Induced hypothermia in critical care medicine: A review

Stephen A. Bernard, MB, BS, FACEM, FJFICM; Michael Buist, MB, BS, FRACP, FJFICM

Background: **Clinical trials of induced hypothermia have suggested that this treatment may be beneficial in selected patients with neurologic injury.**

Objectives: **To review the topic of induced hypothermia as a treatment of patients with neurologic and other disorders.**

Design: **Review article.**

Interventions: **None.**

Main Results: **Improved outcome was demonstrated in two prospective, randomized, controlled trials in which induced hypothermia (33°C for 12–24 hrs) was used in patients with anoxic brain injury following resuscitation from prehospital cardiac arrest. In addition, prospective, randomized, controlled trials have been conducted in patients with severe head injury, with variable results. There also have been preliminary clinical studies of induced hypothermia in patients with severe stroke, newborn hypoxic-ischemic encephalopathy, neurologic infection, and hepatic encephalopathy, with promising results. Finally, animal models have suggested that hypothermia that is induced rapidly following traumatic cardiac arrest provides significant neurologic protection and improved survival.**

Conclusions: **Induced hypothermia has a role in selected patients in the intensive care unit. Critical care physicians should be familiar with the physiologic effects, current indications, techniques, and complications of induced hyperthermia. (Crit Care Med 2003; 31:2041–2051)**

KEY WORDS: hypothermia, induced; anoxic neurologic injury; cardiac arrest; traumatic brain injury; stroke hepatic failure

Induced hypothermia (IH) is defined as the controlled lowering of core temperature for therapeutic reasons and has been used routinely in the operating room since the early 1950s for patients undergoing cardiac surgery (1) and more recently for neurologic surgery (2). Increasingly, mild to moderate IH (32–34°C) is being used in the intensive care unit (ICU) for selected patients with neurologic injury. In particular, recent clinical studies have suggested that IH after resuscitation improves outcome in patients with anoxic neurologic injury following out-of-hospital cardiac arrest (3, 4). Also, there are a number of other proposed applications of IH for patients in the ICU with other types of neurologic injury, including severe traumatic brain injury, major stroke, hepatic encephalopathy, and others. Therefore, critical care physicians should be familiar with the physiologic effects, current indications, techniques, and complications of IH.

From the Intensive Care Unit, Dandenong Hospital, Dandenong, Victoria, Australia.

Address requests for reprints to: Dr. Stephen Bernard, Intensive Care Unit, Dandenong Hospital, Victoria, Australia 3175. E-mail s.bernard@southernhealth.org.au

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History

The earliest recorded clinical use of IH was in 1937 when Dr. Temple Fay cooled a female patient to 32°C for 24 hrs in an attempt to relieve the symptoms of metastatic cancer (5). The IH as a therapy was proposed on the basis of laboratory work suggesting that cancer cells would not divide at a lower body temperature. The IH was undertaken in a general ward, with the patient sedated by using an oral barbiturate before being packed in ice. After 24 hrs, the patient was rewarmed, apparently without ill effect. Subsequently, Fay and colleagues used IH in a further 123 patients with cancer (6). The use of IH appeared to be well tolerated, although there was no apparent effect on cancer progression. In 1941, Smith and Fay also observed that IH improved the conscious state of a patient with head injury, and they subsequently reported the findings in a large series of patients with severe head injury (7).

In 1950, Bigelow et al. (8) introduced IH for neurologic protection during cardiac surgical procedures, and this remains the current practice (1). By 1959, there appeared to be a wide variety of indications for the use of IH outside the operating room, particularly in patients with neurologic injury (9, 10). However, between 1960 and 1996, there were relatively few publications on the clinical use of IH, and this technique apparently was rarely used. In 1996, a review of the literature on IH in critical care medicine found a large number animal studies and anecdotal clinical reports that appeared to support clinical trials of IH in selected patients; however, there had been no properly conducted randomized trials to evaluate this treatment (11). Over the last 5 yrs, several clinical trials of the use of IH in patients in the ICU have been undertaken.

Physiologic Effects of IH

Central Nervous System. The effect of hypothermia on the injured brain is complex. For each 1°C decrease in temperature, the cerebral metabolic rate decreases by 6–7% (12). Since the cerebral metabolic rate for oxygen is the main determinant of cerebral blood flow (13), IH may provide for a relative improvement in oxygen supply to areas of ischemic brain (14). In addition, hypothermia decreases intracranial pressure (15). The mechanism for this is uncertain but may be due to decreased intracranial blood volume because of cerebral vasoconstriction. Finally, hypothermia may act as an anticonvulsant (16).

After an ischemic insult and reperfusion, hypothermia acts through various mechanisms of action. Hypothermia markedly decreases the concentrations of

excitatory amino acids and lactate during ischemia and reperfusion (17). In a microdialysis study of a stroke model, it was demonstrated that hypothermia decreases glutamate, glycerol, lactate, and pyruvate concentrations in the "tissue at risk" area of the infarct but not within the infarct core (18). The adhesion of neutrophils to the endothelium and subsequent transmigration also has been reported to contribute to progression of cerebral ischemia. In a rat model, it was demonstrated that hypothermia reduced the microvessel expression of intercellular adhesion molecule-1 protein and the number of neutrophils migrating into ischemic tissue (19). In head injury patients, IH decreased interleukin-10 concentrations in the cerebrospinal fluid (15).

Cardiovascular System. During accidental hypothermia, there may be intense shivering between 34°C and 36°C. This significantly increases metabolic rate and oxygen demand and may increase the incidence of myocardial infarction in patients with ischemic heart disease (20).

However, during IH, the patient is sedated and/or paralyzed to avoid shivering (3, 4). With shivering abolished, mild hypothermia (32–34°C) decreases heart rate and increases systemic vascular resistance, whereas stroke volume and mean arterial blood pressure are maintained (3). At 33°C, the electrocardiogram may show a notch on the downstroke of the QRS complex (the Osbourne wave) (21).

Although cited as a risk of mild hypothermia, cardiac arrhythmias are rarely seen at 33°C, even in patients with myocardial ischemia (3, 4). However, in accidental hypothermia, there is a risk of ventricular fibrillation if core temperature decreases below 28°C (22).

Respiratory System. Hypothermia has few direct effects on the respiratory system. Since metabolic rate is decreased by 25–30% at 33°C, the ventilator minute volume is decreased to maintain the P_{CO_2} in the normal range.

Pneumonia is a risk of IH; however, this is relatively uncommon during in brief (12–24 hrs) IH (3, 4). In a series of adult patients who underwent more prolonged (mean 7 days) IH as part of a treatment of severe head injury, nosocomial pneumonia was frequent (45%) but not associated with additional adverse effects (23). On the other hand, pneumonia leading to septic shock may be more common in pediatric patients who undergo IH for prolonged periods (24).

Renal System, Electrolytes. During hypothermia, there may be a diuresis because of decreased reabsorption of solute in the ascending limb of the loop of Henle (25). In addition, the induction of hypothermia shifts potassium into the cells (26), and the administration of potassium to correct hypokalemia during induction of IH may lead to significant hyperkalemia during rewarming (27). Hypothermia also decreases phosphate concentrations (28). Therefore, volume status, potassium, and phosphate concentrations require careful monitoring and control during IH.

Acid-Base. The solubility of gases in blood increases as temperature decreases. When arterial blood gases of hypothermic patients are corrected for temperature, patients appear to have a respiratory alkalosis. The measurement of blood gases without correction is known as alpha-stat management. The addition of CO_2 to normalize pH is known as pH-stat management. It is controversial whether blood gases should be corrected for body temperature during IH. Although the evidence currently favors alpha-stat management for hypothermia during cardiopulmonary bypass (29), a recent study has examined the effect of acid-base management on cerebral blood flow, infarct volume, and cerebral edema in a rat model of mild hypothermia (33°C for 5 hrs) and transient focal cerebral ischemia (30). This study found that pH-stat management significantly decreased cerebral infarct volume and edema compared with alpha-stat management during moderate hypothermia.

Gastrointestinal System. During hypothermia, there is decreased gut motility, and this may delay enteral feeding (23). More important, hypothermia increases blood glucose concentrations, probably due to decreased insulin release from the pancreas (31). Since hyperglycemia is associated with additional complications in ICU patients (32), exogenous insulin should be administered to correct this.

Hematologic System. During prolonged IH, the numbers and function of white blood cells decrease, and this may increase the incidence of sepsis, particularly pneumonia during prolonged IH (>24 hrs) (23, 24). Prolonged hypothermia also decreases the numbers and function of platelets (23). Finally, hypothermia prolongs clotting times (33), and this might contribute to an increase in the risk of bleeding in the setting of major trauma.

Clinical Applications of IH

Anoxic Brain Injury. Patients who are admitted to hospital following resuscitation from prehospital cardiac arrest generally have severe anoxic neurologic injury that carries a high mortality rate (34). Previously, the treatment has been largely supportive. Following animal studies suggesting that IH significantly decreased neurologic injury after severe global anoxic brain injury (17, 35–41), a number of preliminary human studies were undertaken (42–45). Subsequently, two prospective, randomized, controlled clinical trials have been published (3, 4).

We reported the first use of IH in adult patients with coma following resuscitation from out-of-hospital cardiac arrest (42). Hypothermia (33°C) was induced in 22 patients in the emergency department by using surface cooling with ice packs and was maintained for 12 hrs in the ICU. Compared with 22 historical controls, there was a significant increase in the numbers of patients with good outcome (50% compared with 13%), and there were no additional complications.

Following this preliminary study, we conducted a prospective, randomized trial of IH in comatose survivors of out-of-hospital cardiac arrest (3). There were 43 patients randomized to IH (33°C for 12 hrs) and 34 patients maintained at normothermia. At hospital discharge, 21 of 43 (49%) in the IH group had good outcome compared with 9 of 34 (26%) in the control group ($p = .046$). Following multivariate analysis for differences at baseline, the odds ratio for good outcome in the hypothermic group was 5.25 (95% confidence intervals, 1.47–18.76; $p = .011$). Although IH was associated with significant hemodynamic effects such as decreased cardiac output and increased systemic vascular resistance, the incidence of cardiac arrhythmias was the same in both groups. There were no apparent adverse effects of IH such as sepsis, lactic acidosis, neutropenia, thrombocytopenia, or coagulopathy.

A multiple-center clinical trial conducted in Europe of comatose survivors of prehospital cardiac arrest enrolled 273 patients, with 136 patients undergoing IH (33°C for 24 hrs) and 137 patients maintained at normothermia. At 6 months, 55% of the IH patients had good outcome, compared with 39% of normo-

thermic controls (risk ratio, 1.4; 95% confidence interval, 1.08–1.81). The complication rate did not differ between the two groups.

However, these studies used surface cooling, which was found to have significant limitations. It was relatively slow, with a rate of core temperature decrease of 0.3–0.9°C/hr. Also, surface cooling was inconvenient for medical and nursing staff and limited the induction of hypothermia to the hospital environment. Since there is good animal model evidence of further improvements in outcome if hypothermia takes place immediately after resuscitation (35, 38), alternative techniques for the rapid induction of hypothermia will be the focus on future clinical trials. Proposed alternate techniques of cooling are discussed later (see Cooling Techniques).

Traumatic Head Injury. Although there were anecdotal reports of the use of IH in the 1950s in patients with severe head injury (46–48), this treatment was largely abandoned after the introduction of ICUs in the 1960s. Current ICU management of patients with severe head injury focuses on strategies that attempt to minimize secondary brain injury by monitoring and controlling cerebral oxygenation (49). However, IH again has been proposed as a therapy in this setting based on the premise that decreasing oxygen consumption and intracranial pressure may protect against secondary ischemic insults.

A number of more recent studies have examined the use of IH following severe head injury. A recent meta-analysis found that hypothermia is not beneficial in the management of severe head injury. However, because hypothermia continues to be used to treat these injuries, the authors concluded that additional studies are justified and urgently needed (50).

The first supportive study was by Marion et al. (51), who compared 40 patients with severe traumatic brain injury who underwent moderate IH (32–33°C for 24 hrs) with 42 patients maintained at normothermia. In patients with an initial Glasgow Coma Score of 5–8, IH was associated with a significant increase in cerebral perfusion pressure without an increase in adverse side effects. The number of patients with good outcome at 12 months was 62% in the IH group compared with 38% in the control group ($p = .05$). However, differences in computed tomography score between the groups and an interim analysis at 40 patients reduced the confidence in the outcome analysis.

The results of a larger multiple-center, prospective, randomized study examining the use of IH in severe head injury have subsequently been published. In this study, Clifton et al. (15) randomized 392 patients to IH (33°C for 48 hrs) or normothermia. Although there was a significant difference in intracranial pressure control (with IH patients less likely to have intracranial pressure >30 mm Hg during the first 96 hrs), there was no difference in outcome at 6 months, with 57% of patients in both groups having poor outcome.

However, there were a number of methodological issues with this study. First, patients were excluded if there was persistent hypoxia or hypotension after initial resuscitation. Given that an effect of hypothermia is protection against cerebral ischemia, there may have been exclusion of patients in whom hypothermia would have significant benefit. Second, hypothermia was not instituted until a mean of 8 hrs after injury, and this may be a period during which hypothermia has the most beneficial effect. Third, patients were rewarmed at 48 hrs regardless of the measurement of intracranial pressure, even though rebound intracranial hypertension may occur during rewarming (52), and many clinicians would consider delaying rewarming patients until intracranial hypertension was controlled. Finally, there were significant differences between the centers in fluid management (53).

A *post hoc* analysis of this study found that some subgroups had different outcomes (54). For example, 81 patients were <45 yrs of age and hypothermic (<35°C) on admission. Of the patients with hypothermia on admission who were assigned to normothermia (and thus rewarmed), there were 76% with poor outcome, compared with the hypothermia-on-admission patients assigned to hypothermia who had a 52% poor outcome ($p = .02$). These data suggest that further studies are needed that examine younger patients who are admitted with hypothermia to assess whether they should be maintained hypothermic for 24 hrs. Future studies also could focus on early IH (within 8 hrs) and include patients with hypoxia or hypotension.

The use of IH in patients without intracranial hypertension following severe brain injury has been studied by Shiozaki et al. (55). They compared IH and normothermia in 91 patients who had normal intracranial pressure after severe head injury and found that IH was associated with an increased rate of pneumonia and diabetes insipidus, with no difference in outcome.

All the preceding studies used IH (32–34°C) for relatively short periods (24–48 hrs) in patients with severe head injury. It is possible that increased benefit might be achieved if hypothermia was maintained for prolonged periods (>48 hrs). We have used moderate IH (32–33°C) for prolonged periods (mean, 8 days; range, 2–19 days) in an observational study of 43 patients with severe head injury (22). We found that nosocomial pneumonia (defined as both new chest radiograph changes and culture of a respiratory pathogen from tracheal aspirate) was common (45%); however, death from sepsis was rare (5%). Other findings included hypokalemia on induction of hypothermia and a significant decrease in total leukocyte and platelet count over 10 days. There were no major cardiac arrhythmias, bleeding complications, or other adverse effects, and there was a satisfactory neurologic outcome in 20 of 43 patients.

Finally, a recent study of cerebral oxygen pressure measured by intracerebral probe in patients with traumatic brain injury suggested that cerebral oxygen pressure declines significantly when temperature is <35°C. The authors suggest that this temperature may be preferable to a lower temperature (56).

At present, clinical studies do not support the use of IH as a routine therapy in severe head injury. However, further studies are required to assess whether IH is beneficial if applied early in severe head injury, particularly when the patient is already hypothermic, or when intracranial pressure requires additional therapy.

Traumatic Cardiac Arrest. Cardiac arrest following trauma and exsanguination carries a very high mortality rate (57). Emergency thoracotomy, aortic cross-clamping, and hemorrhage control may be successful in penetrating trauma but generally are regarded as futile in blunt trauma (58). Even if circulation is successfully restored, there is usually severe anoxic neurologic injury during the period of profound cerebral hypoperfusion.

Recent animal studies have suggested that rapid induction of hypothermia may be applicable for this condition in the future (59–64). In a canine study, cardiac arrest was caused by exsanguination >5

mins (59). After 2 mins of cardiac arrest, a femoral arterial catheter was inserted and an aortic arch flush of 500 mL of isotonic saline was administered, with one group receiving 4°C fluid and the other 24°C fluid. All animals then were resuscitated after 15 mins of cardiac arrest by using cardiopulmonary bypass, return of shed blood, and defibrillation. In the cold flush group, all dogs recovered to normal cerebral performance, whereas in the warm flush group, all dogs remained disabled or comatose.

In another study, 16 dogs were exsanguinated to pulselessness over 5 mins (60). One group received a 25 mL/kg cold (4°C) flush into the proximal aortic via a balloon catheter, which decreased tympanic temperature from 37°C to 33.3°C. The other group received a 100 mL/kg cold fluid flush into the proximal aorta, and this decreased tympanic temperature from 37.4°C to 28.3°C. Circulatory arrest was maintained for 30 mins, followed by external cardiac massage and assisted circulation for a further 2 hrs. Mild hypothermia (34°C) then was maintained for 12 hrs. In the small-volume group, all dogs remained comatose or died, whereas in the large-volume group, all dogs recovered to normal or moderate disability.

In a study in swine, IH was used following exsanguination due to aortic laceration (61). After 5 mins of severe hypotension, an ice-cold (1°C) solution was infused rapidly into the proximal aorta to arrest/preserve the heart and brain. The animals then were placed on cardiopulmonary bypass and cooled to 10°C. The aorta was repaired and the animals were rewarmed after 90 mins. Seven of ten animals survived, four with no clinical or histologic evidence of neurologic injury.

In a study that used a rat model of uncontrolled hemorrhagic shock (tail amputation and 90 mins bleeding), Kim et al. (62) compared hypothermia to normothermia with two different blood pressure targets (no resuscitation vs. resuscitation to 40 mm Hg mean arterial blood pressure), and outcome was assessed at 72 hrs. In animals that remained both normothermic and received no fluid resuscitation, there were no survivors. All animals that received both IH and resuscitation to a mean arterial blood pressure of 40 mm Hg survived.

Hypothermia during exsanguination before definitive surgical care actually may delay or prevent cardiac arrest. In a rat model of lethal uncontrolled hemorrhage, the survival time following tail amputation was increased significantly in animals that were cooled to 34°C compared with controls (63). In the IH group, survival time was 119 mins compared with 51 mins for the control group.

All these animal data suggest that the rapid induction of hypothermia may have a role in maintaining the viability of patients with major trauma who are exsanguinating before definitive surgery (64). The practical application of this approach requires techniques for the rapid core cooling of severely injured patients. Currently, clinical trials are proposed in which trauma patients who are hemorrhaging and suffer cardiac arrest in the emergency department undergo immediate thoracotomy, aortic cross-clamp, and large-volume ice-cold fluid infusion into proximal aorta for cardiac and cerebral protection (65). Cardiopulmonary bypass then could be used for circulatory support during definitive surgical repair and rewarming.

Nevertheless, in contrast to these research directions, (accidental) hypothermia in major trauma is still regarded as an independent risk factor for adverse outcome. In one randomized, prospective, controlled study, 57 hypothermic (<34.5°C), critically injured patients received rapid core rewarming by using continuous arteriovenous rewarming or standard rewarming (66). The patients undergoing continuous arteriovenous rewarming rewarmed significantly faster than did the standard rewarming group, required less fluid during resuscitation, and were more likely to actually rewarm. Only two (7%) of 29 patients who underwent continuous arteriovenous rewarming failed to warm to 36°C and died, whereas all 12 (43%) of 28 patients who failed to reach 36°C with standard rewarming died.

Inadvertent hypothermia that occurs during major surgery also is thought to be associated with additional complications, including an increased rate of wound infections after colon surgery (67) and increased blood transfusion requirements after total hip replacement (68), although these findings have not been found in subsequent studies (69, 70).

The striking differences between accidental hypothermia and IH were studied further by Seekamp et al. (71). They measured adenosine triphosphate concentrations in patients undergoing IH during cardiothoracic surgery and compared these with the concentrations of adenosine triphosphate in trauma patients with accidental hypothermia and normothermic elective surgical patients. There were significant decreases in the adenosine triphosphate concentrations and elevated lactate concentrations in the trauma patients with accidental hypothermia, compared with the elective surgical groups. This data suggested that there are significant differences between accidental hypothermia and IH in oxygen metabolism at a tissue level. It is probable that accidental hypothermia during trauma is associated with anaerobic conditions, whereas IH under controlled conditions is associated with decreased oxygen demand but relative maintenance of oxygen delivery. Therefore, adverse outcomes in studies of accidental hypothermia may not be directly applicable to patient groups in whom hypothermia is induced under controlled conditions.

Stroke. Stroke is the third most common cause of death and the most common cause of adult disability in the Western world (72). Current management priorities include stabilization of airway/breathing/circulation and urgent computerized tomography of the brain. Although aspirin, early thrombolysis, and strict control of blood sugar may be beneficial, the treatment of patients with major stroke is still largely supportive.

In ischemic stroke, a central area of irreversibly damaged tissue is surrounded by a zone of hypoperfusion, the "ischemic penumbra," where neuronal function is impaired but potentially salvageable (73). There is considerable interest in neuroprotective agents that might reduce the effects of ischemia at a cellular level in the so-called ischemic penumbra, and a large number of drugs have been studied in phase II and phase III clinical trials. However, none have yet been shown to be effective.

Preliminary observational human studies have suggested that fever after stroke is associated with increased morbidity and mortality rates (74, 75). In a retrospective study of 110 patients admitted within 24 hrs of stroke, it was found that fever worsened residual deficit (74). In a prospective study of 177 patients with stroke, fever was a major factor that significantly increased morbidity rate (75).

Mild spontaneous hypothermia appears to be associated with a favorable prognosis in stroke. Reith et al. (76) prospectively studied 390 patients admitted within 6 hrs of the onset of stroke and found that mortality rate was lower and

outcome was improved in patients with mild hypothermia on admission. For each 1°C increase in body temperature, the relative risk of poor outcome when using the Scandinavian Stroke Score on discharge increased by 2.2 (95% confidence interval, 1.4–3.5). In another study, Jorgensen et al. (77) reviewed 223 patients with severe stroke and also found that decreased body temperature on admission was associated with improved functional outcome.

There have been numerous animal models (78–83) and preliminary clinical studies of mild IH in patients with stroke (84, 85). Schwab et al. (84) used IH (33°C) for 48–72 hrs in 50 patients with severe ischemic stroke involving the middle cerebral artery territory leading to elevated intracranial pressure because of hemispheric swelling. The important complications included thrombocytopenia (70%), bradycardia (62%), and pneumonia (48%). In addition, 30% of patients had increased intracranial pressure with cerebral herniation during rewarming. Nevertheless, outcome was regarded as improved compared with historical controls. A similar study by Kurokawa et al. (85) also found that IH after middle cerebral artery occlusion was effective in controlling brain swelling.

On the other hand, a recent randomized study compared the clinical course of 36 consecutive patients with severe acute ischemic stroke treated with either hemicraniectomy (n = 17) or moderate hypothermia (n = 19) (86). Mortality rate was 12% in the hemicraniectomy group and 47% in the hypothermia group. One patient treated with hypothermia died as a result of treatment complications (sepsis), and three other patients died due to intracranial pressure crises that occurred during rewarming. Duration of mechanical ventilation and of neurologic intensive care unit stay did not significantly differ, but duration of catecholamine application and maximal catecholamine dosage were higher in the hypothermia group.

The use of mild IH in nonventilated patients has been studied by Kammersgaard et al. (87), who conducted a feasibility and safety study of forced cold air cooling in patients with acute stroke to induce mild hypothermia. In this small case control study (17 cases and 56 controls), decreasing temperature from 36.8°C to 35.5°C for 6 hrs was associated with a 4.8% absolute risk reduction. Although this was not statistically significant, there was no increase in complications or mortality rate in this pilot study. In another preliminary study, Kreiger et al. (88) cooled ten patients with severe stroke to 32°C for 12–72 hrs. This study also concluded that IH was feasible and safe in patients with acute stroke.

Recently, a review of the literature related to IH and stroke was undertaken by the Cochrane Library (89). Although no randomized, controlled trials were identified, this review of the available uncontrolled studies concluded that clinical trials of IH after major stroke were warranted.

However, the cooling of conscious stroke patients is problematic because surface cooling is uncomfortable and sedation is required to suppress shivering (90). Alternatively, core cooling by using intravascular cooling devices may be better tolerated (91, 92). This approach is discussed further in Cooling Techniques.

If the use of IH in stroke patients requires pharmacologic paralysis and mechanical ventilation, admission to the ICU will be required. However, patients with severe stroke who require mechanical ventilation have a high mortality rate (93), and admission to an ICU is not currently considered appropriate use of resources in many cases. On the other hand, if the use of IH in stroke is found to be associated with much improved outcome, this would significantly affect current practice and would result in many additional admissions to the ICU, with major implications for resource allocation in the future.

Newborn Hypoxic-Ischemic Encephalopathy. With strong evidence of a neuroprotective effect of IH in adults with global anoxic brain injury, there is also considerable interest in the use of IH in infants with severe perinatal asphyxia (94–102).

An initial safety and feasibility study was undertaken by Gunn and Gunn (94), who randomized 22 neonates at risk of hypoxic-ischemic encephalopathy to normothermia (36.8–37.2°C), minimal hypothermia (36.0–36.5°C), and mild hypothermia (35.5–35.9°C). Cooling was achieved by using a head cap with circulating water at 10°C. No adverse effects of cooling were observed, and the results suggested improved outcome in the mild hypothermia group, with six of six having good outcome at 12 months compared with five of ten normothermic controls.

In another study, Simbruner et al. (99) treated 21 infants suffering neonatal asphyxia with IH. The complications and outcomes were compared with 15 historical controls. Nasopharyngeal temperature in the IH group was maintained at 34–35°C for 72 hrs. There were no differences in the rates of complications, and neurologic score at day 5 was significantly improved in the IH group.

Thoresen and Whitelaw (100) studied the cardiovascular effects of IH in infants with hypoxic-ischemic encephalopathy. Nine infants with Apgar scores of ≤5 were cooled to 35°C by using surface cooling or a cooling cap. Arterial blood pressure increased during cooling and decreased during rewarming. An important finding was increased oxygen requirements due to pulmonary hypertension; however, these changes were modest and not regarded as hazardous.

Minimal cooling (36–36.5°C) and mild cooling (34.5–35.5°C) were compared with no cooling (37°C ± 0.2°C) in a study of 40 infants with hypoxic-ischemic encephalopathy (101). Although there was a wide range of outcomes in each group, no adverse effects of hypothermia was noted.

The results of a large, multiple-center, randomized, controlled trial in neonates with hypoxic-ischemic encephalopathy are awaited (102).

Hepatic Encephalopathy. Fulminate hepatic failure is associated with altered conscious state and increased intracranial pressure. Since hypothermia is known to lower intracranial pressure in patients with severe head injury (15, 51) and the data from animal models of hepatic encephalopathy are encouraging (103, 104), there is increasing interest in the application of IH in patients with acute liver failure (105–107).

In an animal model, Rose et al. (103) assessed the effectiveness of IH in rats subjected to hepatic devascularization. In the animals undergoing mild IH (35°C), there was decreased brain water, decreased cerebrospinal fluid ammonia, and reduced cerebral extracellular glutamate concentrations compared with normothermic (37°C) controls. In a rat model of hepatic encephalopathy, Cordoba et al. (104) found that IH prevented ammonia-induced cerebral edema.

The use of IH in patients with fulminate hepatic failure and intracranial hypertension has been reported in two separate articles, one with nine patients (105) and one with 16 (106). In the latter study, cooling blankets were used to lower core temperature in patients with

hepatic encephalopathy to 32–33°C for a mean of 32 hrs (range, 8–120 hrs). It was found that IH decreased intracranial pressure from a mean of 54 mm Hg to 19 mm Hg. There was also a significant decrease in the cerebral uptake of ammonia. The nine patients who underwent liver transplantation all survived, whereas one patient died while waiting for a suitable organ to become available and the six patients considered unsuitable for liver transplantation also died. No adverse effects of IH were observed. The authors concluded that IH had a useful role in the patient with increased intracranial pressure awaiting liver transplantation. Further studies are currently in progress (107).

Encephalitis. Only anecdotal reports are available concerning the use of IH in acute encephalitis (108–110). For example, Takata et al. (108) used IH in a 28-yr-old male who was deteriorating due to cerebral edema despite surgical decompression, intravenous immunoglobulin, and corticosteroid therapy. The introduction of IH led to significant clinical improvement and the patient eventually recovered. Another study of IH in four children with encephalitis suggested that hypothermia decreased cerebral edema as determined by computed tomography (109). Two further children with encephalitis due to influenza A also recovered well following the use of IH (110).

Bacterial Meningitis. Recent animal studies have suggested an anti-inflammatory role for IH in bacterial meningitis (111, 112). Angstwurm et al. (111) induced pneumococcal meningitis in a rat model and found that IH lowered regional cerebral blood flow, intracranial pressure, cerebrospinal fluid leukocyte count, and cerebrospinal tumor necrosis factor. In another study, Irazuzta et al. (112) also used a rat model of group B streptococcal meningitis. The use of IH was associated with decreased inflammatory markers and improved biochemical markers of neuronal brain injury; however, IH did not improve overall neurobehavioral performance.

Cardiac Failure. Following cardiac surgery, a persisting low cardiac output state refractory to conventional treatment is associated with a high mortality rate. The use of IH in this setting has been the subject of three reports (113–115). Deakin et al. (113) reported the use of IH in 50 patients, and (from the same center) Dalrymple-Hay et al. (114) reported the use of IH in 57 patients with cardiogenic shock following cardiac surgery. In the latter report (which appears to include the same patients as the Deakin et al. study), cooling to 33°C was instituted in pediatric patients with persistent low cardiac output state, impaired respiratory function, decreased urine output, and metabolic acidosis despite maximal intensive care. Following cooling, hemodynamic parameters improved and good outcome was achieved in 31 of 57 patients.

Yahani et al. (115) used IH (34.5°C) in ten adult patients with severe heart failure following cardiac surgery that was unresponsive to conventional medical therapy and intra-aortic balloon pumping. There were significant improvements in cardiac index, oxygen delivery, and urine output with IH maintained for 38 ± 41 hrs. All patients were successfully weaned from intra-aortic balloon pumping. The authors concluded that mild hypothermia was a simple and useful procedure for improving the circulation of postcardiac surgery patients with severe heart failure despite intra-aortic balloon pumping.

Postoperative Tachycardia. There have been anecdotal reports of IH in pediatric patients with supraventricular tachycardia unresponsive to usual pharmacologic treatment (116, 117).

Adult Respiratory Distress Syndrome. At present, severe adult respiratory distress syndrome (ARDS) is managed with mechanical ventilation and treatment of the underlying condition. Recent studies have focused on strategies for lung protection by using low tidal volumes and permissive hypercapnia. The use of IH to reduce hypercapnia would allow further decreases in minute volume and perhaps minimize barotrauma. Furthermore, IH theoretically would decrease end-organ ischemia, which may be a factor in the development of multiple-system organ failure.

However, studies of IH in ARDS are limited to several case reports (118–120) and one small case-controlled trial (121). The first use of IH in the management of severe respiratory failure was in 1983 when Gilston (118) used IH (34°C) for 3 days in a 16-month-old child suffering severe pulmonary edema. A marked improvement in the Pao_2 at the lower temperature was noted, and the child recovered. In 1985, Hurst et al. (119) used IH (33°C for 10 days) in a 32-yr-old female with severe ARDS, and this patient also eventually recovered. Finally, Wetterberg and Steen (120) used IH (33.3°C for 11 days) in a 20-yr-old male with posttraumatic ARDS, with eventual full recovery.

There has been only one controlled trial of IH in patients with severe ARDS. Villar and Slutsky (121) compared nine patients who underwent IH (33.7C) with ten patients who remained normothermic. The mortality rate was 100% in the normothermic patients compared with 66% in the IH group.

Despite the theoretical benefits of IH in ARDS, there are concerns about the use of prolonged IH in patients with sepsis syndrome, where hypothermia is thought to be an independent risk factor for adverse outcome (122).

Cooling Techniques. When the critical care physician decides to use IH, he or she will need to consider the technique of induction. Ideally, for patients with neurologic injury, regional cooling of the brain only would provide the perceived benefits of IH without any additional risks of side effects. However, attempts at localized brain cooling by using helmets fitted with cooling mechanisms have proved unsuccessful (123). On the other hand, because of the relative blood flow to the scalp compared with skin elsewhere, cooling helmets may slowly decrease core temperature. In one study in 16 patients who were comatose after resuscitation from cardiac arrest, a core temperature of 34°C was reached after 180 mins by using a cooling helmet (124).

In an animal model, Mori et al. (125) used femoral-carotid bypass to provide regional brain cooling. The hypothermic femoral-carotid bypass was accomplished by drawing blood from the right femoral artery, cooling it to 24°C, and returning it to the right carotid artery at a flow rate of 5 $mL \cdot kg^{-1} \cdot min^{-1}$ for 30 mins. With initiation of cooling, brain temperatures decreased rapidly from baseline of 37.2°C to 30.6°C (right frontal lobe) and 33.1°C (left frontal lobe) at 30 mins. Pulmonary artery and rectal temperatures also decreased slightly but never reached mild hypothermic levels.

Currently, cerebral hypothermia requires cooling of the whole body. Different body cooling methods were examined by Plattner et al. (126). They subjected anesthetized volunteers to surface cooling using circulating cold water, surface cooling using fanned cold air, gastric lavage with 500 mL of ice water every 10 mins, bladder lavage using 300 mL of cold lactated Ringer's solution every 10

mins, or ice-water immersion. Gastric lavage provoked diarrhea, and bladder cooling provided only trivial heat loss. Surface cooling techniques that used circulating cold air or water blankets were also relatively ineffective. Ice-water immersion caused a rapid decrease in core temperature of 9.7°C/hr; however, this technique is considered largely impractical for routine use in the emergency department or ICU.

The cooling technique of conduction (when using a water blanket) was compared with convection (by using forced cold air cooling) by Theard et al. (127) in 20 surgical patients. This technique was also relatively slow in both groups, and there were no differences between the groups in the time taken for core temperature to decrease from 35°C to <34°C (mean 178 mins compared with 142 mins).

In our studies of IH in comatose survivors of out-of-hospital cardiac arrest (3, 42), we have used neuromuscular blockade and extensive surface cooling with ice packs. However, this provided for relatively slow core cooling (approximately 0.9°C/hr) and was considered inconvenient by attending medical and nursing staff. Other studies of IH after cardiac arrest in which cold air blankets were used also found slow temperature decreases (0.3–0.5°C/hr) (4, 128). Therefore, alternative techniques are required to induce hypothermia that are convenient, rapid, and inexpensive.

The rapid intravenous infusion of large-volume (30–40 mL/kg), ice-cold (4°C) fluid may be a suitable technique for the induction of core cooling. Baumgardner et al. (129) administered a small volume (5 mL/kg) of 5% albumin (1–4°C) intravenously in neurosurgical patients. Core temperature decreased by 0.6°C following rapid (>100 mL/min) infusion, but this decrease was less (only 0.4°C) following slow intravenous infusion. Larger volumes of rapid intravenous fluid infusions for the rapid induction of moderate hypothermia also have been studied. Rajek et al. (130) infused 40 mL/kg 0.9% saline solution over 30 mins into nine anesthetized volunteers. When 4°C fluid was used, the mean decrease in core temperature was 2.5°C, which was 0.4°C more than expected if the fluid was distributed evenly. It was calculated that 30% of the fluid remained constrained to the core tissues. In another study, Frank et al. (131) examined age-related differences in core cooling by using large-volume intravenous fluid (40 mL/kg) in eight younger volunteers and eight older volunteers. The older subjects had a decreased core temperature at the end of the infusion (35.0°C compared with 35.9°C), presumably because of decreased thresholds for vasoconstriction, heat production, and catecholamine release.

We have recently reported the results of a clinical trial of the rapid infusion of large-volume (30 mL/kg), ice-cold (4°C) lactated Ringer's solution in comatose survivors of out-of-hospital cardiac arrest (132). Our study found that this approach decreased core temperature by 1.6°C over 25 mins and was associated with improvements in mean arterial pressure, renal function, and acid-base. No patient developed pulmonary edema. This technique is inexpensive, convenient, and applicable to the prehospital setting. Also, the increase in blood pressure may be of additional benefit after cardiac arrest (133).

Alternate core cooling techniques include extracorporeal and intravascular devices; however, these are more complex and their use is restricted to experienced physicians in the emergency department or ICU. In a study in eight patients with severe head injury, Piepgras et al. (134) used an extracorporeal heat exchanger for rapid core cooling. A brain temperature of 32°C was reached within a mean of 113 mins and was able to be controlled within a range of 0.1°C for 48 hrs. Although platelet count decreased at day 3, there were no bleeding complications. Other studies also have used extracorporeal techniques (44, 135–136).

Cooling catheters inserted via a central vein into the superior vena cava or femoral vein into the inferior vena cava have been introduced into clinical use, including the Set Point (Radiant Medical, CA) and the Cool Line (Alsius Corporation, CA). These catheters are similar in size to a dialysis catheter and use ice-cold fluid circulating in a closed circuit from an external refrigerator/pump. This effectively cools the blood, and preliminary experience with these catheters suggests that core temperature may be rapidly decreased and then effectively maintained at the set level. An initial trial in a neurologic ICU has confirmed that the intravascular cooling catheter is effective in the control of fever (91). Further clinical trials using these devices to induce hypothermia are currently underway (92). However, the use of these devices also would be restricted to specialized centers because of the cost.

Finally, the safety and efficacy of lung lavage by using cold oxygen-carrying fluids are currently under investigation in animal models (137, 138).

Currently, our practice in postcardiac arrest patients is to induce hypothermia immediately by using large-volume (30 mL/kg), ice-cold (4°C) crystalloid fluid (132). In patients with severe head injury and intracranial hypertension, where rapid induction of hypothermia is not essential, we use surface cooling with ice packs and neuromuscular paralysis. Once 33°C is reached, the patient will remain at this temperature with minimal additional nursing care. Since there is minimal shivering at 33°C, the judicious use of sedation rather than pharmacologic paralysis will maintain core temperature. If the temperature starts to increase (>33.5°C), we give a small dose of sedation (i.e., midazolam) and apply ice packs to the head, neck, and torso of the patient. More aggressive packing in ice is rarely required. If the temperature decreases to <32.5°C, we remove any ice packs, withhold sedation or paralyzing drugs, and apply a heated blanket.

Rewarming From IH. The optimal duration of IH after anoxic neurologic injury is unknown. We have used 12 hrs of IH in our studies (3, 42, 129), and others have used IH for a 24-hr period (4, 45); however, this does not seem to confer an additional improvement above that seen in our studies. Therefore, we currently recommend 12 hrs as a reasonable duration of IH. Should the patient awaken during hypothermia, then earlier rewarming is indicated.

The rewarming after IH must be active, using a heated air blanket and allowing the core temperature increase of 1°C/hr. During this time, shivering must be suppressed as temperature increases. Additional warmed intravenous fluid therapy may need to be given to maintain the mean arterial blood pressure, or additional neurologic injury may occur because of hypotension (139). If IH has been used for a prolonged period (>48 hrs) to control raised intracranial pressure, then slow (1–2°C/day) rewarming may be required to avoid a rebound in intracranial hypertension (52).

Core Temperature Measurement. In patients with neurologic injury, brain temperature is most accurately measured directly by using a thermocouple imbedded in a ventriculostomy catheter that is

We conclude that jugular bulb, pulmonary artery, and bladder temperatures correlate closely with brain temperature.

inserted into the brain. However, alternative techniques for the estimation of brain temperature are required in patients in whom intracranial pressure monitoring is not required or where this equipment is not available.

A number of studies have compared different sites of temperature measurement. In one study in head injured patients, Veerloy et al. (140) compared intraventricular, rectal, bladder, and jugular vein temperatures. Intracerebral temperature was directly correlated with bladder temperature but not rectal temperature.

On the other hand, Henker (141) used IH in patients with severe traumatic brain injury to compare cerebral temperature (measured by using a thermistor in a ventriculostomy catheter) with rectal temperature. In 95% of 4,000 measurements, rectal and brain temperatures did not vary by >0.5°C, and it was concluded that rectal temperature monitoring was satisfactory in this setting. Crowder et al. (142) monitored jugular venous blood temperature in ten patients undergoing neurovascular procedures, by using a 5-Fr catheter advanced to the jugular bulb. In this study, there was a temperature gradient of only 0.2°C between jugular vein, subdural, tympanic membrane, pulmonary artery, and bladder temperatures. This finding was confirmed in other studies (143, 144).

There are also small temperature gradients in the brain itself. In a human study, Mellergard (145) compared surface and deep cerebral temperatures and found that the central brain was slightly warmer than the surface temperature.

From these studies, we conclude that jugular bulb, pulmonary artery, and bladder temperatures correlate closely with brain temperature. Rectal temperature generally will approximate brain temperature but should be considered less accurate when there are rapid changes in core temperature. When it is not possible to monitor brain temperature directly, measurement of bladder temperature appears to be the most convenient estimation of core temperature in patients with neurologic injury in the ICU.

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