Therapeutic hypothermia for stroke: Unique challenges at the bedside

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Therapeutic hypothermia has shown promise as a means to improving neurological outcomes at several neurological conditions. At the clinical level, it has been shown to improve outcomes in comatose survivors of cardiac arrest and in neonatal hypoxic ischemic encephalopathy, but has yet to be convincingly demonstrated in stroke. While numerous preclinical studies have shown benefit in stroke models, translating this to the clinical level has proven challenging. Major obstacles include cooling patients with typical stroke who are awake and breathing spontaneously but often have significant comorbidities. Solutions around these problems include selective brain cooling and cooling to lesser depths or avoiding hyperthermia. This review will cover the mechanisms of protection by therapeutic hypothermia, as well as recent progress made in selective brain cooling and the neuroprotective effects of only slightly lowering brain temperature. Therapeutic hypothermia for stroke has been shown to be feasible, but has yet to be definitively proven effective. There is clearly much work to be undertaken in this area.

KEYWORDS

ischemic stroke, systemic therapeutic hypothermia, selective brain cooling, targeted temperature management, cell death, inflammation, clinical outcomes

Introduction

Acute ischemic stroke is the primary cause of about 85% of strokes worldwide and is most frequently caused by blood clots or atherosclerosis occluding cerebral blood flow (1, 2). Studies have shown that decreasing the time between presentation and intervention can improve clinical outcomes (2, 3). Modern management efforts thus emphasize the time sensitivity of stroke treatment. Antiplatelet and anticoagulant drugs have long been the mainstay of ischemic stroke management, along with the use of acute thrombolysis and mechanical thrombectomy to revascularize thrombosed vessels (4–6). If initiated rapidly, these revascularization strategies reduce morbidity and improve neurological outcomes, although the window for these interventions is on the order of hours (6, 7). Unfortunately, due to a variety of constraints, a majority of patients tend to present too late for these interventions and are not eligible for potentially life-saving and disability-preventing treatments (8–11). Thus, adjunctive treatments may be needed to extend this critical time interval to offer treatments to a broader number of stroke victims.

Therapeutic hypothermia (TH) has been suggested as a potential approach to achieve the goal (12, 13). In 2002, two randomized controlled trials (RCT) showed the induction of mild hypothermia (32–34°C) produced more favorable neurologic outcomes and improved survival after cardiac arrest compared with patients for whom body temperatures were maintained in the normothermic range (14, 15). TH has since been rapidly implemented worldwide and established as a gold standard in the management of comatose survivors of cardiac arrest; however, TH has only been shown to be effective at the clinical level in patients suffering from cardiac arrest and in neonates suffering from hypoxic ischemic encephalopathy (HIE) (16–18). In this review, TH refers to cooling the body in order to preserve organ viability and is so far the most effective therapy for improving neurological outcomes in comatose survivors of cardiac arrest (14, 18, 19). Subsequent studies have also shown that modulation of body temperature to normal and slightly below normal levels may also be beneficial. Thus, the term targeted temperature management (TTM) refers to modulation of body temperature including TH.

In spite of the optimism of TTM in cardiac arrest and neonatal HIE, clinical applications of TTM in other acute brain injuries, such as hemorrhagic or ischemic stroke and traumatic brain injury, have yet to demonstrate improvement in clinical outcomes (20–25). Yet, multiple preclinical studies have consistently shown that TH induces multiple and synergistic effects for neuroprotection in experimental models (16, 26). A major challenge in translating this to the clinical level is that therapeutic hypothermia studies in many experimental models used small species where whole body cooling can be achieved in a short period of time. By contrast, humans have much larger mass, and whole body cooling to achieve target brain temperatures for optimal neuroprotection requires many hours. Furthermore, patients with stroke are typically older with comorbidities, which could complicate TH. Thus, selectively cooling the brain has the potential not only to achieve more rapid cooling but may reduce systemic complications. Efforts to achieve this included using internal catheters to reduce temperatures of the cerebral vessels, which would then cool brain tissue (23, 25), or cooling caps to directly cool the brain (27–29), but these approaches have achieved limited success. Regardless, it is clear that reducing brain temperature can improve neurological outcomes from many acute brain insults. This review covers the current state of TTM as it relates to clinical stroke care.

Mechanisms of hypothermic protection in experimental ischemic stroke

To understand the robust neuroprotective effects of TH, it is important to understand the preclinical works related to understanding why TH seems so effective. TH has long been thought to lead to beneficial effects by decreasing brain metabolism (16), but through multiple experimental studies, it has now been recognized that TH exerts neuroprotection by favorably altering a broad range of pathological pathways, including the regulation of brain metabolism, apoptosis, microglial activation, cerebral blood flow, inflammation, and neurotrophic factors (16, 26). As such, this may be a major reason why lowering brain temperature may lead to preservation of brain tissue and function.

Effect of hypothermia on brain metabolism, blood flow, and excitotoxicity

In ischemic stroke models, hypothermia to brain at temperatures of 33°C (mild hypothermia) showed improved cerebral blood flow and preservation of the cellular metabolic rate (30, 31). During stroke, cerebral blood flow (CBF) is disrupted following vessel occlusion. If blood flow is restored (reperfusion), there is a brief and abrupt overshoot of CBF, followed by gradual deterioration. Microvascular narrowing was thought to underlie this deterioration (32), and TH has been shown not only to improve and maintain CBF by preventing microcirculatory collapse but also seems to prevent this brief overshoot of CBF upon reperfusion (33).

Brain metabolism is also sensitive to temperature. Mild hypothermia reduces oxygen consumption by a $\sim5\%/°C$ decrease in body temperature in the range of 22–37°C (2). Cerebral ischemia also leads to increased accumulation of extracellular glutamate and influx of calcium (34). Hypothermia has been documented to prevent glutamate accumulation and subsequent excitotoxicity mediated by calcium influx (26, 35). More recently, hypothermia also appears to suppress the calcium-sensing receptor (CaSR) expression, which regulates calcium influx and upregulates the inhibitory gamma-aminobutyric acid B receptor 1 (GABA-B-R1) (36). As such, hypothermia appears to induce neuroprotective effects in ischemia models by affecting multiple aspects of brain metabolism and neurotransmission.

Neuroprotection by hypothermia: Cell death pathways

Beyond early observations that hypothermia preserves tissue metabolic reserves and reduces ischemic elaboration of excitotoxins, hypothermia has also been shown to positively influence several ischemic cell death pathways, such as apoptosis (37). Several studies have shown that hypothermia can prevent apoptotic cell death in stroke models (38–40). TH was first

shown to affect several aspects of the intrinsic pathway, ultimately leading to neuroprotection. The intrinsic pathway is initiated within the cell mitochondria *via* release of various factors, such as cytochrome c and apoptosis-initiating factor (AIF), into the cytosol (41). Mild hypothermia has been shown to increase the anti-apoptotic protein Bcl-2, which, in turn, inhibits cytosolic cytochrome c release and subsequent caspase activation (42). A few studies have also shown that mild hypothermia reduces the generation of pro-apoptotic Bax (43–46). Downstream of Bcl2, hypothermia has been shown to influence protein kinase C (PKC) family members, such as anti-apoptotic (PKCε) or pro-apoptotic (PKCδ), so as to lead to overreduction in apoptotic cell death (39).

The extrinsic apoptotic pathway is triggered *via* death receptors, which, when ligated, leads to cell death. A prototypical death receptor, Fas, and its corresponding ligand, Fas ligand (FasL), have also been studied in stroke models, and interrupting this pathway has been shown to improve outcomes in stroke models (47). TH has been shown to decrease the expression of Fas and FasL and subsequent activation of downstream caspase-8 (48–51).

TH can also affect caspase-independent apoptosis. The mitochondrial apoptosis-inducing factor (AIF) pathway involves direct apoptotic cell death and is capable of inducing apoptosis without activating caspases (52). Mild hypothermia suppressed AIF translocation from the mitochondria to the cytosol and led to reduced apoptotic cell death in an ischemic stroke model (53). In sum, TH is capable of influencing many cell death pathways in such a way so as to favor cell survival.

Hypothermia and cell survival pathways

Interestingly, while TH inhibits many molecules associated with apoptotic cell death, it can also upregulate several factors involved in cell survival. Part of the reason may be due to the upregulation of cold stress proteins, which are induced at lower body temperatures. RNA-binding motif protein 3 (RBM3), perhaps the best studied of these cold stress proteins, has been shown to increase under hypothermic conditions after stroke in laboratory and clinical studies (54) and is associated with neuroprotection (55). TH has also been shown to increase the expression of brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GNF), and neurotrophin (NT) in ischemia-injured brain (56–58). Mild hypothermia induced phosphorylation of extracellular signal-regulated kinase-1/2 (ERK1/2), which is downstream of BDNF (56), and has also been shown to activate Akt, which is a serine/threonine protein kinase that has multiple roles in cellular plasticity and migration (59). Downstream of Akt, phosphatase and tensin homolog (PTEN) may lead to apoptosis, but in its phosphorylated state, it promotes cell survival. Phosphorylated PTEN is also known to prevent neuronal cell death in ischemic brain injury (53),

and TH preserves phosphorylated PTEN levels in stroke models (60). These observations indicate that while brain cooling suppresses metabolic and cellular functions, lower temperatures also permit the upregulation of other factors that ultimately promote cell survival.

Anti-inflammatory effects of hypothermia

Following acute ischemic stroke, necrotic cells, cell debris, and increased reactive oxygen species (ROS) induce inflammatory responses, which are related to activating microglia and infiltrating leukocytes from circulating blood to parenchymal brain tissue. The recruitment of both brain and peripheral immune cells in post-ischemic tissue can accelerate and expand an infarct initiated by ischemia (61). Mild hypothermia suppresses microglial activation and tissue viability after ischemic stroke (35) and prevents infiltrating neutrophils from entering ischemic brain tissue. TH has also been shown to reduce levels of many inflammatory mediators, such as adhesion molecules, ROS, and pro-inflammatory cytokines (62–64).

TH also affects the activity of transcription factors involved in inflammatory responses, such as nuclear factor-κB (NF-κB) (65). In brain ischemia models, TH has been shown to prevent NF-κB translocation to the nucleus and preventing the upregulation of target pro-inflammatory genes (66). TH has similarly been shown to inhibit other transcription factors, including mitogen-activated protein kinase (MAPK), and Janus kinases/signal transducer and activator of transcription proteins (JAK/STATs), all of which have been documented to elicit inflammation following stroke (67, 68).

Cytokines, which play an important role in immune system signaling and potentiation of immune responses, are quickly and extensively upregulated in brain tissue after ischemic stroke (69). TH has been shown to suppress many inflammatory cytokines, including transforming growth factor (TGF)-β, tumor necrosis factor-α (TNF-α), and several interleukins (IL) (59, 64). TH has also been shown to induce an anti-inflammatory M2 phenotype in microglia in stroke models (70). Recent work has shown that even a low normal temperature of 36°C can attenuate protein levels of several pro-inflammatory cytokines (71), and temperature modulation to both 33 and 36°C can provide equivalent neuroprotection by decreasing pro-inflammatory M1 activation of microglia and by relatively increasing microglial polarization toward a beneficial M2 phenotype (71). Considering recent concerns at the clinical level that TH to temperatures of 32–34°C may be poorly tolerated in some patients, it is indicated that a body temperature of 36°C may be better tolerated clinically and may have some therapeutic and anti-inflammatory effects (71).

Differential protection within the neurovascular unit

While neuroprotection in laboratory studies has shown fairly consistent and robust results in various disease models, the same cannot be said at the clinical level. Thus, taking into consideration various cells that comprise the neurovascular unit, Lyden et al. (72) systematically examined the protective effects of cooling in cultures of neurons, astrocytes, and brain-derived endothelial cells and found considerable differences in their response to cooling. In particular, they found that cooling inhibited astrocyte activation and seemed to prevent any beneficial effect of paracrine factors that astrocytes provide neurons. The study also found that different cell populations, while showing a similar pattern of dose-dependent responses to the depth and duration of cooling and finite responses to cooling delays, the time frame was different depending on the cell type. In line with prior reports (73), the investigators found that lower temperatures offered more robust protection, and that delaying the onset of cooling required longer cooling times. Yet, they also warned that longer cooling times could also interrupt the paracrine functions of astrocytes, which, in turn, could reduce the effectiveness of the therapy. Subsequent studies by other laboratories have since shown that cooling improves other properties of astrocytes, such as their ability to transfer viable mitochondria to injured neurons (74) and that their phenotype can shift from an activated (A1) to a non-activated (A2) state (75). Thus, these recent laboratory observations should be considered in the design of future clinical trials.

Clinical application and adverse effects of systemic therapeutic hypothermia

The clinical application of TH has become more effective, simpler, and safer by the development of automated cooling devices through intravascular or surface cooling (16, 76, 77). In practice, TH consists of three critical phases: induction, maintenance, and rewarming (16, 78). Induction involves minimizing ongoing irreversible neuronal injury due to ischemia and reperfusion, and target temperature should be reached as rapidly as possible, typically by using ice packs and infusion of cold intravenous fluids (77). During the maintenance phase after the target temperature is reached, core temperature should be maintained by using advanced cooling technologies ($\pm$ 0.5°C of the target temperature) (79). One of the many benefits of TH during the maintenance phase is decreased intracranial pressure (ICP). The most robust clinical benefit of TH on ICP is when systemic body temperature decreases to <35.5°C (16, 17, 80). The rewarming phase can be the most detrimental phase in TH if body temperature is increased too rapidly. This

can lead to systemic vasodilation and hypotension. As a consequence, rapid rewarming can induce cerebral vasodilation and lead to abrupt ICP increases (21, 81, 82), which can lead to bad outcomes, especially in patients with brain edema (83).

In clinical trials, long durations of TH have been limited by feasibility and several complications of cooling (84). Preclinical studies revealed that transient and rebound elevation of ICP may occur during rewarming 18–24 h after stroke, which leads to neurological deterioration (84–86). Short (2.5 h) and ultra-short durations (30 min) of TH could prevent significant ICP elevations (84, 85), although cooling to 34.5°C with ultra-short durations did not significantly prevent ICP elevation and did not decrease infarct volume (84). As such, the authors suggested that milder hypothermia ($\geq$ 34.5°C) requires a longer duration at target temperature (84). It remains to be seen whether short-duration mild hypothermia can provide the same benefits of TH in clinical practice. Although further preclinical studies need to validate the therapeutic benefits of short-duration cooling in patients with stroke, short- and ultra-short-duration cooling could be an alternative to minimize complications and maximize therapeutic effects.

Hypothermia also induces shivering in awake individuals as body temperature reaches about 35.5°C in healthy individuals. It is a major adverse effect as it interferes with the cooling process by making it difficult to reach the target temperature and causes detrimental effects through its massive increase in metabolic demand and energy consumption both systemically and by the brain (16, 76, 87). If shivering can be controlled, TH is then able to decrease systemic and cerebral metabolism and permit the beneficial effects of cooling to proceed. Lowered temperatures are not without risk. In clinical studies, TH has been shown to reduce electrolyte levels, such as that of potassium, phosphate, and magnesium (88). In addition, carbon dioxide partial pressure (pCO2) is lower and blood pH is increased because carbon dioxide becomes more soluble in hypothermic patients (89). This phenomenon called alkaline shift can occur during cooling. Hypothermia can also lead to hyperglycemia due to insulin resistance, while rewarming after hypothermia can induce hypoglycemia through a rapid increase in insulin sensitivity (90). Hypothermia, even mild hypothermia, is capable of inducing cardiac arrhythmias such as atrial and ventricular tachycardia and fibrillation. In general, these arrhythmias can be precipitated when core temperatures fall below 32°C, but those with underlying cardiac conditions may be more sensitive to cooling and develop arrhythmias at higher temperatures. In most cases, the heart tolerates hypothermia in temperature ranges between 32°C and 35°C (90, 91). As hypothermia impairs immune function, coagulation, and platelet function, cooling can increase the risk of infections, such as pneumonia, coagulopathy, and bleeding (16, 92).

Current state of systemic therapeutic hypothermia for acute ischemic stroke

At the clinical level, current practices suggest lowering body and/or brain temperature for 12–24 h to 32–34°C. This is based on both experimental studies and clinical studies in comatose survivors of cardiac arrest (14). Although it is well documented that therapeutic hypothermia has beneficial effects in many animal models of ischemic and traumatic brain injury, further larger clinical trials are needed to validate its therapeutic efficacy and its full translation in humans in the treatment of acute ischemic stroke (73, 93, 94). Currently, there are no large phase III studies to evaluate TTM for acute ischemic stroke. The Cooling for Acute Ischemic Brain Damage (COOL-AID) trial was a small trial conducted to assess feasibility of moderate cooling of 32–33°C using an endovascular device in patients with acute ischemic stroke (95, 96). There was no significant improvement in modified Rankin scores (mRS) and mortality in the hypothermic group in comparison with the control group, although the trial was not intended to study efficacy (95, 96).

The Intravascular Cooling Trial of Acute Stroke (ICTuS) demonstrated safety of 12–24 h of intravascular cooling in patients with stroke (23, 25). It also tested a protocol to reduce shivering in normally awake patients with stroke and found that an anti-shivering regimen with buspirone and meperidine could be given in this patient population. A subsequent trial, the Intravascular Cooling in the Treatment of Stroke-Longer tissue plasminogen activator (tPA) Window (ICTuS-L) trial, also showed acceptable safety and feasibility for intravascular TH in patients who received intravenous tPA (24, 25). Unfortunately, there was no significant improvement in modified Rankin scores (mRS) and mortality in the hypothermic group compared with the control group (24). They also reported significantly increased risks of pneumonia in the ICTuS-L patients who received TH (25, 97). To provide safer, faster TH in patients with stroke, an expanded trial, ICTuS-2, failed to reduce the risk of pneumonia and mortality in the TH-treated group (25). The COOL-AID and the ICTuS-L trials highlighted significant clinical issues associated with TH, such as shivering control, airway management, and prevention of complications (98–100).

In patients with malignant middle cerebral artery (MCA) stroke, TH to 33°C ± 1°C after early decompressive hemicraniectomy had no significant improvement in mortality at 14 days and neurological outcomes at 12 months in comparison to the control group that does not allow actively lowering beneath 36.5°C (101, 102). Unfortunately, the study showed that the TH group after early decompressive hemicraniectomy had a higher rate of serious adverse effects than the control group (102). To identify the benefits of hypothermia on the clinical outcomes of patients with large hemispheric infarction (LHI), Li et al. performed systematic review and meta-analysis (103) and found that there was no significant benefit between application of hypothermia and mortality. They also found that there was a higher risk of several adverse effects. Yet, TH in patients with LHI had improved neurological outcomes compared with patients with LHI who did not receive cooling (103). Future studies are also necessary to demonstrate the safety and effectiveness of hypothermia for LHI.

Despite several clinical trials in ischemic stroke, none have proved the effectiveness of TTM in this patient population (104). Although some studies showed a positive trend toward better outcomes, a systemic review and meta-analysis by Kuczynski et al. (105) did not find that TTM after acute ischemic stroke provided beneficial effects. Unfortunately, TH increased risks of complications in patients with stroke who are typically older with more medical comorbidities than other patient populations (93, 105), although one study by Hong et al. (106) showed lower rates of pneumonia in patients who received TH after stroke than reported in other studies. In their study, all patients receiving TH underwent mechanical ventilation; this may represent a critical difference in the therapeutic protocols for hypothermia in cardiac arrest studies compared with stroke studies and suggest the importance of a secure airway for the prevention of pneumonia (106). Furthermore, most patients with stroke remain awake and breathe spontaneously during the acute phase of stroke (16), compared with studies of TTM in comatose survivors of cardiac arrest. Because of older age and comorbidities in these patients, it may be dangerous to employ sedative and anti-shivering agents, advanced airway management, and mechanical ventilation. Sedation and respiratory depression that may result from the use of pharmacological anti-shivering agents can impede the neurological examination and aggravate hypoxia and hypercarbia. These are additional reasons that any neuroprotective effects of TH may not be observed in patients with stroke (16). Since systemic hypothermia can affect all organ systems in the human body, the use of TTM should be based on the balance between its potential benefits and harm (18).

In spite of many setbacks at the clinical level, TTM still has the strongest evidence for neuroprotection in preclinical studies. There is still much to be learned about the underlying mechanisms of this protection, and aspects of hypothermic neuroprotection could be leveraged to develop an effective yet safe therapy for patients with stroke.

Clinical challenges of therapeutic hypothermia for acute ischemic stroke

Selective brain cooling

Since whole body cooling to achieve lower brain temperatures can inadvertently lead to systemic complications,

selective brain cooling has the potential to avoid these complications while potentially offering robust neuroprotection to the brain. Selective brain cooling lowers temperature of the brain to below the core temperature by inducing a net temperature gradient between the brain and the rest of the body [107]. This approach has been shown to be feasible and resulted in the same benefits of TH in a variety of animal models. Particularly for patients with stroke, this approach is an attractive alternative to systemic hypothermia for neuroprotection [108]. In general, selective brain cooling promotes more rapid, profound, organ-specific induction and maintenance of target temperature of the brain in comparison with systemic hypothermia [107, 108].

Selective brain cooling consists of both non-invasive and invasive cooling methods [109]. Non-invasive approaches include local surface cooling such as a cooling helmet, cap, or a head-and-neck cooling device that could induce a median gradient of temperature between the brain and the core of $3.4°C$. Selective brain cooling was shown to be feasible in newborn pigs subjected to a global ischemic insult [110]. Selective brain cooling in clinical studies of severe traumatic brain injury also led to improved neurological outcomes without severe complications in patients receiving cooling caps and neckbands after severe traumatic brain injury [107, 110, 111]. Another approach is that of intranasal cooling, which leads to heat exchange by direct heat loss to air and evaporation of water, which can reach up to a 10% rate of total body heat loss in normal conditions [107]. Transnasal evaporative cooling has been shown to improve neurological outcomes in patients who received cardiopulmonary resuscitation after cardiac arrest with acceptable feasibility and safety [112, 113]. However, non-invasive cooling using surface cooling and nasopharyngeal cooling is relatively less effective in lowering temperature of the brain parenchyma [20]. Furthermore, since surface cooling will ultimately lead to local cooling of circulating blood, selective surface cooling has the potential to cool other parts of the body as well.

Invasive selective cooling includes epidural, subdural, and subarachnoid cooling; retrograde jugular venous cooling; and intraarterial selective cooling [20]. Despite the effectiveness of invasive selective cooling, these methods lead to increased risks of infection and intracranial hemorrhage, thus limiting the application of these approaches in clinical settings [107].

Nevertheless, selective brain cooling has been increasingly embraced by those involved in the care of patients with acute ischemic stroke due to the challenges of whole body cooling outlined earlier [20]. Since endovascular embolectomy has been shown to have a role in the treatment of acute ischemic stroke in recent years, selective endovascular infusion of cold saline directly into the brain parenchyma offers a promising strategy to induce more rapid target temperature decreases to the brain through preexisting angiographic catheters [20, 114]. In animal models, local endovascular infusion of $23°C$ saline at 2 mL/min for 3–4 min before reperfusion leads to lowering of brain temperature within 10 min, and local endovascular infusion ($10°C$ saline at 0.25 mL/min) after reperfusion leads to decreased brain temperature to $< 35°C$ by 20 min [115]. In the Copenhagen Stroke Study, whole body surface cooling was able to reduce body temperature by a mean of $1.3°C$ without the use of anesthesia in awake patients with stroke [116, 117]. However, a significantly lower mean body temperature was achieved after 1 and 6 h of hypothermic therapy [$t_0 = 36.8°C$ vs. $t_1 = 36.4$, $P = 0.002$ and ($t_0 = 36.8°C$ vs. $t_6 = 35.5°C$, $P < 0.001$)] [116]. Since the time window for therapeutic intervention after ischemic insults is thought to be a matter of minutes to hours, rapid recognition of injury and rapid institution of treatments are highly desirable in patients with acute ischemic stroke [115]. Using selective endovascular infusion, target temperature can be reached more quickly than the classical surface cooling and systemic infusion of cold saline [115]. Initiating selective cooling before reperfusion significantly reduces the infarct volume by 75–90% and preserves motor function after ischemic stroke [114, 118, 119]. Several studies reported that postreperfusion selective hypothermia improved infarct volume and neurological recovery in animal models of stroke [120, 121]. Another neuroprotective benefit of local selective endovascular infusion over systemic infusion is washout of by-products of metabolism induced by ischemia, which can lead to vasodilatation [122]. This washout can minimize the extent of reperfusion injury that may be elicited by hyperperfusion [115]. Selective cooling through local endovascular infusion was recently verified to have acceptable safety and feasibility profiles not only in animals but also in humans [115].

In humans, Choi et al. studied 18 patients undergoing cerebral angiography who received infusion of isotonic saline ($4–17°C$) at 33 mL/min for 10 min into an internal carotid artery [123]. Cold saline infusion led to a $0.84°C$ decrease in jugular venous blood temperature [123], while systemic temperature was changed by $0.15°C$ from baseline [123]. These investigators also did not report any serious complications, such as vasospasm, microemboli, pain, and focal neurologic deficits [123].

In a few small, non-randomized, observational studies, Chen et al. demonstrated that selective brain cooling by at least $2°C$ in brain tissue through intraarterial infusion of $4°C$ cold saline combined with endovascular recanalization was feasible and safe in patients with acute ischemic stroke [122, 124]. A prospective non-randomized cohort study of 113 consecutive patients with acute ischemic stroke reported that infarct volume was reduced at 3–7 days with acceptable safety in a cohort that received mechanical thrombectomy combined with intraarterial selective cooling infusion. However, at 90 days, no differences were found in the proportion of patients who achieved functional independence (mRS 0–2) [20, 109]. To

date, the clinical effectiveness of selective endovascular brain cooling remains to be determined in ischemic stroke patients with large-vessel occlusions to the brain (125). However, vessel recanalization by thrombolytic and mechanical recanalization therapies has been shown to improve functional outcomes in acute stroke and selective endovascular cooling could be fairly easily incorporated into clinical practice (2, 6, 126). Selective brain cooling combined with recanalization can also be a more effective strategy since preclinical studies have shown that TH is more effective when reperfusion occurs (115). Recently, novel selective cooling systems have been developed as a combination of nasopharyngeal brain and endovascular cooling systems (127). As recent technological advances, the application of sensors, artificial intelligence, and smart devices have the potential to reduce complications and maximize the therapeutic effect of selective brain cooling. Further studies are needed to explore optimal protocols for selective brain cooling that lead to improved clinical outcomes in patients with stroke.

Targeted temperature management at or near normothermia

TTM encompasses therapeutic hypothermia, mild therapeutic hypothermia, controlled normothermia, and treatment of fever (128). Subsequent work in the area of TTM for comatose survivors of cardiac arrest has explored the feasibility and therapeutic value of reducing the target temperature to $36°C$ (18). In 2013, a randomized controlled trial compared mortality and neurologic outcomes after the application of TTM in patients with cardiac arrest. Body temperatures of $33°C$ and $36°C$ were compared, and the benefits of TTM at $36°C$ were not inferior to those of TTM at $33°C$ (18). Furthermore, managing shivering and rewarming also maximizes the chances of maximal beneficial effects of TH (19).

Based on these studies and those conducted before, the selection and maintenance of target temperatures between $32°C$ and $36°C$ for at least 24 h were proposed as optimal for TTM by the 2015 Cardiopulmonary Resuscitation and Emergency Cardiovascular Care guidelines (92). TTM at $36°C$ has several advantages over lower temperatures as it may be easier to prevent shivering in the induction phase, reduce the risk of intracranial pressure increases in the rewarming phase, provide a safer margin for serious hypothermia-induced cardiac arrhythmias, and diminish the risk of other systemic detrimental effects of lower temperatures, such as renal dysfunction, coagulopathy, pneumonia, and sepsis. As the effects of TTM at $36°C$ were no different from $33°C$ after cardiac arrest, TTM at $36°C$ may prove more attractive in the treatment of patients with stroke. However, it should be noted that the aforementioned

study did not include a control group, where body temperature was maintained in the normal range for comparison.

Nevertheless, the damaging effects of hyperthermia and fever are well known in stroke (117, 129). In patients surviving cardiac arrest, the development of fever is also known to increase the risk for poor neurologic outcomes (130). Accordingly, the randomized Targeted Hypothermia vs. Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial was conducted to identify the beneficial and harmful effects of hypothermia in comparison with normothermia and early control of fever. As the TTM2 trial was limited to patients with out-of-hospital cardiac arrest (OHCA) of a presumed cardiac or unknown cause, this trial result is not universally accepted for stroke and other presentations of cardiac arrest (131, 132). In addition, there was no group without TTM; thus, this trial did not propose a therapeutic benefit between any active control of core temperature and no control (132). In common practice, TTM applications could be limited (131, 132). Future trials are necessary to answer questions raised by TTM2.

Patients treated with TTM after OHCA did not have reduced mortality at 6 months compared with those with controlled normothermia (132). Aneurysmal subarachnoid hemorrhage guidelines now recommend aggressive control of fever to near normothermia to prevent delayed cerebral ischemia due to vasospasm (133). Piironen et al. (134) studied a cohort of patients with stroke and compared neurological outcomes between those treated with mild hypothermia with $35°C$ with a surface cooling device and standard stroke unit care with the core temperatures maintained at $<37.5°C$ within 6 h of symptom onset. No differences were found in favorable outcomes between the groups at 3 months (134). The rate of adverse events was lower in patients who received mild hypothermia than in those who received moderate hypothermia in previous studies (134). The mortality rate in their study among the hypothermia group was 0% in comparison to 28% in the COOL AID II, 21% in the ICTuS-L, and 12% in the COOLAID Oresund trial (129, 134). Despite the adverse events and small doses of sedatives and anti-shivering medications, mild hypothermia to $35°C$ with a surface cooling device appears safe and feasible in spontaneously breathing and awake patients with stroke who received intravenous thrombolysis (129, 134). From a different perspective, controlled normothermia or TTM near normothermia may lead to similar neurologic outcomes without the requirement of sedative or anti-shivering agents, and with more severe adverse effects. However, further prospective multicenter studies are needed to validate the potential benefits of TTM to controlled or near normothermia.

Perspectives

Therapeutic hypothermia may be the most robust neuroprotective modality in laboratory and preclinical studies.

Neuroprotective effects have been associated with beneficial effects on metabolic, molecular, and inflammation-related events in cell death; however, clinical studies in patients with stroke have yet to demonstrate a clear benefit compared with favorable outcomes shown in other populations such as comatose survivors of cardiac arrest and neonatal ischemic encephalopathy. Recent laboratory observations shed light on differential vulnerabilities to cells that comprise the neurovascular unit that could drive more careful study of how to best apply TTM depending on factors such as the delay in cooling, which could drive the depth and duration of TTM therapy. To improve clinical outcomes by TTM in patients with stroke, numerous studies have collectively contributed important knowledge to overcome clinical obstacles. For TTM to be effective, faster induction, minimal impact on core temperature, and ameliorating systemic adverse effects have been significant challenges. Shivering has been perhaps the most challenging obstacle when using the surface cooling device in awake patients. Airway management has also been shown to be an important factor in good outcomes in patients with stroke treated with TTM to reduce complications, such as aspiration and pneumonia. Safety and feasibility studies of TH have revealed the challenges of TTM in patients with stroke, particularly those of older age and those with multiple comorbidities. It may also be necessary to apply both systemic and selective cooling modalities for optimal TH. Further preclinical and clinical studies are still needed to assess and optimize the indications, target core temperatures, rate, and depth of cooling as well as method, initiation, maintenance, and rewarming for cooling protocols. The potential for normothermia and near normothermia TTM should be further explored in this patient population as well. Much progress has been made for therapeutic cooling and temperature management in patients with stroke, but there is still more work to be undertaken.

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