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Therapeutic hypothermia: Applications in adults with acute ischemic stroke

Andrea M Kuczynski[1], Andrew M Demchuk[1,2], Mohammed A Almekhlafi[1,2,3]

Abstract:

The advent of mechanical thrombectomy and increasing alteplase use have transformed the care of patients with acute ischemic stroke. Patients with major arterial occlusions with poor outcomes now have a chance of returning to independent living in more than half of the cases. However, many patients with these severe strokes suffer major disability despite these therapies. The search is ongoing for agents that can be combined with thrombectomy to achieve better recovery through halting infarct growth and mitigating injury after ischemic stroke. Several studies in animals and humans have demonstrated that therapeutic hypothermia (TH) offers potential to interrupt the ischemic cascade, reduce infarct volume, and improve functional independence. We performed a literature search to look up recent advances in the use of TH surrounding the science, efficacy, and feasibility of inducing TH in modern stroke treatments. While protocols remain controversial, there is a real opportunity to combine TH with the existing therapies to improve outcome in adults with acute ischemic stroke.

Keywords:

Hypothermia, ischemia, neuroprotection, stroke

Introduction

Stroke is associated with high mortality and morbidity worldwide, with approximately 25% of the survivors remaining disabled.[1,2] To date, there are only two clinically approved therapies available to restore normal blood flow (reperfusion) by reopening the arterial occlusion (recanalization) following ischemia to enhance recovery: intravenous recombinant tissue plasminogen activator (rt-PA) and catheter-based thrombectomy. Using a combination of both therapies has shown overwhelming efficacy over alteplase alone.[3] These high recanalization rates are still faced with disproportionally lower recovery. Only 64% of those who achieve reperfusion fast (within 3 h from onset) go on to independent living after thrombectomy.[4] Many patients have ongoing brain injury after recanalization that is potentially salvageable. Studies using diffusion magnetic resonance imaging (MRI) have shown an increase in the size of brain infarction from shortly after recanalization to a 24 h follow-up scan.[5] This is due to deleterious mechanisms that have not been adequately blunted by reperfusion which results in further ischemic damage.

One of the most potent neuroprotectants is therapeutic hypothermia (TH), which has proved to be beneficial not only in animal models but also in patients post cardiac arrest,[6,7] newborns with hypoxia,[8,9] and following traumatic brain injury.[10,11] Moreover, previous work in rat models has suggested that a combination of thrombolysis and TH increases the chances of survival and does not interfere with the enzymatic activity of rt-PA.[12] In adults with ischemic stroke, one trial demonstrated the feasibility and safety of combining thrombolysis with endovascular cooling.[13] There are several factors to be considered in order to maximize the efficacy of hypothermia

[1]Cumming School of Medicine, University of Calgary, [2]Department of Clinical Neurosciences, Hotchkiss Brain Institute, [3]O'Brien Institute for Public Health, Calgary, AB, Canada

Address for correspondence:
Dr. Mohammed A Almekhlafi, 1403 29th Street NW, Foothills Medical Centre, Calgary, AB T2N 2T9, Canada.
E-mail: mohammed.almekhlafi1@ucalgary.ca

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induction and maintenance and to reduce patient complications. In this work, we review some of these factors including the onset of induction, the duration of hypothermia, adjuvant therapy (e.g., reperfusion and/or recanalization), the method of hypothermia, target temperature, and rewarming protocols. Animal studies have suggested that TH is more effective with earlier induction, greater depth, longer durations, and more gradual rewarming measures.[14] However, the translation of these methods and their efficacy in human studies remain uncertain and challenging.

The Ischemic Cascade and Therapeutic Hypothermia

In the acute stage of ischemic stroke, the reduction in blood flow in the affected territory results in anaerobic metabolism and decreased molecular energy production. This in turn causes dysfunction of the sodium-potassium adenosine triphosphate pumps causing increased sodium influx and potassium efflux, disruption of ionic homeostasis and excitatory neurotransmitter (glutamate) release, cellular edema, blood–brain barrier breakdown, and secondary inflammation. Uninhibited glutamate release leads to excitotoxicity and further calcium influx, causing the activation of catabolic proteases, lipases, and nucleases, leading to mitochondrial dysfunction, free radical formation, and expansion of the infarct. In the subacute stage, many hours to days following the initial insult, apoptotic and inflammatory pathways are activated.[15,16]

TH has been proposed to halt the ischemic cascade, unlike other neuroprotective measures which only inhibit a single step in the cell death pathways.[17] Evidence has also suggested that TH suppresses the release of apoptotic[18,19] and pro-inflammatory[20] molecules. In animal models of cerebral ischemia, one meta-analysis demonstrated that TH reduces infarct volume on an average by 44% with temperatures of ≤34°C, and that cooling to 35°C still suggested a moderate effect with a 30% reduction of infract volume.[21] TH has demonstrated a 5% decrease in cerebral metabolism for each 1°C reduction in core body temperature.[22] In a rat model of cerebral ischemia, cooling to 33°C significantly reduced glutamate release and the subsequent excitotoxicity.[23] In a prospective observational study of 12 patients treated with moderate hypothermia (33°C) after middle cerebral artery (MCA) infarction, a rise in glutamate, lactate, and pyruvate was observed with normothermia (>36.5°C).[24] In this same study, microdialysis of the extracellular fluid of the peri-infarct tissue revealed a reduction of glutamate, glycerol, lactate, and pyruvate during hypothermia and after rewarming suggesting inhibition or slowing of the ischemic cascade.

Clinical Trials of Therapeutic Hypothermia in Humans

Table 1 describes the clinical trials of TH in adults with acute ischemic stroke. For this, we conducted a systematic review of the literature and identified 26 studies of TH in adult patients with acute cerebral ischemia and two studies in a population of ischemic and hemorrhagic stroke. We searched MEDLINE using the terms "stroke" AND "hypothermia" OR "cooling." The overall findings suggest functional improvement with the induction of TH but with greater risk of complications. More recently, we conducted a systematic review and meta-analysis of the literature to investigate the efficacy and complications of TH in adults with acute cerebral ischemia.[51] Compared to controls, the results demonstrated an increased number of complications in patients treated with TH, and a shift in functional independence (modified Rankin Scale [mRS]) by 55%. Cooling protocols across the studies varied, leaving many questions regarding the optimal methodology for inducing TH in humans unanswered.

Infarct Reduction in Human Studies of Cerebral Ischemia

There has been limited evidence in human trials regarding whether TH significantly reduces infarct volume. Using MRI brain sequences such as diffusion-weighted imaging, or computed tomography (CT), the volume of the infarct can be estimated. In a randomized clinical feasibility trial, De Georgia *et al*. treated 18 patients with TH and 22 with standard medical treatment.[28] The COOL AID group identified slower infarct growth in patients treated with TH (90.0 ± 83.5% vs. 108.4 ± 142.4% in controls), with an average lesion growth of 72.9 ± 95.2% in patients that cooled well.[28] Using noncontrast CT, Wu *et al*. demonstrated lower average final infarct volumes in patients cooled with intra-arterial selective TH (63.7 ± 31.8 mL vs. 77.9 ± 44.7 mL in controls; $P = 0.038$).[50] Peng *et al*. similarly observed reductions in infarct volume in the mild TH group relative to volumes in the normothermia group at 24 h (TH: 13.45 ± 6.01 mm^3; controls: 25.56 ± 10.22 mm^3) and 7 days (TH: 12.25 ± 7.42 mm^3; control: 26.26 ± 10.86 mm^3) ($P < 0.05$).[44]

Improvements in Functional Independence with Therapeutic Hypothermia in Ischemic Stroke

Several trials in acute ischemic stroke have suggested a trend toward improvements in clinical outcome following cooling. In one study, poor outcome (mRS 4–6) was twice as common in the normothermia group, but shift analysis did not demonstrate a significant improvement with TH.[45] While not

Table 1: Clinical trials of therapeutic hypothermia in adults with ischemic stroke

Study	*n* patients: TH/controls	Induction time from symptoms (h)	Duration (h)	Target temperature (°C)	Time to target temperature (°C)	TH method	Complications	Clinical outcomes
Abou-Chebl *et al*., 2004[25]	18/0	Not specified	Not Specified	32.0	3.2	Systemic surface	Hypotension, bradycardia, hypokalemia, pneumonia, fever, arrhythmia, MI, transtentorial herniation, ICH, coagulopathy, pancreatitis	Not specified
Berger *et al*., 2002[24]	12/0	16.3	Not specified	33.0	Not specified	Systemic surface	Not specified	Not specified
Bi *et al*., 2011[26]	31/62	6.0	24.0	Not specified	0.28	Selective surface; head and neck	Symptomatic ICH, hemorrhage, pneumonia	BI, mRS, NIHSS
Chen *et al*., 2016[27]	26/0	8.0	0.17	Not specified	Not specified	Selective endovascular	Pneumonia, neurological deterioration, vascular spasm, coagulopathy, DVT, melena	Not specified
De Georgia *et al*., 2004[28]	18/22	8.6	24.0	33.0	1.3	Systemic endovascular	Symptomatic hemorrhagic transformation, DVT, pneumonia, pulmonary edema, cardiogenic shock, tachycardia	mRS, NIHSS
Els *et al*., 2006[29]	12/13	Not specified	48.0	35.0	2.0	Systemic combined	Bradycardia	mRS, NIHSS
Georgiadis *et al*., 2001[30]	6/0	28.2	67.0	34.5	3.0	Systemic endovascular	Pneumonia, hypotension, bradycardia, arrhythmia, thrombocytopenia, hypokalemia	Not specified
Georgiadis *et al*., 2002[31]	19/17	24.0	71.0	33.0	4.0	Systemic combined	Pneumonia, arrhythmia, bradycardia, thrombocytopenia, hypokalemia	Not specified
Geurts *et al*., 2017[32]	16/6	4.5	24.0	34.0, 34.5, 35.0	Not specified	Systemic combined	Pneumonia, UTI, neurological deterioration, ICH, hypertension, bradycardia, tachycardia, hypokalemia, hyponatremia	mRS, NIHSS
Hemmen *et al*., 2010[13]	28/30	6.0	24.0	33.0	2.3	Systemic endovascular	ICH, pneumonia, DVT	mRS, NIHSS
Hoedemaekers *et al*., 2007[33]	50/0	Not specified	Not specified	Varied by method	Not specified	Five systemic methods	Hypotension, arrhythmia	Not specified
Hong *et al*., 2014[34]	39/36	3.0	48.0	34.5	6.3	Systemic combined	Bradycardia, hypotension, hypokalemia, pulmonary edema, pneumonia	mRS

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Table 1: Contd...

Study	*n* patients: TH/controls	Induction time from symptoms (h)	Duration (h)	Target temperature (°C)	Time to target temperature (°C)	TH method	Complications	Clinical outcomes
Horn *et al*., 2013[35]	20/0	5.4	12.1	33.0	1.1	Systemic combined	Hemorrhagic transformation, pneumonia, bradycardia, hypotension	mRS, NIHSS
Kammersgaard *et al*., 2000[36]	17/56	3.3	6.0	Not specified	Not specified	Systemic surface	Not specified	SSS
Kollmar *et al*., 2009[37]	10/0	2.1	4.0	Not specified	0.87	Systemic endovascular	Not specified	NIHSS
Krieger *et al*., 2001[38]	10/9	6.2	47.4	32.0	3.5	Systemic surface	Pneumonia, fever, sepsis, bradycardia, hypotension, MI, CHF, melena, groin hematoma, ICH, herniation	mRS
Lyden *et al*., 2016[39]	63/57	3.0	24.0	33.0	≤6	Systemic combined	Pneumonia	BI, mRS, NIHSS
Martin-Schild *et al*., 2009[40]	20/0	5.0	24.0	33.0–35.0	≤2.5	Systemic combined	Neurological deterioration, bradycardia, cardiac arrest, new brainstem stroke	mRS, NIHSS
Milhaud *et al*., 2004[41]	12/0	10.1	448.8	32.0–33.0	14.5	Systemic surface	Hypotension, thrombocytopenia, hyperfibrinogenemia, pnuemonia	BI, NIHSS, mRS
Neugebauer *et al*., 2019[42]	26/24	Not specified	72.0	33.0	Not specified	Systemic combined	Pneumonia, cardiovascular events, neurological events	BI, GCS, mRS, NIHSS
Ovesen *et al*., 2013[43]	17/14	Not specified	24.0	33.0	14.9	Systemic combined	Pneumonia, asymptomatic hemorrhagic transformation, bradycardia, arrhythmia, pneumothorax, respiratory failure, MI	mRS
Peng *et al*., 2016[44]	11/15	Not specified	Not specified	Not specified	Not specified	Selective endovascular	Not specified	NIHSS
Piironen *et al*., 2014[45]	18/18	6.0	12.0	35.0	4.5	Systemic combined	Pneumonia, CHF, arrhythmia, acute MI, symptomatic ICH, symptomatic brain edema	BI, mRS, NIHSS
Poli *et al*., 2014	10/10	Not specified	0.5-1.0	Not specified	Not specified	Systemic or surface endovascular	Not specified	mRS
Schwab *et al*., 1998[46]	25/0	14.0	Not Specified	33.0	Not specified	Systemic combined	Pneumonia, septic syndrome, asymptomatic thrombocytopenia, hypokalemia, cardiac arrhythmias, bradycardia	BI, SSS
Schwab *et al*., 2001[47]	50/0	22.0	55.0	32.0–33.0	6.5	Systemic surface	Thrombocytopenia, bradycardia, pneumonia	mRS, NIHSS

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Table 1: Contd...

Study	*n* patients: TH/controls	Induction time from symptoms (h)	Duration (h)	Target temperature (°C)	Time to target temperature (°C)	TH method	Complications	Clinical outcomes
Steiner *et al*., 2001[48]	15/0	Not specified	72.0	32.0–33.0	Not specified	Systemic surface	Pulmonary infections, septic syndrome, arrhythmia, coagulopathy, pancreatitis	Not specified
Su *et al*., 2016[49]	16/17	42.0	Not specified	33.0–34.0	Not specified	Systemic endovascular	Hemorrhagic transformation, bradycardia, tachycardia, arrhythmia, hypotension, pneumonia, DVT, acute kidney injury, acute liver injury, coagulopathy, GIB	mRS
Wu *et al*., 2018[50]	45/68	5.7	0.17	Not specified	Not specified	Selective endovascular	ICH, pneumonia, UTI, coagulopathy	mRS

Induction of TH from symptom onset, duration of TH, target temperature, and time to target temperature are described as the reported averages. BI: Barthel index, CHF: Congestive heart failure, DVT: Deep vein thrombosis, GCS: Glasgow Coma Scale, GIB: Gastrointestinal bleed, ICH: Intracerebral hemorrhage, mRS: Modified Rankin Scale, MI: Myocardial infarction, NIHSS: National Institutes of Health Stroke Scale, SSS: Scandinavian Stroke Scale, TH: Therapeutic hypothermia, UTI: Urinary tract infection

statistically different, mRS at follow-up was lower in ten patients cooled to 32°C for 12–72 h (3.1 ± 2.3 vs. 4.2 ± 1.6 in controls) in another study.[38] Furthermore, a trend toward better neurological outcome (mRS 0–3) was observed in patients treated with endovascular TH (33°C–34°C) compared to controls with massive cerebral infarction.[49] The ICTuS-2 study[39] and COOL AID study[28] similarly did not observe differences between normothermia and TH groups in terms of follow-up National Institutes of Health Stroke Scale (NIHSS) or mRS scores. While Wu *et al*. did not identify a statistical difference in follow-up mRS, they also found no difference in neurological deterioration between patients treated with selective TH or normothermia.[50] More recently, Neugebauer *et al*. combined hypothermia with decompressive hemicraniectomy and did not observe statistical difference in follow-up NIHSS, Glasgow Coma Scale, or mRS scores between TH and normothermia groups.[42]

In 2014, Hong *et al*. prospectively enrolled patients with ischemic strokes in the anterior circulation.[34] The researchers induced mild hypothermia (34.5°C) for 48 h followed by a 48-h rewarming period in 39 patients, while treated 36 with standard care (normothermia group). Hong *et al*. observed greater functional outcome in patients treated with TH: mRS ≤2 at 3 months (45% vs. 23% in controls, $P = 0.017$) and mRS ≤1 at 3 months (31% vs. 8% in controls, $P = 0.015$).[34] Similarly, Bi *et al*. demonstrated improved mRS (0–1) in patients undergoing a combination of TH and rt-PA relative to controls at follow-up ($P = 0.017$).[26] Using a combination of chemical and surface TH has also shown improvements in clinical outcomes.[40,41]

Clinical Significance of Therapeutic Hypothermia

While most studies report a trend toward improved outcomes, human trials of hypothermia have shown few statistically significant differences in terms of the efficacy of TH in reducing infarct volume and improving functional independence. To our understanding, only three trials have commented on the differences in infarct size pre- and post-intervention with TH, but have not found statistical differences.[28,44,50] The majority of studies reporting clinical outcomes pre- and post-intervention have similarly not found statistically different results between TH and normothermia groups. Only two studies[26,34] utilizing mild hypothermia, with one concomitantly using rt-PA,[26] demonstrated significant improvements in mRS at follow-up compared to controls. These studies may have been limited by relatively small sample sizes; however, it is also difficult to translate the success of the animal models to human trials. Some of these translational difficulties arise from a lack of understanding and consensus on an optimal TH protocol in humans and require a fine balance for effective cooling while minimizing possible complications. Future studies are required to better characterize the optimal TH conditions to improve the clinical outcomes of patients with acute ischemic stroke, while also providing a consensus on neuroimaging biomarkers and protocols to better compare the results across trials.

Therapeutic Hypothermia Methodology and Considerations

Inducing therapeutic hypothermia

TH induction is currently achieved by invasive endovascular means, surface cooling, intravenous infusion of chilled saline, or a combination that targets either (1) systemically cooling the entire body, or (2) selectively cooling the brain only with minimal effects on the core temperature. Surface (external) TH can be used to achieve systemic or selective cooling as it is induced using fans, cooling blankets, cooling pads, cold saline/alcohol washes, and water mattresses with relatively easy-to-use and simple technology. Endovascular methods offer rapid and precise temperature control[16] via external cooling machinery, allow for simultaneous skin warming to avoid shivering and maintain tighter temperature control, and utilize intravenous catheters through the femoral or subclavian veins or, more recently, intra-arterially through direct carotid artery cold saline infusions. The potential advantages and risks of each method are described in Table 2.

External head (and neck) cooling

There is conflicting evidence on whether external cooling of the head using helmets alone can adequately induce and achieve cooling of the cortex or deeper brain parenchyma. Using a quantitative cooling model, Neimark *et al*. demonstrated the inability of cooling helmets alone to achieve lower temperatures deep within the parenchyma.[52] The researchers further observed that adjuvant neck cooling was needed in order to maintain hypothermia, similarly to the findings of Yin *et al*.[52,53] These findings mirror those observed in patients with severe traumatic brain injury, where Qiu *et al*. used a cooling cap and neckband circulating 4°C water to achieve parenchymal temperatures of 33°C–35°C while maintaining normothermic core systemic temperatures.[54]

Although surface TH does not require complex devices and can be induced relatively quickly, reaching target temperature can take longer time,[36,38,40,43,55] and these targets are often not achieved, rendering this method to be inefficient.[56] Cooling using ice packs may more rapidly induce TH, but it does not offer reliable control of temperature during the cooling or rewarming phases.[57] Intranasal administration of cooled air appears relatively safe and has been demonstrated to reduce core, brain, and tympanic membrane temperatures on an average by ≥1°C.[58] The ability to monitor and control temperature during the cooling and rewarming process is difficult when utilizing external cooling of the head and neck and would further require an invasive approach.[57] Despite these potential pitfalls of surface cooling, Kammersgaard *et al*. used surface blanket cooling in 17 ischemic stroke patients for 6 h without anesthesia and demonstrated a reduction of core temperature by 1.3°C.[36] These results suggest that surface cooling is not only less invasive but can also be successfully employed without additional pharmacological interventions.

Endovascular Cooling

Systemic transvenous cooling

The ReCCLAIM trial demonstrated that induction of hypothermia using a special transvenous catheter after intra-arterial reperfusion therapy is feasible.[35] Twenty patients with acute ischemia were cooled to 33°C for 12 h with a gradual rewarming protocol (0.2°C/h) following intra-arterial reperfusion therapy. Pneumonia was seen in 25% of patients, and a majority of patients experienced an episode of hypotension or bradycardia during TH.[35] In a prospective observational trial of fifty adult patients with acute ischemic stroke, Hoedemaekers

Table 2: Therapeutic hypothermia method considerations

TH method	Potential advantages	Potential risks
Selective TH	Avoids cooling of the entire body; avoids systemic side effects	Depending on the type of method used (endovascular versus surface)
Surface cooling	Ease of use; inexpensive equipment; noninvasive; relatively safe with few systemic side effects; possible combination with concurrent thrombolysis	Shivering reduces the efficacy of temperature control; increased risk of skin necrosis; slow rate of cooling; possibly labor intensive; may require intubation and sedation
Cooling helmets	Avoids cooling of the entire body; avoids systemic side effects	Inadequate to maintain deep cooling of the cortex and parenchyma; slow rate of cooling
Nasal cooling device	Avoids cooling of the entire body; avoids systemic side effects	Slow rate of cooling; requires patient intubation
Endovascular cooling	Rapid and tight temperature control; simultaneous skin rewarming to improve patient comfort and thwart the body's thermoregulatory response; may be tolerated in awake patients	Expensive equipment requiring experienced users and monitoring; invasive procedure; risk of infection and bleeding with catheterization; may require intubation and sedation of patients; cannot be used concurrently with thrombolysis
Systemic TH	Rapid cooling	Cooling of the entire body carries greater side effects

TH: Therapeutic hypothermia

et al. evaluated the efficacy of five hypothermia methodologies.[33] Ten patients were allocated into each cooling method: (1) Ringer's lactate solution at 4°C and surface cooling with ice and/or cold packs; (2) water-circulating cooling system (4°C–42°C) with two body blankets and one blanket under the patient's head; (3) air-circulating cooling system (10°C–42°C) utilizing one body blanket; (4) gel-coated external cooling device (4°C–42°C) consisting of four transfer pads placed on the back, abdomen, and both thighs; and (5) intravascular cooling with saline (4°C–42°C) using a central venous catheter inserted into the inferior vena cava via the femoral vein. Cooling was achieved more quickly in patients cooled with the water cooling device, gel-coated external device, and the intravascular method. The intravascular method more reliably kept patients within the target temperature range, likely due to direct temperature exchange between the catheter and the blood; whereas surface cooling methods relied on slow conduction for heat exchange.[33]

Selective intra-arterial cooling

Intra-arterial selective cooling via infusion of ice-cold saline through catheters in the carotid artery promises to achieve rapid (within minutes) and deep (32°C) brain cooling to harness the benefits of TH while avoiding the risks of systemic cooling.[55] This approach has encouraging results in animal studies with benefits even when cooling is delayed after stroke onset and maintained for a relatively shorter duration compared to systemic cooling.[59] In studies of adults with ischemic stroke, there has been a suggested benefit in using chilled saline at 4°C infused at a maximum rate of 30 mL/min for 15 min and with minimal side effects.[50] However, no measurements of brain temperature were obtained to evaluate whether significant warming of the child saline occurred during transit within the uninsulated catheter as it was bathed by warm blood before reaching the brain.[60]

Using intra-arterial cooling may be less effective when cerebral perfusion is compromised, but can be a viable option once reperfusion is achieved in patients with large-vessel occlusion ischemic stroke.[27,61,62] Chen *et al*. combined intra-arterial recanalization with infusion of 4°C ice-cold saline in 26 patients with large-vessel ischemia.[27] Ice-cold saline was administered through the ischemic territory pre-reperfusion via a microcatheter that afterward mechanically removed the clot with a stent retriever. Following reperfusion, ice-cold saline was again infused into the ischemic brain tissue for 10 min. They reported a decrease of cerebral temperature of at least 2°C during induction of hypothermia, with minimal reduction in core temperatures ($\leq$0.3°C). The researchers did not observe unstable vitals or electrolyte imbalance before, during, or after treatment, demonstrating the safety and feasibility of combining TH with intra-arterial recanalization. A similar study combined endovascular thrombectomy with 15°C cold saline infusion into the ischemic tissue in patients that do not improve their NIHSS score following recanalization.[62]

Selective nasal cooling

The nasal passages have a large surface area of vasculature and are close in proximity to the cerebral circulation,[63] making them an ideal target for inducing hypothermia. Significant cooling of the nasal passages and brain can be achieved using liquid coolant–oxygen mixtures sprayed into the nasal cavity. The PRINCE study compared outcomes between 96 intra-arrest patients and transnasally cooled 104 patients receiving standard care prior to reaching the hospital, finding no difference in developing adverse events within 7 days of treatment.[64] The trial further demonstrated the feasibility in reducing tympanic membrane temperature to 34.2°C in approximately 34 min using the RhinoChill device (BeneChill, Inc., San Diego, California, USA). Similarly, reduction of brain temperature by an average of 1.21°C was noted within 1 h in a study of stroke patients.[65] In a study of 15 brain-injured patients, the RhinoChill system demonstrated safety and efficacy in reducing brain and core temperatures on an average by 1.4 ± 0.4°C and 1.1 ± 0.6°C, respectively.[58] Use of vortex tubes for rapid selective brain cooling while maintaining core body temperatures in animal models has also been feasible.[66] In a porcine model, the CoolStat device (CoolTech, MD, Baltimore, Maryland, USA) similarly showed successful induction and maintenance of hypothermia, achieving target brain temperatures within 0.5 ± 0.6 h without damaging the nasal mucosa.[67] The results of these aforementioned studies demonstrate the feasibility and safety of using nasal cooling to induce cerebral hypothermia with minimal systemic side effects.

Endovascular cooling catheters: Closed loop versus infusion catheters

Cooling catheters can achieve cooling either using conduction (closed loop) where chilled fluid are circulated inside the catheter, or by directly infusing chilled fluids into the circulation (infusion). The location of the catheter determines whether it achieves systemic (in the venous circulation) or selective (in the carotid artery or intracranial arterial circulation) cooling. Merrill *et al*. compared continuous closed-loop cooling catheters to commercially available catheters in terms of infusion flow rate, location of the catheter in the body, catheter configuration, and method of cooling.[60] Compared to closed-loop catheters, commercially available catheters demonstrated greater cooling capacity at lower possible temperatures. The researchers found that closed-loop systems struggle to induce lower temperatures at higher flow rates.

In examining heat exchange physics, they found that increasing flow can result in reduced rewarming of the cooling fluid and increased cooling capability of the tissue.[60] In a canine model, King *et al*. demonstrated that focal cerebral TH could be induced quickly through an insulated carotid catheter with minimal impact on core temperature and was associated with smaller infarct volumes compared to controls.[68] With minimal effects on core temperature, these catheter-based methods may offer a highly advantageous protocol to implementing localized TH.

Duration and optimal target temperature of therapeutic hypothermia

Animal models have demonstrated that inducing TH at or before ischemia has better neuroprotective effects. In practice, patients may arrive at the emergency room hours after symptom onset, creating a barrier to the application of TH and its value. While the optimal duration of TH remains unclear, longer durations of cooling following global cerebral ischemia have been associated with better outcomes.[22] When the onset of TH induction is delayed, longer durations may be necessary to achieve the same neuroprotective effects, but there is a lack of compelling evidence supporting that longer durations of TH compensate for longer delays to inducing TH.[69] Although longer durations of cooling may theoretically offer more effective neuroprotection, this may not be tolerated in patients that are not sedated and may carry greater risks of complications.[57] In one study of surface cooling of 32°C maintained for 12–72 h, a trend toward increased risk of complications with longer durations of TH (P = 0.08) was observed in 18 patients with severe acute ischemic strokes.[25] In rat models, mild hypothermia was observed to be as efficacious as moderate hypothermia when the TH was induced for 24 h after delayed induction.[21,70] Similar findings were reported in human studies of cardiac arrest, where TH was effective if maintained for 12 h[6] or 24 h.[7] More studies are needed to clarify the optimal duration of cooling.

The optimal target temperature of TH is also unknown. In a study of MCA occlusion for 90 min, rats were kept at core temperatures of 32°C, 33°C, 34°C, 35°C, 36°C, or 37°C for a total duration of 4 h.[12] The greatest benefit was observed at 33°C–34°C, with significant reductions in infarct size and improved functional outcome.[12] Cooling to temperatures lower than 33°C required sedation and increased natural thermoregulatory responses to cooling (i.e., vasoconstriction and shivering), subsequently affecting the efficacy of cooling and the ability to reach and maintain a target temperature of TH. Shivering may induce direct and indirect mechanisms that thwart the efficacy of TH. For example, increased muscle activity due to shivering rewarms the body, affecting temperature control and prolonging the time to reach the target temperature.[55] Thresholds of 35.5°C and 36.5°C have been proposed for shivering and vasoconstriction in humans, respectively.[71] These thermoregulatory responses are further accompanied by increased sympathetic activation and tone, causing hypertension and tachycardia.[72] Antishivering protocols utilizing intravenous meperidine and oral buspirone, or skin rewarming, can modulate this thermoregulatory response to reduce patient discomfort and aid in achieving target temperatures. Further, the frequency of side effects associated with TH increases with each 1°C decrease in temperature.[57] Many ongoing trials in adults with acute ischemic stroke target core temperature between 33°C and 35°C. In human studies of ischemic stroke, surface cooling to 35°C[36] and endovascular cooling to 33°C[73] have been feasible in awake patients.

Brain temperature monitoring: Core temperature does not equal cerebral temperature

Body temperature during cooling and rewarming periods can be monitored peripherally via bladder, rectal, and esophageal probes. One dilemma surrounding the application of hypothermia in the clinical setting is that core body temperature does not equate to cerebral temperature, and reliable noninvasive methods do not exist to measure brain temperature accurately. Using a theoretical model, Keller *et al*. demonstrated that cooling the head alone was not adequate to cool the deeper brain parenchyma below 36°C.[74] Using an intracerebral pressure probe with a thermistor tip, Schwab *et al*. reported a cerebral temperature of 33.3°C (with an accuracy of temperature measurements of <0.1°C) when the body was cooled to 33°C in patients with severe MCA infarction.[46] These findings should be taken with caution given the small sample size.

Promising methods for noninvasive cerebral temperature monitoring have been more recently investigated. One such method, magnetic resonance spectroscopic imaging (MRSI), maps the temperature of the brain *in vivo* by measuring chemical shift differences between water and compounds such as N-acetylaspartate. In 31 healthy adult volunteers, Thrippleton *et al*. found minimal variation between participants independent of 1.5 T or 3 T field strength.[75] Thrippleton *et al*. demonstrated greater precision using 3 T MRI, and they were able to detect small changes in brain temperature using MRSI. A new temperature sensor (3M SpotOn, later changed to Bair Hugger sensor (3M, St. Paul, Minnesota, USA)) has also been investigated. This sensor uses zero heat flux thermometry, a noninvasive method where an adhesive patch is applied to the lateral forehead which allows heat to transfer between the forehead and core body. When the transfer of heat between the two is complete, the temperature underneath the sensor reflects body

core temperature.[76] In adults undergoing surgery, Iden *et al*. demonstrated that the body temperature measured by the 3M SpotOn sensor was strongly correlated with nasopharyngeal and sublingual measurements.[77] More recently, Bakhsheshi *et al*. observed good congruence in brain temperature measured by the 3M zero heat flux Bair Hugger sensor compared to an invasive intraparenchymal thermocouple probe in pigs.[78] The efficacy and accuracy of these noninvasive sensors require further investigation in adults with cerebral ischemia, as well as their accuracy during rewarming protocols.

Complications of therapeutic hypothermia

While hypothermia carries the potential to improve outcomes, patients are also at risk for developing complications including:

1. Cardiovascular complications such as hypotension, bradycardia,[6] arrhythmias, and myocardial infarction[79]
2. Greater risks of infection including aspiration pneumonia and urinary tract infection due to a reduction in the number of white blood cells[80] and impaired T cell activity.[81] While infection risks are greater in patients undergoing TH, it is important to note that this increased risk may itself be due to the use of mechanical ventilation and sedation[57,82]
3. Coagulopathies because of platelet dysfunction[83] resulting in increased clotting time that could lead to increased bleeding[84]
4. Electrolyte imbalances (e.g., hypokalemia[85,86] and hypophosphatemia[87]) and increased insulin resistance.[88]

Many of these side effects associated with TH depend on the target temperature introduced. For example, cardiac complications are more common below temperatures of 30°C, while coagulopathies occur below 33°C.[82] The frequency of complications further increases with the duration of cooling. In a study of 390 patients with acute ischemic stroke, Kammersgaard *et al*. observed slightly greater rates of infection in patients treated with TH for 6 h relative to a normothermia group.[89]

Endovascular introduction of ice-cold saline does not have reliable temperature modulation and carries risks of volume overload.[16] Endovascular transvenous systemic cooling is further associated with a higher incidence of infections, bleeding, and venous thrombosis. In 2001, Georgiadis *et al*. demonstrated the feasibility of an endovascular cooling (34.5°C for a mean of 67 ± 13 h) method in six patients with severe ischemic stroke.[30] While the endovascular method was feasible, it was associated with complications of pneumonia, bradycardia and arrhythmias, hypokalemia, and thrombocytopenia, but coagulopathies and groin hematomas were not observed. Conversely, surface cooling of the entire body carries risks of shivering and skin necrosis. Despite these complications, a randomized trial of 31 ischemic stroke patients found that the length of hospital stay was comparable between hypothermia and normothermia groups.[43] Moreover, duration of intensive care treatment and mechanical ventilation did not differ between patients cooled with intravenous and surface cooling relative to controls.[29]

Rewarming protocols

The rates of rewarming also significantly impact the side effect profiles in patients treated with TH. For example, rapid rates of rewarming cause rapid vasodilation and rebound of intracranial pressures (ICPs), resulting in a higher association with mortality.[47,90] Rapid rewarming has also been associated with rebound hyperthermia and rapid disseminated intravascular coagulation.[91] Gradual rewarming may be safer and preferable in patients with high ICP[90] or those that have been cooled for a longer duration, but this extends the duration of cooling, therefore, increasing the risk of complications and the need for antishivering measures.

In 1998, Schwab *et al*. induced mild TH (33°C) for 48–72 h in patients with severe MCA infarction using surface cooling via cooling blankets, cold infusions, and ice-cold washes.[46] The researchers concluded that moderate hypothermia significantly reduced ICP in the subacute stage, but was associated with a higher frequency of pneumonia. In 2001, the researchers further concluded that rapid rewarming (<16 h) was associated with greater rises in ICP and suggested more gradual rewarming protocols to reduce the complications of herniation and mortality.[47] Steiner *et al*. also investigated the rate of rewarming and its association with ICP and cerebral perfusion pressure (CPP).[48] Fifteen patients with malignant MCA infarcts were cooled with surface blankets or cooling mattresses for 72 h, with a median controlled rewarming period of 59 h. The authors concluded that increases in temperature correlate with rates of change of ICP ($P = 0.002$) and CPP ($P = 0.017$) and that more gradual rewarming protocols may offer better pressure control.[48]

Conclusions and Future Directions

Brain protection from ischemic injury, whether global or focal, remains an unmet need. Thus, an intervention that shows promising effects will have the potential of wide applications including stroke, postarrest resuscitation, and traumatic brain injury. Studies in animals and humans suggest that TH has a great potential for neuroprotection and improvement of clinical outcomes. Moreover, if hypothermia is shown to halt the ischemic cascade, applications could expand to other organs affected by ischemia such as the heart which affects a

much larger population than stroke. Reducing adverse clinical events associated with TH deserves more attention, and the progression of infarct volumes and ICP should be documented in future studies. Focal cooling methods of the brain offer promising results in improving functional outcome, reducing systemic complications, and reducing infarct expansion following ischemic stroke.

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Conflicts of interest

There are no conflicts of interest.

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