Therapeutic hypothermia for stroke: do new outfits change an old friend?

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Clinically significant neuroprotection for the brain continues to be an elusive quest. All attempts at developing effective pharmacologic agents have failed in clinical trials. Hypothermia has been thought to confer protection after brain injury for many years, but has recently regained interest as a neuroprotectant for focal ischemic stroke in the basic science and clinical literature. The failure to develop safe and efficacious pharmacologic agents along with promising clinical data on the efficacy of hypothermia for cardiac arrest patients have raised a great interest in hypothermia as a neuroprotectant for ischemic stroke. As a clinically meaningful neuroprotectant for stroke, hypothermia confers several theoretical advantages over pharmacologic agents. A major problem with neuroprotectant therapy is instituting therapy within a narrow time window. This obstacle may be easier for hypothermia to overcome as emergency medical service personnel can theoretically initiate it in the field. Additionally, pharmacologic agents are usually restricted to one aspect of the pathophysiologic cascade triggered by focal ischemia, whereas hypothermia acts on several of these pathways simultaneously. The recent advances and future directions in the utilization of hypothermia as a potential therapy for focal ischemic stroke are reviewed.

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Stroke is the second leading cause of death worldwide [1]. Approximately 90% of strokes are ischemic in nature [2] with 15% of patients arriving in the emergency room within a 3-h time window [3]. Thus far, clinical research has yielded positive results only when reperfusion strategies were applied in patients with acute stroke while neuroprotection has consistently been linked with negative results. The results of the National Institutes of Neurological Disorders and Stroke trial showed that patients receiving intravenous tissue plasminogen activator (tPA) within 3 h of symptom onset were significantly more likely to have an improved outcome at 90-day follow-up [4]. Since the publication of the National Institutes of Neurological Disorders and Stroke trial, it has been shown that recanalization is linked to improved clinical outcomes [5]. In addition, it is clear that many patients do not recanalize after administration of intravenous or intra arterial thrombolytics [6,7]. As only a small proportion of patients seek medical attention within the narrow time window and fewer yet receive thrombolytic therapy [3], neuroprotectants have been studied as a method to potentially extend the time window to safely and effectively utilize reperfusion strategies.

Hypothermia has a protective effect on neurons at risk of anoxic damage after focal ischemia [8]. The neuroprotective effects of hypothermia include protection of the blood–brain barrier (BBB), reduction of intracranial hypertension, maintained mitochondrial function, and suppressed release of excitatory amino acids (e.g., glutamate and aspartic acid) or glycine [9–11]. The fundamental mechanism underlying the improvement of these processes is unclear.

Cerebral blood flow & the ischemic penumbra

Following vessel occlusion, two factors determine tissue outcome: regional cerebral blood

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flow (CBF) and duration of vessel occlusion. A drop in regional CBF leads to diminished tissue perfusion. In persistent large vessel occlusion, local perfusion pressure is the main influence on the eventual outcome of tissue [12]. This perfusion pressure depends on several factors including the presence and extent of collaterals, systemic arterial pressure (the ischemic brain has lost the autoregulatory capacity) and is inversely correlated to the local tissue pressure (which is increased by ischemic edema). Depending on the extent of hypoperfusion and time, the tissue supplied by the occluded artery is compartmentalized into areas of brain tissue irreversibly damaged and areas of brain tissue hypoperfused but viable. This led to the concept of ischemic core and ischemic penumbra [13]. The ischemic core represents tissue that is irreversibly damaged. Positron emission tomography studies in humans suggest that beyond a certain time limit (probably no longer than 1 h) it corresponds to CBF values of less than 7 ml/100mg/min [14–16] to 12 ml/100mg/min [17,18]. The ischemic penumbra represents tissue that is functionally impaired but structurally intact and as such potentially salvageable. It corresponds to a range of CBF values from 12 to 22 ml/100mg/min. Salvaging this tissue by restoring its flow to nonischemic levels is the aim of acute stroke therapy. Another compartment termed oligemia represents mildly hypoperfused tissue from the normal range down to approximately 22 ml/100mg/min [19]. It is believed that under normal circumstances this tissue is not at risk of infarction [12]. However, it is conceivable that under certain circumstances such as hypotension, fever and acidosis, oligemic tissue can be incorporated into penumbra and subsequently undergo infarction. Evidence in the literature suggests that there is a temporal evolution of core, which grows at the expense of penumbra [20–22]. One of the proposed mechanisms for growth of the ischemic core is progressive recruitment of penumbral areas into the core caused by ischemic edema [20]. It is known that the ischemic penumbra represents a dynamic phenomenon. If vessel occlusion persists, the penumbra may shrink due to progressive recruitment into the core, a process enhanced by circumstance such as hypotension, acidosis and fever. Alternatively it may return to a normal state following vessel recanalization or neuroprotectant interventions. Theoretically, in hypothermia, the reduction of the oxygen driving pressure matches the diminished demand for oxygen. Additionally, hypothermia induces a reduction of CBF, a significant increase in cerebral perfusion pressure and reduction in intracranial pressure (ICP) in head trauma patients [23]. The effects of hypothermia on CBF and ICP may be related to decreased nitric oxide levels and maintenance of the integrity of the BBB [24,25]. In ischemic stroke, CBF is reduced with hypothermia [26]. *In vitro* models have shown a slight reduction in the efficacy of tPA as the temperature drops [27]. A recent study with rodents considered the effect of combined hypothermia and tPA on final infarct volume and showed that there was no statistical difference when compared with thrombolysis alone. The authors concluded that hypothermia does not have a significant effect on tPA *in vivo* [28]. Additionally, hypothermia does not appear to have a synergistic effect on infarct volume reduction. These are important issues requiring further study especially as newer generation thrombolytics are tested.

Mechanism of ischemic injury to the brain

In the early phase of ischemia, a large surge of amino acid excitotoxicity occurs with elevations of aspartic acid and glutamate. Glutamate causes stimulation of the *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors leading to an influx of calcium ions. At the same time, sodium and chloride enter the neuron via channels for monovalent ions [29]. Water follows passively leading to edema that can further diminish perfusion in regions surrounding the core, leading to recruitment of penumbral areas into the core [20]. As intracellular calcium accumulates, it initiates reactions at the cytoplasmic and mitochondrial levels. At the cytoplasmic level there is an accumulation of free radicals as enzymes such as nitric oxide synthase and cyclooxygenase are activated [30,31]. These free radicals disrupt the inner mitochondrial membrane and oxidation of the proteins that mediate electron transport [32]. The mitochondrial membrane becomes leaky resulting in mitochondrial swelling, intramitochondrial calcium accumulation, impaired energy production and oxygen free radical burst [33]. Cytochrome C is released from mitochondria and is believed to constitute a trigger for apoptosis [34].

An important mechanism responsible for ischemic injury exacerbation is inflammation. Early after onset of ischemia, astrocytes, microglia, endothelial cells and leukocytes are activated. Peripherally derived leukocytes such as polymorphonuclear leukocytes, T-lymphocytes and natural killer cells also accumulate in the ischemic tissue [35–37]. The accumulation of inflammatory cells in the ischemic lesion occurs as a result of intracellular calcium accumulation, increase in oxygen free radicals, as well as hypoxia itself [34]. Activation of inflammatory cells in the ischemic lesion results in the production of cytokines [38]. Tumor necrosis factor (TNF)-α and interleukin-1 cause enhanced expression of adhesion molecules on the endothelial cell surface, including intercellular adhesion molecule-1, P- and E-selectin [39–41]. As a consequence, neutrophils, and later macrophages and monocytes adhere to the endothelium, cross the vascular wall and enter the brain parenchyma. Microvascular obstruction by neutrophils can worsen the degree of ischemia through worsening of microvascular perfusion. Other deleterious effects of inflammation on ischemic tissue include production of toxic mediators (oxygen free radicals, toxic prostanoids and TNF-α) by activated inflammatory cells as well as facilitation of apoptosis [42].

Hypothermia offers the theoretical advantage over other neuroprotectants in that it acts on many of these mechanisms. Cooling leads to a reduction of oxygen consumption thereby reducing the metabolic demands of brain tissue [43]. In addition, there is a reduction of glutamate, inactivation of cytoplasmic enzymes such as nitric oxide synthase [44], attenuation of

cytochrome C release [45], reduction of free radical release [46] and reduction of inflammation [47]. Hypothermia preserves the basal lamina thus maintaining the BBB [48]. This makes hypothermia attractive to the clinician, as its protective targets are not specific.

Hypothermia: friend & foe

The 1960s saw an explosion of interest in the use of moderate and deep hypothermia during aneurysm, spinal cord and cardiac surgery, as well as in the management of head injury. Controlled trials were never reported, however, observations since the early part of the last century, human and animal experiments, and monitoring of surgical patients undergoing induced hypothermia for cardiothoracic interventions or neurosurgical procedures, have provided much information about the physiologic responses to cold. Hypothermic circulatory arrest (HCA) was the first technique to gain wide acceptance for use in surgery of the aortic arch [49]. However, awareness of a relatively high incidence of neurologic complications after aortic arch surgery with HCA led to the gradual recognition that its safety depends on very careful implementation. In addition, HCA cannot be relied on to protect the brain completely during prolonged procedures [50]. Cooling is performed until a temperature of 10–13°C has been reached in the esophagus and the oxygen saturation in the jugular venous bulb is more than 95%, indicating maximal metabolic suppression. Cooling is thorough, lasting at least 30 min prior to cardiac arrest to prevent a gradual updrift of temperature during the interval of HCA. The intracranial temperature is further protected from rising during HCA by packing the head in ice [51]. Scrupulous attention during rewarming after HCA is also indicated to avoid the possibility that oxygen demand will outstrip supply: gradual rewarming and avoidance of high perfusate temperatures are essential. Inappropriate cerebral vasoconstriction has been documented after HCA, mandating careful attention to maintaining stable hemodynamics to assure optimal oxygen delivery during this vulnerable interval, which extends for at least 8 h postoperatively [52]. Even with meticulous attention to cooling and warming techniques, as well as careful monitoring, duration of HCA exceeding 25 min has been shown to produce symptoms characterized as temporary or permanent neurologic dysfunction. In recognition of the limits of safe HCA, the technique of retrograde cerebral perfusion was enthusiastically embraced by many clinicians [53]. The idea of supplying the brain with blood retrograde, via the superior vena cava, had appeal not only as a possible way of delivering nutrients to the brain during a prolonged period of HCA, but also as a possible way of flushing out cerebral emboli [54]. Careful analysis of clinical results has shown that long durations of retrograde cerebral perfusion are associated not only with high rates of temporary neurologic dysfunction, but also, in some studies, with an increased risk of stroke and death after aortic surgery [55]. Selective antegrade cerebral perfusion allows some or all of the cerebral vessels to remain perfused throughout the duration of systemic circulatory arrest, except for very short intervals. Initial results with normothermic or mildly hypothermic cerebral perfusion were disappointing, but the combination of HCA with selective antegrade cerebral perfusion has been very successful in providing cerebral protection both in laboratory studies and clinical practice [56]. The advantage of this technique is that it allows a much longer interval of safe circulatory arrest, since the supply of nutrients and oxygen at a relatively low flow allows maintenance of appropriate levels of oxygen metabolism at hypothermic temperatures [57].

Systemic hypothermia has profound and widespread physiologic effects, which can result in a diverse pathology. The pathophysiologic changes observed may be influenced by underlying disease processes and hypovolemia, and will depend to some extent on the rate as well as depth of cooling, as there is some evidence that more severe problems with acid–base, electrolyte and fluid balance can occur in prolonged hypothermia [58].

Target temperature & rewarming

The depth or duration of hypothermia that is optimal in treating focal ischemic stroke is currently not known. Moreover, rates of rewarming are not standardized. Mild to moderate hypothermia is generally defined as temperatures between 32 and 35°C while severe hypothermia ranges between 28 and 32°C. These variables can profoundly impact on clinical outcomes, as lengthier and deeper hypothermia are associated with systemic complications (TABLE 1). Thus, the vast majority of clinical trials studying brain protection after trauma, global anoxia or focal ischemia have selected the moderate hypothermia range for study. The duration of therapy ranges from 12 to 48 h depending on the study and etiology of brain injury [59–61]. Rates of rewarming also vary depending on the study, but many advocate slow rewarming and a rate of 0.2°/h. In the trauma literature, some advocate following the level of ICP to guide the rewarming process [62]. For stroke patients, there is not an objective marker to guide rewarming rates. Future advances in imaging and monitoring technologies may prove to be useful to this end.

Variables such as depth and duration of hypothermia and rates of rewarming have not been well defined in humans. Studying these parameters more rigorously is required to maintain the efficacy while minimizing the side effects.

Methods to achieve hypothermia

Some of the challenges encountered in safely administering hypothermia to humans is the ability to limit systemic side effects that otherwise reduce the potential benefits of the therapy. Hypothermia induces fluid losses thereby affecting electrolyte balances, increases bleeding time through its effect on platelets and reduces the effectiveness of the immune system. These properties of hypothermia can lead to a host of complications that must be monitored rigorously when caring for these patients (TABLE 1) [58]. In addition, it is vital to rapidly achieve the desired level of temperature because of the limited therapeutic window available when treating acute stroke

Table 1. Known side effects to hypothermia.

Depth of hypothermia	Complications
Mild–moderate hypothermia (32–35°C)	- Diuresis (hypovolemia) - Vasoconstriction - Shivering - Confusion - Electrolyte abnormalities (hypokalemia, hypomagnesemia and hypocalcemia) - Insulin resistance (hyperglycemia) - Prone to infections, sepsis - Pancreatitis (elevations of serum amylase and lipase) - Effects on drug metabolism
Severe hypothermia (28–32°C)	- Ventricular arrhythmias - Stupor - Coagulopathies - Myocardial infarction - Hypotension
Profound hypothermia (<28°C)	- Severe hypotension - Coma - Asystole

patients. Earlier methods of cooling focused on immersion techniques with ice water and alcohol rubs. Since then, newer devices have been tried including surface cooling blankets, endovascular cooling catheters, external head cooling with caps, regional cooling and pharmacotherapy. The pros and cons of these methods are summarized in TABLE 2.

Surface cooling

Surface cooling is a labor-intensive method of achieving mild-to-moderate hypothermia. It is fraught with several disadvantages such as overshooting target body temperatures and discomfort to patients. The method involves sandwiching patients between two blankets that circulate cold water (or air in some models) along with placement of ice packs under the axilla and on the groin. This method takes advantage of heat transfer out of the body through conduction. The process is quite time consuming and achieving target body temperatures can take as long as 8 h [63,64]. Additionally, difficulties exist with maintaining a steady-state body temperature with nine out of ten patients in the COOLing for Acute Ischemic brain Damage (COOLAID) I study overshooting target temperature [64]. The difficulty with cooling patients in a timely fashion is probably the limiting factor of this method. In addition, patients must be intubated and maintained with adequate sedation and medications to suppress shivering. This may obscure neurologic assessments in the intensive care unit making it difficult to determine when patients deteriorate clinically. This method may be practical to initiate in the field by emergency personnel since simply placing ice packs under the axilla and on the torso may reduce core body temperature by 1°C prior to arrival in the emergency room [59].

Selective scalp cooling

Surface cooling has inherent practical difficulties including labor intensiveness, poor control of body temperature and medical complications as a result of systemic hypothermia. These difficulties have prompted a search for selective cooling methods. One such device is the cooling helmet, which may be able to deliver rapid and selective cooling to the brain that may be instituted quickly by emergency medical service personnel [65]. The hope is that this technology will maintain a temperature gradient by cooling the brain to target temperatures while maintaining a milder hypothermia of the body core. This has the potential advantage of minimizing the medical side effects of systemic hypothermia.

Models of temperature distribution in humans call into question whether external scalp cooling can effectively cool the brain: even extreme changes in ambient temperature lead to temperature changes only in the vicinity of the head surface whereas in the brain, the temperature remains practically constant. Reports of placing ice packs on the scalp and neck have failed to show an effective ability to cool the brain via tympanic temperature probes [66]. In contrast, reports of a cooling cap placed around the scalp of newborn piglets was shown to be effective in rapidly cooling the deep brain structures (31°C) while maintaining a more mild hypothermia systemically (35°C for 24 h) [67]. The authors raised a concern about the inability to correlate scalp temperatures to invasive brain parenchymal temperature probes. Another study found that piglets that underwent selective scalp cooling for global hypoxia had large temperature gradients between superficial brain structures and deeper brain structures (i.e., basal ganglia) [68]. This was in contrast to systemic cooling which provided a more uniform cooling of the brain. It is not clear as of yet, if cooling of the more superficial brain structures to deep hypothermia in order to maintain mild-to-moderate hypothermia of deeper structures has deleterious consequences. In addition, this temperature gradient may have profound implications in a focal cerebral ischemia model as it has been shown that after a large middle cerebral artery (MCA)

territory infarct, a temperature gradient occurs with deeper structures having higher temperatures relative to the surface of the brain [69].

Two studies in neonates suffering from global perinatal asphyxia revealed that selective head cooling with mild systemic hypothermia may be performed safely [70,71]. These studies also showed that it is difficult to study the efficacy of this therapy due to the wide range of initial clinical severity of babies suffering from global encephalopathy secondary to anoxia.

A major problem this technology is facing remains the ability to determine the temperature of the brain itself since the best technology to measure it is quite invasive by means of a probe placed within the parenchyma of the brain. Corbett and colleagues have shown that brain temperature can be measured using 1H magnetic resonance spectroscopy to quantify the magnetic resonance frequency of water, which changes as a linear function of temperature in normal brain and stroke [72]. An attractive feature of this method is that temperature from virtually any region of the brain can be measured, allowing the possibility of examining the effectiveness of different protocols to reduce brain temperature in a variety of anatomic locations.

Endovascular cooling

There have been reports of central venous catheters with heat exchange systems being utilized for inducing hypothermia in patients with ischemic stroke. Various companies have introduced models with the principle of heat exchange through infusion of hot or cold saline through a catheter placed in the inferior vena cava. Endovascular heat exchange represents a novel and efficient means of inducing hypothermia that is applicable in the clinical environment. This approach results in a fivefold increase in cooling rates compared with surface methods and many nonconvection enhanced intravascular strategies [73]. Moreover, this cooling technique is applicable at clinically relevant time points (i.e., 3 h after ischemia). This strategy underscores the potential usefulness of hypothermia as a neuroprotective strategy in human stroke.

In a recent, large animal study using 60 kg pigs, the target temperature of 32°C was reached in approximately 1 h, and core temperature was precisely maintained at the target core temperature, indicating that the computerized control system was effective [74]. The saline-to-blood temperature gradient was considerably less during rewarming than during cooling (13 vs. 31°C) because greater saline temperatures may have damaged red blood cells or coagulation elements. The rewarming rate was thus less than the cooling rate (2.5 ± 0.2 vs. 4.5 ± 0.4°C/h). However, slow controlled rewarming is likely to be necessary when hypothermia is used for neuroprotection or control of intracranial pressure. Cooling rates were slightly less in clinical studies in which surface warming is used to inhibit shivering during core cooling [75].

Cooling and warming with the use of the intravascular technique has no effect on platelet or white blood cell count and produced no evidence of hemolysis. There is no evidence of thermal injury to blood vessels or blood elements *in vivo*.

Table 2. Summary of advantages and disadvantages of various methods described in the literature to achieve hypothermia.

Method and status	Advantages	Disadvantages
Surface cooling Status: commercially available	- Can be initiated by emergency medical service personnel - Can be performed at nonspecialized centers thus reaching a larger proportion of stroke patients	- Cumbersome, labor-intensive - Slow induction - Difficult to maintain narrow target temperature range - Systemic side effects are not avoided - Difficulty at regulating rewarming rate - Patient discomfort, requiring pharmacotherapy
Endovascular cooling Status: commercially available	- Rapid rate of induction - Able to maintain a narrow target temperature range - Less labor intensive then surface cooling - Precise regulation of rewarming rate	- Invasive procedure - Cannot be initiated by emergency medical service personnel - Potential groin complications - Systemic side effects are not avoided
Selective scalp cooling Status: Phase I	- Can be initiated by emergency medical service personnel and nonspecialized centers - Theoretical reduction of systemic side effects - Less labor intensive then surface cooling	- Theoretical temperature gradient within brain - Takes longer than endovascular cooling to achieve target temperature - Unclear if narrow target temperature range can be maintained
Regional cooling Status: under development	- Selective cooling of ischemic area only - Theoretical advantage of more rapid achievement of deeper hypothermia in target organ alone - Theoretical reduction of systemic side effects - Can be performed simultaneously with intra-arterial therapies	- Invasive procedure - Side-effect profile unknown - Can be performed at specialized centers only

Similarly, there was no evidence of deep venous thrombosis after *in vivo* use, nor were there any gross or microscopic pulmonary emboli. This method offers the advantage of being able to bring core body temperatures to target levels in under 1 h while maintaining a narrow range of temperatures [73–75]. In addition, these devices can be placed similar to a central venous catheter in the femoral vein. This technology appears safe but has not sparked enough enthusiasm to conduct a large therapeutic trial in the acute stroke setting. These devices, although heparin coated, have the theoretical potential of a thrombus forming on the catheters along with the fact that the procedure is invasive and cannot be performed in the field. In addition, they may be simply not suitable to cool patients rapidly enough as required in the clinical settings of stroke.

Regional cooling

Other techniques described as methods of selective cooling include cold carotid artery perfusion with temperature-reduced blood [76] and selective infusion of cold saline into the ischemic territory via a catheter placed in the vessel supplying the infarcted region [77]. This latter technique involves infusion of cold saline (20°C) through a catheter placed in the blood vessel supplying the ischemic territory. This method has shown that direct cold saline infusion into the ischemic territory led to significantly lower infarct volumes that translated into improved neurologic function in a temporary occlusion rodent model [77]. A reduction of brain temperature to 33°C was achieved rapidly without induction of systemic hypothermia. This method holds promise for patients undergoing intra-arterial therapies through endovascular techniques to recanalize the occluded vessel as evidenced by a recently constructed mathematical model. This model revealed that cooling can be achieved through microcatheters at a rate 30-times faster then cooling blankets and ten-times faster then endovascular cooling devices placed in the inferior vena cava [78].

Clinically, local intra-arterial thrombolytic therapy is used successfully to reperfuse acutely occluded cerebral vessels [7], either by mechanically disrupting [79] or suctioning the clot [80]. One mechanical approach using a corkscrew-shaped wire tip to retract clots, Merci® Retrieval System (Concentric Medical, Inc., CA, USA), has shown promise. The device has recently received US Food and Drug Administration approval and is likely to translate into an increase in patients receiving endovascular treatment for acute stroke [201]. The combined approach of intra-arterial revascularization along with regional infusion of cold saline appears to be a feasible method to achieve neuroprotection but requires further study.

Drug-induced hypothermia

Pharmacologic agents that either increase the rapidity of achieving hypothermia or induce hypothermia themselves have also been described. Endogenous cannabinoids (CB) are upregulated during global and focal cerebral ischemia [81]. The receptor for these endocannabionoids is CB_1. CB_1 agonists can act on the hypothalamus receptors to induce hypothermia [82]. A recent study showed that when a CB_1 agonist was administered intravenously to rats in a permanent MCA occlusion model, mild-to-moderate hypothermia could be achieved [83]. The authors were able to show a reduction of infarct volume and improvement in neurologic outcomes. Part of this effect was postulated to be independent of the hypothermia.

A second receptor closely linked to CB_1 is the 5-HT_7 receptor. An endogenous lipid compound oleamide has been shown to reduce body temperatures [84]. Recently, it has been shown that this agent activates the 5-HT_7 receptors in the hypothalamus and thalamus thereby closely linking its physiologic effects of sleep and reduction of core body temperature [84]. Further study of oleamide revealed that this endogenous substance induces hypothermia in a 5-HT_7 knockout mouse model. This suggests that the agent may act through an additional mechanism or receptor [85].

Magnesium sulfate may help to increase the speed of systemic cooling [86], while also theoretically having a synergistic neuroprotectant effect in reducing infarct volumes due to its antagonist effect on the NMDA receptor [87]. Topiramate is an antiepileptic drug known for its neuroprotective properties through inhibition of AMPA receptors and modulation of GABA receptors [88]. A recent report has shown that this neuroprotectant can increase the time window for hypothermia initiation in rats and still maintain its benefits [89]. Lastly, Coenzyme Q10 (cofactor for the mitochondria) has recently been shown to improve neurologic outcomes when combined with mild hypothermia in comatose patients after cardiac arrest [90]. The mechanism is unclear but elucidates that combination therapy may prove to be more efficacious.

Pharmacologic agents may play an adjunctive role to thermoregulation and hypothermia in future studies.

Thermoregulation

The major drawback of therapeutic cooling is that the body is forced below an individual setpoint that may be counteracted by normal physiologic responses. Heat loss occurs through an increase in basal metabolic rate mostly through radiation, but shivering and conduction make smaller contributions. When the temperature is between 37 and 32°C, vasoconstriction, shivering, and nonshivering basal and endocrinologic thermogenesis generate heat. From 32 to 24°C, a progressive depression of the basal metabolic rate occurs without shivering thermogenesis. At temperatures below 24°C, autonomic and endocrinologic mechanisms for heat conservation become inactive. Such responses may potentially negate the beneficial effects of hypothermia. Regulated reductions in body temperature via a reduction in the set point appear to be a much better method of achieving a hypothermic state. Rodent models of ischemia when unregulated appear to have a mild hypothermic response as a result of the injury [91]. This reduction in setpoint may have a profound clinical impact in larger species such as humans and requires further investigation.

Additional research in pharmacologic agents that may reduce shivering also hold promise going forward. Meperidine is an opioid with known antishivering properties. The

downside to this drug is that larger doses may induce respiratory depression thereby placing a tenuous stroke patient at risk of requiring mechanical ventilation. As discussed earlier, magnesium sulfate has antishivering properties allowing it to speed the rate of cooling [86]. Two other target receptors of recent interest include α_2-agonists and 5-HT_{1A} agonists as these receptors are not associated with respiratory depression. Dexmedetomidine is an α_2-agonist that blunts the central sympathetics thereby providing analgesia without altering the respiratory drive significantly [92]. The combination of meperidine and dexmedetomidine in healthy subjects can reduce the shivering threshold without respiratory depression [93].

Buspirone is a 5-HT_{1A} agonist that affects thermoregulatory centers within the hypothalamus. In certain animals it can induce hypothermia. When given alone, it can reduce the shivering threshold of healthy humans and is synergistic with meperidine in its antishivering properties [94]. The combination allows for smaller doses of both drugs thereby reducing the risk of respiratory depression in patients.

Pharmacologic interventions to reduce the shivering threshold require further study in patients treated with hypothermia but can potentially aid in quickly achieving target temperature goals.

Animal data

There are two rodent models that have been utilized to test the effectiveness of hypothermia: the temporary MCA occlusion model and permanent MCA occlusion model.

Temporary MCA occlusion model

With the temporary occlusion model, the rat's MCA is occluded with preformed embolic material or a temporary clip and then reperfused with thrombolytics or removal of the clip. The aim of this model is to mimic the clinical scenario where the vessel is recannalized along with institution of hypothermia. It is important to understand that in a human trial, hypothermia would need to be studied with reperfusion strategies concomitantly in order to mimic this type of an animal model. There have been numerous studies reproducing similar results using the temporary occlusion models [95–97]. The differences of these studies have been with regards to timing of initiating hypothermia and degree of hypothermia. It appears that mild-to-moderate hypothermia is effective in infarct volume reduction and that earlier initiation of therapy offers the most clinical and radiographic benefit. The degree of improvement varies according to the rodent model and time to initiate hypothermia [98].

Permanent MCA occlusion model

The permanent occlusion model assumes the hypothesis that, despite persistent MCA occlusion, hypothermia will lead to a reduction of infarct volume. The results of this model have been more inconsistent. Moreover, the models showing benefit have all initiated hypothermia within 1 h [99,100]. In clinical practice, it may be difficult to replicate this model as a very small percentage of patients seek medical attention within 1 h of a stroke. These studies emphasize the importance of designing trials aimed at utilizing neuroprotection in conjunction with recanalization therapies.

Clinical trials

Therapeutic mild-to-moderate hypothermia has been tested in the clinical setting for two purposes: reduction of ischemic stroke volume as well as reduction of swelling after a large middle cerebral artery territory infarction. Until today, no definitive controlled therapeutic trial has been attempted to assess hypothermia in acute stroke. To explore the field the recent data from two major trials showing benefit of hypothermia in patients suffering from ventricular fibrillation cardiac arrest are reviewed [59,61].

These prospective randomized controlled studies showed a benefit corresponding to better clinical outcomes in patients who underwent hypothermia over patients who remained normothermic. In the Melbourne study, 77 patients were randomized to moderate hypothermia (33°C) and normothermia [59]. Patients were enrolled at the scene of cardiac arrest. Once resuscitation was performed and the patient was found to be comatose, the ambulance team would place ice packs on the patient's head and torso. Upon arrival to the emergency room more aggressive surface cooling techniques were employed to bring the patient to goal core temperature. After controlling for age and time to collapse, the patients who were treated with hypothermia were five-times more likely to be discharged to acute rehabilitation or home (odds ratio [OR] 5.25 [95% confidence interval; 1.47–18.76]; $p < 0.011$) [59]. A second study from Vienna revealed a similar benefit with hypothermia after cardiac arrest [61]. They enrolled 275 patients and randomized them to hypothermia and normothermia. It took an average of 8 h to achieve target-cooling temperature with an external surface-cooling device. This study also revealed a significantly higher proportion of patients receiving hypothermia with a favorable neurologic outcome when compared with the normothermia group (55 vs. 39%, OR 1.4 [1.08–1.81]; $p < 0.009$) [61].

Management of cerebral edema after massive middle cerebral territory infarct has been a challenge. Medical measures such as osmotherapy, elevation of the head of bed, barbiturates and hyperventilation often have transient benefits and do not ultimately alter the course of tissue shifts that occur with swelling. Mortality rates from this syndrome have been reported to be as high as 80% with medical treatment [101]. A reduction of mortality rates has been shown with decompressive craniectomy, a surgical procedure that removes the bone flap on the side of the stroke to relieve intracranial pressure. Currently, it is unclear as to which patients benefit from this surgery, although its benefit may be limited to younger patients [102]. Reports from the head trauma literature have shown that elevated ICP can be reduced with hypothermia [103]. This prompted the first clinical evaluation of hypothermia to treat cerebral edema after

massive middle cerebral artery territory infarction [63]. In total, 25 patients were cooled with surface cooling and required a range of 3.5–6.2 h to achieve the target temperature of 32–34°C. There was a reduction of ICP in patients who were cooled from 21 mmHg to a mean of 14.5 mmHg. The overall mortality for the group was found to be lower than historical controls (44 vs. 80%). Of note, as patients were being rewarmed, 30% of them developed rebound intracranial hypertension as a result. Thus it is unclear if the therapy was delaying the inevitable as is seen with other medical therapies.

This prompted the same group to compare decompressive craniectomy and hypothermia to treat massive middle cerebral artery territory infarction [104]. The results showed that patients who underwent surgical decompression had a lower mortality rate when compared with hypothermia (12 vs. 47%). It was noted that three out of 19 (16%) patients allocated to hypothermia died during the rewarming phase. These studies revealed that hypothermia is effective in reducing intracranial pressure, but the rewarming phase can often lead to a rebound increase in ICP. Animal data suggests that combining hypothermia with decompressive craniectomy may have an additive benefit [99]. Doerfler and colleagues found that combined hypothermia and craniectomy reduced infarct volumes and improved neurologic function in Wistar rates when compared with control and craniectomy alone. This may prove to be one of the roles of hypothermia going forward [99].

The last set of clinical trials have centered on initiating hypothermia early to reduce infarct volume and thus improve functional outcomes. A summary of these trials is listed in TABLE 3. The COOLAID I [64] and Copenhagen Study Group [105] used surface cooling as a means to achieve target body temperatures while COOLAID II used an endovascular device [75]. TABLE 1 summarizes these studies. All of these studies concluded that hypothermia is safe and feasible in patients suffering from severe ischemic stroke.

A recently initiated Phase I study entitled 'Intravascular cooling in the Treatment of Stroke-Longer tPA window' will address the question of whether hypothermia can extend the time window to administer tPA intravenously in acute ischemic stroke [202]. The trial will utilize an endovascular cooling device and enroll awake patients that arrive within 6 h from symptom onset. A second randomized control study that is currently enrolling patients is entitled the 'Nordic Cooling Stroke Study' [203]. This study is using surface cooling in acute stroke patients with the intent of being able to target a larger population of acute strokes. Currently, no randomized controlled trials are available to determine the efficacy of hypothermia.

Conclusions

Hypothermia currently has great potential at being shown to be a clinically significant neuroprotectant. Questions with regards to time to initiating hypothermia, safest methods to achieve hypothermia and duration still need to be answered. Ongoing clinical trials are currently focused on showing safety, with newer approaches being designed to reduce the systemic side effects.

Expert opinion

Hypothermia is the most powerful neuroprotectant available as it acts upon multiple aspects of the metabolic cascade thought to initiate ischemic death to brain tissue. It is beneficial in patients who have suffered global anoxia secondary to cardiac arrest and is likely to be beneficial in focal ischemic stroke with correctly designed studies. Further study in the form of randomized controlled studies are required to define the time window to initiate therapy, depth and duration of therapy, and precise patient population that is most likely to benefit from this therapy.

Five-year view

The future of hypothermia appears bright with many aspects of this therapy currently being studied and more promising approaches are yet to be tested in the future. These approaches to reduce the systemic side effects will help to design studies with a higher chance of showing clinical benefit. A focus on initiating hypothermia early in conjunction with other receptor targets via pharmacologic agents may also provide synergistic neuroprotective effects. A better understanding of thermoregulation and finding methods to lower the body's setpoint may be safer and more efficient at achieving therapeutic hypothermia. The role of this neuroprotectant for the management of cerebral edema after massive stroke will need to be studied as an

Table 3. Clinical trials testing hypothermia in acute ischemic stroke.

	COOLAID I*	Copenhagen‡ Group	COOLAID II	Georgiadis and colleagues
N	10	17	18	6
Age (years)	71 ± 14	69 ± 16	61 ± 12	65 ± 8
Mean NIHSS	20 ± 3	26 ± 12*	15 ± 4	
Mean time to initiate hypothermia (hours)	6 ± 1	3	9 ± 3	28 ± 17
Mean time to achieve target temperature (hours)	3.5 ± 1.5	6	77 ± 44 min	3 ± 1

*Scandanavian Stroke Scale.
‡Surface cooling techniques.
COOLAID: COOLing for Acute Ischemic brain Damage; NIHSS: National Institutes of Health Stroke Scale.

adjunct to decompressive craniectomy. Patients who are treated with hypothermia may have a longer time window where reperfusion strategies with thrombolytics or mechanical disruption may prove to be beneficial. This benefit may come in the form of a reduction of secondary hemorrhages that will in turn help to show the benefit of revascularization procedures.

Key issues

- Hypothermia is a nonspecific neuroprotectant making it advantageous as it acts on many aspects of the metabolic cascades involved with neuronal injury.
- Hypothermia may be utilized for different aspects of ischemic stroke management: management of elevated intracranial pressure, extending the time window for reperfusion therapy and revent secondary hemorrhage through stabilization of the blood–brain barrier after administration of thrombolytics.
- Selective methods of delivering hypothermia to the brain will reduce the significant medical complications that occur with systemic hypothermia, thereby increasing the effectiveness of the therapy.
- Clinical trials going forward will help to elucidate the patient population best served by hypothermia and the appropriate time window to initiate therapy.

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Webites

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