), it is common practice after cardiac arrest to maintain normothermia after decooling and until 72 hrs have elapsed since ROSC (29). When a commercial cooling device is utilized, this is easily achieved by leaving the device in place after the patient reaches goal temperature, resetting target temperature to 36.5°C to 37.5°C, and employing an aggressive shiver-control protocol (Appendices 1 and 2). When conventional cooling techniques are employed, controlled decooling and subsequent maintenance of normothermia require particular nursing vigilance, with attention to the onset of fever spikes, and frequent adjustments to the application of cooling measures. An algorithm for therapeutic normothermia in nonintubated patients is offered in Figure 2.

Fundamental to the induction, maintenance, and withdrawal of TTM are the following concerns:

1. After cardiac arrest, serum potassium should be aggressively replaced if <3.8 mEq/dL at the onset of TH, and should be reassessed every 3 to 4 hrs during the induction phase.
2. Accurate, continuous core temperature measurement must guide TTM, preferably by bladder, rectal, central venous, or esophageal measurement. In oliguric patients, bladder temperature may poorly reflect core temperature, and other monitoring sites are preferred.
3. When neuromuscular blockade (NMB) is employed to control shivering or aid in induction, a rapid and thorough neurological examination and verification of adequate sedation should precede NMB administration. Either empirical heavy sedation or sedation monitoring with processed electroencephalography (EEG) are appropriate during the full period of NMB (Fig. 3).
4. Although the U.S. Food and Drug Administration has approved multiple

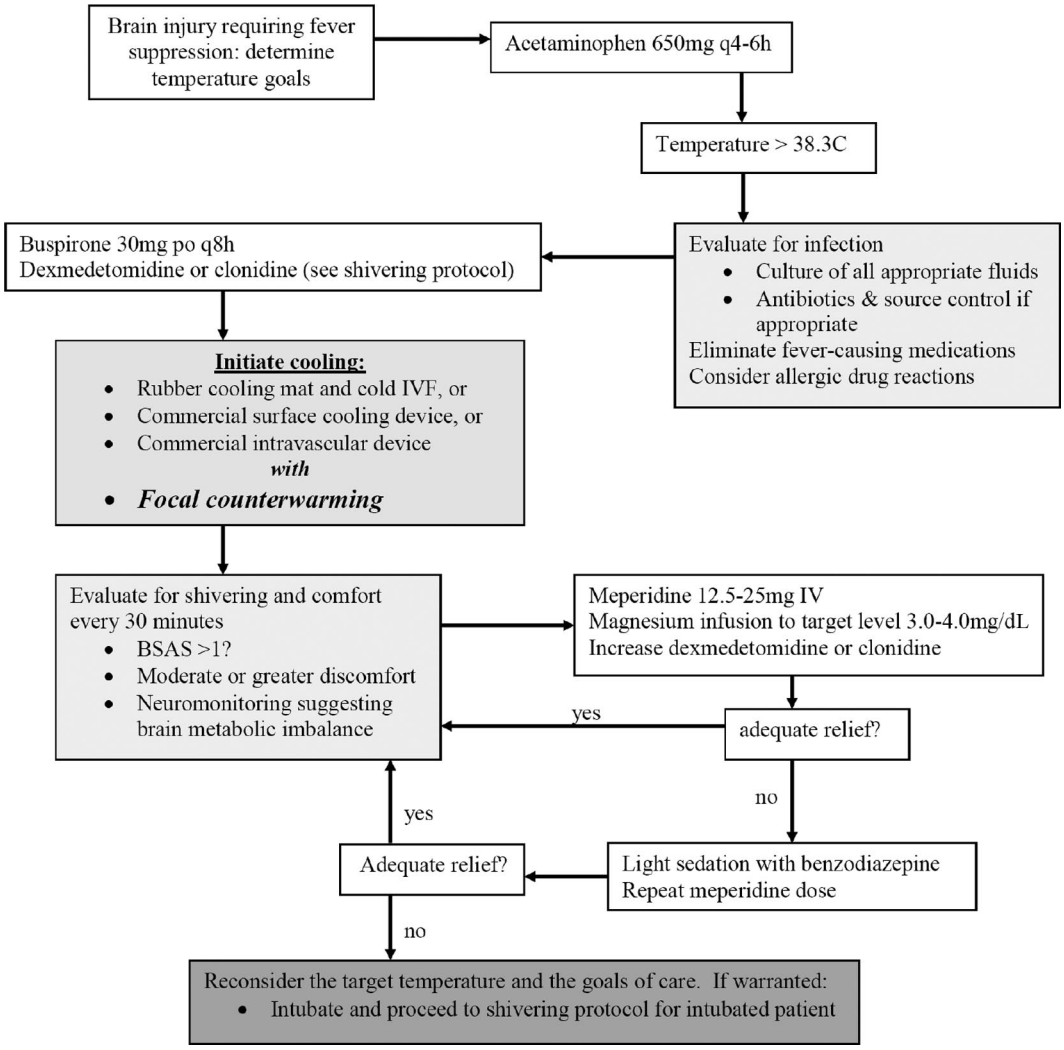


Figure 2. Suggested algorithm for therapeutic normothermia in the nonintubated patient. *IVF*, intravenous fluid; *BSAS*, Bedside Shivering Assessment Scale (Appendix 1).

devices for temperature modulation, and although these devices have been routinely utilized in cardiac arrest survivors, no device is currently approved for treatment of hypoxic-ischemic encephalopathy after cardiac arrest, so the application of any temperature management device constitutes "off-label" application in that population.

5. The incidence of pneumonia is between 30% and 50% in intubated cardiac arrest survivors treated with hypothermia (10, 66, 67), presumably due to aspiration at the time of cardiac arrest and the immunosuppressive effects of TTM (68, 69). Preliminary data suggest that when pulmonary aspiration is suspected at the onset of TH, prophylactic antibiotics should be strongly considered (51, 52).
6. The incidence of seizures after cardiac arrest is between 19% and 34% (48, 49, 70–72), and cannot be detected without EEG monitoring in the paralyzed patient. Continuous EEG monitoring should be considered if convulsive or nonconvulsive seizures are suspected. If continuous EEG is not available, then patients should be sedated with antiepileptic sedatives during therapeutic hypothermia (Fig. 3).
7. During decooling, hemodynamic instability is common, and as cutaneous vasodilation and an inflammatory post-arrest state develop, clinicians should be prepared to administer intravenous isotonic fluids to maintain adequate preload. When shock is present, monitoring of cardiac output, global tissue perfusion, or brain perfusion is suggested to guide interventions. Options for hemodynamic monitoring include invasive or noninvasive cardiac output measurement (73), assessment of urine output if kidney function is normal, repeated assessments of adequate tissue perfusion by either central venous or jugular venous oxyhemoglobin saturation measurement (74), or direct invasive monitoring of brain metabolism (75–79).
8. Although neuromuscular blockade agents (NMBAs) are commonly provided during the entire period of induction and maintenance, it is reasonable to forego additional NMBA after induction is achieved, by aggressive application of a shivering protocol (Appendix 2). Because of the extreme metabolic costs involved, shivering at Bedside Shivering Assessment Scale 2 or 3 (80) should not be tolerated. When NMBA is provided, corticosteroids should be avoided, due to the

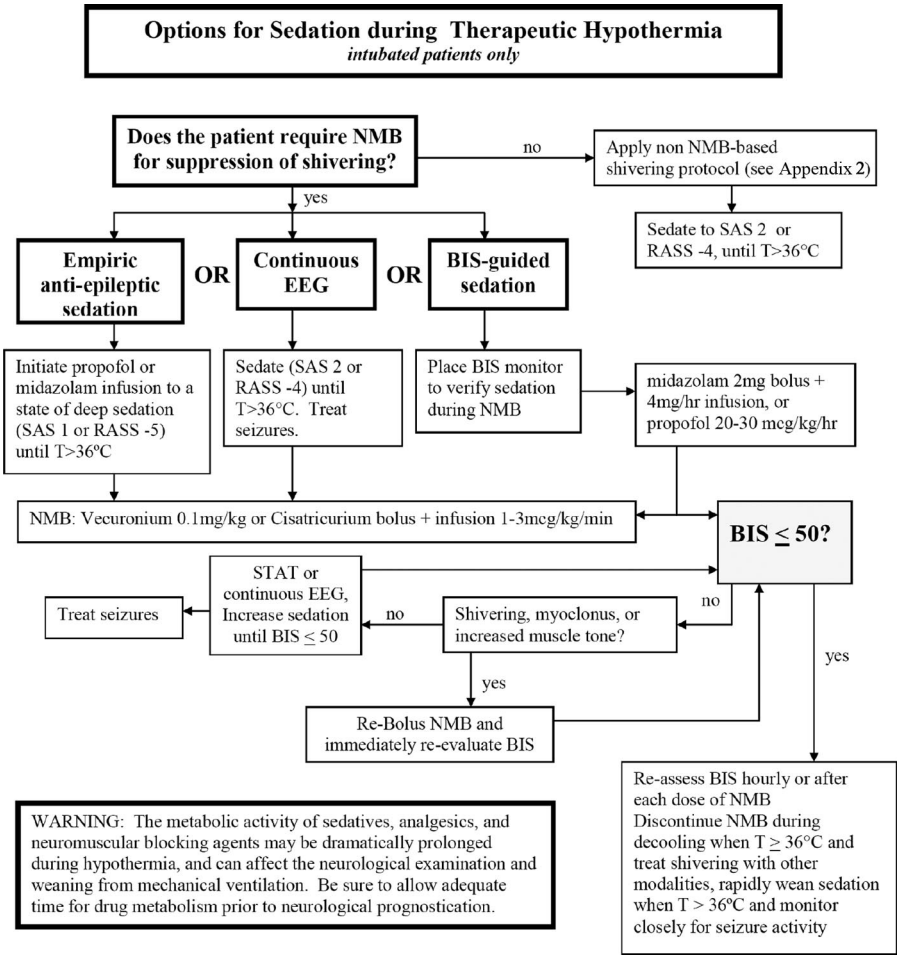


Figure 3. Options for sedation during therapeutic normothermia. *NMB*, neuromuscular blockade; *SAS*, Sedation and Agitation Scale (137); *RASS*, Richmond Agitation and Sedation Scale (138); *T*, temperature; *BIS*, bispectral index; *EEG*, electroencephalography.

additive risk for critical illness myopathy and prolonged neuromuscular weakness (81–82).

9. Focal counterwarming—in which the face, neck, and extremities are actively warmed while the torso or central venous system is cooled—reduces shivering and discomfort, while paradoxically augmenting the cooling process through the mechanism of cutaneous vasodilation.

Cooling Methodologies

Conventional Surface Cooling and Cold Fluids. After neurological assessment, sedation, the placement of a continuous core temperature monitor, and neuromuscular blockade, cold saline or Ringer's lactate solution (4°C) is administered at a dose of 30 to 40 mL/kg. This intervention—which has been shown to decrease temperature by 2°C to 4°C without causing a decrease in left ventricular systolic function or cardiac output and without frequent pulmonary edema (83–85)—is the best-studied method of TH induction, supported by multiple safety and efficacy trials, and should be the first line for induction in conventional cooling methodology. Subsequently, cooling can be maintained with ice packs applied to the neck, groin, and axillae, and with widely available rubber cooling blankets or mats routinely utilized in the operating room. Because these mats can cause skin damage at contact points when placed under the patient, some centers advocate placing these mats over the patient, with sheets draped above to create a tent in which cold air is trapped around the patient. Ongoing infusion of cold fluid has not shown to be an effective method to maintain therapeutic hypothermia (86).

Conventional cooling techniques are clearly effective at reducing body temperature, and should be considered a good method of inducing hypothermia, and an adequate, although tricky, means of maintaining 32°C to 34°C when other technologies are unavailable. Drawbacks include the lack of an internal feedback loop (making accurate temperature maintenance difficult), a high incidence of overcooling (87), the need for extreme nursing vigilance and experience to maintain the goal temperature, and difficulty in controlling the rate of decooling. Conventional cooling is inexpensive and convenient, utilizing widely available technology on hand in almost all hospitals, but because of the potential for overcooling and high level of nursing vigilance required should be evaluated in a cost-effectiveness analysis against techniques involving commercial cooling devices.

Commercial Surface Cooling Devices. The widely available Arctic Sun device (Medivance, Louisville, CO) employs proprietary heat-exchange pads that adhere to the skin, utilizing a hydrophilic gel that conducts heat and maintains close contact between the skin and pads. These pads cover approximately 40% of the body surface area, and circulating water temperature is continuously modulated by a servo mechanism to maintain core body temperature at goal. Generally well tolerated, this system has advantages that include temperature control that may be less rigid than with intravascular systems (88) but remains well within the target range studied in the Hypothermia After Cardiac Arrest trial (10); relative safety due to the infrequency of overcooling and lack of vascular complications; relative ease of maintenance of normothermia after cooling; thoughtful design sparing the femoral and subclavian sites for catheterization, allowing for defibrillator pad placement under the heat-exchange pads; and compatibility with cardiac catheterization by virtue of the radiolucent nature of the device (89–91). Disadvantages include the high cost of the unit and the disposable pads, and the potential for rare but serious skin complications (92), which should be considered in patients receiving high-dose vasoconstrictors or with severely impaired left ventricular function.

CoolBlue (Innercool Therapies, San Diego, CA), KoolKit (Cincinnati SubZero Products, Cincinnati, OH), and ThermoWrap (MTRE Advanced Technologies, Rehovot, Israel) are among the recently introduced, somewhat less expensive gar-

ment-type surface cooling devices without the gel-adhesion system discussed above. These systems all employ servo mechanisms, which enhance safety and decrease nursing work, cooling by conduction as water circulates through pads that encircle the patient but do not adhere directly to the skin. These devices may be acceptable surface cooling alternatives to the Arctic Sun system, but experience with the systems is relatively limited, and both safety and cooling efficacy should be demonstrated in clinical trials.

The fastest cooling system now on the market is probably the Thermosuit System (Life Recovery Systems, Kinnelon, NJ), a cold water immersion system that has been shown to cool human-sized swine to 33°C in only 30 to 45 mins, a remarkable feat (93). Unfortunately, a reasonable pool of human safety data is not yet available (94), and real caution should be exercised with the technology, due to the risks of rapid cooling causing unrecognized electrolyte shifts, the inherent dangers of defibrillating a patient immersed in water, and the potential for overcooling. Furthermore, the system is for induction only, with no mechanism for the maintenance of goal temperature, so conventional or other commercial techniques must be used for the maintenance and decooling phases. Because of the radical difference in both rate and method of cooling compared with other devices, we believe this promising system should undergo additional clinical testing to demonstrate safety in human subjects before it is routinely utilized to induce therapeutic hypothermia in cardiac arrest survivors.

Commercial Intravascular Cooling. Intravascular cooling devices are subject to the complications of central venous catheterization, including injury during placement, catheter-related bloodstream infection, and venous thrombosis (95). Nonetheless, intensivists are experienced with central venous catheterization, and employ validated central line bundles to minimize the likelihood of catheter-related bloodstream infection (96). Furthermore, central venous catheters are frequently required for vascular access and hemodynamic monitoring in cardiac arrest survivors, and the placement of an intravascular cooling device does not always require additional venous access.

The Alsius temperature management system, compatible with several different proprietary intravascular cooling catheters, has been used to cool thousands of cardiac arrest patients in Europe and North America, providing excellent control of the induction, maintenance, decooling, and normothermia phases (63, 97–99). Furthermore, the Alsius system serves as both cooling device and central venous catheter, allowing for the administration of vasopressors and caustic medications, blood draws, monitoring of central venous pressure, and central venous sampling for intermittent $ScvO_2$ analysis to assess systemic oxygen delivery. As with the surface cooling systems described, a servo mechanism varies circulating water temperature, preventing large core temperature variations during therapy.

The Celsius Control System (Innercool Therapies) is a servo-controlled temperature modulation system in which water circulates through a metallic catheter with a textured surface in the inferior vena cava (100, 101). It is highly effective in providing precise temperature control (102). The turbulent blood flow induced by the catheter's surface and intended to facilitate heat exchange raises concerns about venous thrombosis and catheter-related bloodstream infection. Because the Celsius Control system does not serve as a central venous line, it requires an independent central venous access. The system is not appropriate for mobile or awake patients requiring TTM, because the large-bore femoral insertion site requires that the patient be still and minimally bent at the waist. Additionally, some clinicians have expressed concerns about how the device is secured: If the patient were inadvertently bent at the waist, the catheter could migrate beyond the intended depth of insertion.

Like the commercially available surface cooling systems, intravascular cooling systems are expensive (88, 103, 104) to purchase and utilize, but cost-effectiveness data, currently unavailable, may well demonstrate that these up-front expenses are offset when nursing time, complications, and patient outcomes are taken into consideration.

Less Commonly Used Cooling Techniques and Devices. There are other feasible methods of inducing hypothermia, including medications (such as neurotensin), extracorporeal circuits, body cavity lavage, whole-body ice water immersion, continuous veno-venous hemofiltration, and air-conduction hypothermia devices such as that used in the landmark Hypothermia After Cardiac Arrest randomized trial (10). Cooling helmets have been extensively studied (105–108), but in adults are less effective in maintaining the goal temperature than other modalities, and are not widely in use. These modalities have recently been reviewed at length elsewhere (109), and although they may be promising or appropriate in individual circumstances, none is in widespread enough use, has amassed adequate clinical safety and efficacy data, or is convenient and cost-effective enough that it may be considered a routine part of a therapeutic hypothermia program at the time of this writing.

Comparison of Common Methods of Cooling. Direct comparison of methods of TTM suffers from a paucity of controlled trials comparing efficacy and safety. One recent nonblinded study of 50 patients with an indication for either hypothermia or normothermia prospectively and sequentially assigned them to one of five different cooling modalities, and the rate of cooling and ability to maintain a tight temperature range was evaluated. In groups matched poorly for severity of illness and primary diagnosis, the investigators found water circulating blankets, adherent gel pads, and the intravascular cooling device to be more efficient means of induction than conventional modalities (ice packs and cold fluids) or a surface air-cooling system, whereas the intravascular cooling device was the most effective at maintaining temperature within 0.2°C of the goal temperature (88)—a goal of uncertain importance, because the randomized controlled trial data supporting TH after cardiac arrest allowed a full 1°C variation from the target temperature (10).

The tight temperature control achieved with intravascular catheters was supported by an uncontrolled and retrospective study of patients receiving therapeutic hypothermia to 33°C with either the Innercool intravascular cooling device or rubber cooling mats and ice packs. Although the conventional surface cooling group achieved the goal temperature and suffered an "acceptable" incidence of complications (mostly shivering), conventional surface cooling methods were more likely to result in overcooling, and were associated with greater temperature variability than intravascular catheter devices. Unfortunately, infectious and thrombotic complications were not reported (102).

In febrile, brain-injured patients, the Arctic Sun in conjunction with focal

Table 1. Neuromonitoring options during therapeutic hypothermia

Modality	Rationale for Use	Advantages	Disadvantages
Continuous EEG	Convulsive and nonconvulsive seizures are common in HIE	Immediate identification of seizures	Requires expertise and continuous attention to monitor
	Neuromuscular blocking agents may obscure seizures	Early identification of shivering Prognostication	
BIS monitoring	Less severely injured patients may be aware during TH and paralysis	Titration of sedation Early identification of shivering Prognostication Ease of use	Shivering confounds processed EEG signal
ICP monitor	Elevated ICP is common after cardiac arrest	Titrate MAP to appropriate CPP	Invasive
	ICP rises during decooling and may exacerbate HIE	Monitors ICP during decooling	Slight elevation in procedural bleeding risk due to TH
Partial pressure of brain oxygen ($PbtO_2$)	Measure of the adequacy of cerebral perfusion	Accuracy of direct measurement No increased morbidity when bundled with ICP monitor	Invasive
Brain temperature	Brain temperature and systemic temperature often correlate poorly	Measures brain temperature directly during decooling and after TH No increased morbidity when bundled with ICP monitor	Invasive
Microdialysis	LPR is a direct measure of brain ischemia	Titrates therapy to drive down the LPR No increased morbidity when bundled with ICP monitor	Invasive
Jugular oximetry ($SjvO_2$)	Verifies adequacy of CBF during TH and decooling	Titrates MAP to $SjvO_2$ >60% Prognostication	Multiple confounders Requires expertise to interpret readings
	Cerebral oxygen extraction is a surrogate for metabolic activity	Low morbidity	

EEG, electroencephalography; HIE, hypoxic-ischemic encephalopathy; BIS, bispectral index; TH, therapeutic hypothermia; ICP, intracranial pressure; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; LPR, lactate-pyruvate ratio; CBF, cerebral blood flow.

Reproduced with permission from Seder and Jarrah (41).

counterwarming was compared with rubber cooling mats for the maintenance of normothermia. Use of the Arctic Sun decreased overall fever burden (associated with higher Glasgow Coma Scale), while requiring more antishivering interventions (110). A larger study in a similar population comparing the use of acetaminophen plus cooling blankets to these modalities plus the Alsius Cool Line catheter-based cooling system demonstrated a significant reduction of fever burden with the catheter, and line-related adverse events equivalent to a routine central venous catheter (98).

One retrospective, nonrandomized study of a large population of patients undergoing TH after cardiac arrest with intravascular cooling catheters suggested that the use of an intravenous cooling catheter was independently associated with a higher odds ratio of survival (111). This study had design flaws, but reflects a growing body of data supporting the safety and efficacy of intravascular catheters for TTM.

In Norway, 59 intensive care nurses familiar with multiple means of delivering TTM were asked to rate ease of application, visual patient monitoring, work load, hygiene, and noise level related to four different hypothermia techniques: towels soaked in ice water, the Coolgard intravascular cooling system, the Thermowrap surface cooling system, and the Arctic Sun surface cooling system. Although the cold towels were rated as quiet, the commercial systems were all rated as significantly easier to use. The Arctic Sun and Coolgard systems rated higher in hygienic aspects, whereas the Coolgard system was rated as the best for visual evaluation of the patient. Controlled decooling and subsequent therapeutic normothermia were not described (112).

Neuromonitoring During Therapeutic Hypothermia and Normothermia

Although therapeutic hypothermia is routinely performed without neuromonitoring of any kind, cardiac arrest survivors are vulnerable to several important causes of secondary neurological injury, and clinicians should consider employing neuromonitoring to detect and guide the treatment of seizures, elevated ICP, and inadequate cerebral blood flow due to low CPP or the excessive cerebral and systemic metabolic demands of shivering. Table 1 outlines neuromonitoring options during TH.

Seizures

Because seizure activity after cardiac arrest is common (47, 48), the detection of seizures is a pressing neuromonitoring concern. Most cardiac arrest survivors are paralyzed during TH, and therefore seizure activity will rarely be clinically apparent. This alarming situation is somewhat offset by the facts that hypothermia in itself is probably antiepileptic (113–115), and that most hypothermia protocols include continuous infusions of propofol or benzodiazepines. We suggest that clinicians must either monitor with continuous EEG, unavailable in most centers, or treat empirically during the period of neuromuscular blockade with antiepileptic sedation (Fig. 3), a commonly employed option. When convulsive seizure activity is noted in the periarrest period, at least one EEG should be performed on unresponsive patients at the time of admission, to rule out a state of continuous nonconvulsive status epi-

lepticus (116). Intermittent EEG is likely to miss the majority of seizure activity, however, and is a poor substitute for continuous monitoring (47). Clinicians should be vigilant for seizure activity during the decooling phase (117), even if medication dosing and the clinical examination are unchanged.

Because it is difficult or even impossible to determine the true severity of brain injury from the clinical examination and the circumstances of the arrest at the time of hospital admission (118), therapeutic hypothermia may occasionally be performed on patients with only mild injury, who are therefore at risk for awakening, paralyzed, during TH. To prevent this possibility, we routinely employ the BIS A2000 monitor (Aspect Medical Systems, Newton, MA) during hypothermia to verify the adequacy of sedation underlying NMB, and prevent awareness and recall of the paralyzed state (119–121). When the A2000 monitor is employed in this way, it can also be used to detect subtle shivering, which is reflected in a visible increase in fine muscle activity, and higher "electromyography power" measurements. Our standard protocol for use of BIS monitoring to guide sedation and prevent awareness during TH is described in Figure 3. We have also reported on the use of this technology for very early neuroprognostication (122, 123).

Cerebral Blood Flow

A recent consensus statement called for greater study of "goal-directed" hemodynamic targets in cardiac arrest survivors (73). Beyond the usual measures of systemic perfusion, there is strong reason to consider the use of ICP monitoring devices in survivors of cardiac arrest with severe brain injury, to assure adequate CPP, and thereby prevent ICP crisis leading to transtentorial herniation and brain death. French investigators placed invasive extradural ICP monitors in 84 consecutive patients with hypoxic-ischemic encephalopathy, and found that the frequency of ICP >25 mm Hg was 21.4% on day 1 and 26.3% on day 2, with 55.9% of patients experiencing sustained CPP <50 mm Hg on the second day. No patient with elevated ICP survived (75). Although performed before the era of TH, this study and two smaller series (76, 77) suggest that ICP and CPP may in fact be significant contributors to morbidity and mortality after cardiac arrest, and that mean arterial pressure goals may be most appropriately guided by invasive neuromonitoring data in place of empirical strategies. When head computed tomography shows cerebral edema or noninvasive ICP measurement with transcranial Doppler technology suggests elevated ICP (124) in a patient with prolonged downtime and low initial Glasgow Coma Scale, it is reasonable to consider the insertion of a parenchymal ICP monitor to guide therapy, especially during decooling (75–77, 125).

ICP monitoring is increasingly accompanied by brain tissue oxygen monitoring (Licox; Integra Neurosciences, Plainsboro, NJ). In acute brain injury, the improvement in systemic metabolism with hypothermia may be completely offset by the metabolic demands of shivering (126). Measurement of brain tissue oxygen levels ($PbtO_2$) can be a powerful indirect means of monitoring the metabolic profile of TTM, or to detect brain ischemia when the most appropriate CPP is uncertain (127, 128). One group recently reported their results with cerebral microdialysis in a small number of cardiac arrest survivors, showing a pattern of increased brain lactate, glutamate, glycerol, and lactate-pyruvate ratio characteristic of neuronal injury, and suggested that this form of monitoring may provide real-time assessment of ongoing neuronal injury against which to titrate therapies (77).

A simpler and less invasive monitoring strategy to verify adequate CPP during therapeutic hypothermia is jugular bulb oximetry (74, 129). The insertion of a small catheter retrograde into the dominant internal jugular vein allows for either continuous oximetric measurement or interval sampling of the cerebral venous drainage. When cerebral blood flow is inadequate, overextraction of oxygen occurs, resulting in a widened arteriovenous oxygen gradient, or $AVDO_2$. When the arterial hemoglobin content and saturation are constant, it is appropriate to simply follow the jugular venous oxyhemoglobin saturation; a measurement O_2 <55% indicates either increased cerebral metabolic activity, or more commonly, inadequate CPP. This indirect means of verifying adequate cerebral blood flow is associated with low morbidity, and may be a less invasive means of guiding CPP optimization. Several groups have noted an association of cerebral oxygen extraction, calculated by jugular bulb oximetry, and prognosis (79, 130).

CONCLUSION

All TTM should be performed under institution-specific protocols that take advantage of available expertise, resources, and equipment. Protocolized temperature management requires interdisciplinary and interdepartmental buy-in from medical subspecialists, nursing, pharmacy, and hospital administration (131–133). In the case of hypoxic-ischemic encephalopathy after cardiac arrest, a system to facilitate concurrent cardiac and neurological evaluation and treatment must be in place. Multiple devices and techniques to control heat production and remove existing heat are now available, simplifying temperature control. Hospitals should select the most appropriate means of TTM based on both patient factors and institutional concerns. Because cardiac arrest outcomes are better in large centers (134, 135), and because transfer time between institutions has not been shown to be an important factor in patient outcomes (136), cardiac arrest patients should routinely be transferred to cardiac arrest centers, where urgent cardiac revascularization, appropriate neuromonitoring, and aggressive neuroprotective therapies can be rapidly initiated.

REFERENCES

1. Incropera FP, De Witt DP: Fundamentals of Heat and Mass Transfer. Third Edition. New York, John Wiley & Sons, 1990
2. Bickler P, Sessler DI: Efficiency of airway heat and moisture exchangers in anesthetized humans. *Anesth Analg* 1990; 71: 415–418
3. Stertz F, Safar P, Tisherman SA, et al: Mild hypothermic cardiopulmonary resuscitation improves outcome after cardiac arrest in dogs. *Crit Care Med* 1991; 19:379–389
4. Kuboyama K, Safar P, Radovsky A, et al: Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study. *Crit Care Med* 1993; 21:1348–1358
5. Nolan JP, Morley PT, Hoek TL, et al: Therapeutic hypothermia after cardiac arrest: An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Resuscitation* 2003; 57:231–235
6. Silfvast T, Tianen M, Poutianinen E, et al: Therapeutic hypothermia after prolonged cardiac arrest due to non-coronary causes. *Resuscitation* 2003; 57:109–112
7. Alzaga AG, Cerdan M, Varon J: Therapeutic hypothermia. *Resuscitation* 2006; 70: 369–380

8. Safar P: Resuscitation of the ischemic brain. *In:* Albin MS (Ed). Textbook of Neuroanesthesia With Neurological and Neuroscience Perspectives. New York, McGraw-Hill Health Professions Division, 1997, pp 557–593
9. Margraf C, Clifton G, Moody M: Treatment window for hypothermia in brain injury. *J Neurosurg* 2001; 95:979–983
10. The Hypothermia After Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002; 346:549
11. Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557
12. Shah PS, Ohlsson A, Perlman M: Hypothermia to treat neonatal hypoxic ischemic encephalopathy. *Arch Pediatr Adolesc Med* 2007; 161:951–958
13. Shankaran S, Laptook AR, Ehrenkranz RA, et al: Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; 353:1574–1584
14. Vaquero J, Butterworth RF: Mild hypothermia for the treatment of acute liver failure—what are we waiting for? *Nat Clin Pract Gastroenterol Hepatol* 2007; 4:528–529
15. Jalan R, Rose C: Hypothermia in acute liver failure. *Metab Brain Dis* 2004; 19:215–221
16. Merkow M, Singer S, Fernandez L, et al: Risk for nosocomial infections during therapeutic temperature modulation in neurocritically-injured patients. Abstr. *Neurocrit Care* 2008; 9:S6
17. Steiner T, Friede T, Aschoff A, et al: Effect and feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarctions of the middle cerebral artery. *Stroke* 2001; 32:2833–2835
18. Takasu A, Saitoh D, Kaneko N, et al: Hyperthermia: Is it an ominous sign after cardiac arrest? *Resuscitation* 2001; 49:273–277
19. Bergman R, Tjan DH, Adriaanse MW, et al: Unexpected fatal neurological deterioration after successful cardio-pulmonary resuscitation and therapeutic hypothermia. *Resuscitation* 2008; 76:142–145
20. Fernandez A, Schmidt JM, Claassen J, et al: Fever after subarachnoid hemorrhage: Risk factors and impact on outcome. *Neurology* 2007 68:1013
21. Stocchetti S, Rossi ER, Zanier A, et al: Pyrexia in head-injured patients admitted to intensive care. *Intensive Care Med* 2002; 28:1555
22. Azzimondi G, Bassein L, Nonino F, et al: Fever in acute stroke worsens prognosis: A prospective study. *Stroke* 1995; 26:2040
23. Diringer MN, Reaven NL, Funk SE, et al: Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Crit Care Med* 2004; 32:1489
24. Polderman KH: Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008; 7:371:1955–1969
25. Polderman KH: Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality—Part 2: Practical aspects and side effects. *Intensive Care Med* 2004; 30:757–769
26. Negovsky VA: Postresuscitation disease. *Crit Care Med* 1988; 16:942–946
27. Adrie C, Laurent I, Monchi M, et al: Postresuscitation disease after cardiac arrest: A sepsis-like syndrome? *Curr Opin Crit Care* 2004; 10:208–212
28. Neumar RW, Nolan JP, Adrie C, et al: Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication: A consensus statement from the International Liaison Committee on Resuscitation. *Circulation* 2008; 118:2452–2483
29. Steiner T, Meisel F, Mayer SA: Complications of Rewarming. *In:* Mayer SA, Sessler DI (Eds). Therapeutic Hypothermia. New York, Marcel Dekker, 2005, pp 211–227
30. Shiozaki T, Sugimoto H, Taneda M, et al: Selection of severely head injured patients for mild hypothermia therapy. *J Neurosurg* 1998; 89:206–211
31. Shiozaki T, Nakajima Y, Taneda M, et al: Efficacy of moderate hypothermia in patients with severe head injury and intracranial hypertension refractory to mild hypothermia. *J Neurosurg* 2003; 99:47–51
32. Mayer SA, Chong JY: Critical care management of increased intracranial pressure. *J Intensive Care Med* 2002; 17:55–67
33. Oddo M, Ribordy V, Feihl F, et al: Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: A prospective study. *Crit Care Med* 2008; 36:2296–2301
34. Kilgannon JH, Roberts BW, Reihl LR, et al: Early arterial hypotension is common in the post-cardiac arrest syndrome and associated with increased in-hospital mortality. *Resuscitation* 2008; 79:410–416
35. Kämäräinen A, Virkkunen I, Tenhunen J, et al: Prehospital induction of therapeutic hypothermia during CPR: A pilot study. *Resuscitation* 2008; 76:360–363
36. Kim F, Olsufka M, Longstreth WT Jr, et al: Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4°C normal saline. *Circulation* 2007; 115:3064–3070
37. Wolfrum S, Radke PW, Pischon T, et al: Mild therapeutic hypothermia after cardiac arrest—a nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. *Resuscitation* 2007; 72:207–213
38. Laver SR, Padkin A, Atalla A, et al: Therapeutic hypothermia after cardiac arrest: A survey of practice in intensive care units in the United Kingdom. *Anaesthesia* 2006; 61: 873–877
39. Merchant RM, Soar J, Skrifvars MB, et al: Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. *Crit Care Med* 2006; 34:1935–1940
40. Majersik JJ, Silbergleit R, Meurera WJ, et al: Public health impact of full implementation of therapeutic hypothermia after cardiac arrest. *Resuscitation* 2008; 77:189–194
41. Seder DB, Jarrah S: Therapeutic hypothermia for cardiac arrest: A practical approach. *Curr Neurol Neurosci Rep* 2008; 8:508–517
42. Wolfrum S, Pierau C, Radke PW, et al: Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med* 2008; 36: 1780–1786
43. Skulec R, Kovarnik T, Dostalova G, et al: Induction of mild hypothermia in cardiac arrest survivors presenting with cardiogenic shock syndrome. *Acta Anaesthesiol Scand* 2008; 52:188–194
44. Hovdenes J, Laake JH, Aaberge L, et al: Therapeutic hypothermia after out-of-hospital cardiac arrest: Experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. *Acta Anaesthesiol Scand* 2007; 51:137–142
45. Werling M, Thorén AB, Axelsson C, et al: Treatment and outcome in post-resuscitation care after out-of-hospital cardiac arrest when a modern therapeutic approach was introduced. *Resuscitation* 2007; 73:40–45
46. Knafelj R, Radsel P, Ploj T, et al: Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 2007; 74:227–234
47. Claassen J, Mayer SA, Kowalski RG, et al: Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 2004; 62:1743–1748
48. Jordan KG: Nonconvulsive status epilepticus in acute brain injury. *J Clin Neurophys* 1999; 16:332–340
49. Wijdicks EF, Parisi JE, Sharbrough FW: Prognostic value of myoclonus status in comatose survivors of cardiac arrest. *Ann Neurol* 1994; 35:239–243
50. Sundgreen C, Larsen FS, Herzog TM, et al: Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. *Stroke* 2001; 32:128–132
51. Sirvent JM, Torres A, El-Ebiary M, et al: Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med* 1997; 155: 1729–1734
52. Acquarolo A, Urli T, Perone G, et al: Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. *Intensive Care Med* 2005; 31:510–516
53. Oddo M, Schmidt JM, Carrera E, et al: Impact of tight glycemic control on cerebral

glucose metabolism after severe brain injury: A microdialysis study. *Crit Care Med* 2008; 36:3233–3238
54. Losert H, Sterz F, Roine RO, et al: Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12 h after cardiac arrest might not be necessary. *Resuscitation* 2008; 76:214–220
55. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al: Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360:1283–1297
56. Badjatia N, Kowalski RG, Schmidt JM, et al: Predictors and clinical implications of shivering during therapeutic normothermia. *Neurocrit Care* 2007; 6:186–191
57. Acka O: Complications of hypothermia. *In:* Mayer SA, Sessler DI (Eds). Therapeutic Hypothermia. New York, Marcel Dekker, 2005
58. Tortorici MA, Kochanek PM, Poloyac SM: Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. *Crit Care Med* 2007; 35:2196–2204
59. Arpino PA, Greer DM: Practical pharmacologic aspects of therapeutic hypothermia after cardiac arrest. *Pharmacotherapy* 2008; 28:102–111
60. Walcott GP, Killingsworth CR, Ideker RE: Do clinically relevant transthoracic defibrillation energies cause myocardial damage and dysfunction? *Resuscitation* 2003; 59: 59–70
61. Laurent I, Monchi M, Chiche JD, et al: Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2002; 40:2110–2116
62. Kilgannon JH, Roberts BW, Reihl LR, et al: Early arterial hypotension is common in the post-cardiac arrest syndrome and associated with increased in-hospital mortality. *Resuscitation* 2008; 79:410–416
63. Pichon N, Amiel JB, Francois B, et al: Efficacy of and tolerance of mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. *Crit Care* 2007; 11:R71
64. Greer DM, Funk SE, Reaven NL, et al: Impact of fever on outcome in patients with stroke and neurologic injury: A comprehensive meta-analysis. *Stroke* 2008; 39: 3029–3035
65. Oddo M, Frangos S, Milby A, et al: Induced normothermia attenuates cerebral metabolic distress in patients with aneurysmal subarachnoid hemorrhage and refractory fever. *Stroke* 2009; 40:1913–1916
66. Gadkary CS, Alderson P, Signorini DF: Therapeutic hypothermia for head injury. *Cochrane Database Syst Rev* 2002; 1:CD001048
67. Bernard SA, Buist M: Induced hypothermia in critical care medicine: A review. *Crit Care Med* 2003; 31:2041–2051
68. Wenisch C, Narzt E, Sessler DI, et al: Mild interoperative hypothermia reduces production of reactive oxygen intermediates by polymorphonuclear leukocytes. *Anesth Analg* 1996; 82:810–816
69. Van Oss CJ, Absolam DR, Moore LL, et al: Effect of temperature on chemotaxis, phagocytic engulfment, digestion, and O2 consumption of human polymorphonuclear leukocytes. *J Reticuloendothel Soc* 1980; 27:561–565
70. Snyder BD, Hauser A, Loewenstein RB, et al: Neurologic prognosis after cardiopulmonary arrest: III. Seizure activity. *Neurology* 1980; 30:1292–1297
71. Krumholz A, Stern BJ, Weiss HD: Outcome from coma after cardiopulmonary resuscitation: Relation to seizures and myoclonus. *Neurology* 1988; 38:401–405
72. Rundgren M, Rosen I, Friberg H: Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. *Intensive Care Med* 2006; 32: 836–842
73. Jones AE, Shapiro NI, Kilgannon JH, et al: Emergency Medicine Shock Research Network (EMSHOCKNET) investigators. Goal-directed hemodynamic optimization in the post-cardiac arrest syndrome: A systematic review. *Resuscitation* 2008; 77:26–29
74. Lemiale V, Huet O, Vigue B, et al: Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. *Resuscitation* 2008; 76:17–24
75. Gueugniaud PY, Garcia-Darennes F, Gaussorgues P, et al: Prognostic significance of early intracranial and cerebral perfusion pressures in post-cardiac arrest anoxic coma. *Intensive Care Med* 1991; 17: 392–398
76. Iida K, Satoh H, Arita K, et al: Delayed hyperemia causing intracranial hypertension after cardiopulmonary resuscitation. *Crit Care Med* 1997; 25:971–976
77. Nordmark J, Rubertsson S, Mortberg E, et al: Intracerebral monitoring in comatose patients treated with hypothermia after a cardiac arrest. *Acta Anaesthesiol* 2009; 53: 289–298
78. Macmillan CSA, Andrews PJD: Cerebrovenous oxygen saturation monitoring: Practical considerations and clinical relevance. *Intensive Care Med* 2006; 26:1028–1036
79. White H, Baker A: Continuous jugular venous oximetry in the neurointensive care unit—a brief review. *Can J Anaesth* 2002; 49:623–629
80. Badjatia N, Strongilis E, Gordon E, et al: Metabolic impact of shivering during therapeutic temperature modulation. The Bedside Shivering Assessment Scale. *Stroke* 2008; 39:3242–3247
81. Deem S: Intensive-care-unit-acquired muscle weakness. *Respir Care* 2006; 51: 1042–1052
82. De Jonghe B, Sharshar T, Lefaucheur JP, et al: Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA* 2002; 288:2859–2867
83. Kim F, Olsufka M, Carlbom D, et al: Pilot study of rapid infusion of 2 L of 4°C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005; 112:715–719
84. Polderman KH, Rijnsburger ER, Peerdeman SM, et al: Induction of hypothermia in patients with various types of neurological injury with use of large volumes of ice-cold intravenous fluid. *Crit Care Med* 2005; 33: 2744–2751
85. Bernard S, Buist M, Monteiro O, et al: Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: A preliminary report. *Resuscitation* 2003; 56: 9–13
86. Kliegel A, Janata A, Wandaller C, et al: Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. *Resuscitation* 2007; 73:46–53
87. Merchant RM, Abella BS, Peberdy MA, et al: Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med* 2006; 34: S490–S494
88. Hoedemaekers CW, Ezzahti M, Gerritsen A, et al: Comparison of cooling methods to induce and maintain normo and hypothermia in intensive care unit patients: A prospective intervention study. *Crit Care* 2007; 11:R91
89. Mayer SA, Kowalski RG, Presciutti M, et al: Clinical trial of a novel surface cooling device for fever control in neurocritical care patients. *Crit Care Med* 2004; 32: 2508–2515
90. Haugk M, Sterz F, Grassberger M, et al: Feasibility and efficacy of a new non-invasive surface cooling device in post-resuscitation intensive care medicine. *Resuscitation* 2007; 75:76–81
91. Scott BD, Hogue T, Fixley MS, et al: Induced hypothermia following out-of-hospital cardiac arrest; initial experience in a community hospital. *Clin Cardiol* 2006; 29: 525–529
92. Varon J, Acosta P, Wintz R, et al: Unusual side effect from hydrogel pads during therapeutic hypothermia. *Resuscitation* 2008; 78:248–249
93. Janata A, Weihs W, Bayegan K, et al: Thermosuit after prolonged cardiac arrest in pigs. *Resuscitation* 2006; 69:145
94. Holzer M, Janata A, Haugk M, et al: Efficacy and safety of a novel rapid non-invasive surface-cooling device for induction of therapeutic hypothermia in patients after cardiac arrest. Abstr. *Circulation* 2007; 116:II_930
95. Simosa HF, Petersen DJ, Agarwal SK, et al: Increased risk for deep venous thrombosis with endovascular cooling in patients with traumatic head injury. *Am Surg* 2007; 73: 461–464
96. Pronovost P, Needham D, Berenholtz S, et al: An intervention to decrease catheter-

related bloodstream infections in the ICU. *N Engl J Med* 2006; 355:2725–2732
97. Schmutzhard E, Engelhardt K, Beer R, et al: Safety and efficacy of a novel intravascular cooling device to control body temperature in neurologic intensive care patients: A prospective pilot study. *Crit Care Med* 2002; 30:2481–2488
98. Diringer MN: Neurocritical Care Fever Reduction Trial Group. Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system. *Crit Care Med.* 2004; 32:559–564
99. Arrich J, The European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007; 35: 1041–1047
100. Badjatia N: Celsius Control system. *Neurocrit Care* 2004; 1:201–203
101. Badjatia N, O'Donnell J, Baker JR, et al: Achieving normothermia in patients with febrile subarachnoid hemorrhage: Feasibility and safety of a novel intravascular cooling catheter. *Neurocrit Care* 2004; 1:145–156
102. Flint AC, Hemphill JC, Bonovich DC: Therapeutic hypothermia after cardiac arrest: Performance characteristics and safety of surface cooling with or without endovascular cooling. *Neurocrit Care* 2007; 7:109–118
103. Polderman KH, Callaghan J: Equipment review: Cooling catheters to induce therapeutic hypothermia? *Crit Care* 2006; 10:234
104. Hinz J, Rosmus M, Popov A, et al: Effectiveness of an intravascular cooling method compared with a conventional cooling technique in neurologic patients. *J Neurosurg Anesthesiol* 2007; 19:130–135
105. Hachimi-Idrissi S, Corne L, Ebinger G, et al: Mild hypothermia induced by a helmet device: A clinical feasibility study. *Resuscitation* 2001; 51:275–281
106. Wang H, Olivero W, Lanzino G, et al: Rapid and selective cerebral hypothermia achieved using a cooling helmet. *J Neurosurg* 2004; 100:272–277
107. Storm C, Schefold JC, Kerner T, et al: Prehospital cooling with hypothermia caps (PreCoCa): A feasibility study. *Clin Res Cardiol* 2008; 97:768–772
108. Qiu W, Shen H, Zhang Y, et al: Noninvasive selective brain cooling by head and neck cooling is protective in severe traumatic brain injury. *J Clin Neurosci* 2006; 13: 995–1000
109. Holzer M: Devices for rapid induction of hypothermia. *Eur J Anaesthesesiol* 2008; 25(Suppl 42):31–38
110. Mayer SA, Kowalski RG, Presciutti M, et al: Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. *Crit Care Med* 2004; 32: 2508–2515
111. Holzer M, Müllner M, Sterz F, et al: Efficacy and safety of endovascular cooling after cardiac arrest: Cohort study and Bayesian approach. *Stroke* 2006; 37:1792–1797
112. Vaga A, Busch M, Karlsen TE, et al: A pilot study of key nursing aspects with different cooling methods and devices in the ICU. *Resuscitation* 2008; 76:25–30
113. Corry JJ, Dhar R, Murphy T, et al: Hypothermia for refractory status epilepticus. *Neurocrit Care* 2008; 9:189–197
114. Vastola EF, Homan R, Rosen A: Inhibition of focal seizures by moderate hypothermia: A clinical and experimental study. *Arch Neurol* 1969; 20:430–439
115. Sourek K, Travnicek V: General and local hypothermia of the brain in the treatment of intractable epilepsy. *J Neurosurg* 1970; 33:253–259
116. Hovland A, Nielsen EW, Kluver J, et al: EEG should be performed during induced hypothermia. *Resuscitation* 2006; 68:143–146
117. Battin M, Bennet L, Gunn AJ: Rebound seizures during rewarming. *Pediatrics* 2004; 114:1369
118. Wijdicks EF, Hijdra A, Young GB, et al: Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; 67:203–210
119. Riker RR, Fraser GL: Monitoring sedation, agitation, analgesia, neuromuscular blockade, and delirium in adult ICU patients. *Semin Respir Crit Care Med* 2001; 22: 189–198
120. Myles PS, Leslie K: Bispectral index monitoring to prevent awareness during anaesthesia: The B-Aware randomised controlled trial. *Lancet* 2004; 363:1757–1763
121. Ekman A, Lindholm ML, Lennmarken C, et al: Reduction in the incidence of awareness using BIS monitoring. *Acta Anaesthesiol Scand* 2004; 48:20–26
122. Seder DB, Bruce H, Robbins T, et al: Bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Abstr. *Crit Care* 2007; 11:S135
123. Riker RR, Seder DB, Fraser G, et al: Validation of the bispectral index and suppression ratio as early predictors of outcome with therapeutic hypothermia after cardiac arrest. Abstr. *Neurocrit Care* 2008; 9:S13
124. Saqqur M, Zygun D, Demchuk A: Role of transcranial Doppler in neurocritical care. *Crit Care Med* 2007; 35(Suppl 5): S216–S223
125. Steiner T, Friede T, Aschoff A, et al: Effect and feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarction of the middle cerebral artery. *Stroke* 2001; 32:2833–2835
126. Hata JS, Shelsky CR, Hindman BJ, et al: A prospective, observational clinical trial of fever reduction to reduce systemic oxygen consumption in the setting of acute brain injury. *Neurocrit Care* 2008 9:37–44
127. Nortje J, Gupta AK: The role of tissue oxygen monitoring in patients with acute brain injury. *Br J Anaesth* 2006; 97:95–106
128. Wartenberg KE, Schmidt JM, Mayer SA: Multimodality monitoring in neurocritical care. *Crit Care Clin* 2007; 23:507–538
129. Feldman Z, Robertson CS: Monitoring of cerebral hemodynamics with jugular bulb catheters. *Crit Care Clin* 1997; 13:51–77
130. Zarzuelo R, Castaneda J: Differences in oxygen content between mixed venous blood and cerebral venous blood for outcome prediction after cardiac arrest. *Intensive Care Med* 1995; 21:71–75
131. Kilgannon JH, Roberts BW, Stauss M, et al: Use of a standardized order set for achieving target temperature in the implementation of therapeutic hypothermia after cardiac arrest: A feasibility study. *Acad Emerg Med* 2008; 15:499–505
132. Søreide E, Sunde K: Therapeutic hypothermia after out-of hospital cardiac arrest: How to secure worldwide implementation. *Curr Opin Anaesthesiol* 2008; 21:209–215
133. Brooks SC, Morrison LJ: Implementation of therapeutic hypothermia guidelines for post-cardiac arrest syndrome at a glacial pace: Seeking guidance from the knowledge translation literature. *Resuscitation* 2008; 77:286–292
134. Carr BG, Goyal M, Band RA, et al: A national analysis of the relationship between hospital factors and post-cardiac arrest mortality. *Intensive Care Med* 2008; 35:505–511
135. Keenen SP, Dodek P, Martin C, et al: Variation in intensive care unit stay after cardiac arrest: Where you are is as important as who you are. *Crit Care Med* 2007; 35: 836–841
136. Spaite DW, Bobrow BJ, Vadeboncoeur TF, et al: The impact of prehospital transport interval on survival in out-of-hospital cardiac arrest: Implications for regionalization of post-resuscitation care. *Resuscitation* 2008; 79:61–66
137. Riker RR, Picard JT, Fraser GL: Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med* 1999; 27:1325–1329
138. Sessler CN, Gosnell M, Grap MJ, et al: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care patients. *Am J Respir Crit Care Med* 2002; 166:1338–1344

APPENDIX 1: THERAPEUTIC TEMPERATURE MANAGEMENT SHIVERING PROTOCOL

Nonintubated patient

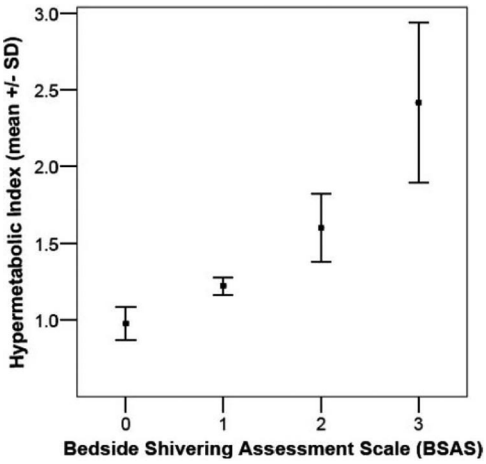
1. Acetaminophen 650 mg every 6 hrs when temperature $<35°C$ and 650 mg every 4 hrs when temperature $>35°C$.

2. Focal counterwarming: warm air blanket or warm packs to face, neck, and extremities.
3. Buspirone 30 mg (enteral) q8h plus: a. meperidine 12.5 to 25 mg intravenously every 4 hrs.
4. Dexmedetomidine 0.3 to 1.5 ng/kg per min or clonidine 0.1 to 0.3 mg (enteral) every 8 hrs.
5. Magnesium infusion to target serum level of 2.5 to 3.5 mg/dL.
6. Cautious intermittent administration of a low dose benzodiazepine for comfort.
7. Reconsider therapy: If Bedside Shivering Assessment Scale is 2 or 3, neuroprotective gains of therapy are likely overbalanced by the metabolic cost (80). If therapy is determined to be necessary, intubate and proceed as below.

Intubated patient

1. Acetaminophen 650 mg (enteral) every 6 hrs when temperature <35°C and 650 mg every 4 hrs when temperature >35°C.
2. Focal counterwarming: warm air blanket or warm packs to face, neck, and extremities.
3. Sedate: intravenous propofol, midazolam, or bolus-dose lorazepam. Place bispectral index monitor and follow sedation and neuromuscular blockade algorithm (Fig. 3). Sedation *must* be maintained throughout the period of neuromuscular blockade.
4. Administer 25 to 50 μg/hr intravenous fentanyl or equivalent narcotic.
5. Monitor the Bedside Shivering Assessment Scale and bispectral index every 30 to 60 mins.
6. Administer vecuronium 0.1 mg/kg by intravenous bolus whenever Bedside Shivering Assessment Scale >1, or cisatricurium 0.15 mg/kg by intravenous bolus and 3 μg/kg per min infusion.
7. If bispectral index >50, evaluate for and treat shivering; if index remains >50 after shivering is eliminated, obtain immediate electroencephalography and increase sedation until bispectral index <50.
8. Discontinue neuromuscular blockade daily for neurological examination and several hours before weaning sedation.
9. Neuromuscular blockade is associated with long-term neuromuscular weakness, and should be avoided when the synergistic factors of corticosteroids and sepsis are present.

APPENDIX 2: THE BEDSIDE SHIVERING ASSESSMENT SCALE AND ASSOCIATED ENERGY EXPENDITURES



Score	Definition
0	None: no shivering noted on palpation of the masseter, neck, or chest wall
1	Mild: shivering localized to the neck and/or thorax only
2	Moderate: shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe: shivering involves gross movements of the trunk and upper and lower extremities