Therapeutic Hypothermia for Neurological Injuries: Balancing Neuroprotection with Risks

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Liang Zhu

Abstract

While the therapeutic potential of hypothermia for treating tissue damage has been investigated for over 90 years, its effectiveness is still debated. This review introduces the history of hypothermia in medicine first, followed by a description of cellular mechanisms behind its neuroprotective effects observed in animal studies and some clinical studies. The next section focuses on current cooling approaches/devices, as well as cooling parameters recommended by researchers and clinicians to maximize the benefits of hypothermia. Animal and clinical studies of implementing hypothermia for spinal cord and brain tissue injury are presented next. The outcomes in treating conditions like traumatic brain injury (TBI), spinal cord injury (SCI), stroke, and cardiopulmonary issues will be discussed in detail. The review also examines the risks and benefits of hypothermia, supported or disputed by clinical studies. Contributions from bioengineers in the research field are presented in the last section, with details of cooling device design and theoretical simulations. Ultimately, the review highlights that successful hypothermia treatment hinges on achieving targeted tissue cooling quickly after injury, with mild hypothermia often being proven as effective as deeper cooling, provided a slow rewarming rate is implemented.

Keywords

Cooling · Hypothermia · Cooling device · Brain injury · Bioengineering

18.1 The Evolution of Cooling in Medical Treatment

In ancient times, heating and cooling were used for various medical applications. Heating was used to disinfect wounds, while cooling was employed for managing bleeding on battlefields and for reducing fever. The broader medical benefits of cooling were not well understood and fully explored until the nineteenth century. During Napoleon's war against Russia in the 1810s, physicians observed that soldiers left in the snow had an improved survival rate than those given a warm blanket and/or placed close to a fire. They also noticed the dangers of extreme heating, such as open fires, to the frostbite of soldiers. Medical practices in the twentieth century incorporated insights from the nineteenth century, leading to the development of devices that could precisely regulate human tissue temperature by actively removing heat. These devices utilized precise temperature regulation mechanisms to manage

L. Zhu (✉)
Department of Mechanical Engineering, University of Maryland, Baltimore County, Baltimore, MD, USA
e-mail: zliang@umbc.edu

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heat transfer in the body. One pioneer in this field is Dr. Temple Fay, who speculated that cooling inhibited tumor cell multiplication and progression, due to the rarity of tumor development in the relatively cold body extremities. He later tested this hypothesis in cancer patients and implemented cooling to relieve pain. Dr. Fay published his first case study of using hypothermia for cerebral injury patients in the 1940s (Fay 1945). The concurrent industrial revolution in refrigeration in the twentieth century also played a crucial role in the advancement of controlled cooling techniques in sophisticated medical applications.

Human tissue cannot survive without a constant supply of oxygen-rich blood. Among all tissues, heart and brain tissues in the head and spinal regions are most vulnerable to ischemia, a medical condition characterized by restricted blood flow to a tissue region. Due to a lack of storage for glucose in the brain, a reduced oxygen delivery to the brain would immediately deprive the affected brain tissue of the oxygen and nutrients the brain needs to function properly. It is well documented that brain tissue cannot recover after only 5 min of brain ischemia in normothermic conditions at 37 °C. However, physicians observed that this duration increased to 45 min when the brain tissue was cooled to 10 °C (Wass et al. 1995). Since the 1940s, cooling has been studied as a means to protect the brain from ischemia (Kabat 1940; Fay 1945; Miller 1949; Bigelow et al. 1950; Lazorthes and Campan 1958; Sedzimir 1959; Vandam and Burnap 1959a, b; Drake and Jory 1962). Another application utilizing cooling is in open-heart and open-neck surgeries when surgeons need to repair malformations in those regions. Surgeons would prefer to operate on a bloodless field and minimize the risk of hemorrhage. In the 1950s and 1960s, cardiopulmonary bypass in conjunction with induced hypothermia was performed to provide cardiac surgeons sufficient time for many cardiac and neural procedures. They introduced cerebral hypothermia to cardiac arrest patients to maximize the ability of the brain tissue to survive anoxic no-flow states. In the 1970s, numerous animal experiments and clinical studies showed the benefits of hypothermia in prolonging the tolerance of brain tissue to ischemia. Hypothermia contributed significantly to reduced patient mortality, especially in patients with previously inoperable cardiac and cerebral pathologies.

Early animal and clinical studies often used deep states of hypothermia with temperatures ≤30 °C. For example, in Dr. Fay's initial experiment, he lowered the body temperature of the patients to 27 °C. However, detrimental systemic complications, such as pneumonia, ventricular fibrillation, and acidosis, were widely reported, especially fatal to elderly and fragile patients. In the 1970s and 1980s, research on hypothermia to enhance brain tissue recovery after ischemic attack became dormant. This was probably due to medical advancements with other, less risky, and more manageable treatment methods. In addition, difficulties in managing temperature and administering energy removal made it hard to demonstrate the benefits of deep hypothermia on neuroprotection. In the 1980s, researchers began to reinvestigate the cooling approach of mild hypothermia since it could be relatively easy to control and implement. Extensive experimental studies on canine, swine, and rodent models were conducted in the 1980s to evaluate the efficacy of different cooling strategies, including temperature reductions, cooling durations, initiation of hypothermia relative to the ischemic/damage event, and rewarming rates on tissue recovery from ischemia. The neuroprotective mechanisms of hypothermia at the cellular level have been increasingly better understood in the past three decades due to animal experiments using various animal models (Yan et al. 2022). Unfortunately, supporting data of neuroprotection by cooling in human subjects are still limited, especially for randomized multi-center clinical trials (Clifton et al. 2001, 2011; Hirst et al. 2020). In clinical studies, hypothermia therapy seems more successful in open-heart and open-neck surgery than in traumatic head injury (TBI). This is not unexpected because hypothermia initiation after traumatic head injury cannot be implemented until several hours later following the event. The delay of cooling may be a critical factor in not maximizing the benefits conferred by

hypothermia. However, these challenges can create opportunities for future investigations to develop more effective and well-controlled approaches for patients suffering from tissue ischemia. Hypothermia, if it is implemented properly, will be proven as an effective method to limit and eliminate injury and death associated with ischemic attack and benefit a vast patient population.

18.2 Neuroprotective Mechanisms of Cooling in Injury Response

Deprivation of oxygen and nutrients to tissue could occur after ischemic stroke, cardiovascular and respiratory disorders, and external physical trauma. If the initial damage is limited, the affected tissue may be able to recover. However, if the injury is extensive, secondary tissue damage occurs, including intracranial hypertension, hemorrhage, hypoxia, and edema. It is well known that brain energy stores become exhausted within 5 min after global ischemia, and an even shorter exhaustion duration of 15 s in the brain oxygen stores occurs following ischemia (Wass et al. 1995). A series of biochemical reactions and cascades triggered by the initial damage then follow, leading to depolarization of cell membranes. It is common to see increases in extracellular K^+, energy depletion, disruption of the blood-brain barrier, release of free radicals and glutamate, excitotoxicity, and inflammation as typical consequences of those cascade events. The loss of selective neurons following global or local brain ischemia may lead to permanent neurologic deficit and even death. Thus, secondary injury can be more fatal to patients than the initial injury. The gradual progression of these secondary effects can mask the severity of the injury, sometimes resulting in delayed fatalities. Many patients did not notice the severity of the damage since those cascade events may evolve gradually and last several days after the initial trauma. It is not uncommon to hear news reports on human deaths occurring several hours or several days after the initial trauma.

Originally, researchers suggested that the major neuroprotection by cooling may be related to its ability to decrease blood perfusion in the injured region, like cold-induced blood vessel constriction in halting bleeding. It is well known that brain oxygen consumption could decrease by approximately 5%–7% for every degree Celsius decrease in tissue temperature. Thus, it is evident to see a profound reduction in the energy expenditures of cerebral metabolic rates of glucose and oxygen in patients with deep hypothermia implementations. However, this mechanism was questioned after people observed protective benefits associated with introducing mild hypothermia, lowering tissue temperature by only 1 or 2 °C.

In the past several centuries, many researchers have begun to suggest that cooling may play an important role in deterring deleterious biochemical actions in the secondary tissue injury triggered by the initial tissue damage. It has been illustrated that cooling modifies a wide range of cell necrosis mechanisms (Marion et al. 1996; Yenari et al. 2000; Maier et al. 2002). Cooling decelerates the progression of the ischemic cascade and pathological neuroexcitation. In brain tissue hypothermia, cooling may hinder the opening of the blood-brain barrier, restrain glutamate release, attenuate inflammation, and minimize free radical generation and release. It may also modify glutamate-mediated calcium influx or directly hamper calcium-mediated effects on calcium/calmodulin kinase. As a result, hypothermia may lead to the maintenance of cell membrane integrity during ischemia, limit edema formation, lower intracranial pressure, and interrupt necrosis and apoptosis via preserving high-energy phosphates (Xu et al. 2002). All the underlying mechanisms modified by tissue cooling may lead to prolonged cell survival and can improve treatment outcomes after reperfusion and rewarming.

18.3 Cooling Parameters Affecting the Protective Outcomes of Hypothermia

Precooling is an option only for circumstances under which the occurrence of tissue injury is anticipated, such as in animal studies and clinical settings involving open-heart and open-neck

surgeries. In controlled animal studies, brain cooling (hypothermia) after injury significantly reduces brain damage. The consensus is to initiate cooling as soon as possible after injury, although some studies show benefits even with delays of up to 6 h (Colbourne and Corbett 1995). Brain injury mechanisms typically progress rapidly within 6 h after the initial injury. Hypothermia can reduce the initial inflammatory response after head trauma and minimize or prevent secondary brain injury. It is well accepted that for animal models, there is a 1–2 h treatment window after which the benefits of hypothermia are strongly diminished. Researchers reported that initiation of hypothermia before the injury completely prevented secondary brain damage in gerbils (Welsh et al. 1990). Although it is difficult to correlate animal data directly to humans, recent clinical data have reported positive effects of cooling in patients. A clinical study using CT in young adults with acute subdural hematoma (SDH) patients found that implementing early mild hypothermia of 32–34 °C (reaching the targeted temperature within 35 min) combined with surgical intervention showed favorable outcomes compared to fever control alone at 37–38 °C (Kobata et al. 2022). Specifically, quicker achievement of targeted temperatures was associated with improved outcomes (Kobata et al. 2022). A recent clinical study (Hughes et al. 2024) evaluated the effect of cooling in patients before their aortic arch surgery, demonstrating positive outcomes including significant reductions in cerebral gray matter volume, cortical thickness, and regional brain functional connectivity. Unfortunately, for other brain injuries, such as TBI, reducing the time between the injury and cooling can be challenging in practice, as patient transport to the hospital often adds delay. Minimizing delays in cooling initiation, potentially through portable sensors and emergency medical services, could improve outcomes, according to researchers.

Because tissue temperature significantly impacts cellular activity and metabolism, the extent of hypothermia used in treatment is expected to influence the outcome of minimizing secondary tissue damage. Hypothermia is classified into deep or severe (less than <28 °C), moderate (28–32 °C), and mild (32–35 °C) (Kirkpatrick et al. 1999; Olah et al. 2021; Hughes et al. 2024). While traditionally a "colder is better" (Michenfelder 1988) was preferred, later, researchers have questioned this idea due to systemic complications at lower temperatures to potentially outweigh neuroprotective benefits of cooling (Tisherman et al. 1999). As brain temperature decreases, systemic toxicity is frequently observed, with the adverse effects outweighing the neuroprotection mechanisms associated with therapeutic hypothermia (Chambers 1999). Deep hypothermia is linked to complications like arrhythmias (Mouritzen and Anderson 1966), cardiac complications (Frank et al. 1993), coagulopathies (Rohrer and Natale 1992), and pulmonary infections (Bohn et al. 1986). A recent study (Li et al. 2025) on patients undergoing acute type A aortic dissection (ATAAD) found that cooling temperatures above 28 °C were associated with less acute kidney injury than cooling between 20 and 28 °C. Moreover, patients in the higher cooling temperature group (above 28 °C) did not experience increased rates of stroke, spinal cord injury, or in-hospital mortality (Li et al. 2025). Additionally, deep and moderate cooling often necessitates sedation and mechanical ventilation, limiting their use to intensive care settings and situations that medically justify the collateral complications. Conversely, recent studies suggest that a mild hypothermia range (32–35 °C) is preferable for neuroprotection (Colbourne and Corbett 1995; Gunn and Gunn 1998; Yan et al. 2022). Many studies show improved neurological outcomes with mild hypothermia compared to both deep cooling and normothermia. Some research also illustrates the specific mechanisms of mild hypothermia. In Yan et al. (2022), the researchers illustrated specific mechanisms connecting the protective effects of mild hypothermia (32–35 °C) with upregulation of the Nrf2-ARE pathway in mouse models (Yan et al. 2022). It is possible that the desirable cooling temperature to maximize neuroprotection is injury-specific, warranting additional research.

Brain injury can cause secondary effects like edema (swelling) and elevated intracranial pressure (ICP) that can persist for several days after an initial event like focal cerebral ischemia (Dirnagl et al. 1999). Therefore, prolonging brain hypothermia therapy may offer benefits to those patients. Experimental studies have investigated the safety and optimal duration of cooling. A duration of 24 h was proposed initially, and it was later extended to 48 h by Bernard and Rosalion (2008), Clifton et al. (1993), McIntyre et al. (2003), and Shiozaki et al. (1993). A review in 2008 (Peterson et al. 2008) indicated that extending cooling beyond 48 h could have profound neuroprotective advantages. However, while extended cooling can maximize neurological benefits, it may also increase the risk of systemic complications, particularly in patients with pre-existing health issues. The optimal duration of hypothermia therapy remains unclear for broader clinical use, especially when other factors might influence the patient's treatment outcomes. Therefore, carefully monitoring patients undergoing hypothermia therapy is crucial.

The rate of rewarming brain tissue after hypothermia significantly impacts recovery. Studies, including one on spinal cord injury patients (Gallagher et al. 2020) and a mouse model (Linardi et al. 2020), showed that slow rewarming reduces inflammation and edema and improves cerebral blood flow compared to rapid rewarming. One study found the diminishing of the benefits of local cooling at 33 °C in spinal cord injury patients post-rewarming (Gallagher et al. 2020). In a mouse model undergoing cardiopulmonary bypass (CPB), deep hypothermia was implemented to cool the body temperature to 19 °C, followed by either a fast rewarming rate or a slow rewarming rate (Linardi et al. 2020). Magnetic resonance imaging (MRI) analysis in the mouse group with the slow rewarming demonstrated a larger reduction in the inflammatory response and cerebral edema, less inflammatory cell activation in the brain, and better cerebral blood perfusion than that with fast rewarming (Linardi et al. 2020). Rapid rewarming can lead to dangerous intracranial pressure increases and a mismatch between cerebral perfusion and metabolism. The importance of gradual rewarming has been emphasized in multiple clinical studies (Shiozaki et al. 1993). Previous theoretical analysis (Diao et al. 2003) simulating brain temperature fields in passive (and uncontrolled) rewarming by removal of a head-cooling device yielded an average rate of approximately 3 °C/h. Animal experiments conducted on rats (Diao and Zhu 2006) suggest that a fast rewarming rate might result in a mismatch between local blood perfusion and metabolism. As suggested in a study (Thoresen and Wyatt 1997), the rewarming rate in tissue should be conducted slowly at 0.25–0.5 °C/h. Therefore, the research demonstrated the pressing need for a system designed to achieve controlled and adjustable rewarming, alongside rapid cooling, for effective hypothermia management.

18.4 Currently Used Cooling Approaches/Devices

Effectively cooling deep tissues like the brain and spinal cord presents significant challenges dictated by the second law of thermodynamics. Unlike heating, which can be dissipative, effective cooling requires creating a negative temperature gradient. When relying on conduction, the amount of cooling is limited by the small temperature gradient and the tissue's low thermal conductivity. Alternatively, under normothermic conditions, high blood perfusion rates in tissue regions can be used as the primary mechanism to remove heat from the body core and redistribute it to the surface area to dissipate. This mechanism is dependent on the level of blood perfusion through the cutaneous circulation in conjunction with conduction through the skin and cooling on the surface. Furthermore, the brain and spinal cord's high blood perfusion rates, while crucial for normothermic heat regulation, actively work against cooling efforts, since warm blood from the heart rewarms the tissue and restricts temperature reduction. A different option for cooling is by advection, which involves introducing a cold liquid directly into the circulatory system. However, this highly invasive approach has its

inherent risks. Both approaches have been adopted for inducing tissue hypothermia, but heat removal by conduction through the overlying tissue has limited efficacy due to cooling-induced vessel constriction in cutaneous regions and the low thermal conductivity of body tissue. Generally, achieving faster cooling necessitates more invasive procedures.

Most of the clinical studies to date have examined systemic (whole-body) hypothermia. Either the whole-body mass or the blood in circulation is cooled using this approach. The major methodological drawback of whole-body cooling is the inherently slow cooling rate (~0.5 °C/h) due to the large volume of the human body to be cooled and the increase in thermal resistance due to arteriovenous shunt vasoconstriction (Marion et al. 1997; Schwab et al. 1998a, b; Krieger et al. 2001). Among all methods, skin surface cooling is the most studied in hypothermia. It can be achieved through different techniques, including convective air circulation, cooling blankets or jackets, water mattresses, ice packs, and alcohol or ice-water bathing. Surface cooling is a practical approach, and it does not require sophisticated equipment. However, potential side effects include shivering and vasoconstriction. Full-body immersion into cold water, although effective, can make it difficult to attach and maintain monitoring sensors to patients (Olsen et al. 2003). Moreover, vasoconstriction induced by skin surface cooling greatly increases the thermal resistance of the skin, further hindering heat transfer from the body core to the surface, counteracting the cooling effects.

Directly cooling the circulating blood offers a promising method for inducing rapid cooling, bypassing the resistance of surface tissues. Intravascular cooling catheters, as described in numerous studies, are designed for this purpose. Early clinical trials conducted in the 2000s explored its safety and effectiveness in patients who had experienced ischemic events affecting the brain (Dixon et al. 2002; Doufas et al. 2002; Inderbitzen et al. 2002; Dae et al. 2003; Mack et al. 2003; de Georgia et al. 2004; Holzer et al. 2005; Hemmen et al. 2010; De Fazio et al. 2019; Duan et al. 2020; Cattaneo et al. 2021; Jiang et al. 2022; Ramadanov et al. 2022). This technique involves inserting a cooling catheter into the femoral vein and advancing it to the inferior vena cava using X-ray guidance. Coolant circulated within the catheter allows for efficient heat removal from the venous blood, with a potential cooling capacity of up to 150 W. The technique would result in cooling rates from 0.9 to 6.9 °C/h. The large variation of the reported cooling rate may be due to different design parameters, such as coolants used, flow rates, sizes, and structures of the catheter by those companies. Intravascular cooling has been evaluated in clinical trials for both brain and spinal cord injuries, demonstrating its effectiveness and safety profile. However, the use of this technique is limited by the surgical procedures involved in catheter insertion, which require specialized training and expertise. This invasive nature restricts its availability primarily to specialized hospitals. While intravascular cooling offers benefits like faster and more stable temperature control, it is also associated with more risks, such as catheter-related thrombosis. Despite some promising findings, large-scale randomized controlled trials are still needed to definitively determine if endovascular cooling leads to significantly improved clinical outcomes in ischemic stroke patients (Georgiadia et al. 2001).

Chilled saline is considered a favorable resuscitation fluid for patients with neurological and neurosurgical injuries due to its affordability, ease of storage, and routine use as a hydration fluid in hospitals (Polderman et al. 2005; Kollmar et al. 2009; King et al. 2024). Research involving a swine model demonstrated that intravenous infusion of chilled saline at a high rate (120 mL/min) achieved a core temperature cooling rate of up to 18 °C/h. (Vanden Hoek et al. 2004). Similarly, in a clinical study involving patients who experienced non-traumatic cardiac arrest, Ringer's solution administered at 100 mL/min did not lead to serious adverse hemodynamic complications and proved effective in achieving rapid cooling (Virkkunen et al. 2004). Intravenous coolants, when administered on demand, guided by temperature, and under supervision, provide a practical and safer way to cool the core by avoiding

excessive fluid and lengthy infusions. However, concerns remain regarding patients' tolerance for such a high infusion rate, especially in those with compromised kidney function. Studies suggest that while fluid resuscitation is vital in sepsis management, caution is often exercised in patients with chronic or end-stage renal disease due to the risk of fluid overload in the bloodstream.

In sports medicine, maintaining a stable body temperature is linked to athletic performance. Research by Enomoto and Grahn supports this connection (Enomoto et al. 1996; Grahn et al. 1998, 2005, 2008). One method for temperature control utilizes negative pressure applied to the non-hairy (glabrous) skin, like the hands. This pressure expands arteriovenous anastomoses, significantly increasing blood flow to the skin. The circulatory system then becomes a conduit, transferring warm blood from the core, including the brain, to the hand area to cool the blood before it returns to the circulation. Initial human studies using this approach have demonstrated rapid core temperature cooling rates, exceeding 10 °C/h in healthy athletes. This rapid cooling of blood should, in theory, be sufficient for inducing hypothermia in brain injury patients. Although this approach is promising, neurosurgeons cautioned about the adverse effects of potential blood pressure drops in patients with compromised health. Nevertheless, this technique may still be useful for localized cooling and hypothermia induction in specific brain or spinal cord regions without disrupting other treatments.

Localized cooling has been utilized in the past decades for patients suffering from tissue injury. It is the brain or spinal tissue that requires temperature reduction, not the entire body mass. Therefore, local cooling has been utilized in the past when the targeted tissue region becomes accessible to implement the cooling devices. Selective brain cooling to target temperature reduction in the brain tissue alone has been well studied in the past. Feasible approaches include head surface cooling relying on cooling penetration from the scalp to the brain tissue, neck collars or interstitial cooling devices targeting arterial blood supplied to the brain tissue, intracarotid flushing, and cooling in the ventricular space. Cooling on the head and neck surface requires several hours to reach steady state with a penetration depth limited to the superficial regions of the brain cortex (Wang et al. 2004; Eginton 2007; Poli et al. 2013).

To provide direct cooling to injured brain tissue, a cooling device can be utilized in conjunction with routine neurocritical care procedures like monitoring interstitial pressure or draining ventricular fluid. These integrated approaches offer the ability to reduce brain temperature for therapeutic benefit (Zhu and Rosengart 2008). Similarly, an interstitial cooling device placed directly on the surface of the common carotid artery was proposed and tested (Wang and Zhu 2007; Wang et al. 2008; Wei et al. 2008). The approach might be too invasive for stroke patients, but it may be suitable for open-neck surgery when the carotid artery has already been exposed.

Intracarotid flushing, like intravascular cooling, employs a cooling catheter advanced into the carotid artery for rapid brain cooling. This method shows potential for achieving a 4 °C temperature reduction in the cerebral cortex within 10 min (Ding et al. 2004). Although endovascular cooling may appear invasive, its application aligns with common practices like endovascular recanalization in brain injury and cardiopulmonary bypass surgeries involving circulatory arrest (Bachet and Guilmet 2002; Choi et al. 2006). In a clinical trial utilizing cold saline (4–17 °C) at 33 mL/min, the approach demonstrated the risks of systemic volume overload and hemodilution (Choi et al. 2010; Esposito et al. 2014). The measured reduction in the jugular venous bulb temperature was below 1 °C within 10 min, which fell short of the theoretical prediction. However, investigators argued that jugular venous bulb temperature may not accurately indicate deep brain temperatures.

Nasopharyngeal cooling utilizes the rich blood supply in the nasal cavity to potentially cool nearby brain regions, as suggested by studies from Esposito et al. (2014) and Ferreira et al. (2021). In a recent clinical trial involving five patients with severe TBI, a novel nasopharyngeal

catheter was employed to evaluate its effectiveness and safety. This device successfully achieved a brain temperature reduction of 2.5 °C within 9.5 h and was well-tolerated by patients (Ferreira et al. 2021). As shown in the study, ventilation of cold air into the nasal cavity might be less efficient due to the low thermal capacity of air, resulting in prolonged cooling times to achieve targeted temperature reduction in the brain region. Another approach is to insert a cooling catheter using a coolant like the RhinoChill™. It has demonstrated rapid and significant temperature reduction in the brain. However, some earlier clinical trials exploring nasopharyngeal cooling faced challenges, including limited temperature drops and potential increases in blood pressure (Andrews et al. 2005; Harris et al. 2007; Abou-Chebl et al. 2011; Covaciu et al. 2011; Poli et al. 2013; Springborg et al. 2013).

Cooling the cerebrospinal fluid (CSF) presents another strategy for lowering brain temperature. This can be achieved by placing a cooling catheter in the brain's lateral ventricles while keeping the rest of the body at its usual temperature. Experiments using this method in sheep demonstrated a reduction in brain temperature to 34.5 °C within 3 h (Moomiaie et al. 2012). The impact of ventricular infusion on cerebral oxygen supply has also been explored in clinical studies, where a decrease in brain temperature was noted. Furthermore, a mathematical simulation suggested the feasibility of cooling the brain by targeting the CSF via the torso (Smith and Zhu 2010b).

18.5 Clinical Outcomes of Tissue Hypothermia: Applications and Evaluation

18.5.1 Traumatic Brain Injury

Traumatic brain injury, caused by external force, represents a significant nondegenerative and noncongenital damage to brain tissue (McIntyre et al. 2003). The consequences of head injuries can be severe, including bone fractures, bleeding within the skull, increased intracranial pressure, and bruising of the brain. While strokes typically affect older populations, TBIs are more prevalent in young individuals, largely due to motor vehicle accidents. Efforts to utilize hypothermia for neuroprotection in TBI patients have yielded inconsistent outcomes in clinical trials, a situation complicated by considerable variability among the studies (Shaefi et al. 2016). The lack of conclusive results of improved neurologic functions in TBI patients has deterred clinicians from implementing cooling as a standard treatment.

Following years of promising but inconsistent results from smaller studies, a large, multi-center, phase III trial (Clifton et al. 2001) was initiated in 1994 to investigate the effectiveness of systemic hypothermia for severe TBI in addition to a previously extensive phase II clinical trial (Clifton et al. 1993). Conducted across seven medical centers in the United States, the study recruited 392 patients aged 16–65 who were in a coma due to brain injury, excluding those with other major traumas. One group received standard care aiming for a core temperature of 37 °C, while the other group received the same care with a target temperature of 33 °C. Cooling began at an average of 4.1 h post-injury and was completed by 8.3 h, utilizing surface cooling methods. Hypothermia was sustained for 48 h, followed by an 18-h rewarming period. A subgroup of patients who were already hypothermic (≤35 °C) upon hospital admission was included in the treatment group. Ultimately, the study found only a minimal difference in outcomes between the two groups, although better outcomes were observed in the subgroup who were hypothermic upon admission (Clifton et al. 2001). This outcome highlighted the importance of achieving hypothermia quickly after TBI for potential benefits (Marion et al. 1997; Markgraf et al. 2001).

Further large clinical trials produced similarly disappointing results. A 2008 study involving 225 children with severe TBI also showed that hypothermia did not improve outcomes and might even increase mortality in the cooling group, despite early cooling (6.3 ± 2.3 h after injury) and slow rewarming (0.5 °C/h)

(Hutchison et al. 2008). The Clifton group conducted another clinical study aiming for earlier hypothermia initiation (within 5 h) and prolonged duration (48 h) with slow rewarming. They still found no significant difference in outcomes compared to normothermia, except for a possible benefit in patients with surgically treatable lesions (Clifton et al. 2011). Additional trials in Japan and Europe also failed to demonstrate neurological benefits from hypothermia in TBI patients (Andrews et al. 2015; Maekawa et al. 2015). The POLAR Randomized Clinical Trial (2010–2018), which included over 500 patients, also concluded that there was no statistically significant difference in outcomes between the hypothermia and control group (Cooper et al. 2018).

On the other hand, several studies have shown promise in reducing mortality and enhancing neurological recovery in patients with severe head injuries. These studies, including those by Shiozaki et al. (1993), Marion et al. (1997), and Metz et al. (1996), demonstrated that hypothermia can lead to improved outcomes compared to normothermia groups. Specifically, Marion et al. (1997) found benefits in patients with a coma score of 5–6 at 3 and 6 months, with over 62% achieving good outcomes in the hypothermia group compared to 39% in the control group. Jiang et al. (2000) reported a 40% reduction in mortality and a 70% increase in favorable outcomes at 1 year after the initial injury in the hypothermia group. A common benefit observed across studies was a reduction in intracranial pressure after treatment. A retrospective and cross-sectional meta-analysis by Li and Yang (2014) concluded that moderate hypothermia benefited TBI patients by resulting in better neurological outcomes, and a reduced death rate was shown, although the data were not statistically significant.

Furthermore, studies were conducted to identify factors that may contribute to the beneficial effects of hypothermia. Cooling has been investigated for its potential to counteract fever, which can exacerbate secondary brain injury through mechanisms like excitotoxicity and blood-brain barrier breakdown (Saxena et al. 2015). Puccio et al. (2009) found that hypothermia reduced fever burden in TBI patients, potentially mitigating secondary injury, and recommended maintaining cooling until intracranial pressure normalizes. While some studies (Safar and Kochanek 2001) have pointed to delayed cooling initiation as a factor in the lack of observed benefits in some trials (Clifton et al. 2001), other trials (Gal et al. 2002) have demonstrated high rates of good neurological outcomes with hypothermia, suggesting methodological variations. Qiu et al. (2005) and Liu et al. (2006) reported improved extradural pressure, reduced mortality, and improved neurological outcomes with hypothermia, even 2 years after treatment. A review by Peterson et al. (2008) highlighted the importance of cooling duration (longer than 48 h) and cautioned against pneumonia risk. Zhao et al. (2011) linked improved outcomes to a reduction in blood glucose and lactate levels with cooling. A more recent analysis (Olah et al. 2021) of the original POLAR study data (Cooper et al. 2018) found that a subgroup of those severe TBI patients in the POLAR study benefited from cooling. They identified the subgroup of the TBI patients having a large "cooling index" (COIN), which assesses temperature, duration, and rewarming rate, implying the importance of maintaining deep cooling temperature with a long cooling duration.

Overall, there is a lack of well-controlled, large clinical trials that provide convincing evidence of the benefits and safety of brain hypothermia as a treatment for traumatic head injury patients. The latest edition of the Guidelines for the Management of Severe Traumatic Brain Injury, issued by the Brain Trauma Foundation, does not recommend routine hypothermia (cooling) as a primary treatment (Carney et al. 2017). While hypothermia has theoretical benefits like reducing intracranial pressure and cerebral metabolic rate, the guidance is against the implementation of cooling due to inconsistent results. Hypothermia may be considered if other treatments to control ICP (e.g., osmotherapy, hyperventilation) are ineffective. Otherwise, the guidance emphasizes adequate pharmacologic intervention (Carney et al. 2017).

18.5.2 Brain Ischemic Injury from Stroke

While hypothermia shows promise in research for acute stroke treatment, the American Stroke Association emphasizes the need for robust clinical trials before widespread adoption. A review by Van Der Worp et al. (2007) concludes that hypothermia improved outcomes of animals suffering from ischemic stroke by more than 30%. Transient ischemia models, where blood flow is temporarily interrupted, have shown more pronounced benefits than permanent ischemia models (Marion et al. 1997; Morikawa et al. 1992). This result is especially true in well-controlled animal stroke models (Barone et al. 1997). Animal studies, particularly in well-controlled models, have demonstrated that hypothermia can significantly improve outcomes, with reductions in infarct volume and edema. Further, it is relatively easier to have reproducible models of transient global brain ischemia via occlusion of the distal middle cerebral and ipsilateral common carotid arteries than that of focal brain ischemia, for which it is more difficult to define experimental conditions. Computerized images of cerebral infarct volume and edema are commonly used to evaluate ischemic damage to the brain tissue. If the animals are kept alive after the injury, a cognitive evaluation can be conducted to assess the long-term protective outcome of cooling.

Lower target temperatures (28 and 30 °C) and earlier initiation of cooling (before or during ischemia) appear to enhance its effectiveness (Kurasako et al. 2003; Linardi et al. 2020). A study by Kurasako et al. (2003) on a spontaneously hypertensive rat model demonstrated a strong, linear, temperature-dependent reduction in infarct volume and edema progression in transient focal ischemia. Recent studies, including those using rat models and canine models, have shown positive neurological outcomes like reduced infarct volume, preserved blood-brain barrier, and improved neurological function with targeted cooling, either via direct injection or infusion of chilled saline. One recent animal study utilized a coolant directly injected into the jugular veins (Duan et al. 2020) in ischemic stroke rat models. They reported positive neurological outcomes in terms of significant decreases in infarct volume, maintenance of the blood-brain barrier, and preservation of neurological functions (Duan et al. 2020). Another recent animal experiment using a canine model of temporary middle cerebral artery occlusion (MCAO) found that infusion of chilled saline into the vein slowed down post-MCAO infarct progression (King et al. 2024). On the other hand, an animal experiment using sheep ischemic stroke models showed the safety and efficacy of intravascular cooling; however, it failed to illustrate statistically significant differences between the cooling group and the control group in infarct volumes and neurological outcomes (Cattaneo et al. 2021).

While limited clinical trials exist for hypothermia in acute ischemic stroke, they suggest potential benefits. Studies like Schwab et al. (1998a, b, 2001) showed >50% survival after 72 h of 33 °C hypothermia, with most deaths during rewarming. Though not controlled, the mortality rate (38%) was lower than typical severe stroke mortality (70%) in other studies (Hacke et al. 1996; Berrouschot et al. 1998). A mild hypothermia trial (35 °C) by Kammersgaard et al. (2000) showed a 12% mortality compared to 23% in controls. However, the Schwab study had complications, while the Kammersgaard trial primarily caused shivering. In the study by Kasner et al. (2002), they used acetaminophen-induced hypothermia and showed inconclusive benefits of cooling. A randomized trial in infants with hypoxic-ischemic encephalopathy demonstrated reduced death/disability with hypothermia (Shankaran et al. 2005). A smaller 2006 trial that included 25 patients with malignant supratentorial cerebral ischemia reported better 6-month outcomes in the hypothermia group utilizing endovascular cooling to 35 °C with comparable side effects (Els et al. 2006). Another clinical trial using mild hypothermia (target temperature of 33 °C) for 48 h with endovascular cooling in 75 acute ischemic stroke patients found less cerebral edema, lower incidence of hemorrhagic transformation, and better outcomes

in the cooling group than the control group (Hong et al. 2014). Neurological outcomes, as measured by the modified Rankin Scale (mRS) score 3 months after treatment, showed more than half of the cooling group scoring as "good" compared to only 22% of the control group.

However, some trials failed to show statistically significant differences in clinical outcomes. A study involving 59 ischemic stroke patients using endovascular cooling to reach a body temperature of 33 °C found no statistically significant difference in 90-day mortality between the hypothermia and control groups (Hemmen et al. 2010). Other studies (Krieger et al. 2001; de Georgia et al. 2004) did not demonstrate clear neuroprotection. According to a study published in the Journal of Neurotrauma, robust randomized trials with large patient cohorts are still needed to confirm hypothermia's efficacy in stroke patients (Wu et al. 2020).

18.5.3 Cardiac Arrest

Therapeutic hypothermia following cardiac arrest is supported by clinical trials demonstrating its beneficial effects. A 2016 review by Schenone et al. (2016) extensively analyzed studies on systemic hypothermia in cardiac arrest patients. Out of 149 initial papers, 24 clinical trials were evaluated, including 11 randomized controlled trials and observational cohort studies. Most of these reports indicated that implementing hypothermia for out-of-hospital cardiac arrest patients significantly increased the odds of survival with positive neurological outcomes.

Several studies have explored the impact of therapeutic hypothermia (TH) on outcomes after out-of-hospital cardiac arrest (OHCA). Two early randomized controlled trials published in 2002 involving a total of 352 adult comatose survivors of OHCA demonstrated a positive effect (Bernard et al. 2002; Holzer et al. 2002). Patients in the hypothermia groups were cooled to approximately 33 °C, while those in the normothermia groups had temperatures above 37 °C, sometimes with fever control. After 6 months, those in the hypothermia groups exhibited improved neurological outcomes (around 50% vs. 30%) and low mortality rates compared to the normothermia groups.

Subsequent research further investigated the role of hypothermia. A randomized study in 2005 examined high-volume hemofiltration with or without hypothermia on mortality rates in 61 cardiac arrest patients and found improved overall prognosis with hemofiltration, suggesting potential benefits of early hypothermia in reducing mortality within weeks (Lauren et al. 2005). Retrospective studies by Oddo et al. (2006) also supported these findings. In the 2006 study, it compared 55 hypothermia and 54 normothermia patients and showed lower mortality and better neurological outcomes in the cooling group, particularly for short cardiac arrest durations (Oddo et al. 2006). A 2007 study using ice packs for external cooling found significantly higher survival rates in the hypothermia group and noted the ease and safety of the method (Belliard et al. 2007). Another retrospective study in 2009 involving 75 patients showed a significant increase in survival (67% vs. 42%) and favorable neurological outcomes (51% vs. 19%) with cooling, whether external or endovascular cooling was used (Ferreira et al. 2009). A retrospective study also found TH reduced mortality rates in cardiac arrest patients from 81% to 44% (Petrovic et al. 2011). A recent meta-analysis of data from more than 4000 cardiac arrest patients demonstrated positive neurological outcomes and better survival with systemic hypothermia (Ramadanov et al. 2022).

Evidence indicates that specific target temperatures are important during hypothermia treatment. Research has examined the impact of cooling initiation timing and the delay in reaching the desired temperature. Fukuda (2016) found that both delaying the start of cooling and postponing the attainment of the target temperature were associated with increased risks of death or unfavorable neurological outcomes. A recent study by Callaway et al. (2020) reported that patients experiencing severe post-cardiac arrest with mild cerebral edema exhibited high survival rates when treated with mild hypothermia at 33 °C compared to 36 °C. In the context of

cooling initiation, some investigations have explored the effectiveness of starting hypothermia before the patient arrives at the hospital or before the return of spontaneous circulation. These preliminary studies, though small in scale, have yielded promising results, suggesting that prehospital cooling and cooling before the return of spontaneous circulation can improve survival and neurological outcomes.

Overall, the current landscape of therapeutic hypothermia for cardiac arrest patients is more supportive than that for TBI patients. Some clinical trials are still ongoing, including the ICECAP trial (Meurer et al. 2024), which will compare different durations of hypothermia. Future trials may also revisit the potential benefits of earlier and more rapid cooling for patients suffering a cardiac arrest.

18.5.4 Brain Ischemic Injury During Surgery

Implementing neuroprotective hypothermia for conditions like traumatic brain injury, ischemic stroke, and cardiac arrest poses challenges because initiating cooling *before* the injury is often difficult. However, cardiopulmonary surgery, where brain ischemia is a known complication, presents an opportunity for pre-emptive. Prior animal studies consistently highlighted the importance of early cooling for maximizing the neuroprotective benefits of hypothermia (Welsh et al. 1990; Dietrich et al. 1993). Cardiopulmonary surgery, a procedure known to frequently result in postsurgical brain injury due to regional or global ischemia caused by circulatory arrest and embolism, presents a unique opportunity for precooling strategies (Miller 1993; Roach et al. 1996; Nussmeier 2002; Wagner and Zuccarello 2005). Leveraging this surgical context could enable the initiation of hypothermia before the injury-inducing event, potentially improving neurological outcomes.

Cooling the brain during heart surgery has been shown in many studies to help the brain withstand a temporary lack of blood flow (ischemia) and improve a patient's recovery after surgery. In situations where blood flow needs to be stopped during open-heart or open-neck surgery, a technique called hypothermic circulatory arrest is used. This involves reducing the patient's body temperature to a very low level, which dramatically slows down cellular activity in the brain, allowing for a temporary cessation of blood flow without causing significant harm. This also provides the surgeon with a clear, bloodless surgical field to perform the necessary repairs, for example, during ascending aortic surgery. It is uncommon to find recent research comparing outcomes with and without therapeutic hypothermia during these types of surgeries because it has been a standard part of international medical guidelines since the 1970s.

Previous animal research has explored the neuroprotective benefits of hypothermia, particularly in the context of brain injury and recovery from cardiac events. Studies conducted by Gillinov et al. (1993) and Zeiner et al. (1996a, b) revealed that inducing profound hypothermia in the brain significantly improved neurological outcomes, with a notable reduction in neuro-deficit scores. Specifically, scores decreased from 48 in control groups to 19 in cooling groups, where a score of 0 indicates normal function and 100 represents brain death. Similar improvements were observed in a dog model of cardiac arrest (Sterz et al. 1991). Further investigations by Moyer et al. (1992) demonstrated that spontaneous cerebral hypothermia at 33 °C led to a 75% reduction in focal infarction volume in rat brains. More recently, a 2017 study by Mihara et al. (2017) on dogs undergoing mitral valve plasty surgery with deep hypothermia (20 °C) during cardiopulmonary bypass (exceeding 90 min) reported a high 70% survival rate, indicating the potential for hypothermia in complex surgical procedures. These findings highlight the potential therapeutic role of hypothermia in mitigating neurological damage and improving outcomes in various animal models.

Recent research in the medical field has focused on evaluating the effects of cooling levels and different reperfusion techniques (Hughes et al. 2024). Profound hypothermia is typically

defined as a core temperature of less than 28 °C. Deep hypothermia involves reducing body temperature to 20 °C or below and can allow up to 40 min of cardiac arrest time for repair during cardiac procedures (Gutsche et al. 2014; Gocoł et al. 2021). One clinical study found no significant difference in patient mortality between utilizing profound hypothermia (approximately 15 °C) and deep hypothermia (approximately 20 °C) (Gong et al. 2016). The authors of that study suggested that deep hypothermia is a safe and easily implementable approach without the complications associated with profound hypothermia (Gong et al. 2016). Another study investigating hypothermia at 31 °C during bypass surgery also reported similar mortality rates compared to deep or profound hypothermia (Guo et al. 2014). Mild brain hypothermia has been shown to reduce cerebral impairment in patients undergoing pulmonary endarterectomy (Jamieson et al. 2003). Hypothermia has also demonstrated protective effects in carotid endarterectomy patients, preventing early postoperative strokes and reversible ischemic neurologic deficits (Kouchoukos et al. 1994). Current research focuses on determining if moderate hypothermia is as effective as profound hypothermia in providing tissue protection, and on understanding how to extend bypass duration to allow surgeons more operating time in complex procedures.

18.5.5 Spinal Cord Injury

Each year, more than 12,000 new cases of spinal cord injury are reported in the United States, and it affects all ages. Only 1% of those patients were discharged neurologically normal, and most patients suffered from either complete quadriplegia or paraplegia that required significant medical costs following their discharge from the hospital. It is a great challenge to develop new treatment options to preserve spinal cord tissue, thus facilitating recovery of partial motor functions controlled by the spinal cord (Steeves et al. 2011). The nervous system includes the brain, spinal cord, and a complex network of neurons. Like the brain, the spinal cord is covered by the meninges and contains both gray matter and white matter. Also, like the brain tissue, the spinal cord is subjected to severe damage after injury, and hypothermia may provide neuroprotection after acute spinal cord injury (Al-Nashash and All 2022).

There have been many animal studies conducted to evaluate the efficacy of spinal cord cooling under well-controlled injury settings (Strauch et al. 2004; Yoshitake et al. 2004; Ha and Kim 2008; Morino et al. 2008; Batchelor et al. 2010; Maybhate et al. 2012; Grulova et al. 2013; Purdy et al. 2013). Animal studies, particularly in rats and pigs, have demonstrated that spinal cord cooling can mitigate the damage from injuries. The injuries are usually induced in a controlled manner, such as contusion (impact), compression, or transection (severing), allowing researchers to study the effects of hypothermia in isolated injury types (Cheriyan et al. 2014). One study using controlled injury models like contusion and compression has demonstrated that hypothermia (32–33 °C) can improve motor function and reduce tissue damage (Yu et al. 2000). The results were encouraging, showing improvement in locomotor deficits and reduction of the damaged area. In another study using terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) stain as an index of cell damage on rats with spinal cord contusion injuries, the authors observed a marked decrease in TUNEL in the hypothermia group of 32 °C in the evaluation at both the 72-h and 7-day follow-ups as compared to that of the control and sham groups (Shibuya et al. 2004). In a separate contusion model study, brief (4-h) hypothermia led to significant increases in white and gray matter volumes and preserved neurons compared to normothermic controls. The cooled rats also exhibited faster recovery of open-field locomotion and improved forelimb strength (Lo Jr et al. 2009). Research indicates the therapeutic potential of hypothermia for spinal cord injury (SCI). A study by Wang and Pearse (2015) demonstrated that hypothermia enhanced the survival of neural stem cells transplanted for SCI recovery,

compared to control groups. Further evidence comes from Teh et al. (2018), who observed that local cooling at 30 °C in rats with SCI led to quicker recovery of both somatosensory evoked potentials (SSEP) and motor function than that in untreated control groups. More recently, Fu et al. (2022) conducted an experimental study on rats with SCI, finding that mild hypothermia delayed the onset of paralysis, and they attributed these improvements to underlying mechanisms, including the enhancement of microglia activity. The consistency of these findings across various studies suggests that hypothermia could be a potential therapeutic strategy for managing spinal cord injuries in humans.

In clinical settings, cooling initiation for spinal cord injury patients may not be introduced as early as that in well-controlled animal experiments. This is largely due to the transportation of patients to trauma centers and the time required to obtain a patient's consent to include hypothermia as an experimental treatment option. Therefore, results from clinical studies vary on neuroprotection and functional recovery after hypothermia intervention. Early studies in the 1970s typically used an ice pack or cold saline infusion to the injured spinal cord for several hours. Unfortunately, those studies are often associated with small sample sizes and a lack of control groups (Selker 1971; Tator 1972; Negrin Jr 1973; Meacham and McPherson 1973; Bricolo et al. 1976). A clinical study using local cooling via an extradural saddle device on 20 SCI patients suggested an improved ASIA (American Spinal Injury Association) grade (Hansebout and Hansebout 2014). Although there was no control group of patients in normothermic conditions, the authors state that the outcomes due to cooling were better than those of traditional treatments (Hansebout and Hansebout 2014).

In recent years, systemic hypothermia for spinal cord injury has attracted a lot of attention due to the development of an endovascular catheter that induces fast cooling and can quickly reach targeted temperature reductions. Unlike local cooling, when a laminectomy is needed before cooling can be applied, systemic hypothermia can be implemented immediately after injury by cooling the blood using ice-cold saline or endovascular cooling catheters. Several clinical studies implementing systemic cooling to SCI patients showed encouraging results. Some studies were carried out to evaluate the safety of implementing the device in a small group of patients (Cappuccino et al. 2010; Tripathy and Whitehead 2011). Initial results by Levi et al. (2009, 2010) show improved patients' AIS (ASIA Impairment Scale) grades with normal complications, and their follow-up study demonstrated favorable outcomes in those patients. A clinical trial by the same group enrolled more than 35 acute SCI patients (Dididze et al. 2013). At the 10-month follow-up evaluation, more than 43% of the patients improved at least one ISNCSCI (International Standards for Neurological Classification of Spinal Cord Injury) grade despite the relatively late cooling initiation of approximately 6 h after injury (Dididze et al. 2013). A prospective multi-center study was conducted recently to compare the complications of modest systemic hypothermia to 33 °C and normothermia for acute cervical spinal cord injury patients (Vedantam et al. 2022). With small sample sizes (27 in hypothermia vs. 23 in normothermia), they reported comparable complications in both groups, leading to a conclusion that systemic hypothermia did not result in increased risks to SCI patients (Vedantam et al. 2022). There were several clinical studies with small sample sizes (<100) utilizing cooling in SCI patients. Those studies illustrated a small improvement in long-term neurological outcomes, although slight increases in respiratory risks were observed (Ransom et al. 2022). Although animal and clinical studies have demonstrated that hypothermia is beneficial for acute SCI patients, further multi-center, randomized clinical trials are critically needed to provide convincing evidence of the efficacy of hypothermia on the recovery of a devastating injury with poor treatment outcomes (Shin et al. 2022).

18.6 Engineering Contributions in Brain Hypothermia

18.6.1 Development of Cooling Devices

The major contribution of engineering in therapeutic brain hypothermia is the design of reliable and safe devices that achieve target cooling rates and temperatures. New technologies are typically evaluated for thermal efficacy and safety in small and large animal models to determine their suitability for testing in humans. During the design, patient safety is a primary consideration, and potential issues include leakage of coolant, induced freezing damage to tissue, and physical trauma. Sterilizability, size minimization consistent with thermal performance requirements, and physical packaging are typical design considerations during the development of the device. Another important concern often neglected by engineers is how the cooling device may interfere with normal medical treatments.

Engineers design devices for therapeutic hypothermia. The devices are primarily categorized into surface and endovascular cooling methods. Surface cooling devices, like blankets and pads, are non-invasive and widely used in clinical trials. Companies such as Medivance, MTRE, Seabrook, Cincinnati Sub-Zero, Birchbrook, and Garnar manufacture these devices. AVAcore™ offers an alternative surface cooling approach via applying negative pressure to the skin in conjunction with cooling. The negative pressure opens arteriovenous anastomoses to draw a large amount of blood to the location of the device to be cooled. The cooled blood, once returned to the body's blood circulation, offers faster cooling rates of the body's core temperature.

Endovascular cooling involves inserting catheters into large vessels to cool the blood as it flows past the device. Companies like ThermopeutiX and ZOLL Medical have developed these types of catheters. While endovascular cooling provides rapid cooling, it carries drawbacks, including an increased risk of blood clotting, invasive insertion procedures, and potential complications in whole-body cooling. Endovascular cooling using catheters may also be associated with catheter-related thrombosis. These methods also have potential drawbacks, such as those discussed in a recall notification from ZOLL Medical regarding leakage in their catheter balloons. Furthermore, endovascular cooling catheters are more expensive than surface cooling blankets and wraps. Other early-stage approaches, including intracarotid cooling, interstitial neck cooling, and intravenous coolant infusion, are currently being tested in animal models, and they have not been tested in large multicenter randomized clinical studies.

18.6.2 Mathematical Simulations of Cooling and Rewarming Processes

In the past three decades, clinicians have realized the importance of closely monitoring brain temperature during hypothermia. Even a small reduction in brain temperature can improve the neurological outcomes of patients suffering from brain injury. Temperature variation within normothermic brain tissue is usually small. However, especially during therapeutic hypothermia, temperature gradients can develop not only between the brain and body core but also within regions of the brain (Busto et al. 1987; Mellergard et al. 1990; Stone et al. 1995; Wass and Lanier 1996; Schwab et al. 1997, 1998a, b). Information on internal temperature gradients is difficult to obtain clinically by temperature probes owing to the risk of inducing additional tissue damage. Current non-invasive temperature measurements, such as magnetic resonance imaging (±2 °C), lack the desired resolution to monitor small temperature variations in the brain region. Therefore, analytical methods for understanding the transient and spatial temperature distribution in brain tissue during hypothermia therapy are clinically valuable.

Theoretical modeling provides clinicians with powerful tools to improve their ability to deliver safe and effective therapy. Most importantly, thermal modeling helps identify critical

monitoring sites to assess the cooling extent and to assure patient safety. Most of the current theoretical heat transfer models in brain hypothermia implement the Pennes bioheat equation (Pennes 1948) that models the thermal contribution of local blood vessels as a lumped simple heat source term added to the traditional heat conduction equation (Zhu and Diao 2001; Diao et al. 2003; Dennis et al. 2003; Ley and Bayazitoglu 2003, 2004; Janssen et al. 2005; Wang and Zhu 2007; Neimark et al. 2008; Zhu and Rosengart 2008; Zhu et al. 2009; Silva et al. 2018). Advanced computational methods also allow researchers to model the head with a more realistic geometry than a simple hemispherical structure. The head geometry is reconstructed based on magnetic resonance images (MRIs), which can be imported into grid-generating algorithms and then interfaced with numerical software for temperature simulation (Van Leeuwen et al. 2000; Dennis et al. 2003; Ley and Bayazitoglu 2003; Li et al. 2018; Yin et al. 2019). However, the results obtained from the more complicated head models to date are very similar to those predicted by a simple, layered head geometry (Li et al. 2018; Yin et al. 2019). A recent theoretical study (Silva et al. 2018) utilized three-dimensional human geometry with detailed individual tissue structures and components to simulate the temperature distribution during hypothermia. It incorporated the lumped system approach (Zhu et al. 2009) to not only predict the temperature distribution of the entire body but also the blood temperature reduction during hypothermia (Silva et al. 2018).

When point-to-point temperature nonuniformities are important, a model that incorporates perfusion through the vasculature is necessary to accurately predict the tissue temperature field in the vicinity of large blood vessels. There were several attempts in the past to model large blood vessels, including the carotid arteries and jugular veins in the neck, during brain hypothermia (Zhu 2000; Bommadevara and Zhu 2002; Eginton 2007; Wang and Zhu 2007). In those studies, temperature decay along the large arteries was used to evaluate whether various techniques could induce sufficient cooling to the arterial blood that supplies the brain. Owing to the complicated vascular structure, it is difficult to model the thermal effects of individual blood vessels in the brain region. Van Leeuwen et al. (2000) predicted temperature contours based on detailed vasculature in the brain. It was found that they agree very well with those predicted by the Pennes bioheat equation. This may be mainly due to the large rate and distribution pattern of blood perfusion in the brain tissue, for which the Pennes bioheat equation is a preferred approach.

Mathematical simulations are a crucial tool for assessing the thermal feasibility of various cooling methods targeting specific tissue regions, providing insights into detailed temperature contours and the time required to reach a steady state. These simulations are essential for determining precise cooling rates at various locations. Initial investigations focused on cooling the brain hemisphere via a scalp helmet, but these studies (Van Leeuwen et al. 2000; Zhu and Diao 2001; Diao et al. 2003) revealed that cooling penetration into brain tissue was limited to less than 8 mm unless the region was ischemic, making brain white matter cooling impractical. Later, with advancements in computational resources during the 2000s, more sophisticated simulations were conducted using realistic head models derived from image scans (Dennis et al. 2003; Janssen et al. 2005; Ley and Bayazitoglu 2003, 2004). Interstitial cooling on the common carotid artery was also simulated to understand how the cooling device‘s length impacts brain temperature reduction (Wang and Zhu 2007; Wang et al. 2008). These studies indicated that high blood flow rates in the common carotid artery would limit cooling effectiveness.

Another proposed method for brain cooling in warm climates involved a neck collar; however, simulations of the temperature field in the neck and head region showed that this approach would achieve less than 0.3 °C of blood temperature reduction, despite providing a sensation of cold to the neck (Eginton 2007). In the context of spinal cord injuries, a non-invasive torso cooling approach was suggested to cool the spinal cord and cerebrospinal fluid. Since CSF is interconnected between the spinal cord and

head, simulations were performed to predict temperature reductions in the spinal cord tissue and the potential for hypothermia in brain tissue due to the pulsation of the cooled CSF (Smith and Zhu 2010a, b). The resulting temperature field after endovascular infusion of cold saline into blood vessels was theoretically modeled before implementation (Rosengart et al. 2009; Zhu et al. 2009). Computational models were used to simulate this kind of infusion at rates ranging from 7.5 to 50 mL/min (Konstas et al. 2007; Neimark et al. 2007a, b, 2008, 2013; Slotboom et al. 2004; Slotboom 2007), demonstrating a rapid brain temperature drop to 34 °C within 10 min. However, it is crucial to note that these simulations likely represent the upper limit of temperature reduction as they do not account for the thermal resistance of the catheter or the loss of cooling to surrounding tissues.

Predicting temperature changes during cooling and rewarming using mathematical models is challenging due to the significant influence of blood perfusion. Studies on rat models during head surface cooling revealed a considerable discrepancy between experimental and simulated characteristic times for reaching a steady state. For instance, experimentally measured steady-state times ranged from 5 to over 40 min, whereas simulations predicted times under 5 min (Diao and Zhu 2006). This difference highlights the crucial role of variable blood perfusion rates, which are not always accounted for in the simulations. Further research using other animal models and cooling methods has confirmed these findings, emphasizing the need to integrate dynamic blood perfusion into temperature regulation models for more accurate predictions (Zhu and Rosengart 2008; Wang et al. 2008). While previous theoretical models accurately predict steady-state temperature distribution within the brain, a considerable disparity exists between theoretical predictions and experimental observations regarding the time required to achieve a steady state during both cooling and rewarming. This disparity highlights the need for more nuanced and dynamic representations of blood perfusion in mathematical models to better reflect the complex physiological responses during these hypothermia interventions.

Current simulations often oversimplify blood perfusion models by assuming it is constant or that it decreases solely based on local temperature following the Q_{10} law (Bering 1961; Hoffman et al. 1982). The Q_{10} law states that for every 10 °C drop in temperature, the metabolic rate, such as the cerebral metabolic rate of oxygen consumption ($CMRO_2$) or overall metabolic rate, reduces by a factor of Q_{10}. This Q_{10} factor can range from 2 to 4.4, based on experimental data. For instance, a Q_{10} of 2 implies a 5% reduction in cerebral metabolic rate for every 1 °C temperature decrease, and a halving of the rate with a drop of 10 °C.

Normally, cerebral blood flow (CBF) and cerebral metabolism are coupled, so that CBF would follow a similar pattern. Many temperature simulations currently incorporate the Q_{10} law, but they face a critical issue: as local blood perfusion continues to decrease during cooling, the cold temperature can spread further into the brain, causing a cycle of even more perfusion reduction (Dennis et al. 2003; Diao et al. 2003; Janssen et al. 2005; Zhu and Rosengart 2008). This continuous temperature-dependent perfusion reduction can then significantly extend the time it takes for the system to reach a stable state.

Cerebral ischemia, caused by reduced blood flow to the brain, and head injuries can alter the brain's Q_{10} value and decouple cerebral blood flow (CBF) from metabolism. Several studies have explored how systemic hypothermia (whole-body cooling) affects CBF. Using radioactive microspheres in newborn pigs, Busija and Leffler (1987) found that systemic hypothermia decreased CBF because it depressed the cerebral metabolic rate. Verhaegen et al. (1993) used a laser Doppler flowmeter (LDF) in anesthetized rats and similarly observed reduced CBF during moderate hypothermia. Okubo et al. (2001) used colored microspheres to measure regional CBF in newborn piglets, showing that lowering the cerebral cortex temperature reduced blood flow in all brain regions.

In contrast to systemic hypothermia, there are fewer studies on selective brain cooling (cooling

only the brain), and the results are inconsistent. Laptook et al. (2001) found that both whole-body and selective brain cooling reduced global CBF in newborn swine. Ibayashi et al. (2000) also demonstrated decreased regional CBF during selective brain cooling in rats. However, an earlier study by Kuluz et al. (1993) using the LDF technique found that cortical CBF increased during selective brain cooling in normal, lightly anesthetized rats. Diao and Zhu (2006) used an in vivo LDF to measure the blood flow rate of the common carotid artery during selective brain cooling and rewarming with a cooling helmet. They observed similar transient profiles for brain temperature and common carotid artery blood flow rate in rats. However, more rigorous experimental verification is needed to confirm the correlation between the CBF and the blood flow rate in the common carotid arteries. The accuracy of mathematical simulations used to study these phenomena will remain questionable until they can be validated with experimental data that simultaneously monitors local blood perfusion rates during cooling and rewarming.

18.7 Concluding Remarks

Therapeutic hypothermia has been applied to a wide variety of medical conditions, including spinal cord injury, traumatic brain injury, stroke, cardiopulmonary surgery, and cardiac arrest. Overall, an accumulating body of clinical evidence, along with several decades of animal research and mathematical simulations, has not provided a definite conclusion on the efficacy of hypothermia. However, most researchers agree that the success of therapeutic hypothermia hinges on achieving temperature reductions in the target tissue before or soon following the occurrence of the injury. Mild hypothermia appears equally effective as deeper cooling with fewer collateral/systemic complications that are often associated with deep hypothermia. It is widely documented that controlling the post-cooling rewarming rate to be lower than 0.5 °C/h minimizes a mismatch between local blood perfusion and metabolism, but controlled rewarming is crucial. The development of diverse cooling methods has yielded mixed results, highlighting the ineffectiveness of a one-size-fits-all approach to treatment. There is an urgent need for personalized treatment protocols and collaborative efforts between engineers, researchers, and clinicians to optimize hypothermia for individual patient needs. Although the problem is quite challenging, it offers significant potential for bioengineers to continue to design new cooling methods and devices that can safely and effectively induce hypothermia in targeted tissue regions without interfering with routine medical interventions.

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