Hypothermia Therapy for Brain Injury

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Abstract
Induced hypothermia is an acknowledged useful therapy for treating conditions that lead to cell and tissue damage caused by ischemia, including traumatic brain injury, stroke, and cardiac arrest. An accumulating body of clinical evidence, together with several decades of research, has documented that the efficacy of hypothermia is dependent on achieving a reduced temperature in the target tissue before or soon following the ischemia-precipitating event. The temperature must be lowered to within a rather small range of values to effect therapeutic benefit without introducing collateral problems. Rewarming must be much slower than cooling. Many different methods and devices have been used for cooling, with mixed results. There are existing opportunities for bioengineers to improve our understanding of the mechanisms of hypothermia and to develop more effective methods of cooling the brain following trauma.
Hypothermia: state in which the body core temperature is reduced at least 2°C below the normothermia value (37°C)

Ischemia: restriction in blood supply, with resultant damage to the affected tissue

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1. HISTORY OF HYPOTHERMIA TREATMENT IN MEDICINE

Cooling processes have been applied in medicine since ancient Greece. Over the intervening millennia, developing an understanding of the function of the human thermoregulatory system has been a subject of great interest, and eventually attempts were made to manipulate it for therapeutic applications. During Napoleon's invasion of Russia, French surgeons noticed that the soldiers left in snow had a better survival rate that those with a warm blanket. During and following World War II, devices were developed for the explicit purpose of removing heat from the body core via surface cooling garments that were worn by airplane pilots and astronauts. The availability of cooling garments provided a method for inducing hypothermia (or avoiding hyperthermia) with a greater level of control than afforded by more passive techniques such as whole-body immersion into cold water or ice baths.

It is well documented that unconsciousness occurs within 15 s after complete occlusion of cerebral arteries and that brain tissue cannot recover fully after only 5 min of normothermic brain ischemia (1). Induced hypothermia has been studied as a means to protect the brain from ischemia...
Hypoxia: deficiency of oxygen in tissues

since the 1940s (2–10). Resuscitative cerebral hypothermia was introduced first in cardiac arrest for cerebral resuscitation in the 1950s (11). Later research focused on maximization of the ability of the brain tissue to survive anoxic no-flow states as enhanced by hypothermia. In the 1960s and 1970s, animal experiments and clinical studies showed the benefits of hypothermia in prolonging the brain time-tolerance to cardiac arrest. Hypothermia was also implemented in open-chest and open-heart surgeries, including intracranial aneurysm clipping and arteriovenous malformation resection to minimize injury to the heart and brain. Cardiopulmonary bypass was usually employed for patients undergoing neurovascular surgical procedures, to allow for a bloodless field for the surgeon and to lessen the risk of hemorrhage. Bypass in conjunction with induced hypothermia provides cardiac surgeons sufficient time for many procedures while avoiding permanent brain injury. The surgical interruption time can be sustained for more than 45 min at 10°C versus less than 8 min at 32°C (12). This application of hypothermia contributes significantly to reduced mortality associated with previously inoperable cardiac and cerebral pathology. Most of the neuroprotective effects have been more evident in animal experiments than in patients.

Because early studies commonly used deep states of hypothermia ≤30°C, it is not surprising that many years of experimentation were required to identify the therapeutic bounds for which hypothermia presents a clear efficacy. Research in hypothermia to enhance brain tissue recovery after ischemic attack became dormant in the 1970s and the 1980s owing to thermal management difficulties and uncertainty of benefits as well as detrimental systemic complications associated with deep hypothermia. The idea of mild hypothermia has been re-investigated by researchers since 1987 owing to encouraging animal experiments on canine, swine, and rodent models. Because of the ability to better control the state of hypothermia in animals, extensive experimentation on such models has been conducted to evaluate effects of cooling methods, temperature depression, hypothermia duration, cooling initiation relative to the ischemic event, and rewarming rate on the brain recovery from ischemia. There is a large amount of experimental evidence of hypothermia-induced neuroprotection from ischemia injury in laboratory animals. The neuroprotective mechanisms of hyperthermia have become increasingly better understood in the past two decades. Supporting data in human subjects are still limited, especially for randomized multicenter clinical trials (13). In clinical studies, hypothermia therapy seems more successful in open-heart and neck surgery than in traumatic head injury. This is not unexpected, because initiating cooling before ischemia attack has been demonstrated to maximize the benefits conferred by hypothermia, although delay in initiation by 2 h or more has also shown limited benefits in both animal models and clinical studies. These foregoing studies in brain hypothermia have set the stage for future investigations to develop more effective and well-controlled approaches for treating brain ischemia. It is anticipated that hypothermia will be proven as an effective method to limit and eliminate injury and death associated with brain ischemia, to the benefit of a large patient population.

2. BIOLOGICAL AND CHEMICAL REACTIONS TO INJURY IN THE HUMAN BRAIN

Brain ischemia can be the result of ischemic stroke, cardiovascular and respiratory disorders, and external physical trauma. If the initial damage is limited, the brain may be able to recover. If the injury is extensive, secondary brain damage occurs, including intracranial hypertension (brain swelling), hemorrhage, hypoxia, and edema. It is well known that brain oxygen stores become exhausted within 15 s and brain energy stores become exhausted within 5 min after global ischemia (1). Energy loss results in depolarization of cell membranes. A series of biochemical reactions and cascades initiated by the trauma will then follow. Those cascade events evolve gradually and may last.
Reperfusion: reestablishing of blood flow in a vascular bed following a period of ischemia

TBI: traumatic brain injury

several days after the initial trauma. Increase in extracellular $K^+$, energy depletion, disruption of the blood-brain barrier, free radical release, excitotoxicity, and inflammation are typical consequences of those cascade events. Loss of selective neurons following global or local brain ischemia may lead to permanent neurologic deficit and even death.

3. NEUROPROTECTIVE MECHANISMS ASSOCIATED WITH BRAIN HYPOTHERMIA

It has been suggested that hypothermia may modify a wide range of cell necrosis mechanisms. Early studies have attributed the protective effects of hypothermia to reducing the energy expenditures of cerebral metabolic rates of glucose and oxygen. Brain oxygen consumption can decrease by approximately 5–7% for every degree Celsius decrease in tissue temperature. However, the improved outcomes associated with mild hypothermia suggest that it may play a role in deterring deleterious biochemical actions following brain injury (14–16). Hypothermia retards progression of the ischemia cascade and pathologic neuroexcitation. The major mechanisms of neuroprotection by hypothermia are attenuation in the opening of the blood-brain barrier, reduction of glutamate release, alleviation of inflammation, and slowing of free radical generation and release. It may impair glutamate-mediated calcium influx or directly inhibit calcium-mediated effects on calcium/calmodulin kinase. As a result, hypothermia preserves high-energy phosphates that may facilitate the maintenance of membrane integrity during ischemia, limit edema formation, lower intracranial pressure, and interrupt necrosis and apoptosis (17). All of the mechanisms lead to long neuronal survival and improve outcomes after reperfusion.

4. APPLICATIONS WITH IMPROVED CLINICAL OUTCOMES BY BRAIN HYPOTHERMIA

4.1. Traumatic Brain Injury

Traumatic brain injury (TBI) is a nondegenerative, noncongenital insult to the brain tissue due to externally inflicted trauma (18). The major consequences of head injury include skull fractures, intracranial hemorrhages, elevated intracranial pressure, and cerebral contusion. Unlike stroke, which is often associated with senior citizens, TBI affects a predominantly young population.

Neuroprotective outcomes in clinical trials that treated head injury using hypothermia are not consistent. There is marked heterogeneity among available clinical studies. In 1994, a multicenter, randomized, prospective phase III study of systemic hypothermia in severe brain injury, involving seven medical centers in the United States (13), was initiated based on the promise of decades of somewhat sporadic experiments and anecdotal positive clinical outcomes for hypothermia used to treat TBI in addition to an extensive phase II clinical trial (19). This study enrolled 392 patients, ages 16–65, who suffered coma from brain injury in the absence of other major traumas. A control group received standard management with a nominal core temperature of 37°C. The treatment group received the same management protocol at a target temperature of 33°C. There was a large variation in the cooling induction time due to many individual circumstances. The cooling process began at 4.1 ± 1.2 h post injury via surface cooling technology, with completion by 8.3 ± 3.0 h. Hypothermia was maintained for 48 h, following which slow rewarming was distributed over 18 h. Some of the patients were already hypothermic ($\leq 35°C$) owing to independent circumstances on admission to the hospital and were retained in a treatment subgroup. Overall, a very minimal difference was observed between the treatment and control groups (13), with the exception of the subgroup, already hypothermic at admission, which had significantly better outcomes (20).
Although the results of this study were discouraging, they led directly to an enhanced appreciation for the need to achieve a hypothermic state quickly following a TBI for the therapy to be effective (21, 22). Thus, the stage was set for current developments in the application of hypothermia for TBI.

Several clinical studies (23–25) tested hypothermia therapy in patients with severe head injury and achieved improved outcomes compared with normothermia groups. Hypothermia benefits were evident in patients with a coma score of 5–6 at months 3 and 6 (23). It is reported that more than 62% of patients achieved good outcome in the hypothermia group versus 39% in the control group. Jiang et al. (26) evaluated the long-term benefits of hypothermia in patients with severe traumatic head injury. It was found that mortality decreased by 40%, and the rate of favorable outcome increased by 70% in the hypothermia group one year after the head injury. One of the common benefits identified in the above studies was a marked reduction of the intracranial pressure in the hypothermia group after days of treatment. It was recommended that cooling should be maintained at least until after the intracranial pressure returns to the normal range (25, 26). Some researchers (27) attributed the failure of demonstration of benefits by hypothermia to the delay of cooling initiation, which is often more than 4 h after the injury in clinical treatments (13). A more recent paper (28), which showed that more than 87% of patients have achieved good neurological outcome in the hypothermia group, suggested certain methodological discrepancies in the Clifton study. The latest clinical trial of hypothermia on traumatic head injury (29) showed improved extradural pressure and reduced mortality from 51% in the control group (43 patients) to 26% in the hypothermia group (also 43 patients). Another clinical study by the same group (30) documented improved neurological outcome in TBI patients two years after the hypothermia treatment, with complications that were manageable. A recent review by Peterson et al. (31) of hypothermia-related neuroprotection on TBI patients identifies a cooling duration longer than 48 h as a favorable factor; however, it cautions the risk of pneumonia. Based on the review, the strong evidence of the long-term (more than one year) benefits of hypothermia suggests following up with patients for one to two years in future hypothermia studies for TBI patients (31). Overall, there is a lack of well-controlled, large clinical trials that provide convincing evidence of the benefits and safety of brain hypothermia for traumatic head injury patients. In the third edition of the Guidelines for the Management of Severe Traumatic Brain Injury, issued by the Brain Trauma Foundation in 2007, it is stated that mild hypothermia should be exercised with caution for patients with TBI (32).

4.2. Brain Ischemic Injury from Stroke

The 2005 Guidelines on Acute Stroke Treatment by the American Stroke Association identify hypothermia after stroke as a promising field of research. A recent review by van der Worp et al. (33) concludes that hypothermia improved outcomes of animals suffering from ischemic stroke by more than 30%. This result is especially true in well-controlled animal stroke models (34). It is relatively easier to have reproducible models of transient global brain ischemia via occlusion of the distal middle cerebral and ipsilateral common carotid arteries than of focal brain ischemia, for which it is more difficult to define experimental conditions. Computerized images of cerebral infarct volume and edema are commonly used to evaluate ischemic damage to the brain tissue. If the animals are kept alive after the injury, cognitive evaluation is conducted to assess the long-term protective outcome of cooling. The efficacy of hypothermia is better with lower target temperature (35) and/or when initiated before or during the onset of ischemia. A study by Kurasako et al. (36) on a spontaneously hypertensive rat model demonstrated a strong, linear temperature-dependent reduction in infarct volume and edema progression in transient focal
ischemia. Neuroprotection by hypothermia is more prominent in lower-temperature (28°C and 30°C) groups. More improvements are found in temporary than in permanent ischemic models (35, 37).

There are limited clinical trials to test the efficacy and safety of various hypothermia approaches for acute ischemic stroke patients. Clinical studies by Schwab et al. (38–40) showed that more than half of the patients survived severe stroke after up to 72 h of moderate hypothermia at 33°C. Most of the 38% mortality rate of the stroke patients occurred during the rewarming process, which suggests the important role played by gradual rewarming after hypothermia. Although the clinical studies were not conducted using a control group, the observed 38% mortality rate is much lower than a typical death rate of 70% in severe stroke patients (41, 42). A small clinical trial by Kammersgaard et al. (43) that used mild hypothermia (35°C) in 17 patients also showed marked improvement of mortality rate, from 23% in controls to 12%. Unlike the Schwab studies associated with many serious systemic complications, including thrombocytopenia, bradycardia, and pneumonia, the only reported side effect in the Kammersgaard trial was shivering, which was treated by pethidine. Kasner et al. (44) conducted a clinical trial with mild hypothermia induced by acetaminophen administration in an attempt to achieve brain cooling rapidly. The results were inconclusive because acetaminophen produced only a very mild state of hypothermia, <36.5°C, bringing question to its clinical efficacy. A randomized trial of hypothermia in infants with hypoxic-ischemic encephalopathy showed reduced risk of death or disability (45); however, neuroprotection from hypothermia was not obvious in another two clinical studies (46, 47), although the results favored hypothermia.

4.3. Brain Ischemic Injury during Surgery

Cardiopulmonary bypass–related brain injury is a common postsurgical observation. A multicenter study by Roach et al. (48) demonstrated that more than 6% of patients suffered adverse neurological outcomes after coronary artery bypass grafting. Neuropsychological deficits (cognitive changes) were reported in more than 20% of patients eight weeks after bypass surgery (49). It is believed that neurological dysfunction results from regional or global brain ischemia as a consequence of hypoperfusion. Early experimental studies on animals suggested that brain tissue remained partially ischemic after resuscitation from circulatory arrest, and delayed ischemia was observed during the following hours. In both intracardiac and extracardiac surgeries, formation of emboli is the major factor contributing to most neurological complications (50). Animal and clinical studies showed that some patients developed severe neurological deficits after surgeries involving unilateral common carotid occlusion (51). The deficits were attributed to lack of posterior communicating arteries following carotid occlusion.

The main effects of brain hypothermia include decrease in intracranial pressures and cerebral edema, reduction of tissue oxygen demands, and amelioration of numerous deleterious cellular biochemical mechanisms, including calcium shift, excitotoxicity, lipid peroxidation and other free radical reactions, DNA damage, and inflammation (52). Hypothermia during experimental cerebral ischemia provides potent, dose-related and long-lasting neuroprotection (53, 54). Conversely, an elevated brain temperature of only 1–2°C strikingly worsens experimental neuronal injury and clinical outcome (55). Experimental studies have shown that brain hypothermia enhances the brain’s tolerance to ischemia and thereby improves neurological outcomes. Therapeutic mild hypothermia was implemented as a standard therapy in the international resuscitation guidelines. Several animal studies (56–58) have been performed to assess neuro-deficit score in dogs after bypass surgery. Profound brain hypothermia improved significantly the neuro-deficit score of the control group (48.3) to 19.2 in the cooling group (0 = normal and 100 = brain dead). Improved
neurological outcome was shown in a dog model of cardiac arrest (59). In a study by Moyer et al. (60), spontaneous cerebral hypothermia of 33°C decreased focal infarction volume in a rat brain by 75%. Mild brain hypothermia was reported to minimize cerebral impairment in 1500 patients undergoing pulmonary endarterectomy (61). The protective effect of hypothermia was also evident in patients undergoing carotid endarterectomy (62), wherein there were no early postoperative strokes or reversible ischemic neurological deficits following the surgery. Two randomized clinical trials in large groups of patients with global cerebral ischemia after cardiac arrest reported that the number of patients with good outcome increased at least 40% in the hypothermic group, although the mortality rate was similar in both groups (63, 64). Recently, an FDA-approved cooling system (ChillerPadTM and ChillerStripTM System, Seacoast Technologies, Inc., Portsmouth, NH) was employed in a clinical trial of aneurysm repair, and hypothermia markedly reduced vasogenic edema and protected the blood-brain barrier (65). However, this technology only superficially cools the surface of the skull and does not provide deep brain cooling.

4.4. Multiple Sclerosis

Multiple sclerosis (MS) is a neurological disease associated with the destruction or loss of myelin surrounding nerves. The major symptoms experienced by MS patients include spasticity, fatigue, dizziness, loss of visual acuity, tremor, pain, and cognitive disability. The symptoms tend to get worse when the body temperature is even slightly elevated. Early experiments using in vitro preparations of demyelinated nerves (66, 67) demonstrated that a small increase in temperature shortened the duration of the action potential, and the available current was insufficient to excite the Ranvier node connecting myelin sheath cells. Since demyelination may lead to conduction block, disuse, and finally cell death, an increase in neuronal activity by decreasing nerve temperature can, in theory, prolong the action potential duration and induce sufficient current to depolarize the Ranvier node. Studies have shown that the restored neuronal activities may lead to proliferation, migration, and maturation of myelin-producing cells (68, 69). Therefore, cooling has the potential to slow the progression of multiple sclerosis by fostering remyelination and protecting the axon from degeneration.

There are several types of body cooling garments, based on heat removal from the surface via evaporation, ice pack, or refrigeration, that are available to this patient population. Most MS patients using a lightweight cooling vest found that the symptoms were alleviated (70). A cold bath or swimming also provides better management of heat-related symptoms. In a controlled experiment, improvements in acuity, timed walk and muscle strength, and reduction in cytokine production were demonstrated in a cooling group when compared with controls (71). Localized cooling on the wrist and forearm while keeping the heart rate and body core temperature unchanged illustrated a clear reduction of overall tremor amplitude and frequency during a step-tracking task in MS patients (72). Aerobic exercise is usually recommended to mild-to-modest MS patients because it provides fitness and psychological benefits similar to those in a healthy subject, including increased strength and endurance, reduced depression, increased positive moods, and improved cardiovascular fitness (73–78). However, exercise will lead to a rapid increase in body temperature, which compromises the patients’ ability to function. The detrimental effects of body temperature increase can be offset by cooling before or during exercise. A new device that enables highly effective heat removal from the body core reduces exercise-related heat stress and thereby increases the physical performance capacity of heat-sensitive individuals with MS (79). As a consequence, cooling may help MS patients gain greater independence and may improve their quality of life.
4.5. Heat Stroke

Heat exhaustion and heat stroke are the most common heat-related diseases involving dysfunction and/or failure of temperature control in the human body. They usually occur when the body is subjected to elevated ambient temperature and during strenuous exercise. When body hyperthermia lasts for a prolonged period of time, neurological abnormalities such as hallucinations, seizures, and coma can occur, with the further effects of organ failure, permanent brain damage, and death. More than 300 heat stroke-related deaths are reported in the United States annually. Heat stroke resulted in more than 14,000 deaths in France during the 2003 summer heat wave (80).

The primary treatments of heat stroke include immediate cooling and support of organ-system dysfunction (81). There are several approaches for rapidly cooling the body after the onset of heat stroke. The first steps are always moving the patient to a cool place away from environmental heat sources and removing excess clothing. Internal cooling approaches include water irrigation lavage or an intravascular catheter. External cooling can be produced with convection or conduction sources applied to the skin surface. Internal methods are obviously more invasive than external methods, are usually associated with collateral risks, and may cause water intoxication in patients with compromised health. Some external methods aim to promote evaporative cooling on the skin surface via spraying tepid water and/or using fans to increase air circulation (82–86). Unfortunately, these methods tend to be counterproductive because they promote vasoconstriction, which increases the thermal resistance between the body core and the skin surface, where heat can be rejected to the environment. The median time for evaporative cooling to achieve a target rectal temperature of 38°C varies widely with the presenting state of hyperthermia and is often well over an hour. This method has limited efficacy if the humidity of the surrounding environment is near saturation. Other external cooling techniques are accomplished by increasing the temperature gradient through the tissue. Practical approaches include immersion in cold water (82, 87, 88) and surface application of a cooling blanket (87, 89) or ice packs (90). Immersing patients in iced water is messy and poorly tolerated, and it does not allow attachment of some types of monitoring equipment. The challenge in implementing the conduction method is to prevent the skin temperature from falling below 30°C to trigger shivering. Numerous studies have demonstrated the detrimental effects of vasoconstriction and shivering on patients. Vasoconstriction results in decreased cutaneous blood perfusion, which impedes convective heat transfer from the body core to the skin and therefore, compromises the body’s ability to lose heat fast. The application of cooling to the surface of glabrous skin in which the arteriovenous anastomoses are distended and flowing enables blood circulation to the body core to provide an effective convective pathway for rejection of core heat in thermally stressed individuals (91).

5. FACTORS AFFECTING THE PROTECTIVE OUTCOMES ASSOCIATED WITH BRAIN HYPOTHERMIA

5.1. Time of Cooling Initiation

Numerous controlled animal experiments have demonstrated the benefit of initiation of cooling before the brain injury to confer significant neuroprotective outcomes. Of course, precooling is an option only for circumstances under which the onset of brain ischemia is foreseen. Precooling is a clinical option for open-heart and neck surgery. Experimental data from a rat model demonstrated the greatest benefits of neuroprotection when hypothermia was induced during global ischemia (92). Initiation of hypothermia before the injury completely prevented secondary brain damage in gerbils (93).
For all the other clinical applications involving human subjects, precooling is not usually possible. The general consensus is to initiate brain hypothermia as early as possible following an ischemia-precipitating event, although some studies have shown neuroprotective effects even when the treatment was delayed by up to 6 h (94). Brain injury mechanisms typically progress rapidly within 3–6 h after the initial injury. Hypothermia can reduce the initial inflammatory response after head trauma so as to minimize or prevent secondary brain injury. It is well accepted that there is a 1–2 h treatment window for animal models, after which the benefits of hypothermia are strongly diminished. However, it is difficult to correlate rodent data directly to humans. On the basis of the present data, it may be concluded that the treatment window is probably very brief for postischemic hypothermia to be effective in humans. A randomized and controlled experimental study in a rat model by Markgraf et al. (95) showed significant reduction of neurological deficits if the cooling is initiated within 60 min rather than 90 min after the injury. A recent clinical study (96) demonstrated a reduction of hypoxic brain injury and improvement of neurological outcome after cardiac arrest if mild hypothermia is initiated within the 90 min treatment window. However, experimental data also imply that delayed cooling can provide neuroprotection if the cooling period is long with gradual rewarming (97, 98).

The inconsistency in patient outcome in various clinical studies, particularly involving head trauma, might be due to the delay of hypothermia initiation and possible other uncontrolled factors. A paper by Clifton et al. (13) has been cited widely in the hypothermia community as evidence of ineffectiveness of hypothermia therapy for head trauma. However, as pointed out by Safar & Kochanek (27), the negative results for clinical trials on head-injured patients may be due to the delay in initiating cooling for up to 8 h after the injury in most patients studied. Clifton subsequently noted that the apparent window of opportunity for gaining the benefit of hypothermia extends to only 90 min post trauma (21), and he is currently conducting a large clinical trial to measure the effect. It is still a challenge to shorten the time between the injury and induction of hypothermia. Usually, the process of transporting the patients to the hospital is unproductive for this objective. A portable sensor attached to the patient to alert the medical center of the impending case can minimize delay of treatment. Further, simple cooling approaches that can be implemented by the Emergency Medical Service (EMS) personnel in the ambulance have been suggested.

### 5.2. Cooling Extent

Because tissue temperature has profound effects on local metabolism and cellular activities, it is expected that different depths of hypothermia have varying effects on the clinical outcome of minimizing secondary brain injury. Brain hypothermia can be categorized as deep/severe (<28°C), moderate (28–32°C), and mild (32–35°C) (99). The traditional view that colder is better (100) has been questioned in the past decade (101). As brain temperature is decreased, greater systemic toxicity is observed, and the adverse effects outweigh the neuroprotection mechanisms associated with therapeutic hypothermia (102). Deep hypothermia is associated with arrhythmias (103), cardiac complications (104), coagulopathies (105), and pulmonary infections (106). In addition, severe or moderate cooling usually requires sedation and mechanical ventilation. Therefore, deep cooling approaches are limited to facilities that have intensive care units and that medically justify the collateral complications. Many animal studies suggest that the preferred cooling temperature for neuroprotection is between 32 and 35°C (94, 107). Many studies have shown improved neurological outcome using mild hypothermia, compared with either the deep cooling group or the normothermia group. Typically, these studies use whole-body cooling. One may conjecture whether the associated systemic complications of hypothermia can be avoided if only the brain
tissue is cooled and the rest of the body kept normothermic. In addition, when whole-body cooling is implemented, the brain can be assumed to be isothermal due to its high blood-perfusion rate. Under these circumstances, there is minimal differential between the body core temperature and the brain temperature, but large temperature variations may be created within the brain tissue if cooling is applied to the head surface. Temperature gradients in the brain make control of the hypothermia state in a target tissue region a difficult task. More studies are needed to understand the tolerance of brain tissue to local cooling.

5.3. Cooling Duration

Secondary effects of brain injury, including edema and elevated pressure, are known to persist several days after focal cerebral ischemia (108). Therefore, prolonging brain hypothermia therapy for an equivalent period may benefit those patients. Cooling for less than 1 h provided no neuroprotection in a rat model (92). Short periods of cooling may lead to transient rather than permanent neuroprotection. Experimental studies have tested whether a long cooling duration is safe for patients. Initially, 24 h were proposed, and later, the cooling duration was extended by Bernard & Rosaljon (134), Clifton et al. (19), McIntyre et al. (18), and Shiozaki et al. (25) to 48 h. A recent review by Peterson et al. (31) documents profound neuroprotective benefits observed in patients with more than 48 h of hypothermia. Iwata et al. (109) note that the cooling extent and cooling duration may not be two independent factors in determining patient outcomes. Although prolonged cooling may maximize clinical neurological benefits, it may also increase systemic complications associated with cooling, especially in patients having compromised health. The optimal duration of treatment remains unknown for clinical application, especially when other confounding factors are involved. Closely monitoring patients during hypothermia therapy should be an important planning consideration.

5.4. Rewarming Rate

The importance of controlling the rewarming rate in the brain tissue from a state of hypothermia has been widely documented. Rapid rewarming may result in a dangerous rebound of intracranial pressure elevation and cerebral perfusion pressure reduction; the importance of gradual rewarming has been emphasized in multiple clinical studies (25). Previous theoretical analysis (110) of simulated passive (and uncontrolled) rewarming by removing the cooling device yields an average calculated rate of approximately \(3^\circ\text{C} \cdot \text{h}^{-1}\). Recent animal experiments on rats (111) suggest that the fast rewarming rate might result in a mismatch between the local blood perfusion and metabolism. As suggested by Thoresen & Wyatt (112), the rewarming rate in tissue should be conducted slowly at \(0.5^\circ\text{C} \cdot \text{h}^{-1}\). In some clinical trials, rewarming from hypothermia is conducted with a feedback control system over 18 h. It is critical to develop a thermoregulating system that allows not only fast cooling but also an adjustable rewarming rate.

6. CURRENTLY USED BRAIN HYPOTHERMIA APPROACHES

6.1. Overview

The ability to cool deeply embedded interior tissue such as the brain is limited by considerations of the second law of thermodynamics. Unlike the heating process, which can be dissipative, cooling requires that a negative temperature gradient be applied across the interstitial transport medium. If conduction is used to effect the heat transfer process, the magnitude of cooling that can be produced is directly proportional to the gradient that can be established across the medium and
the thermal conductivity of the medium. Alternatively, convective blood flow can be used as the primary mechanism to remove heat from the body core and redistribute it to the surface area. This mechanism is dependent on the level of blood perfusion through the cutaneous circulation in conjunction with conduction through the skin and cooling on the surface. A different option for cooling by convection is to introduce a chilled perfusate solution directly into the circulatory system, although this approach is highly invasive and has inherent risks. Both approaches have been adopted for inducing brain hypothermia, although heat removal by conduction through the overlying tissue, including the skull, is of limited efficacy owing to the poor thermal conductivity of bone.

6.2. Whole-Body versus Selective Brain Cooling

Most of the clinical studies to date have examined only systemic (whole-body) hypothermia. Either the whole body mass or the cardiac output is cooled using this approach. The major methodological drawback of this approach is the inherently slow cooling rate (~0.5 °C h⁻¹) due to the large volume of the human body to be cooled and the increase in thermal resistance due to arteriovenous shunt vasoconstriction (23, 39, 47). When extracorporeal blood cooling is applied, the cooling rate can be greatly improved; however, the procedures are highly invasive and require extensive supporting equipment. With either approach, the major concern relating to whole-body cooling is that it may produce deleterious systemic effects such as metabolic, cardiovascular, pulmonary, coagulation, and immunologic complications (23, 113). The increased risk of systemic complications when using whole-body hypothermia may outweigh the neuroprotective benefits of such therapy. Further, because of the long characteristic time of the human body, whole-body hypothermia may easily miss the treatment window when hypothermic protection of the brain can be maximized.

Cooling the entire body to achieve a temperature reduction in the brain may not be necessary because the human brain represents only 2% of body mass, and it receives 20% of resting cardiac output. Thus, blood circulating to the brain could be an effective transport medium if there were a method by which it could be cooled. Accordingly, in recent years, selective brain cooling (SBC), in which the brain temperature is reduced while the rest of the body is kept normothermic, has been proposed. A selective brain cooling technique would minimize serious adverse systemic complications (114) and maximize the protective benefits of hypothermia if it is initiated before or during the ischemic event. In this approach, the brain tissue is cooled directly or the blood supplied to the brain is cooled. The small mass of the head makes the cooling relatively fast compared with whole-body cooling. The common carotid and vertebrate arteries are the major blood vessels supplying blood to the brain and are somewhat accessible to cooling from the overlying skin surface. Arterial blood temperature can be reduced via intravascular cooling, for which commercial devices are available, or through skin surface cooling, if an imposed temperature gradient can adequately penetrate the tissue and reach the blood vessels. Conducting heat from the brain through the skull results in an unacceptably long process for inducing hypothermia.

6.3. Whole-Body Hypothermia

6.3.1. Skin surface cooling. Skin surface cooling is the most studied method in hypothermia. This approach can promote heat transfer by evaporation from the skin and by imposing a temperature gradient from the body core to the skin. Various methods have been used to cool the skin, including convective air circulation, cooling blankets/jackets, water mattresses, ice packs, and alcohol or ice water bathing. Surface cooling is an easy approach and does not require sophisticated equipment. A clinical study by Mayer et al. (115) compared two surface cooling systems (Subzero
and Arctic Sun) in controlling fever in neuro-critical-care patients and found positive outcomes in reducing fever burden in both systems. Arctic Sun–treated patients spent less time febrile, and the cooling rate to achieve normothermia was faster than in the Subzero group. The side effects included shivering, which occurred more often in the Arctic Sun group. To control shivering, another clinical study gave a stroke patient pethidine while implementing a cooling blanket with a flow of cool air at 10°C (43). Hypothermia reduced mortality at 6 months after stroke by 50% from the control group. However, neurological impairment was only slightly improved and was not significantly different from the controls. Inducing mild whole-body hypothermia for 34 h in head trauma patients with a coma score of 5–7 greatly improved the patients’ outcome (62% in the hypothermia group versus 38% in the control group) in a randomized, controlled clinical trial on 87 severe head injury patients (23). A pilot study by Eicher et al. (116) on moderate whole-body hypothermia (33°C) versus normothermia in excephalopathic neonates demonstrated favorable neurological outcomes.

In addition to introducing vasoconstriction and shivering, there are other drawbacks. Full body immersion makes it difficult to attach monitoring sensors to patients, and fast reduction of temperature is prevented by large body mass, thus elongating the time it takes to achieve the target temperature (117). Also, vasoconstriction induced by skin surface cooling greatly increases the thermal resistance of the skin, further hindering heat transfer from the body core to the surface. It is reported that 3.5–11 h are needed to reach 33°C using a cooling blanket (118). In the Copenhagen Stroke Study (43), it took more than 5 h to decrease the body temperature by 2°C; however, surface cooling may be more appropriate for children because they inherently have a smaller thermal mass than adults. Less than 1.5 h were required to achieve a body temperature of 33.5°C in newborn infants using a blanket precooled to 5°C (45).

6.3.2. Blood cooling

6.3.2.1. Intravascular cooling catheter. Veno-venous extracorporeal blood cooling was proposed as a method to induce a fast cooling rate (119–125). This is a very attractive technique because it bypasses the thermal resistance of tissue and connects directly to the cardiac output. This method uses a covered cooling catheter that is inserted into the femoral vein and advanced to the inferior vena cava via abdominal X-ray guidance. The catheter is coated with antithrombotic coverings to prevent clotting. Coolant is pumped to the catheter to achieve a fast heat removal from the venous blood, with a cooling capacity of up to 150 W. In well-controlled studies using large and small animal models, the targeted brain temperature of 33°C was reached within a reasonable time frame after cooling initiation. The reported clinical trials have shown cooling rates varying between 0.9 and 6.9°C h⁻¹, with hypothermia well tolerated by the patients. Some of the typical complications associated with body surface cooling, such as infections, coagulopathy, and cerebral edema, were not observed in animal experiments using the cooling catheter (125). In addition, by keeping the skin warm, shivering did not occur, because shivering is, in part, driven through skin receptors. However, the surgical procedure involved is invasive, and vessel access time varies greatly with the skill of the surgeon. Therefore, its clinical use has been limited to special hospitals, and it is not a technology available to personnel with limited training and resources (122).

There is no dispute that the cooling catheter is capable of reaching a targeted brain hypothermia state within a short time owing to its powerful cooling capacity (126–128). In well-controlled animal experiments, the neuroprotective effects induced by the cooling catheter were all positive. One clinical study (46) showed slight decrease in lesion size measured by diffusion weighted imaging (DWI); however, the decrease was not significantly different from that in the control group. Conflicting reports concerning the effect on brain function suggest that other uncontrolled
factors may play a role. For example, in most clinical studies, the cooling was usually not initiated until several hours following the injury. The delays in cooling may diminish or even abrogate the beneficial effects of hypothermia. This approach was also implemented to reduce the size of myocardial infarct in a pig model weighing from 60 to 80 kg (119, 129). Only 9% of the left ventricular myocardial area is at risk of infarct with hypothermia compared with the normothermia group (45%). Similar to other clinical trials for cardiac arrest, a recent clinical trial (126) found short-term favorable neuroprotection in the hypothermia group using an endovascular cooling approach. A fast cooling rate (1.2°C h⁻¹), long cooling duration (24 h), and gradual and well-controlled rewarming rate (0.5°C h⁻¹) may be contributing factors that improved the survival rate with favorable neurological outcomes and reduced patient mortality (127). Additional well-controlled and randomized clinical studies are still needed to demonstrate the safety and long-term efficacy of endovascular cooling.

6.3.2.2. Intravenous flushing. Chilled normal saline has been suggested as a preferred resuscitation fluid for patients with neurological and neurosurgical injuries. It is inexpensive, easy to store, and frequently utilized as hydration fluid in hospitalized patients. This method of inducing hypothermia was tested in a swine model (129). For an extremely high intravenous infusion rate of 120 ml min⁻¹, a core cooling rate was measured at up to 18°C h⁻¹. In a clinical study (130), ringer’s solution was infused at a rate of 100 ml min⁻¹ to patients after resuscitation from nontraumatic cardiac arrest, and no serious adverse hemodynamic complications occurred. This approach is certainly very effective in achieving fast cooling. However, it is questionable whether the patients can tolerate such a large infusion rate. A theoretical analysis (131) was performed recently to simulate the reduction of body temperature using this approach. Unlike the animal study during which the flow rate was very high, the simulation focused on a realistic and safe upper limit of the infusion rate of either cold saline or 50% ice slurry saline mixture. The model identified a cooling rate of 0.48 and 0.24°C h⁻¹ using 50% ice slurry and chilled saline, respectively, at 450 ml h⁻¹.

The use of cooled peripheral infusion is safe and likely without significant side effects if the patients can tolerate the additional fluid. Inducing mild hypothermia in awake stroke patients using cooled intravenous fluid seems unlikely to cause discomfort. 30 ml kg⁻¹ of Ringer’s solution was infused at a rate of 100 ml min⁻¹ into the antecubital vein in a clinical study by Badjatia et al. (132), which was successful in controlling fever in patients within 2 h. Within approximately 3 h, it was possible to cool the body temperature from 36 to 34°C using two liters of cold saline at 4°C (133). The observed cooling rate is similar to that predicted by the theoretical model (131). In a recent case report by Bernard & Rosaljon (134), a large volume of chilled saline at 4°C was injected intravenously during cardiopulmonary resuscitation, and the patient made a satisfactory recovery. Lopez et al. (135) infused four to six liters of 3°C lactate ringer at ~0.1 ml kg⁻¹ min⁻¹ into healthy, awake volunteers to demonstrate the lack of side effects. Shivering, which was observed in controls between 35.6 and 36.8°C, was avoided, as the subjects’ skin temperature was maintained above 36.7°C (135). Infusing healthy, awake volunteers with 4°C intravenous fluids at 40 ml kg⁻¹ h⁻¹, Frank et al. (136) demonstrated that the first signs of thermal discomfort occurred only when the body temperature reached 36°C. Because of a lower shivering threshold, elderly may be susceptible to infusions of coolants when compared with the younger population. No cardiac abnormalities were observed during or after the cold fluid infusions (137). Based on mathematical modeling, peripheral infusions of saline in chilled or ice slurry form can be used as an adjuvant therapy to achieve mild hypothermia or to control fever. Intravenous coolants administered in an on-demand, temperature-guided, and supervised setting seem a reasonable...
approach for core cooling to avoid potentially unsafe use of extended fluid volumes and infusion time periods.

6.4. Selective Brain Cooling

6.4.1. Head surface cooling. Head surface cooling via a helmet or an ice pack is practicable and easy to apply, even in the prehospital setting. Saline perfusion to the subdural space has also been suggested to cool the brain (138). Previous studies have indicated that it takes less than 1 h to establish a steady-state temperature field after head surface cooling. This gives EMT personnel an advantage when cooling is initiated in the field to maximize neuroprotection of hypothermia treatment. One clinical study evaluated the performance of a cooling helmet based on a NASA spin-off technology (114). In the hypothermia group of eight enrolled patients, brain temperature dropped more than 1.8°C within 1 h of the helmet application. Systemic cooling occurred only after a prolonged cooling of more than 6 h. Minimal systemic complication was observed using the helmet cooling. The clinical study (114) demonstrated that head surface cooling using a helmet is a relatively effective way to induce and maintain brain hypothermia while keeping the rest of body at normothermia.

An ice pack can more efficiently cool the brain tissue than a cooling helmet with the same coolant temperature of 0°C. Recent theoretical modeling showed the effects of a large thermal resistance between the coolant and scalp. Experiments on MS patients (139) and theoretical simulations (110) showed that the head skin temperature is approximately 20°C using a cooling helmet with 0°C coolant circulating inside. Improving the thermal contact between the coolant and scalp would, in theory, shorten the time required to achieve targeted cerebral hypothermia and improve cooling penetration to the deep brain tissue. In the experiment performed in a cat model, 20°C cold saline was induced to the subdural space of the cerebral hemisphere by a catheter inserted into a parietal burr hole (138). The temperature was well tolerated by the subjects and effective in lowering the brain temperature. It showed that hypothermia has enhanced the recovery of somatosensory evoked potential in the animal model after 1 h of transient middle cerebral artery occlusion (138). A similar design of a cooling chamber was used to induce brain hypothermia by placing it on the cerebral cortex of the anterolateral temporal lobe of 18 patients (140). Chilled saline was infused to the chamber. Temperatures lower than 25°C were established in the cortex 6 mm below the surface of the cooling chamber. The changes in spontaneous and stimulus-evoked electroencephalogram (EEG) activity were due to local cooling. This approach is considered safe because no adverse effects were observed, although more rigorous clinical study is needed to evaluate the risks and benefits of this hypothermia technique on patient neurological outcomes.

Head surface cooling relies on heat conduction from the scalp to the inner region of the brain hemisphere. Thus, because of the imposed radial temperature gradient, head surface cooling provides more preferential cooling of the superficial areas of the brain than the deep regions. This method of hypothermia induction can involve an interplay of conduction and convection effects. Large temperature gradients occur in the brain tissue, and temperature variation depends strongly on the local blood perfusion rate. A temperature variation of more than 7°C across the brain has been reported (141). Theoretical simulations of temperature fields of head structures during head surface cooling demonstrated similar trends as observed in the animal experiments. Cooling from the head surface has to overcome the thermal barrier of the scalp and skull as well as the large blood perfusion rate in the brain tissue (110, 142). Significant cooling of the white matter is not feasible unless the brain tissue is ischemic.

The beneficial effects of selective brain cooling using a cooling helmet are more evident in infants owing to their smaller head size. A cooling cap filled with −30°C solution was introduced
to infant piglets after cardiac arrest and resuscitation (143). Brain temperature was reduced from 37°C to 31°C within 1 h. Although the temperature of the coolant in the cap was below 0°C, no necrosis was observed. This implies that there was no freezing damage to the skin surface owing to the thermal barrier of the cap material and the air gap between the cap and the skin. A recent clinical trial on infants with moderate to severe neonatal encephalopathy demonstrated favorable neuro-developmental outcomes in infants with less severe amplitude-integrated electroencephalogram (aEEG) changes after 72 h of selective head cooling using a cooling cap (144). Experimental measurements of brain temperatures on newborn swine showed temperature reductions at all brain sites (141).

6.4.2. Neck collar. Unlike head surface cooling, chilled neck collars aim to cool the arterial blood that supplies the brain tissue. There are several prototypes on the market. The feasibility of this approach for inducing selective brain hypothermia has been evaluated theoretically by researchers over the past 10 years. The major blood vessels in the neck region can be modeled as straight tubes embedded in the neck cylinder. Theoretical simulation showed limited temperature reductions (<1°C) along the carotid arteries even when the neck surface temperature was reduced to 0°C (145). The limitation on cooling predicted in this study is largely due to the deep locations of the carotid arteries. Temperature reduction along the arteries depends on not only the length of the cooling collar but also on the blood flow rate of the arteries. This model was later modified to include the vertebral arteries owing to their relatively superficial locations and their small blood flow rates (146). Depending on the cooling collar temperature, up to 37 W of heat could be removed from the arterial and venous blood in the neck region. Although the theoretical analysis failed to demonstrate significant potential for a neck collar to reduce brain temperature, it did indicate that the cooling collar has the potential to decrease the body temperature by as much as 0.69°C h⁻¹ by cooling blood flow through the superficial jugular vein. Therefore, the neck collar's small size and portable nature may make it suitable to provide an initial downward trend in the body temperature while a patient is transported to the hospital.

6.4.3. Interstitial cooling in the neck. Considering that the tissue between the cold neck surface and an embedded blood vessel is the major thermal barrier for effective removal of heat from the arterial blood, an interstitial cooling device was proposed to bypass the barrier. Wang & Zhu (147) first proposed inserting a cooling device into the neck muscle to ensure close physical contact with the arterial blood, thereby enhancing the contact surface area. The advantages of this approach include the small size of the thermal source device, its powerful cooling capacity, fast cooling capability, and adjustable rewarming rate. The physical principle of the cooling approach was demonstrated by the theoretical simulations of the neck and head temperature fields. The simulations predicted a reduction in the temperature of the common carotid arterial blood by at least 2°C within 30 min. A prototype of the device was tested independently in a rat model by two research groups. Wang et al. (148) used a small version of that proposed by Wang & Zhu (147) and inserted it into the neck muscle of adult rats. Unlike head surface cooling, this device produces a nearly uniform temperature field in the rat brain tissue because the chilled arterial blood is circulating throughout the brain structure, where it exerts a convective cooling effect (148). A similar experiment was performed by Wei et al. (149) to not only monitor the brain temperature reduction but also test whether it reduces the infarct volume in the brain tissue. Both the incidence of peri-infarct depolarization and infarct volume were reduced by more than 70% (149). Both experimental studies demonstrated the feasibility and efficacy of this approach in small animal models. Large animal models are needed to evaluate the safety and effectiveness of the technique.
6.4.4. Intracarotid flushing. Because most of the noninvasive cooling methods are not effective in reducing the brain temperature quickly, more aggressive techniques have been suggested. By adapting the approach of veno-venous blood cooling, researchers have proposed selective cooling of only the blood supply to the brain. Because cold saline infusion is able to produce a relatively fast cooling rate in the whole body, infusing cold saline via a catheter inserted into the femoral vessels and advanced to the carotid artery should have considerable potential for achieving rapid brain cooling. Several theoretical studies were performed to evaluate the clinical feasibility of this approach. On the basis of a three-dimensional (3D) mathematical model developed by Neimark et al. (150), it was shown that an infusion flow rate of 30 ml min$^{-1}$ is sufficient to induce moderate brain cooling within 10 min in the brain, after which hypothermia can be maintained. A fast cooling rate (4°C 10 min$^{-1}$) was observed when 6 ml cold saline was infused to the middle cerebral artery in a rat model (151). In this study, brain cooling significantly improved the motor behavior of the tested rats; however, reduction in the infarct volume was not substantial. Because a rat brain is much smaller than a human brain, the cooling extent and rate for the rat experiments may not be applied directly to the humans. Although the theoretical models have provided proof of the principle, future experimental study on large animals and clinical trials are needed to examine the feasibility of this technique.

6.4.5. Intraparenchymal cooling. Given that thermal conduction resistance between the skin and core tissue is the major factor that affects the effectiveness of surface cooling of the brain, inserting a cooling device directly into the brain tissue may address the limitation. A recent patent by neurosurgeons and researchers at the University of Chicago and Argonne National Laboratory describes such a cooling probe. The cooling device consists of a 2.5 cm long, dual-lumen stainless steel shaft with cold water circulating from a slurry ice bath to the device. The diameter of the device is approximately <2.7 mm.

A recently published paper (152) analyzes the temperature distribution in the brain tissue surrounding the intraparenchymal cooling device. The temperature of the device surface can be lowered to 6°C with a circulating ice-slurry solution. The theoretical simulation illustrated how the cooling field penetrates into the brain tissue. One important factor is the local blood perfusion rate, which is well known to be as high as 0.0133 s$^{-1}$. The effect of blood perfusion will limit the zone of influence of the cooling device, because the cooled blood is rapidly redistributed and diluted throughout the entire blood circulation. In contrast, in clinical settings where brain perfusion is either not present at all (e.g., the ischemic core within a brain infarction) or markedly reduced (e.g., penumbra region around an ischemic brain core), both the blood perfusion rate and the temperature will have a reduced counteracting influence on the probe, thus allowing the cooling zone to extend further laterally from the device when compared with the cooling of a noninjured brain. Depending on the extent of blood perfusion, cooling penetration achieved by the probe ranged from 10 to 25 mm, with a larger cooling penetration being obtained in injured (less perfused) brain regions. A major advantage of the device is the potential for fast cooling. Final steady state of therapeutic hypothermia can be achieved in less than 16 min after probe insertion.

One of the major concerns of the device is patient safety, because the proposed approach is too invasively aggressive to be applied in many therapeutic scenarios. The inventor argues that the device can be used side by side with other routine neuro-critical-care procedures, including insertion of both rigid and flexible catheters to drain ventricular fluid, as well as the use of probes to monitor cerebral pressures. If these catheters are inserted via a small hole drilled in the skull, it is conceivable that modifications of those catheters to include the cooling device can be implemented with no added risk or complication.
7. ENGINEERING CONTRIBUTIONS IN BRAIN HYPOTHERMIA

7.1. Development of Cooling Devices

The major contribution of engineering in therapeutic brain hypothermia is to design reliable and safe devices to achieve target cooling rates and temperatures. New technologies are typically evaluated for thermal efficacy and safety in small and large animal models to determine their suitability for testing in humans. During the design, patient safety is a prime consideration, including issues such as leakage of coolant, induced freezing damage to tissue, physical trauma, etc. Sterilizability, size minimization consistent with thermal performance requirements, and physical packaging are typical design considerations during the development of the device.

In general, there are two categories of device designs that are used clinically for therapeutic hypothermia: skin surface and endovascular cooling. More than six companies (Medivance, MTRE, Seabrook, Cincinnati SubZero, Birchbrook, and Garnar) manufacture surface cooling devices such as cooling blankets, garments, helmets, and pads. This category of devices is based on noninvasive methods and, to date, has been most broadly applied in clinical trials. An alternative approach is presented by AVACore in which an applied negative pressure to glabrous skin in conjunction with cooling is used to enhance blood perfusion through arteriovenous anastomoses, thereby increasing convective energy transport with the body core. This technique has the potential for providing much faster cooling rates. There are three companies (Radiant Medical, Innercool Therapies, and Alsius) that have developed endovascular catheters for cooling human blood as it flows past the device when inserted into a large vessel. Endovascular cooling is superior in providing a fast cooling rate; however, its major drawbacks are blood clogging and clotting, invasive surgical insertion procedures, and complications associated with whole-body cooling. Other approaches, such as intracarotid cooling and interstitial cooling in the neck, are in their infant stage and are yet to be tested in large animal models and clinical studies.

7.2. Mathematical Simulations of Cooling and Rewarming Processes

In the past two decades, clinicians have realized the importance of closely monitoring brain temperature during hypothermia. Even a small reduction in brain temperature can improve neurological outcomes of patients suffering brain injury. Temperature variation within normothermic brain tissue is usually very small; however, especially during therapeutic hypothermia, temperature gradients can develop not only between brain and core but also within regions of the brain (38, 53, 118, 153–155). Information on internal temperature gradients is difficult to obtain clinically by measurement with temperature probes owing to the risk of inducing additional tissue damage. Current noninvasive temperature measurements such as magnetic resonance imaging (±2°C) lack the desired resolution to monitor small temperature variations in the brain region. Therefore, analytical methods for understanding the transient and spatial temperature distribution in brain tissue during hypothermia therapy are clinically valuable.

Quantitative thermal modeling aids in identification of an optimal treatment protocol, and with appropriate constitutive input data, affords the opportunity for designing personalized therapeutic regimens. Theoretical modeling provides clinicians with powerful tools to improve the ability to deliver safe and effective therapy. Most importantly, thermal modeling permits the identification and evaluation of critical monitoring sites to assess the cooling extent and to assure patient safety. Most of the current theoretical thermal models in brain hypothermia implement the Pennes bioheat equation (156) that simplifies the thermal contribution of local blood vessels as a simple heat source term added to the traditional heat conduction equation (110, 142, 147, 150, 152,
With the advancement in computational resources, researchers have the capability to simulate the 3D temperature field of the head and neck and to consider multiple large blood vessels individually in the model. When point-to-point temperature nonuniformities are important, a model that incorporates perfusion through the vasculature is necessary to predict accurately the tissue temperature field; however, because of the complex vascular geometry, one may model only selected large blood vessels individually and neglect the others. There were several attempts in the past to model large blood vessels, including the carotid arteries and jugular veins in the neck, during brain hypothermia (145–147, 162). In those studies, temperature decay along the large arteries was used to evaluate whether various techniques could induce sufficient cooling to the arterial blood supplied to the brain. Owing to the complicated vascular structure, it is difficult to model effects of individual blood vessels in the brain region. Van Leeuwen et al. (163) predicted temperature contours based on a detailed vasculature in the brain and found that they agree very well with those predicted by the Pennes model. This may be mainly due to the large rate and diffuse pattern of blood perfusion in the brain tissue, for which the Pennes bioheat equation is a preferred approach. Advanced computational methods also allow researchers to model the head with a more realistic geometry than a simple hemisphere structure. The head geometry is usually based on magnetic resonance images (MRIs), which can be imported into grid-generating algorithms and then be interfaced with numerical software for temperature simulation (157, 159, 163). However, the results obtained from the more complicated head models to date are very similar to those predicted by a simple, layered head geometry.

One of the major challenges in mathematic simulation of cooling and rewarming processes is assessment of local blood perfusion variations in response to cooling. In most theoretical simulations, blood perfusion is usually considered a constant during cooling or is considered to be decreasing as a function of the local tissue temperature following the $Q_{10}$ law (164, 165). The predicted temperature distribution in the brain is in agreement with the observed temperature field during steady state; however, there is a large discrepancy between theory and experiment on how long it takes to establish a steady state during cooling and rewarming.

In an experimental study performed on a rat model during head surface cooling, thermocouples were inserted into the brain to monitor the temperature reduction and recovery (111). The measured characteristic time to establish a steady state varied from 5 min to longer than 40 min, whereas the theoretical simulation predicted a much smaller characteristic time (less than 5 min) for the small size of the rat head, when the blood flow rate is unchanged during the simulation. These results imply that the change of the blood perfusion rate in tissue contributes significantly to the characteristic transient time. A similar conclusion can be drawn from other animal models (152) and alternative cooling approaches (148).

The $Q_{10}$ law represents a linear relationship between $1/T$, where $T$ is tissue temperature, and log CMRO$_2$ (the cerebral metabolic rate of oxygen consumption). A mathematical expression of this relationship is given by

$$CMRO_2 = CMRO_{2,n} \cdot Q_{10}^{\frac{T-37}{10}} ,$$

where $CMRO_{2,n}$ is the normal cerebral metabolic rate of oxygen consumption, and $Q_{10}$ is a constant factor, which has been reported (165) to vary between 2 and 4.4 based on correlations with experimental measurements. This law states that the metabolic rate decreases by a factor of $Q_{10}$ with each 10°C reduction in temperature. Based on a $Q_{10}$ value of 2, it has been calculated that hypothermia decreases cerebral metabolic rate by an average value of 7% for the first 1°C reduction in temperature, whereas metabolic rate is reduced to one-half of the normal value when the temperature reduction is 10°C. This type of relation is analogous to the Arrhenius equation. During normal conditions, cerebral blood flow (CBF) may follow the same pattern.
as that of cerebral metabolism owing to their direct coupling. Several temperature simulations have incorporated the $Q_{10}$ law (110, 152, 157, 158). Because the local blood perfusion keeps decreasing with the temperature during cooling, the temperature field from the cold surface can penetrate more readily into the deep brain region, which, in turn, would further trigger perfusion reduction. If the temperature dependence of perfusion progresses during cooling, the result would be an extended time to reach a steady state.

During cerebral ischemia or head injury, not only may the $Q_{10}$ value change but also CBF may be decoupled from metabolism. A number of studies have examined the variation of CBF during systemic hypothermia. Using the radioactive microsphere technique, Busija & Leffler (166) measured CBF in anesthetized newborn pigs. They concluded that systemic hypothermia reduced CBF secondarily to the depression of cerebral metabolic rate. Verhaegen et al. (167) measured the cortical blood flow in anesthetized rats using a laser Doppler flowmeter (LDF) and found that CBF was reduced during moderate hypothermia. Okubo et al. (168) examined the effect of systemic cooling on cerebral metabolism and regional CBF variation in newborn piglets. They measured the regional CBF with colored microspheres and demonstrated that a reduction of cerebral cortex temperature resulted in a decrease in the blood flow in all brain regions. Unlike many experimental studies on CBF response during systemic cooling, there have been only a few studies on the effect of selective brain cooling on CBF, and the various results are inconsistent. Laptook et al. (141) examined the differences of CBF in newborn swine during selective brain cooling versus whole-body cooling and illustrated that the global CBF was reduced during both whole-body cooling and selective brain cooling. Ibayashi et al. (169) demonstrated that the regional CBF decreased when selective brain cooling was implemented on rats. However, a previous study (170) using the LDF technique showed that the cortical CBF in normal lightly anesthetized rats increased during selective brain cooling.

LDF has been used to monitor blood perfusion in superficial areas of the brain. To measure the blood perfusion rate of brain tissue, the LDF probe must be inserted into the brain to have access to the measured region because its sensing signal cannot penetrate the skull. Another limitation of LDF is that it may not be suitable for measuring global blood flow changes in the brain. Microspheres of a selected diameter, a standard and popular technique for measuring local blood perfusion rate in tissue, are injected into blood and allowed to circulate freely until they become lodged in the smaller capillaries. It is possible to determine the blood perfusion at different times using different colored and sized microspheres introduced serially into the circulation. However, the microsphere can provide only a low temporal resolution. In previous studies (53, 171, 172), CBF was measured only once or twice during hypothermia in the animal models. More recently, MRI has been used to detect the cerebral perfusion in animal models during brain hypothermia (16). Because of the relatively long acquisition time for a 3D MRI scan, the technique may not be suitable for studying the response of blood perfusion during cooling. It has also been proposed that the variation of the blood flow rate of the common carotid artery should be considered as an index of the global CBF and how it changes during brain hypothermia should also be considered (111). It is estimated that more than 80% of the blood supplied to the brain is from the common carotid arteries. The blood flow rate of the common carotid artery can be measured continuously using an LDF applied in an in vivo setting to study the transient behavior of temperature and blood flow responses during selective brain cooling and rewarming (111). Very similar transient profiles of the brain temperature and blood flow rate of the common carotid artery as characterized by their characteristic time constants were observed in rats (111). Nonetheless, more rigorous experimental verification is needed to establish the correlation between the CBF and blood flow rate of the common carotid artery. The accuracy of theoretical simulations is still questionable unless the simulations can be verified with
experimental data that continuously monitor the local blood perfusion rate during cooling and rewarming.

8. OPPORTUNITIES FOR BIOMEDICAL ENGINEERING CONTRIBUTIONS

As the mechanistic basis of the therapeutic application of hypothermia for ischemic brain injury improves and becomes more complete, it may become possible to accurately and predictably design treatment protocols to achieve specific outcomes. For example, there is an accumulating body of evidence that points to the need for a rapid reduction in brain temperature following a trauma event in order to realize the potential benefit of hypothermia therapy. The minimum temperature drop is thought to be at least $2^\circ$C, and the window of opportunity in which it can be effective is limited to 90 min or less. Quick initiation of rapid cooling is apparently an essential feature of hypothermic therapy. The practical implementation of rapid brain cooling would benefit greatly from a cooling process that could be started in the field by first responders for whom specialized training and skilled procedure requirements are minimal. Further, the requirement for cooling the brain at a rate of $1.5^\circ$C h$^{-1}$ or higher imposes limitations on the types of technology that can be used for removing heat rapidly from the interior of the body. The combined criteria of simple, safe, and fast cooling define the considerations facing biomedical engineers in designing new devices and procedures.

Recent advances by thermal physiologists have opened an opportunity for achieving the rapid cooling of the body thermal core (79, 91, 172, 173). Their technology uses an applied negative pressure on glabrous skin to mechanically distend arteriovenous anastomoses, thereby greatly increasing the cutaneous blood perfusion. By diverting a significant fraction of the cardiac output to the skin, where there can be an effective heat transfer with the environment, it is possible to use the circulatory system as a convective conduit for thermal energy between the body surface and the thermal core, including the brain. In initial studies with humans, it has been possible to achieve rates of change of core temperature of $10^\circ$C h$^{-1}$ and higher, which would be adequate for hypothermia induction in cases of TBI. One concern raised by neurosurgeons is decrease in blood pressure, which can be dangerous to patients with compromised health. Although this technology may not be suitable for clinical applications in hypothermia, it illustrates that there are possibilities for extending the currently limited performance range of technologies into the domain in which methods of hypothermia therapy could be made available for widespread adoption.

SUMMARY POINTS

1. Hypothermia has a documented efficacy in treating tissues subjected to ischemic stress, including complications of TBI and stroke as well as cardiac arrest.

2. The magnitude of hypothermia necessary to derive its prophylactic benefit is not defined clearly, although there are indications that it may as little as $2^\circ$C to a brain temperature of $35^\circ$C.

3. Clinical evidence is accumulating that shows time is of the essence for implementing hypothermia in the target tissue. The window of opportunity appears to be 90 min or less. However, the treatment window may be wider if the cooling is prolonged.

4. Although rapid cooling to a state of hypothermia is demonstrated to be of direct benefit, it is important to avoid rapid rewarming from hypothermia.
FUTURE ISSUES

1. The therapeutic mechanism of action of hypothermia is not well understood, and therefore the ability to design treatment protocols for optimal efficacy is compromised. Although the problem is quite challenging, it presents a major opportunity for significant contributions.

2. Effective cooling of the brain remains a major difficulty in the practical use of hypothermia. Engineering methodologies should play a key role in identifying new and effective technologies and devices and adapting them for clinical application.

3. It is widely held that treatment of brain ischemia requires a quick reduction in temperature of the affected tissue to a state of mild hypothermia, possibly within an hour of the precipitating event, in order to achieve full neuroprotective benefit. New methods and devices are needed to quickly and safely produce mild hypothermia of the brain by minimally skilled personnel in a field environment.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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