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HYPOTHERMIA AS A CYTOPROTECTIVE STRATEGY IN ISCHEMIC TISSUE INJURY

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Abstract

Hypothermia is a well established cytoprotectant, with remarkable and consistent effects demonstrated across multiple laboratories. At the clinical level, it has recently been shown to improve neurological outcome following cardiac arrest and neonatal hypoxia ischemia. It is increasingly being embraced by the medical community, and could be considered an effective neuroprotectant. Conditions such as brain injury, hepatic encephalopathy and cardiopulmonary bypass seem to benefit from this intervention. It's role in direct myocardial protection is also being explored. A review of the literature has demonstrated that in order to appreciate the maximum benefits of hypothermia, cooling needs to begin soon after the insult, and maintained for relatively long period periods of time. In the case of ischemic stroke, cooling should ideally be applied in conjunction with the re-establishment of cerebral perfusion. Translating this to the clinical arena can be challenging, given the technical challenges of rapidly and stably cooling patients. This review will discuss the application of hypothermia especially as it pertains to its effects neurological outcome, cooling methods, and important parameters in optimizing hypothermic protection.

Keywords

hypothermia; ischemia; injury; cytotprotection

INTRODUCTION

Hypothermia has been widely used by several biomedical disciplines, and recognized as an effective cytoprotectant. It has been studied to improve outcome from myocardial infarction (Holzer and Behringer 2008,Schefold et al. 2008), organ transplantation (El-Wahsh 2007,Anaya-Prado and Delgado-Vazquez 2008), cardiopulmonary bypass (Drinkwater and Laks 1993), spinal cord injury (SCI) (Yoshitake et al. 2007), intestinal ischemia (Stefanutti et al. 2008), and neonatal hypoxia-ischemia (Wagner et al. 2002,Mishima et al. 2004,Zhu et al. 2004,Edwards and Azzopardi 2006). At the clinical level, it has been shown from a small number of prospective randomized studies to improve neurological outcome from cardiac

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arrest (Bernard et al. 2002,HACA 2002) and neonatal hypoxia ischemia (Gluckman et al. 2005,Shankaran et al. 2005).

A physiological example of hypothermia can be observed in species that normally hibernate. In these animals, body temperature and metabolism drops in a manner reminiscent of that observed when intentional hypothermia is applied (Johansson 1996,Drew et al. 2001,Nathaniel 2008). In fact, these parallels have led some investigators to wonder if human hibernation is possible (Lee 2008). Hypothermia has once been thought to be the “gold standard” to which the other laboratory studies investigation cytoprotection should be compared (Krieger and Yenari 2004).

Hypothermia can be classified based on the depth of cooling from a normal body temperature of 37-38 °C: mild hypothermia (32-35°C), moderate hypothermia (28-32°C) and deep hypothermia (<28°C). While deep hypothermia has been embraced by various surgical subspecialties, the neuroprotective effect of mild to moderate hypothermia appears to be similar to deep (Huh et al. 2000). Thus, less drastic decreases in body temperature have been favored by other disciplines, as it is easier to cool nonsurgical patients to these target temperatures, and the risks of medical complications such as infection, arrhythmia, hypokalemia, coagulopathies and even heart failure in older patients are lower.

There are many mechanisms by which hypothermia may be cytoprotective. Earlier literature has focused on its ability to preserve metabolic stores and thus render the tissue or organism in a state of ‘suspended animation’ (Bellamy et al. 1996). Hypothermia has generally been viewed as a means by which protein synthesis can be suppressed. However, the widely held notion that hypothermia protects because lower temperatures slow metabolism is not completely accurate (Yenari et al. 2004). Recent research has shown that hypothermia can alter a plethora of cell death and cell survival pathways including gene regulation resulting in the inhibition of apoptosis and inflammation (Han and Yenari 2005,Liu and Yenari 2007) and the upregulation of anti-apoptotic (Slikker et al. 2001) or trophic factors (D'Cruz et al. 2002). In fact, in some systems, hypothermia has been shown to upregulate a family of ‘cold shock proteins’ at temperatures between 25-33C (Han and Yenari 2007), which could potentially regulate cell survival at a proximal point in the cell death pathway(s). Two cold shock proteins include cold inducible RNA binding protein (CIRP) and RNA-binding motif protein 3 (RBM3). CIRP has been speculated to protect and restore native RNA conformations during stress, and protects against apoptosis by upregulating extracellular signal-regulated kinase (ERK), which is involved in a cell survival pathway (Sakurai et al. 2006). RBM3 may also protect cells from death by acting in a manner similar to the X-linked inhibitor of apoptosis (XIAP) (Holcik et al. 1999). Thus, hypothermia has the potential to affect multiple aspects of cell physiology to promote protection.

A major goal of hypothermia for several indications is often to improve neurological outcome. Thus, this review will mainly focus on hypothermia as a means of preserving or improving neurological function and mortality.

NEUROLOGICAL CONDITIONS

Prior work has shown that the extent of neuroprotection by hypothermia is not related to the amount of cooling, but the time when cooling is begun and its duration (Tang et al. 2009). Similar amounts of neuroprotection have been observed where cooling to 30-34C is similar to that observed at 25C (Huh et al. 2000). At the clinical level, cooling to 35 °C appeared to be as beneficial as 33 °C while causing fewer complications (Tokutomi et al. 2009). Timing of the initiation of cooling is also important, in that the likelihood of a better outcome seems to depend on earlier initiation (Maier et al. 2001). Prolonged cooling (24-48 h) is essential for long term and robust protection (Colbourne et al. 1999,Colbourne et al. 2000).

Hypothermia in combination with a second potential neuroprotective agent has also been studied by several investigators, and was recently reviewed by us (see also Tang and Yenari (Tang et al. 2009)). While therapeutic hypothermia has shown robust protection especially in the laboratory, investigators have shown synergistic effects in combination with a second neuroprotectant such as magnesium (Scholler et al. 2004,Meloni et al. 2009), xenon (Ma et al. 2005,Dingley et al. 2008,Hobbs et al. 2008,Thoresen et al. 2009), trophic factors (Berger et al. 2004) or anti-oxidants (Pazos et al. 1999), or triple therapy with magnesium and tirilazad ("MTH" therapy) (Schmid-Elsaesser et al. 1999,Zausinger et al. 2003) or caffeine, ethanol and hypothermia (Aronowski et al. 2003). A few studies failed to show synergistic effects with a second agent, and these negative results could have been due to the already robust protective effects of hypothermia alone (Tang et al. 2009). Thus, combination therapy may also be used to enhance hypothermic protection where hypothermia is no longer or less effective. For example, delayed hypothermia for a relatively short period of time (3 h) in forebrain ischemia fails to provide long term protection (Dietrich et al. 1993), but in combination with a glutamate antagonist (Dietrich et al. 1995) or an anti-inflammatory agent (Dietrich et al. 1999), long term protection can be regained. Hypothermia could also be combined so as to lengthen the temporal therapeutic window another neuroprotectant (Nito et al. 2004,Zhao et al. 2004). Combinatorial approaches are beginning to be studied at the clinical level, with a trial of triple therapy with caffeine, ethanol and hypothermia underway (Martin-Schild et al. 2008).

Many mechanisms have been proposed regarding the neuroprotective effect of hypothermia. Several studies have shown that brain protection from hypothermia is associated with preserved metabolic stores, reduced blood flow, reduced generation of excitotoxins, decreased inflammation, decreased apoptosis and alterations in gene expression (Han and Yenari 2005,Liu and Yenari 2007,Zhao et al. 2007). About 5% of the oxygen and glucose consumption are reduced per degree centigrade when the brain is cooled. Hypothermia is also thought to couple both the brain energy and blood flow to a lower rate for the cerebral tissue (Sakoh and Gjedde 2003). Probably a specific phenomenon in brain, injury triggers the release of excitatory amino acids. Glutamate is now recognized to potentiate brain injury by binding to its ionotropic receptors and allow entry of toxic levels of calcium. A key mechanism in hypothermic brain protection is to prevent this toxic increase (Busto et al. 1989,Baker et al. 1991,Huang et al. 1993). Activation of peripheral leukocytes and brain resident microglia also occurs after brain injury, and mild hypothermia has been shown by multiple investigators to inhibit this activation and thus provide protection against ischemic injury (Inamasu et al. 2000,Wang et al. 2002). Suppression of this activation could be explained by the observation that hypothermia inhibits the pro-inflammatory transcription factor NFκB (Han et al. 2003,Yenari and Han 2006,Webster et al. 2009). Anti-apoptotic effects of hypothermia have also been documented by several investigators. Hypothermia decreases numbers of apoptotic cells (Inamasu et al. 2000,Ohmura et al. 2005,Sahuquillo and Vilalta 2007) and reduces expression of pro-apoptotic genes including Bax and several caspases (Zhao et al. 2007) while increasing anti-apoptotic genes such as Bcl-2 (Prakasa Babu et al. 2000,Zhang et al. 2001,Zhao et al. 2007,Hu et al. 2008). Hypothermia also appears to upregulate cell survival pathways such as activating the Akt pathway (Zhao et al. 2005,Lee et al. 2009) and increasing trophic factor expression (Schmidt et al. 2004,Vosler et al. 2005).

1. HYPOTHERMIA IN CARDIAC ARREST (CA)—Several experimental studies have consistently shown that mild hypothermia is neuroprotective (Krieger and Yenari 2004,Lyden et al. 2006). Cooling in the range of 30-34C have consistently shown robust neuroprotection. Critical factors in the application of hypothermia seem especially relevant in terms of the timing and duration of cooling. Dietrich and colleagues first demonstrated that post ischemic cooling to 30C for 3 h in a model of forebrain ischemia led to neuroprotection that lasted for a few days, but this was lost by one month (Dietrich et al. 1993). However, long term post ischemic

hypothermic protection could be observed if cooling were prolonged to 48 h (Colbourne et al. 1999).

Clinical studies now show that mild hypothermia improves neurological outcome from cardiac arrest (Bernard et al. 2002,HACA 2002). A multi-center clinical trial in Europe studied 274 patients with CA due to ventricular fibrillation, and showed that cooling to 32°C to 34°C over a period of 24 hours had a significant protection. As a consequence of therapeutic hypothermia, the 6 month mortality was reduced from 76/138 (normothermia) to 56/137 (hypothermia, $P<0.05$). The cooled patients also had improved neurological outcome 6 months later, compared to those who were not cooled (HACA 2002). Another clinical trial in Australia included 77 patients who had CA and randomly treated the patients with either hypothermia (33°C within 2 hours after the return of spontaneous circulation and maintained for 12 hours) or remained normothermic. In this second study, 49% of the patients who received hypothermia survived and had a good neurological outcome, while 26% of the patients survived in the normothermia group ($P<0.05$) (Bernard et al. 2002). Based on these findings, hypothermia is being increasingly used at centers worldwide. Therapeutic hypothermia is even recommended in pediatric populations for similar indications (International 2005).

2. HYPOTHERMIA IN BRAIN TRAUMA—Hypothermia also been studied in experimental models of brain trauma with similar beneficial effects (Dietrich et al. 2009). It has been used in the setting of brain trauma for many years, and results of several small clinical trials have been published (Sydenham et al. 2009). One study showed modest but transient benefit in patients with head trauma, provided the Glasgow Coma Score (GCS) was between 5-7. (Marion et al. 1997). However, larger clinical trials, *including a recent one in pediatric populations*, failed to show a convincing benefit (Clifton et al. 2001,Hutchison et al. 2008). However, the study by Clifton and colleagues indicated that trauma victims who presented hypothermic and were not rewarmed fared better than those who were, further studies in adults are ongoing to clarify whether earlier intervention might result in a favorable outcome.

3. HYPOTHERMIA IN NEONATES—Perinatal brain injury is a significant problem in the United States (Gunn and Bennet 2008). Hypoxic-ischemic encephalopathy can complicate the newborn period and lead to long term neurological disability. Animal studies in neonatal and juvenile animals (Taylor et al. 2002,Wagner et al. 2002,Yager et al. 2004) have shown that hypothermia can provide neuroprotection after hypoxia-ischemia, but, like in adult animals, that the severity of injury and timing, depth and duration of hypothermia are major variables (Verklan 2009). Mechanisms of protection, while not as extensively studied as in adult animals, suggest similar underlying mechanisms such as decrease of excitatory amino acids and preservation of energy metabolites (Thoresen et al. 1995,Amess et al. 1997) as well as inhibition of caspase activation (Zhu et al. 2004,Zhu et al. 2006).

Clinical trials of therapeutic hypothermia in neonates with hypoxic encephalopathy also suggest a benefit in this patient population. To date, there have been *three* large, multicenter randomized studies of newborn infants with hypoxic ischemic encephalopathy. One trial showed that term infants with moderate, but not severe neonatal encephalopathy and abnormal EEGs subjected to head cooling for 72h (rectal temperature 34-35C), within 6h of birth showed a benefit that persisted at 18 months of life (CoolCap)(Gluckman et al. 2005). A second trial of whole-body cooling to 33.5C for 72h in infants with moderate or severe encephalopathy reduced the risk of death or moderate or severe disability assessed at 18 to 22 months (Shankaran et al. 2005). A recently published third study, Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY) showed similar benefits in newborns with perinatal asyphyxia who received whole body cooling within a similar timeframe, but somewhat different cooling paradigm (Azzopardi et al. 2009). The primary outcome at 18 months of age showed that cooled infants had better survival and neurological outcomes than those that were

not cooled. However, defining the optimal candidate for hypothermia has yet to be defined, and subsequent studies are ongoing. Further, an important question in pediatric neuroprotection is the need for long term follow up (no trial has yet studied outcomes beyond 18 months of age) and persistent, lifelong benefit (Shankaran 2009).

4. HYPOTHERMIA IN STROKE

HYPOTHERMIA AND ISCHEMIC STROKE: Abundant experimental stroke studies have shown the neuroprotective effects of hypothermia when cooling was applied in the range of 24°C to 33°C (Krieger and Yenari 2004), with temperatures in the mild to moderate range being better tolerated. The timing of cooling is also important, in that hypothermia should be initiated within 2-3 hour of ischemia onset. In contrast to that observed in models of forebrain ischemia or cardiac arrest, the duration of cooling is less clear. Delays of 2-3 h have documented protection where cooling was maintained for a few hours (Maier et al. 2001) or 48 h (Colbourne et al. 2000). Collective experimental studies also suggest that recanalization, or reperfusion after stroke increases the likelihood of a good outcome (Krieger and Yenari 2004,Tang et al. 2009). Studies where the middle cerebral artery is only transiently occluded (tMCAO) consistently showed protection, whereas the results from studies where the MCA was permanently occluded (pMCAO) were conflicting. While on permanent MCAO (pMCAO) models, studies showed contradictory results. Thus, the role of combining therapeutic hypothermia with recanalization strategies in clinical trials becomes important (Lyden et al. 2006).

A few clinical studies of therapeutic hypothermia in acute ischemic stroke have been published or are ongoing (Lyden et al. 2006,Hemmen and Lyden 2007). In essence, these studies have collectively shown that mild therapeutic hypothermia is feasible, though not completely without complications. A significant challenge in applying hypothermia to stroke patients is that unlike other neurological conditions, stroke patients are generally awake and do not tolerate cooling. Like that encountered in the cardiac arrest and brain injury studies, attaining target temperature and maintaining it, especially in adult humans, is challenging. Another issue in applying hypothermia to patients with stroke is the rebound increased intracranial pressure experienced during rewarming, a phenomenon not well studied in laboratory models (Schwab et al. 2001).

Two clinical studies have utilized intravascular cooling devices to cool acute stroke patients. In COOL-AID (De Georgia et al. 2004), most patients tolerated hypothermia, and clinical outcomes were similar in both groups although there was a suggestion of reduced lesion growth on diffusion-weighted imaging (DWI). ICTuS, another non-randomized clinical trial using a different intravascular cooling device, also addressed administration of rt-PA to improve chances of recanalization (Lyden et al. 2005). Overall, these patients also tolerated cooling, and the incidence of cerebral hemorrhage did not appear increased. Thus, the benefit of hypothermia for treatment of acute ischemic stroke in humans is not yet clear.

HYPOTHERMIA AND HEMORRHAGIC STROKE: Hemorrhagic stroke accounts for about 15% of all strokes, but the mortality and morbidity result from this is much higher than ischemic stroke. Stroke due to brain hemorrhage can be caused by primary parenchymal hemorrhage (intracranial hemorrhage, ICH) often due to hypertension, subarachnoid hemorrhage due to aneurismal rupture, or hemorrhagic transformation where ischemically weakened blood vessels permit the passage of blood (hemorrhagic transformation, HT) (Mohr et al. 2004). Significant HT can also complicate treatment with thrombolytic agents such as rt-PA, which are used to pharmacologically reperfuse occluded cerebral vessels.

Though its pathophysiology is complicated, an obvious consequence of hemorrhage, particularly arterial hemorrhage, is the mass effect caused by extravasated blood leading to

increased intracranial pressure and brain herniation. It is also recognized that both inflammatory and oxidative factors are involved in damaging brain cells caused by the extravasation of blood to the brain parenchyma. Exposing neurons to hemoglobin and heme causes oxidative injury to neurons (MacLellan et al. 2009). Further, neurons take up more hemoglobin metabolites than other brain cells, thus they are more vulnerable to ICH injury (Lara et al. 2009). Unfortunately, less has been studied with regard to therapeutic hypothermia for brain hemorrhage.

Models of ICH are frequently studied where bacterial collagenase was instilled into the striata to cause hemorrhage due to proteolytic disruption of the basal lamina, or autologous blood is directly injected into the brain (Strbian et al. 2008). Unlike that observed in ischemic brain ischemia models, studies of therapeutic hypothermia in brain hemorrhage are less consistent. While a few studies have shown salutary effects of hypothermia in ICH, others have not (MacLellan et al. 2009). The parameters of optimal hypothermic treatment may also be quite different from that used for other conditions. For instance, in one study of collagenase induced ICH, mild hypothermia (33–35°C) was begun 1, 6 or 12 hours after collagenase infusion. In contrast to findings in other types of brain injuries where earlier intervention was associated with better outcome, only the group cooled 12 h post injury had any benefit. No neuroprotection was observed in the groups where cooling was instituted sooner. The reasons for these observations are not clear, but the authors noted that hypothermia in their model increased blood pressure soon after collagenase injection (MacLellan et al. 2004). Another reason why the response of hemorrhagic stroke is so varied is that cooling can also affect endogenous coagulant and thrombolytic systems, and predispose to bleeding.

Hemorrhagic transformation (HT) normally follows many ischemic strokes, but not of sufficient consequence to cause clinical deterioration. With the use of thrombolytic agents, symptomatic HT has been recognized and is a major concern surrounding the use of these agents. However, experimental studies have emphasized the need for recanalization to occur in order to optimize the response to therapeutic hypothermia. Since temperature can differentially affect spontaneous and pharmacological clot lysis (Yenari et al. 1995), it is important to understand whether rt-PA might affect the risk of significant HT. However, rt-PA in combination with mild hypothermia does not appear to worsen HT (Tang et al. 2009).

Subarachnoid hemorrhage (SAH) is often due to aneurysmal rupture, and hypothermia is used by many surgeons during aneurym repair. Models to study SAH consist of inserting a monofilament into the carotid artery in order to rupture the intracranial portion of the vessel, or instill autologous blood into the subarachnoid space (Strbian et al. 2008). A few preclinical studies of hypothermia in SAH have been published and recently reviewed (MacLellan et al. 2009). These studies seem to show improvement in metabolic derangements and alterations in gene expression caused by experimental SAH, but there are no systematic studies to address overall functional benefit. Clinical studies of intraoperative hypothermia for aneurysm surgery to date do not show a convincing benefit of cooling (Todd et al. 2005,Samra et al. 2007). Since ischemia due to vasospasm can complicate SAH, the role of therapeutic hypothermia might apply here in a manner similar to that of ischemic stroke.

5. HYPOTHERMIA IN SPINAL CORD INJURY (SCI)—Deep hypothermia for spinal cord injury was extensively studied in the 1960's and 70's, but was somewhat abandoned due to the side effects of cooling in the range of 6-18C. However, with the resurgence of interest in hypothermia in the 1980s and 90s, fueled by the observation that even small decreases in brain temperature protected the brain from injury, similar work in SCI was also begun anew. In contrast to other areas of neurological injury, an important issue in SCI focuses on optimal cooling methods, such as local cooling using epidural or subarachnoid approaches versus systemic cooling. Regardless, multiple preclinical studies have examined cooling in the range

of 4-33C of varying durations (mostly brief) with beneficial results using histologic and/or functional measures (reviewed by Guest and Dietrich (Guest and Dietrich 2005)). Importantly, the collective literature on hypothermia in SCI suggests that the temporal therapeutic window might be rather brief, as short as 5 minutes post injury, although other studies have demonstrated longer time windows. These discrepancies might be explained by the severity of the insult or the type of insult (e.g. contusion vs ischemia), or the duration of hypothermia. There do not appear to be systematic studies addressing these issues. Mechanisms of hypothermic protection in SCI, like other brain pathologies, were associated with decreased inflammation and excitotoxic and oxidative stress (Inamasu et al. 2003). Mild hypothermia also decreased astrocyte and capillary proliferation which could affect regeneration of axons. However, laboratory studies mostly seem to suggest that hypothermia improves axon recovery (Lo et al. 2009). This could potentially be explained by differential effects of hypothermia on decreasing astrocyte proliferation and scar formation, while increasing trophic factor expression.

A few non randomized trials of hypothermia in SCI have been published and show some promise (Guest and Dietrich 2005). However, controlled prospective trials are lacking. In the meantime, studies to define optimal cooling methods, depth and duration of cooling, timing of cooling and ideal candidates for cooling are still needed.

6. HYPOTHERMIA IN HEPATIC ENCEPHALOPATHY—Severe liver failure may increase toxic metabolite accumulation in the body with portal blood being shunted into the systemic circulation. Hyperammonemia ensures leading to increased permeability of the blood brain barrier (BBB), brain edema and increased intracranial pressure (ICP) (Larsen and Wendon 2008). Systemic inflammation which accompanies liver failure is also being increasingly recognized to contribute to adversely affect brain function and edema (Rolando et al. 2000,Jiang et al. 2009). Laboratory studies of hypothermia in experimental liver failure showed that cooling in the range of 32-35C can reduce brain edema and increased ICP (Jalan and Rose 2005). Mild hypothermia can improve detrimental effects of liver failure by improving ammonia metabolism, suppressing inflammation, normalizing brain osmolarity and cerebral blood flow (Vaquero and Blei 2005). By using the cooling blankets to lower core temperature to 32-33°C in patients with liver failure awaiting organ transplantation, Jalan et al (Jalan et al. 2004,Jalan and Rose 2005) observed reduced arterial ammonia levels, decreased cerebral uptake of ammonia and brain cytokine production with reduced ICP and brain edema. While less is known about the use of cooling in this condition, promising outcomes from a few clinical studies have prompted many in the medical community to embrace this approach to reduce neurological complications in patients with liver failure awaiting transplantation.

CARDIOVASCULAR SYSTEM

Hypothermia is widely used in open cardiac surgery not only to protect against peri-operative brain ischemia that could potentially develop (Grocott and Yoshitani 2007), but also the myocardium (Hale et al. 2005). The topic of hypothermia for myocardial protection was reviewed recently (Parham et al. 2009), but we summarize salient points here.

Following coronary artery occlusion, myocardial tissue consequently endures oxygen and energy depletion and thus cell death if not rescued. For several decades, cardiac surgeons have been using hypothermia to protect the non-working heart during open heart surgeries (Bigelow et al. 1950). In the ischemic working heart, mild hypothermia (34°C) preserved microvascular flow and maintained cardiac output (Dae et al. 2002). In addition to maintaining myocardial contractility after ischemia, studies in a rabbit model of acute myocardial infarction showed that regional myocardial hypothermia (32°C) initiated 10 minutes before reperfusion and maintained for 2 hours significantly improved the reflow, reduced the “no-flow” phenomenon,

myocardial necrosis and infarct size (Hale et al. 2003). Like the brain, timing of hypothermia is a major concern in order to rescue the heart from ischemia. Several studies have shown salutary effects of hypothermia in cardioprotection when cooling began prior to the onset of ischemia (Hale and Kloner 1997,van der Pals et al. 2009). While consistent and robust effects have been demonstrated, such a paradigm would have limited clinical utility, except in cases of prophylactic cardioprotection in high risk procedures such as aortic aneurysm repair (Coselli and LeMaire 2008) and infants with aortic coarctation and ventricular septal defect (Kanter 2007). However, prolonged deep hypothermia in neonatal procedures may increase the risk of post operative seizures (Gaynor et al. 2005). Post insult hypothermia has also been shown to benefit experimental myocardial ischemia (MI). Whether initiated before or after ischemia onset, mild hypothermia resulted in protection provided the target temperature (left atrial temperature 2-2.5C lower than normal) was reached at the time of coronary artery reperfusion resulted in a marked protection (Kanemoto et al. 2009).

Possible mechanisms of protection seem to parallel those described for brain ischemia. Studies have shown correlations between protection and reduced energy demand (Ning et al. 2007), delayed ATP depletion (Ruiz-Meana et al. 2003), induced HSP70 expression (Ning et al. 1999), decreased apoptotic cell death through reduced expression of tumor suppressor gene p53 translational product (Ning et al. 2007) and improved blood flow to the myocardial microvasculature (Hamamoto et al. 2009).

Clinical application of hypothermia for cardioprotection has largely been used in the intraoperative setting, but some smaller studies have been conducted in patients with acute myocardial infarction. Considerations somewhat specific to the heart include compromised cardiac function with cooling. In a study where canine core temperatures were cooled to 25 °C for 5 hours, cardiac output reduced to 37% of the baseline level and this change remained persistent even after rewarming (Tveita et al. 1994). Further, myocyte morphology is altered when rats were exposed to −8 °C for 4 hours (Meneghini et al. 2008). Nevertheless, in one study of 42 patients with acute MI, endovascular cooling to 33C led to a trend towards smaller infarct size and no adverse events (Dixon et al. 2002). Retrospective analysis of the HACA study (HACA 2002) that showed neurological benefit of hypothermia in cardiac arrest failed to show a similar myocardial benefit (Koreny et al. 2009). Certainly, it appears that defining the optimum parameters for myocardial protection still need to be defined, and studies to address this in acute MI are ongoing (Parham et al. 2009).

COOLING METHODS

NON-INVASIVE METHODS

Non-invasive cooling is mainly achieved by surface cooling devices. These approaches range from simple ice packs to sophisticated machines with automatic feedback control (Holzer 2008). Traditional non-invasive cooling methods and endovascular approaches are detailed elsewhere (Dae et al. 2002,Dixon et al. 2002,De Georgia et al. 2004,Lyden et al. 2005,Guluma et al. 2006). Here we discuss recent novel approaches.

Intranasal cooling—Intranasal cooling might be especially useful for selective brain cooling where neuroprotection is desired. The effect of hypothermia and neuroprotection has been linked to how rapidly the cooling is initiated and how quickly the hypothermic target zone is reached. One group showed in sheep experiments that by spraying evaporative aerosolized perfluorochemicals (PFC) into the nasopharyngeal space, selective brain cooling was more rapidly achieved compared to the whole body spraying. The authors attributed this to the nasopharyngeal vascular network being anatomically closer to the cerebral circulation, cavernous sinus, and carotid arteries (Wolfson et al. 2008). It may also avoid other undesirable

side effects of whole body cooling such as shivering, predisposition to infection and cardiac arrhythmias.

Pharmacologic cooling—There is also a growing body of literature reporting pharmacological approaches to cooling. Neurotensin is an endogenous peptide involved in circadian temperature regulation, and analogues have been developed that penetrate the BBB. Single intraperitoneal injections to rats decreased body temperatures by about 5C within 1 h, and cooling could be maintained for about 7 h (Tyler-McMahon et al. 2000,Gordon et al. 2003,Katz et al. 2004). 3-iodothyronamine (T1AM), a naturally occurring derivative of thyroxine, rapidly induced hypothermia in rodents.(Scanlan et al. 2004) to temperatures as low as 28C persisting as long as 3-4h. Hydrogen sulfide (H2S), possibly by buffering unrestricted oxygen consumption, has also been reported to reduce body temperature to as low as 15C within 6 h (30C in less than 1 h) and reduce metabolic rate by 90%. It also appears to prolong survival in mice exposed to lethal hypoxia.(Blackstone and Roth 2007) Whether any of these approaches could be applied in humans has yet to be addressed, but are clearly worthy areas of investigation.

INVASIVE COOLING METHODS

These include the administration of ice-cold fluids intravenously, the use of intravascular cooling catheters, body cavity lavage, extra-corporeal circuits and selective brain cooling.

Circulatory and cardiac cooling—With respect to localized cooling for cardiac indications, atrial fibrillation (AF) is a complication of on-pump coronary artery bypass grafting. By cooling the right atrium, transient post-operative AF can be reduced. Atrial cooling can be achieved through a modified dual-stage venous drainage by circulating cold sterile saline through an intracavity, shape-memory balloon (Huybregts et al. 2008). Right atrial and nodal cooling was achieved with this method, the body temperature could be maintained at 36 °C while for 30 minutes while the right atrium is held at 19-20 °C.

Systemic cooling in the setting of cardiac resuscitation can be achieved through cooling of withdrawn blood. In a porcine model of cardiac arrest, pigs were instrumented with micromanometers and thermocouple probes, two 8Fr catheters were canalized through femoral vein. Five minutes after experimental heart arrest, the blood was withdrawn from one of the catheters, cooled externally, then returned the circulation through another catheter. The authors claimed that this method could provide a rapid induction of mild hypothermia in the setting of cardiac arrest (Zviman et al. 2004). At the clinical level, a small study of patients suffering cardiac arrest, hypothermia was applied by direct cooling of the blood using a coil (Nagao et al. 2000). In this study, many patients who were cooled had favorable survival and neurological indices.

CONCLUSIONS

Hypothermia is a robust cytpoprotectant, and its effects have perhaps been most realized with respect to the nervous system. However, beneficial effects have also been explored in other organ systems, namely the heart. While robust protection has been observed in numerous experimental studies, only a few clinical studies have convincingly demonstrated a role in humans. To date, its use in neurological improvement following cardiac arrest and neonatal hypoxia ischemia appear to be the most convincing, but its use in related disorders is being aggressively studied.

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