Therapeutic Hypothermia: Applications in Pediatric Cardiac Arrest

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Abstract

There is a rich history for the use of therapeutic hypothermia after cardiac arrest in neonatology and pediatrics. Laboratory reports date back to 1824 in experimental perinatal asphyxia. Similarly, clinical reports in pediatric cold water drowning victims represented key initiating work in the field. The application of therapeutic hypothermia in pediatric drowning victims represented some of the seminal clinical use of this modality in modern neurointensive care. Uncontrolled application (too deep and too long) and unique facets of asphyxial cardiac arrest in children (a very difficult insult to affect any benefit) likely combined to result in abandonment of therapeutic hypothermia in the mid to late 1980s. Important studies in perinatal medicine have built upon the landmark clinical trials in adults, and are once again bringing therapeutic hypothermia into standard care for pediatrics. Although more work is needed, particularly in the use of mild therapeutic hypothermia in children, there is a strong possibility that this important therapy will ultimately have broad applications after cardiac arrest and central nervous system (CNS) insults in the pediatric arena.

Key words: asphyxia; cooling; drowning; neonate; newborn; resuscitation

Introduction

THERAPEUTIC HYPOTHERMIA has deep roots in the area of pediatric resuscitation. Early case reports of dramatic recovery from prolonged cardiac arrest and resuscitation after cold-water drowning represented some of the groundwork for the ultimate clinical application of this important therapy (Siebke et al., 1975). In the late 1970s, Conn and his group in Toronto pioneered the use of “HYPER” therapy, which included moderate therapeutic hypothermia for use in pediatric drowning victims (Conn, 1979). In the late 1970s and early 1980s, therapeutic hypothermia was used after asphyxial cardiac arrest in children in many pediatric intensive care units (Conn et al., 1979; Nussbaum and Maggi, 1988). Many, including the first author of this report, gained a great deal of experience with this therapy based on its application in clinical practice in that era in pediatric critical care. It is also important to recognize that in that era Reye syndrome was also a relatively common condition in pediatric critical care, and the response of these patients to therapies directed at intracranial hypertension, such as hypothermia, could be dramatic-with normal recovery despite prolonged deep coma and even fixed and dilated pupils (Frewen et al., 1982; Lansky et al., 1977). Success of therapeutic hypothermia in Reye syndrome and other diagnoses produced a spill-over effect, and this therapy was often applied to other pediatric conditions such as cardiac arrest and traumatic brain injury. Although publications on pediatric applications of therapeutic hypothermia in that era were somewhat limited, in part, this was likely the result of the fact that it was, in many centers, felt to be the standard of care and already described. Curiously, despite the fact that cold water drowning in children and the use of “HYPER” therapy in pediatric drowning victims represented a key early experience for the use of therapeutic hypothermia in clinical practice, it is only an option in the current pediatric guidelines for treatment of cardiac arrest in children (American Heart Association Guidelines for Cardiopulmonary Resuscitation, 2006).

In the late 1980s, two reports had a “chilling” effect on the use of therapeutic hypothermia in children and beyond. Bohn et al. (1986), and Biggart and Bohn (1990) presented follow-up reports from the Toronto group, describing their experience with pediatric drowning victims (after therapeutic hypothermia had been abandoned) and suggested that hypothermia...
 afforded no improvement in outcome and increased infectious complications. In retrospect, however, these studies were limited in scope. For example, the study of Bohn et al. (1986) described results from only ~40 drowning victims treated over 5 years, and the hypothermia that was used was applied in a heterogeneous fashion (i.e., target temperature as low as 30–31°C in some patients and applied for as long as 13 days in one patient). In addition, in that era, therapeutic hypothermia was generally used in combination with aggressive hyperventilation, fluid restriction, and often with rapid re-warming—interventions that would be considered potentially detrimental in current management. It is rather ironic that the report of Bohn et al. (1986) appeared at about the same time as the seminal report of Busto et al. (1987), which described the successful application of extremely mild levels of hypothermia in experimental cerebral ischemia—a report that re-energized the field of experimental brain injury research which ultimately culminated in its successful clinical application in ventricular fibrillation cardiac arrest in adults.

**Cardiac Arrest in Infants and Children: Unique Considerations**

There are two important factors that merit special discussion: (1) the unique pathobiology of the asphyxial cardiac arrest and (2) developmental differences in the response of infants and children to central nervous system (CNS) insults. Both of these factors deserve a brief discussion to put the current status of the use of therapeutic hypothermia after cardiac arrest in infants and children into perspective. Cardiac arrest in children often results from asphyxia rather than ventricular fibrillation. For example, Young et al. (2004), in a prospective study of 599 children, reported that only 9% resulted from ventricular fibrillation. Most children suffer cardiac arrest from a respiratory etiology such as drowning or choking. The consequences of asphyxial cardiac arrest appear to be particularly detrimental. For example, most reviews and texts on this topic cite an overall survival of ~13% for asphyxial cardiac arrest in children and a particularly poor ~9% survival in out-of-hospital pediatric cardiac arrest. Reports on out-of-hospital asphyxial cardiac arrest in children have also suggested extremely poor outcome in survivors (O’Rourke, 1986). The fact that in asphyxia a period of hypoxic or anoxic perfusion precedes the arrest appears to result in a particularly unfavorable injury (Kochanek, 1988; Vaagenes et al., 1997). One other factor with regard to mechanism of injury in infants and children with cardiac arrest that may be very relevant to the application of therapeutic hypothermia relates to the fact that in neonatal resuscitation, the overwhelming majority of cases are witnessed. In contrast, the majority of cases of asphyxial cardiac arrests in children occur out-of-hospital. Delays in initiating CPR and advanced cardiac life support can critically limit the potential for successful resuscitation and the opportunity to promptly implement therapeutic hypothermia.

There are also many age-related differences in the response to brain injury; a few key points may be relevant to therapeutic hypothermia. First, there are critical age-related differences in excitotoxic pathways, most notably comparing pre-term and term infants to older infants, children, and adults. Based on numerous studies across species from rodents to humans (McDonald and Johnston, 1993; Johnston, 2005), there appears to be heightened vulnerability to NMDA receptor activation in term newborns. For example, postnatal-day 7 (PND7) rats (commonly felt to model term newborn human for brain development in many regards) show markedly enhanced vulnerability to injection of glutamate agonists (McDonald and Johnston, 1993). In addition, the GABA switch occurs near term in humans, and this represents the transition from GABA as an excitatory to inhibitory transmitter (Jenkins and Kochanek, 2008). Enhanced vulnerability of newborns to excitotoxicity may represent a target for therapeutic hypothermia given the fact that excitotoxicity is known to be attenuated by this therapy (Marion et al., 1997; McDonald et al., 1991). In addition, apoptosis is an essential facet of normal brain development, and the pre-term and term newborn brain appears to be primed for apoptosis. For example, caspase-3 levels are generally increased relative to adult levels in the first 2 postnatal weeks in rat brain (Shimohama et al., 2001). This could be of special relevance to the use of therapeutic hypothermia in newborns and infants, if an apoptotic neuronal death pattern predominates. Recently, Berger and colleagues assessed serum levels of the biomarkers neuron-specific enolase (NSE) after cardiac arrest and reported delayed increases in pediatric cardiac arrest victims, which is consistent with possibility of apoptotic delayed neuronal death in this setting. Study of the impact of therapeutic hypothermia on biomarkers of brain injury in serum or urine of pediatric cardiac arrest victims is needed (Berger et al., 2006; Berger and Kochanek, 2006). A third mechanistic difference germane to unique injury in the developing brain relates to the important role of injury to oligodendrocyte precursor cells (OPCs) in the pathobiology of perinatal asphyxia relative to pediatric or adult insults. OPCs appear to have enhanced vulnerability with very defined temporal windows in the pre-term human brain, and insults to them produce the classic pattern of periventricular leukomalacia seen in perinatal brain injury (Yasuda et al., 1995). Another unique and potentially important age-related difference relates to developmental differences in cerebral blood flow, metabolism, and synaptic number. All three of these parameters appear to peak in rodents around PND17, which would equate to a toddler. Cerebral blood flow, for example, is low in newborns, peaks in young children, and then plateaus downward slowly in adulthood (Nehlig, 1997). The impact of these physiological differences on injury and plasticity remain to be fully defined. Finally, a number of other potential age-related differences in injury mechanisms may be operating, such as inflammation, cell signaling, white matter damage, and neurogenesis, among other pathways may be important but are beyond the scope of this targeted review.

**Therapeutic Hypothermia in Pediatric and Neonatal Resuscitation: Studies in Experimental Models**

A potential benefit of therapeutic hypothermia in perinatal asphyxia was suggested by Edwards in 1824 (Edwards, 1824). In perinatal asphyxia in newborn kittens, hypothermia prolonged the duration of asphyxia required to terminate gasping. These findings were later confirmed (Westin et al., 1962). However, subsequent studies in 1966 in a primate model of perinatal asphyxia (12 or 15 min) suggested that brain damage at 9–28 days after the insult was not attenuated by therapeutic hypothermia (24–26°C until spontaneous breathing
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recovered) (Daniel et al., 1966). Similarly, in 1976, no benefit from therapeutic hypothermia was seen in asphyxiated newborn rabbits (Oates and Harvey, 1976). These findings, along with the well-recognized deleterious effects of cold stress in normal pre-term infants combined to reduce interest in therapeutic hypothermia in perinatal brain injury.

Following the experimental work of Busto et al. (1987) in adult rats, which re-introduced the concept of therapeutic hypothermia using very mild temperature reductions, a number of early reports emerged relevant to neonatal and pediatric brain injury. As discussed, at that time, therapeutic hypothermia was used as standard of care in many pediatric intensive care units for drowning or Reye syndrome (Lansky et al., 1977; Frewen et al., 1982), although its use was beginning to wane. Yager et al. (1993) reported that mild or moderate intra-ischemic hypothermia attenuated neuronal damage in the Rice/Vannucci model of 3 h of hypoxic-ischemia in PND7 rats, which models a newborn child. In that model, unilateral carotid artery ligation is followed by transient exposure to reduced FiO2, resulting in unilateral hypoxic-ischemic neuronal damage (Yager et al., 1993). However, despite benefit with intra-ischemic application, no benefit was seen when hypothermia was initiated after the insult. Mansfield et al. (1996) demonstrated reduced brain edema by moderate hypothermia applied early after experimental TBI in PND21 rats, modeling a toddler or young child. Similar to the work of Yager et al. (1993), a long-term benefit on lesion volume at 7 days after insult was not seen. One potential explanation for these mixed findings in these pediatric and neonatal models, particularly on long-term outcome, may relate to the use of brief periods of hypothermia, since 72 h of cooling was recently shown to produce permanent protection in the Rice/Vannucci model (Ohmura et al., 2005). The initial clue in perinatal asphyxia of the need for prolonged cooling came from the work of Gunn et al. (1997), who reported marked benefit from 72 h of selective head cooling in a fetal sheep model of perinatal asphyxia, even when cooling was delayed 90 min. In subsequent work, attenuation of oligodendrocyte damage, microglial activation, and caspase-3 activation was shown in this model (Roelfsema et al., 2004).

Finally, despite having the earliest clinical adoption of therapeutic hypothermia in clinical care, studies in experimental brain injury in pediatric cardiac arrest modeling children, have only been recently published. Fink et al. (2005) demonstrated beneficial effects of therapeutic hypothermia on neuronal death after asphyxial cardiopulmonary arrest in PND17 rats, modeling toddlers suffering insults such as drowning. Benefit of therapeutic hypothermia on cognitive function as assessed with Morris water maze testing was also shown in those studies.

Taken together, this body of laboratory work has supported the clinical trials in neonatology and pediatric neurocritical care, and also support continued investigation to optimize and define all of the potential therapeutic targets for this potent therapy in the pediatric and neonatal arenas.

Therapeutic Hypothermia in the Treatment of Birth Asphyxia: Clinical Studies

Birth asphyxia, defined as critically decreased oxygen delivery near birth, which results in profound metabolic acidosis and neurological dysfunction (as measured by the Apgar score and continuing encephalopathy in the hours after birth) affects up to 5 per 1000 live births (Levene et al., 1986) and is associated with up to 50% poor neurological outcome (Vannucci, 1990). Over the past decade, a dramatic advance has been made in treating afflicted infants with hypothermia, ultimately leading to improved survival and neurological outcome. In 1997, an expert review stated “there is no uniform standard of care in the brain-oriented therapy of full-term newborn infants sustaining cerebral hypoxia–ischemia, and it remains for future research to uncover new and effective strategies” (Vannucci et al., 1997), and human studies in hypothermia were not mentioned. A decade later, hypothermia is becoming accepted treatment (and approaching “standard therapy”) because investigators demonstrated feasibility, verified the safety of the therapy while ensuring modifying enrollment criteria, and showed efficacy in well-designed phase III trials with clinically relevant outcomes.

Hypothermia was widely regarded as hazardous for human neonates because of their impaired ability to regulate body temperature. This opinion was largely based on a study demonstrating that warmer incubator temperatures (for the first 5 days of life) were associated with an ~20% improved survival in preterm infants (Silverman et al., 1958). While emphasizing the importance of maintaining normal temperature in uninjured preterm infants, these data dampened any interest in hypothermia as a neuroprotection strategy in brain-injured infants.

This dogma was challenged using two unique hypothermia devices—selective head cooling utilizing a head covering maintained at 10°C (called a “Cool Cap”) and whole body hypothermia using a servo-controlled blanket—both titrated to systemic temperatures. Advocates for selective head cooling believe that this method might allow decreased brain temperatures with minimal side effects, but this remains to be proven. Pilot studies using selective head cooling carefully decreased the degree of hypothermia to avoid complications, eventually ensuring that moderate hypothermia (33.5–34°C) was safe (Gunn et al., 1998). A photo of the cool cap system in operation is available elsewhere (http://medgadget.com/archives/2006/12/coolcap_system.html). Initial studies using whole body cooling defined encephalopathy with amplitude-integrated EEG (aEEG), ultimately finding that normal aEEG after birth was associated with normal outcome in both hypothermic and normothermic infants (Azzopardi et al., 2000). Both devices succeeded in achieving target temperatures (both devices were used to achieve target core temperatures as monitoring brain temperatures are not feasible in this population) within hours and with minimal side effects (Battin et al., 2001, 2003; Debillon et al., 2003; Shankaran et al., 2002). By considering eight trials using either strategy (n = 638 combined), therapeutic hypothermia seemed to be a significant neuroprotectant after birth asphyxia (relative risk, RR, for mortality or severe disability at 18 months = 0.76 [0.65–0.89]) (Jacobs et al., 2003).

Finally, both strategies were tested in phase III trials with relatively similar study designs (hypothermia for 72 h, controlled-rewarming, and neurodevelopmental outcomes at 18–22 months). The selective head cooling trial enrolled 234 children and found a significant decrease in mortality in all children with moderate encephalopathy at study enrollment (RR 0.42 [0.22–0.80], p = 0.009) but not for those with the most severe dysfunction (Gluckman et al., 2005). Conversely, the
NICHID-sponsored phase III trial of whole body hypothermia (conducted by the Neonatal Research Network) enrolled 208 infants and found a reduction in the composite outcome of death/severe neurological dysfunction (44% vs. 62%, RR = 0.72 [0.54–0.95], \( p = 0.01 \)) and a trend toward decreased development of cerebral palsy in survivors (Shankaran et al., 2005). In summary, these trials suggest that six children would need to be treated with hypothermia in order to have one more superior outcome. Table 1 summarizes the findings of these studies.

In summary, hypothermia for birth asphyxia has become more accepted over the past decade, based on two breakthrough clinical studies, and is poised as the only therapy that improves long-term neurological outcome and mortality. It is likely that the large surface area of the infant’s head allows for the potential utilization of the cool cap as a method of inducing systemic hypothermia. Continued studies on the mechanisms of neuroprotection and the various devices that might be useful need to be completed, and it is likely that refinement of study design and patient selection will be required, as exemplified by the NICHD Hypothermia workshop that “recommended the formation of national and international HIE registries, so that scientific progress in this field can be assessed continuously to develop, refine, and optimize therapies” (Higgins et al., 2006).

### New Data on Therapeutic Hypothermia in Children after Cardiac Arrest: Clinical Studies

Is it appropriate to extrapolate the results from the successful clinical studies in adults and newborns to children with cardiac arrest? The answer is unclear. Arguments in support of the use of therapeutic hypothermia include the fact that the mortality rate of cardiac arrest in children is high, ranging from 45% to 92%, neurological morbidity occurs in half of survivors, and there are no new proven therapeutic options (Nadkarni et al., 2006; Young et al., 2004). In addition, there was no increase in adverse events between cooled and non-cooled patients in these adult and neonatal trials. Extrapolating from the adult RCTs, the 2005 American Heart Association’s Pediatric Advanced Life Support guidelines recommended the consideration of hypothermia for 12–24 h in comatose children after cardiac arrest, acknowledging that the optimal duration of cooling and rewarming is unknown, and cautioning about hypothermia’s associated side effects (American Heart Association Guidelines for Cardiopulmonary Resuscitation, 2006). Arguments against the adoption of therapeutic hypothermia in children include the fact that the primary etiology of cardiac arrest in children is asphyxia, which has a unique pathophysiology from that of arrhythmia-induced cardiac arrest (Young and Seidel, 1999; Vaagenes et al., 1997). In addition, most patients in the neonatal RCT cohorts did not suffer from cardiac arrest, had perinatal-related causes of hypoxia-ischemia, and are in a different stage of brain development than children after cardiac arrest, as previously discussed. Similarly, delays in initiating resuscitation in out-of-hospital pediatric asphyxial arrest can be significant, even relative to ventricular fibrillation cardiac arrest in adults.

As we approach the 2010 guidelines, we still do not have prospective data in the pediatric population, but planning is underway for a multi-center RCT (Frank Moler, M.D., et al., 2010).

### Table 1. Summary of the Clinical Evaluation of Hypothermia in Neonates and Children with Global Hypoxia-Ischemia

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Type of study</th>
<th>Age (yr)</th>
<th>Target temperature (°C)</th>
<th>Duration of hypothermia (h)</th>
<th>Major findings</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluckman et al., 2005</td>
<td>RCT</td>
<td>Newborn (234)</td>
<td>32-34</td>
<td>72</td>
<td>RR 0.42 [0.22–0.80]</td>
<td>↓ mortality if moderate but not severe hypothermia; electrolyte replacement</td>
</tr>
<tr>
<td>Shankaran et al., 2005</td>
<td>RCT</td>
<td>Newborn (208)</td>
<td>32-34</td>
<td>72</td>
<td>RR 0.72 [0.52–0.99]</td>
<td>↓ mortality, severe disability, severe electrolyte replacement</td>
</tr>
<tr>
<td>Fink et al., 2007</td>
<td>Retrospective, non-randomized</td>
<td>1 week to 21 years (181)</td>
<td>34.1±0.8 mean±SD (un-protocolized use of hypothermia)</td>
<td>34</td>
<td>↓ infections in HT group, no difference in bleeding, arrhythmias</td>
<td>( p = 0.05 )</td>
</tr>
<tr>
<td>Topjian et al., 2007</td>
<td>Prospective, randomized controlled trial</td>
<td>Children, unspecified (5)</td>
<td>32-34</td>
<td>24</td>
<td>T &lt; 32 occurred in 2%, T &gt; 34 occurred in 7%</td>
<td>( p = 0.06 )</td>
</tr>
</tbody>
</table>

aThe etiology of hypoxia-ischemia in the neonatal studies was heterogeneous (i.e., placental lesions, cardiac arrest, fetal deceleration, hemorrhage), while in children the etiology was solely cardiac arrest.

bHead cooling only; other listed studies involved whole body cooling.

cCardiac arrest only; other listed studies involved whole body cooling.

|T| Temperature |
|SD| Standard deviation |
personal cooling incidence of > (32–34°C). After cardiac arrest showed that the target temperature of 31.8°C ± 0.8°C, mean ± SD, were maintained at the target temperature for 31.8 ± 19.2 h, and re-warmed over 7.5 ± 5.9 h (Fink et al., 2007). Children in the hypothermia group had more electrolyte replacements in the first 4 days after cardiac arrest compared to children who were not cooled (standard group, n = 141), but the incidence of bleeding, and arrhythmias was similar. There was a trend toward more infections in the first 4 days in the hypothermia group (p = 0.06). Cooling to a temperature below the target range (“overcooling,” < 32°C) occurred in 15.8%. There was no difference in mortality between groups (55.0% hypothermia group, 55.3% standard group); however, the cooled cohort had more severe asphyxial insults, as reflected by a number of parameters.

A preliminary prospective study testing a protocol in five pediatric patients using surface cooling to initiate hypothermia after cardiac arrest showed that the target temperature of 32–34°C was achieved quickly and maintained for 24 h, with an overcooling incidence of > 20% (Toppian et al., 2007). Hyperthermia was uncommon, and three methods of temperature measurement using rectal, esophageal, and urinary catheter probes were deemed equivalent. Table 1 summarizes the findings of these studies. In a separate study at the same institution, electroencephalograms taken during the first week after cardiac arrest in children were graded in severity and were found to be predictive of outcome, highlighting the need for advanced neurological monitoring in this cohort, many of whom are comatose or require neuromuscular blockade to prevent shivering (Nishisaki et al., 2007).

While we await an RCT to determine the efficacy of hypothermia for neuroprotection in children after cardiac arrest, other questions remain regarding the optimal duration of hypothermia therapy and re-warming, methods of initiation and maintenance of cooling, and contemporary monitoring modalities.

Conclusion

There is a rich history for the use of therapeutic hypothermia after cardiac arrest in infants and children. Indeed, early laboratory reports date back to 1824 in experimental perinatal asphyxia and clinical reports in cold water drowning victims represented key initiating work in the field. Hypothermia in pediatric drowning victims represented some of the seminal clinical application of therapeutic hypothermia in modern neurointensive care. Uncontrolled application (too deep and too long) and unique facets of asphyxial cardiac arrest in children (a very difficult insult to affect any benefit) likely combined to result in abandonment of therapeutic hypothermia. Important studies in perinatal medicine have built upon the landmark clinical trials in adults, and are once again bringing therapeutic hypothermia into standard care for pediatrics. Although more work is needed, particularly in the use of mild therapeutic hypothermia in children, there is a strong possibility that this important therapy will ultimately have broad applications after cardiac arrest and CNS insults in the pediatric arena.

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