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State of the Art in Therapeutic Hypothermia

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Abstract

Historically, hypothermia was induced prior to surgery to enable procedures with prolonged ischemia, such as open heart surgery and organ transplant. Within the past decade, the efficacy of hypothermia to treat emergency cases of ongoing ischemia such as stroke, myocardial infarction, and cardiac arrest has been studied. Although the exact role of ischemia/reperfusion is unclear clinically, hypothermia holds significant promise for improving outcomes for patients suffering from reperfusion after ischemia. Research has elucidated two distinct windows of opportunity for clinical use of hypothermia. In the early intra-ischemia window, hypothermia modulates abnormal cellular free radical production, poor calcium management, and poor pH management. In the more delayed post-reperfusion window, hypothermia modulates the downstream necrotic, apoptotic, and inflammatory pathways that cause delayed cell death. Improved cooling and monitoring technologies are required to realize the full potential of this therapy. Herein we discuss the current state of clinical practice, clinical trials, recommendations for cooling, and ongoing research on therapeutic hypothermia.

Keywords

cardiac arrest; intra-arrest cooling; intra-ischemia cooling; ischemia; reperfusion; reperfusion injury

HISTORY OF THERAPEUTIC HYPOTHERMIA

A remarkable example of the ability of the human body to endure low temperatures and extended hypoxia occurred during a skiing accident in 1999 when a 29-year-old medical resident spent 80 minutes suspended by her skis, upside down in a crevasse between rocks and ice, in rapidly flowing water. Extraction was difficult and she endured three hours of no or low blood flow. Ultimately, a cardiopulmonary bypass pump was used to resuscitate her from asystole. At the time of bypass implementation, her body temperature was 13.7°C, the lowest recorded temperature for a survivor of prolonged cardiac arrest. Resuscitation required nine hours before she was stabilized. During that time, she was supported by both cardiopulmonary bypass and extracorporeal membrane oxygenation, and her core temperature was slowly increased using these devices. After a long period in an intensive care unit and rehabilitation, she has completed her medical training and is hiking and skiing (1).

Clinicians have studied the impact of cold on the human body for millennia. Hippocrates advocated packing bleeding patients in snow and ice (2). Hypothermia, frostbite, and gangrene have been recorded as significant obstacles to winter warfare since the time of Alexander the Great; however, the realization that tissues could recover from low temperatures was recognized ~180 years ago by Baron Dominique-Jean Larrey. Recognizing that rapid rewarming of hypothermic tissues led to more severe frostbite and gangrene, he developed rewarming strategies to salvage very cold body tissues (3, 4).

Despite this history, hypothermia remains poorly understood as a therapy. Our most impressive clinical successes (such as nine-hour resuscitations, pulseless open heart surgery, and organ transplant) all involve significant cooling prior to any ischemia. Using hypothermia to treat ongoing ischemia (i.e., myocardial infarction, stroke, and cardiac arrest), or during reperfusion after the ischemia, requires a more detailed understanding of ischemia as an injury and hypothermia as a treatment. Several important clinical questions remain unanswered: What is the optimal target temperature, how quickly should someone be cooled, how long should someone be cooled, how rapidly should someone be warmed, should ischemia be prolonged to allow time for cooling, and if so, how long can reperfusion be delayed?

Additionally, therapeutic hypothermia suffers from a lack of technological development. Cooling technologies are in their infancy. Current technologies provide reasonable control of body temperature, but they cool patients too slowly to target the intra-ischemia treatment window during cardiac arrest. In addition, devices for temperature monitoring should be improved. Clearly the temperature of the ischemic tissue is of critical interest, but our current technologies, e.g., bladder, rectal, tympanic, or esophageal temperature probes, provide only local temperatures. Although these measurements are clinically accepted and can sometimes be correlated to core temperature, it seems unlikely that the successful treatment of stroke will require a hypothermic bladder, particularly as new technologies to target brain cooling are developed.

HYPOTHERMIA PROTECTS AGAINST ISCHEMIA/REPERFUSION INJURY

The term ischemia/reperfusion (I/R) injury refers to pathologies that are created by the acute reintroduction of oxygenated blood following a period of ischemia. Therapeutic hypothermia is believed to confer protection against I/R injury through multiple mechanisms. Among the many cited cellular pathways that may be responsible for the beneficial effects of cooling, a central hypothesis is that hypothermia reduces cellular metabolism and oxygen demand while maintaining acceptable ATP levels (5). Additionally, hypothermia attenuates abnormal free radical production (6), improves cellular ion handling, and improves cellular pH balance (7). Hypothermia also reduces cell death and inflammatory signaling (8).

Although different tissues have different sensitivities to ischemia, I/R injury has been observed in many tissue types (9). Paradoxically, cells can tolerate ischemia for hours, but the reintroduction of oxygen accelerates the onset of cell death (10-19).

The pathology of I/R injury can be separated into two mechanisms that play out over two time scales: hypoxia-induced cellular dysfunction and reperfusion-induced cell death. Reperfusion following ischemia results in a short period of excessive free radical production. Experimental measurements of post-I/R free radical production demonstrate that oxygen- and carbon-centered free radical production peaks within 5 min of reperfusion (20-24), and that hydroxyl generation in cardiomyocytes peaks within 15 min (25). Reperfusion-induced free radical production suggests that I/R injury is mediated by oxidative stress (9). Although several cellular enzymes and organelles are known to produce free radicals, data suggest that the mitochondrial electron transport chain is an important site of post-reperfusion free radical generation (26-34). Mitochondrial free radical production is an important target mechanism during the first window of opportunity for hypothermia treatment. This window likely requires intra-ischemia cooling or intra-arrest cooling so that the blood is already cooled at reperfusion.

A second window of opportunity for hypothermia after I/R injury targets the inflammatory cascade and cell death pathways known as apoptosis and necrosis. Data suggest that the mitochondrial permeability transition may be the point of no return in both of these cell death pathways (35-37). Necrosis and apoptosis are complex mechanisms involving biochemical processes such as gene expression and protein migration, as well as biophysical processes such as lipid bilayer breakdown. Apoptosis is ATP dependent, whereas necrosis is not. Both processes play out over hours to days and are associated with poor calcium and sodium management, activation of caspases and proteases, and release of mitochondrial cytochrome c, a potent initiator of apoptosis (37, 38). These cell death processes represent the second window for treatment with hypothermia. This window lasts several hours and is targeted by our current clinical practice of cooling a patient after reperfusion or blood flow has been restored. A schematic of these processes is provided in Figure 1.

CLINICAL APPLICATIONS OF THERAPEUTIC HYPOTHERMIA: THE PRESENT

References to the use of therapeutic hypothermia during surgical treatment on brain aneurysms in the circle of Willis date back to the 1950s (39). Therapeutic hypothermia has been advocated as standard treatment in on-pump open heart surgery (40). Deep hypothermia is a critical component of organ preservation during organ transplant procedures (41), where ischemic organ preservation has been pushed to days (42).

The current upswing in the emergent use of therapeutic hypothermia is being driven by national and international recommendations that cooling after cardiac arrest should be the standard of care. In 2002, two randomized clinical trials demonstrating the benefit of therapeutic hypothermia on neurologically intact survival in patients who were cooled to 33–34°C within 8 h of the return of spontaneous contraction (ROSC) following an out-of-hospital ventricular fibrillation (VF) cardiac arrest were reported (43, 44). In 2003, the International Liaison Committee on Resuscitation published a “special report” recommending that patients who achieve ROSC following an out-of-hospital cardiac arrest with a VF rhythm should be cooled as quickly as possible, and that those patients achieving ROSC following a nonshockable out-of-hospital cardiac arrest “might” also benefit from

cooling (45). In 2005, the American Heart Association (AHA) (46) and European Resuscitation Council (47) reviewed and re-endorsed these recommendations for cooling (see sidebar “Text of the AHA Recommendation”). Since 2005, hospitals throughout the United States and Europe have made hypothermia a standard of care for patients with neurological abnormalities after both in-hospital and out-of-hospital cardiac arrest. Public health officials in the city of New York have passed regulations that will allow emergency medical service personnel to transport cardiac arrest patients to hospitals that provide therapeutic hypothermia, even if this requires bypassing other hospitals that have emergency facilities but do not cool (48). Recent reports from the Netherlands (49) and from the United Kingdom (50) document that the routine use of therapeutic hypothermia in the intensive care unit after cardiopulmonary resuscitation has risen to 92% and 85.6%, respectively, by doctors and hospitals.

ESTABLISHING THERAPEUTIC HYPOTHERMIA PROTOCOLS

Hypothermia requires a team approach for effective implementation. Although cooling a patient is simple in concept, it is a complex medical procedure that requires coordination of efforts from multiple staff along with preparedness for the management issues that may arise with hypothermia. This team approach involves nursing personnel, physician personnel, and administration, and often must be transportable across different units and locations in the hospital. For example, a physician in the emergency department initiates cooling with 2 L of iced saline and a cooling blanket. However, the patient needs to travel to radiology for a head CT and to the cardiac catheterization lab before finally ending up in the intensive care unit. The staff in each of these locations needs to be familiar with the cooling protocol and cooling devices being applied to the patient.

STEPS IN THE IMPLEMENTATION OF THERAPEUTIC HYPOTHERMIA WITHIN A HOSPITAL

Although a full discussion of the challenges to implementation is beyond the scope of this review, a few simple recommendations will be useful at most institutions:

1. Develop a leadership group with representatives from emergency departments, cardiac care, intensive care, neurological and neurosurgical care, and imaging. Involve medical and nursing staff, with the understanding that physicians typically order cooling to be performed, but the hard work of patient cooling and management will primarily fall to the nursing staff.
2. Develop an institutional cooling protocol, with signoff by all stakeholders, that describes the induction of hypothermia, specific devices for cooling, target temperatures, temperature monitoring, hypothermia timing intervals, warming protocols, drugs and protocols for shivering, seizure surveillance monitoring and treatments, and the role of the leadership group for cooling.
3. Develop an institutional plan to educate medical and nursing staff broadly on the cooling protocol, cooling methods, and vigilance for possible adverse effects related to cooling.

4. Hold a regular review of cooled patients in which the stakeholders discuss emerging issues related to compliance with protocol and possible changes to the protocol.
5. Collect data on cooled patients that can be reviewed by leadership.

COMMON ADVERSE EFFECTS AND PITFALLS

Hypothermia treatment has a wide range of possible adverse effects. Early complications of cooling include a somewhat decreased cardiac output, a slowed heart rate, increased coagulation times, electrolyte shifts, shivering, the necessity for intubation, and possible over-cooling (51, 52). Although most of these are relatively minor, shivering should be dealt with aggressively. Later complications may include pulmonary infections, immunosuppression, electrolyte shifts, and prolonged metabolism of many commonly used drugs. Complications may also arise during the rewarming period. Of particular concern is the tendency of most patients to become hyperthermic during rewarming. Warming should be done gradually with strict protocols designed to avoid hyperthermia (53).

HYPOTHERMIA IS ONLY ONE PART OF POST-RESUSCITATION CARE FOLLOWING CARDIAC ARREST

Post-resuscitation care is becoming more complex, driven in part by the recent evidence of the efficacy of therapeutic hypothermia as a treatment for cardiac arrest. The “post-resuscitation care bundle” includes not only cooling but also aggressive hemodynamic support for acute heart failure or stunned myocardium following arrest, early cardiac catheterization for correction of possible acute coronary artery occlusions, neurologically directed intensive care, and attention to continuity of care. In the case of cardiac arrest, aggressive hemodynamic support could include the use of an intra-aortic counterpulsation balloon or extracorporeal hemodynamic support (54). To improve continuity of care, some hospitals have even developed a “resuscitation consult service” to advocate for patients as they travel through multiple services requiring the expertise of many subspecialty consultations. Although cooling is important for outcomes, optimal post-resuscitation care also integrates many other interventions.

COST/BENEFIT ANALYSIS OF THERAPEUTIC HYPOTHERMIA

The few papers on cost/benefit analysis or cost-effectiveness analysis suggest that cooling is cost effective. A search of the literature identifies two formal analyses (55, 56), which focus on therapeutic hypothermia for the treatment of cardiac arrest and perinatal asphyxial encephalopathy; both are conditions where hypothermia has become the standard of care.

Both analyses use Monte Carlo simulations to generate data on 10,000 simulated patients. The simulations are based on treatment decision trees that were designed to mimic the clinical experience gained in the clinical trials for each treatment. The analyses allow for uncertainties in treatment costs and patient populations. Merchant et al. (55) use cost per quality-adjusted life year (QALY) as their metric, whereas Regier et al. (56) use cost per disability-free life year (DFLY) as their metric. Both analyses conclude that, over the long

term, therapeutic hypothermia is cost effective. Merchant et al. find that 91% of all simulations result in a cost per QALY less than or equal to \$100,000 (an accepted upper limit on cost), with an average cost of \$47,168. The primary cost driver in the treatment of cardiac arrest is long-term care for cardiac arrest survivors with neurological disabilities. The analysis that Regier et al. conducted on the costs and benefits of hypothermia for perinatal encephalopathy estimated that the cost per DFLY was £1,421 over the first 18 years of life. If the willingness-to-pay threshold is £8,300, ~95% of the population would approve of this cost. Interestingly, the cost/benefit is not so clear in the first 18 months of life, when the cost per DFLY is £19,931. If the willingness-to-pay threshold is £20,000, ~52% of the population would approve of the cost. The simple take-away lesson from these analyses is that when compared to the cost of neurologically impaired survivors, cooling is a very cost-effective therapy.

CLINICAL TRAINING PROGRAMS

The logistical issues involved in the treatment and the potential for adverse effects have been a barrier to adoption of the recommendations of the International Liaison Committee on Resuscitation and the AHA (57). Several training programs are being developed to help break down these barriers. The Hypothermia Training Institute at Penn (HTIP) program at the University of Pennsylvania is a two-day intensive Continuing Medical Education (CME) accredited course with didactic and hands-on training in the clinical use of therapeutic hypothermia. The hands-on training is simulation based and designed to familiarize clinicians with practical problems that arise during induction and maintenance of hypothermia. A variety of hypothermia-induction devices are presented (<http://www.med.upenn.edu/resuscitation/hypothermia/HypothermiaTraining.shtml>). The Society of Critical Care Medicine offered a similar CME accredited two-day program entitled Keeping It Cool in April of 2010 (<http://www.sccm.org/Conferences/Topics/ClinicalFocus/Pages/default.aspx>). A four-hour lecture or instructional DVD is available from Cardiac Care Critique (<http://www.cardiaccarecritique.com/programs/HypothermicLifeSupport/>). The goal of these programs is to train people who will return to their institutions as local therapeutic hypothermia champions.

REVIEW OF RECENT CLINICAL TRIALS OF THERAPEUTIC HYPOTHERMIA: THE NEAR FUTURE

The clinical trials covered here are not meant to be all inclusive. Instead, they have been chosen because they highlight the current state of knowledge or because they highlight common issues experienced with therapeutic hypothermia. Select information from the clinical trials is shown in Table 1.

Cardiac Arrest

To date, the efficacy of therapeutic hypothermia as a treatment for cardiac arrest is the best demonstration of the potential of therapeutic hypothermia to treat ongoing I/R injury in the clinical setting. Two trials of therapeutic hypothermia following cardiac arrest have demonstrated a significant increase in long-term survival (43, 44). The results of the clinical

effort over the past eight years have been analyzed recently, and the analysis demonstrates that results similar to the early clinical trials have been replicated in hospitals throughout the world (52).

Clinical trials investigating the use of pre-hospital cooling for the treatment of cardiac arrest have been recently reported. The trial by Bernard et al. investigated the administration of ice-cold saline by paramedics to treat survivors of out-of-hospital cardiac arrest (58). Although it demonstrated that this treatment was safe, this trial was stopped early for futility. Potential confounders were the time to hypothermia induction and the temperature of the saline at infusion. (Normal IV sets allow a significant amount of heat transfer, and it is not clear what the temperature of the IV solution was as it passed into the body.)

A second study named PRINCE (Pre-ROSC Intranasal Cooling Effectiveness) investigated the safety and efficacy of inducing nasopharyngeal cooling in patients before ROSC. This is the first study to attempt intra-arrest cooling. The PRINCE investigators concluded that the procedure was safe and that it dramatically reduced time to target core temperature (59). The study was not designed to find a survival benefit; however, a favorable trend was seen in survival for patients with VF and for patients who were attended by rescuers in <10 min.

Perinatal Asphyxial Encephalopathy

Several clinical trials investigating the efficacy of hypothermia to treat perinatal asphyxial encephalopathy have been conducted. The results of these trials correlate well; they indicate therapeutic hypothermia does not statistically improve survival but does confer long-term (18-month) neurological protection to the survivors of perinatal asphyxial encephalopathy (60, 61).

Stroke

A search of the stroke trials registry finds that 19 clinical trials have investigated therapeutic hypothermia for treatment of brain ischemia since 1999. Six trials are ongoing, and eight have published data as of 2009. So far, the results indicate that therapeutic hypothermia can be induced in a clinically relevant time frame in stroke patients, and that receiving the treatment does not result in a higher number of adverse outcomes. The preferred hypothermia-induction technique was endovascular cooling catheters aimed at whole-body cooling (62, 63).

Myocardial Infarction

Several clinical trials have investigated the safety and efficacy of therapeutic hypothermia for the treatment of ongoing I/R injury in myocardial infarction. Feasibility and safety trials include Noninvasive Cooling for Acute Myocardial Infarction (NICAMI, surface cooling), Lowering Adverse Outcomes with Temperature Regulation Feasibility (LOWTEMP, endovascular cooling), and an endovascular cooling study conducted by Dixon et al. An ongoing feasibility study named the Rapid MI-ICE-Pilot is currently recruiting patients to study the efficacy of an endovascular cooling system. Two randomized controlled trials were conducted, namely the COOL MI and the ICE-IT trials. These two trials were negative. In both trials there were problems with achieving target temperature before reperfusion (an

express goal of the therapy) and in both trials patients that did reach target temperature demonstrated significant reduction in infarct size, especially for anterior infarcts (64, 65, 66).

EXPERIMENTAL THERAPEUTIC HYPOTHERMIA: THE FAR FUTURE

The protective effects of therapeutic hypothermia have been studied for a variety of I/R pathologies in multiple animal models. Often temperature control is easier in animal models, which have provided significant new insight into the protective effects of therapeutic hypothermia.

Intra-Ischemia Cooling

In our lab, we have pioneered research into intra-arrest hypothermia in a murine model of cardiac arrest. We have demonstrated that intra-arrest cooling is superior to post-ROSC cooling (67). In addition, we have demonstrated that it is preferable to delay ROSC by 90 s to allow time for intra-arrest cooling (68). Similar results were found in a rabbit model of myocardial infarction. In these studies, the cooling of the left atrium by 2–2.5°C resulted in significant reduction of the infarct region (69). Although cooling was always protective, the authors found that cooling before reperfusion was most protective, and that temperature at the time of reperfusion had the strongest correlation with the degree of cardioprotection conferred. In a sheep model of myocardial infarction (1 h of coronary occlusion followed by 3 h of reperfusion), the cooling of the left atrium by 1°C improved microvascular flow. The authors found that therapeutic hypothermia conferred the most protection to the apex of the left ventricle (70). Similarly, intra-ischemia cooling has been found more protective than post-ischemia cooling in animal models of stroke. These results are summarized in an excellent review article (71).

Hypothermia in Aggressive Extracorporeal Pump Resuscitation

In our lab, we have established a rodent model of emergency cardiopulmonary bypass (ECPB) to treat refractory cardiac arrest. We investigated the role of core body temperature in hypothermic protection. In these experiments, hypothermic ECPB was found to be significantly better than normothermic ECPB. In addition, moderate hypothermia trended toward better 72-h survival as well as better neurological outcomes. The conclusion of these studies would promote the use of cooling when ischemic injuries or cardiac arrest require the use of ECPB for refractory arrest patients (72).

Profound therapeutic hypothermia is a key component in the novel emergency preservation and resuscitation (EPR) treatment of hemorrhagic shock–induced cardiac arrest (73). In a slow-exsanguination model, cardiac arrest occurred after 2 h of hemorrhage. Profound hypothermia (brain temperature of 10°C) was induced and resuscitation efforts were supported by cardiopulmonary bypass for 2 h. Mild hypothermia was then maintained for 12 or 36 h. This treatment was compared to the current standard of care. In this study, no animals survived in the standard-care group, whereas six of seven animals survived to 96 h in the two EPR groups. It was found that prolonged mild hypothermia conferred more neuroprotection.

CURRENT CONTROVERSIES IN THERAPEUTIC HYPOTHERMIA

The research discussed above suggests that the efficacy of hypothermia treatment decays rapidly over the first minutes after reperfusion and then stabilizes for several hours. This supports the concept that there are two windows of opportunity for the use of hypothermia as a treatment. Intra-ischemia hypothermia in the early window provides the most protection in cardiac arrest (67, 68), myocardial infarction (69), and stroke (71). However, long-term hypothermia induced in the second window 1 h after reperfusion may provide the same protection as long-term hypothermia induced 4 h after reperfusion (74).

The notion of prioritizing cooling over reperfusion should cause concern, as it does not fit with a large body of clinical practice wherein “reperfusion first” is the highest priority for myocardial salvage and stroke care. Our lack of understanding on timing is underscored by a clinical trial for myocardial infarction that attempted to address this topic by cooling patients to 33°C before cardiovascular percutaneous reperfusion (75). The study of 42 patients was designed to test the hypothesis that cooling before percutaneous cardiac reperfusion in the setting of acute myocardial infarction would be superior to normothermic reperfusion. The study was neutral. However, less than half of the patients in the cooling group actually achieved target temperature. The study failed to answer the question and highlighted the problem of inadequate devices that are just too slow in cooling.

No coherent story arises from the literature correlating target temperature to treatment efficacy. Generally, it is understood that cooler tissue temperatures result in longer periods of tissue preservation (41, 76), and moderate hypothermia (30°C) trended toward better neurological outcomes than mild hypothermia (34°C) in our rat model of ECPB (72). However, cooler temperatures increase the challenges of patient management, and complications such as pneumonia and fibrillation will become more prevalent (51). Although there is little evidence that 34°C is the optimal target temperature, there is equally little evidence that the target temperature should be different.

Two questions that have been largely unexplored are the effects of hypothermia duration and the effects of rewarming rate. Although there is considerable variability in the duration of hypothermia in the literature, there has been no systematic study of the effect of hypothermia duration. This makes comparison of efficacy in the existing studies impossible. Although the pathology of I/R injury is not completely understood, there are reasons to think that treatment duration and rewarming rates could affect outcomes. Apoptosis and necrosis are processes that play out locally over many hours (37). The systemic inflammatory response could take days to stabilize, and hypothermia could prolong those dynamics. If hypothermia improves the outcomes of those processes, then it could be beneficial to titrate the length of cooling to these physiological processes. Rewarming rates are equally uncontrolled. Often, the animal is not actively rewarmed but is instead left to normalize body temperature independently. Rewarming could be of particular interest, as Baron Larrey realized that it was the rate of rewarming, not duration of cold exposure, which most closely correlated with extent of cold injury (4). It was later determined that rewarming rates influenced the degree of post-reperfusion capillary shunting (77).

ENVISIONING THE FUTURE OF THERAPEUTIC HYPOTHERMIA

Despite the volume of work indicating that therapeutic hypothermia is a viable clinical tool to combat I/R injury, and despite the significant amount of clinical experience with this therapy, there is still considerable progress to be made in order to optimize cooling. Until it is possible to cool the entire body in times on the order of minutes instead of hours, we will not be able to properly address questions of intra-ischemia cooling in the clinical setting.

Focal cooling is likely to be advantageous for the pathologies of stroke and myocardial infarction. In these cases of focal ischemia, it seems likely that a reduction of local tissue temperature is all that is required to confer protection. One might envision a catheter-based heat exchanger that can be locally placed, with the capacity to ensure that the blood flowing to the local environment is maintained at a specific temperature. This approach would reduce the heat load significantly and would likely reduce the time to target temperature to seconds instead of minutes or hours.

There are emerging phase-change technologies that have the promise to significantly reduce cooling time. One device, RhinoChill™, is a nasopharyngeal cannula that mists the nasal cavity with liquid perfluorocarbon. The perfluorocarbon evaporates on contact with the body, facilitating rapid and significant heat transfer. This device has shown promise in both experimental and preliminary human studies (59). A device developed in our lab creates a pumpable ice particulate slurry out of medical saline. This ice slurry is a biocompatible phase-change coolant that has almost twice the heat capacity of saline alone (78).

A current clinical limitation is temperature monitoring. Temperature monitoring is almost exclusively focal and is most often distal to the region of clinical interest. Clearly, we do not have the capacity to monitor hippocampal neuron or ventricular muscle temperatures. Given that ischemic tissue temperature is likely to correlate more closely with conferred protection than esophageal, rectal, or bladder temperature, it would be a significant improvement to be able to compare ischemic volume centroid temperatures at the time of reperfusion.

Finally, improvements in physiological monitoring could allow for the titration of hypothermia target temperature and hypothermia treatment duration to the individual ischemic insult. I/R injury is a very dynamic pathology. Therefore, the clinician is currently unable to determine the severity of the injury at treatment. Information such as time of ischemic onset (when it is known) is insufficient to provide true insight into the nature of the injury. Clearly, 10 min of cardiac arrest is very different in a 14-year-old than in a 90-year-old. The ability to monitor the cellular processes that are disrupted by ischemia and reperfusion will allow greater insight into the protection mechanisms that are utilized by therapeutic hypothermia. This insight would lead to better titration of treatment.

It is almost certain that cooling will continue to play an important role in clinical medicine. It is currently used routinely for patients resuscitated from cardiac arrest and a few other clinical syndromes that feature ischemic injury. Furthermore, it is almost certain that we have not yet optimized our use of cooling as a therapy. The optimization of therapeutic hypothermia will occur in the coming years. It will include the creation of new devices, an

enhanced knowledge of the critical timing for hypothermia, and an expanded understanding of the basic mechanisms that produce its beneficial effects.

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Glossary

I/R	ischemia/reperfusion
ROSC	return of spontaneous contraction
VF	ventricular fibrillation
ECPB	emergency cardiopulmonary bypass

TEXT OF THE AHA RECOMMENDATION

Recommendation of the American Heart Association (46) for use of therapeutic hypothermia to treat comatose survivors of cardiac arrest: “Thus, unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was VF (Class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).”

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SUMMARY POINTS

1. Therapeutic hypothermia should be performed for selected patients following cardiac arrest and some other clinical conditions that share ischemia as the primary pathological process. After cardiac arrest, cooling should be induced as rapidly as possible, targeted to 33°C, carefully maintained for 24 h without overcooling, and followed by rewarming without overheating. It is a complex medical procedure that requires a skilled team approach for maximal benefit.
2. I/R injury is a complex biochemical cascade that is initiated with a period of ischemia, and then paradoxically exacerbated by the return of blood flow and oxygen. The two injuries, ischemia and reperfusion, are most often encountered as a pair but have different mechanisms of action. Ischemia is associated with cellular free radical production, poor ion management, and poor pH management. Reperfusion is associated with a second burst of cellular free radical production, apoptosis, necrosis, and inflammation.
3. Hypothermia is a multimodal treatment. Mechanisms of protection include reduction of cell metabolism, maintenance of ATP, reduction of enzymatic reaction rates, reduction of gene expression and protein production, improved ion management, and improved pH management. The time between ischemia onset and hypothermia induction likely determines which of these protections are conferred to the patient.
4. At least two distinct time windows exist for the use of therapeutic hypothermia to treat I/R injury. The first window is during ischemia or during the first minutes of reperfusion. It is a narrow window and could require intra-arrest or pre-reperfusion cooling. Cooling during this window targets free radical production, pH maintenance, and ion management. The second window is delayed after reperfusion. This window is hours long and is targeted by current clinical practice. Cooling during this window targets inflammatory processes, necrosis, apoptosis, and delayed pathways to cell death.

Figure 1.

Schematic illustrating the effects of hypothermia on ischemia/reperfusion injury. Post-reperfusion cooling confers protection but is thought to target only the later cell death and inflammatory signaling. Intra-ischemia protection is thought to target ischemia-induced cellular abnormalities as well as post-reperfusion cell signaling.

Table 1

Data from selected clinical trials

Injury	Trial name	Cooling method	Target temperature	Hypothermia duration	Time to target temperature	Temperature measurement	Trial design	Outcomes	Comments	Reference
Cardiac arrest	Hypothermia After Cardiac Arrest (HACA)	TheraKool®, Kinetic Concepts, Wareham, UK (external)	32–34°C	24 h	~8 h	Bladder	Randomized, controlled	Improved survival	16% improvement in good outcomes	43
	Bernard Hospital Study	Cold packs, CoolCare, Cheltenham, Victoria, Australia (external)	33°C	12 h	~2 h	Tympanic, bladder, vascular	Randomized, controlled	Improved survival	23% improvement in survival. Odds ratio of 5.25 for improved outcome due to hypothermia	44
	Pre-ROSC Intranasal Cooling Effectiveness (PRINCE)	RhinoChill™, BeneChill, San Diego, CA, USA (nasopharyngeal)	33°C	Not published	102 min	Tympanic, bladder, vascular, rectal	Safety and feasibility	Method feasible, reduced time to target temperature	First intra-arrest cooling study, cooling initiated pre-hospital	59
	Rapid Infusion of Cold Hartmanns (RICH)	~2 L ice-cold Hartmanns solution bolus (intravenous)	33°C	24 h (~18 at temp)	~6 h	Bladder, esophageal	Randomized, controlled	Method feasible, discontinued owing to lack of efficacy	Post-ROSC cooling initiated pre-hospital	58
Perinatal asphyxial encephalopathy	The Cool Cap Trial	Olympic Medical Cool Care System®, Olympic Medical, Seattle, WA, USA (external)	34–35°C	72 h	~0.5 h	Rectal	Randomized, controlled	No survival benefit, improved neurological outcomes for severe aEEG changes	Within 5.5 h of birth	60
	Total Body Hypothermia for Neonatal Encephalopathy (TOBY)	Cold gel packs, discontinuation of active warming, and cooling blankets (external)	33.5°C	72 h	~2 h	Skin, rectal	Randomized, controlled	No benefit for survival or severe disability, but improved secondary neurological outcomes among survivors	Within 6 h of birth	61
Stroke	Cooling for Acute Ischemic Brain Damage (COOL AID)	Repreve® Endovascular Temperature Management System, Radiant Medical,	33°C	24 h	77 min	Esophageal	Safety and feasibility	Method feasible	Within 12 h of onset	62

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Injury	Trial name	Cooling method	Target temperature	Hypothermia duration	Time to target temperature	Temperature measurement	Trial design	Outcomes	Comments	Reference
Myocardial infarction		Redwood City, CA, USA (endovascular) Redwood City, CA, USA (endovascular) Redwood City, CA, USA (endovascular)								
	Intravascular Cooling in the Treatment of Stroke (ICTuS)	Celsius Control System [®] , InnerCool Therapies, San Diego, CA, USA (endovascular)	33°C	12 or 24 h	Never hit target temperature	Tympanic, esophageal, bladder	Safety and feasibility	Method feasible	Within 12 h of onset	63
	Noninvasive Cooling for Acute Myocardial Infarction (NICAMI)	Arctic Sun [®] , Medivance, Louisville, CO, USA (external)	34.5°C	3 h	79 min	Tympanic	Safety and feasibility	Method feasible	Within 6 h of onset	64
	Lowering Adverse Outcomes with Temperature Regulation Feasibility (LOWTEMP)	Fortius [®] Catheter, Alsius, Irvine, CA, USA (endovascular)	32–34°C	4 h	~1 h	Bladder, tympanic	Safety and feasibility	Method feasible	Within 6 h of onset	65