Supportive Care During Neuroprotective Hypothermia in the Term Newborn: Adverse Effects and Their Prevention

Marianne Thoresen, MD, PhD

KEYWORDS

• Asphyxia • Encephalopathy • Newborn
• Hypodermic • Neuroprotection • Adverse effects

WHICH INFANTS SHOULD BE COOLED?

The entry criteria in the two large published trials,[1–5] the CoolCap trial[2] and National Institute of Child Health and Human Development (NICHD) trial,[3] recruited infants of similar severity (moderate and severe encephalopathy). As such, the percentages of poor outcome in the untreated arm in the two trials were 66% and 62%, respectively. A series of feasibility studies undertaken in New Zealand[5] and the United Kingdom[6] led to the CoolCap trial, which recruited 235 infants. These studies combined selective head cooling (SHC; circulating cold water in a cap fitted around the head) with mild body hypothermia to 34.5°C rectal temperature, using a protocol that was then applied in the CoolCap trial (and, later, the Whole Body Hypothermia for Perinatal Asphyxial Encephalopathy [TOBY] trial).[7] In the United States, the NICHD used total body hypothermia by means of two cooling blankets, reducing infant temperatures to a rectal temperature of 33.5°C in its 2005 trial (n = 204).[3]

Currently, we are awaiting the outcome of 650 randomized infants from three international studies, with the largest being the United Kingdom–led TOBY trial (Primary Investigator: Dennis Azzopardi)[6,7] with 325 infants recruited. Two other trials were stopped prematurely because of lack of equipoise among the participants: the Australian Infant Cooling Evaluation (ICE) trial (n = 204, Primary Investigator: Sue Jacobs) and the European, induced hypothermia in asphyxiated newborns trial (Neo nEuro Network) (n = 121, Primary Investigator: George Simbrunner). Many centers have decided to delay introducing hypothermia treatment into their protocols until these

Child Health, St. Michael 's Hospital, Level D, University of Bristol, Southwell Street, BS2 8 EG Bristol, UK
E-mail address: marianne.thoresen@bris.ac.uk

Clin Perinatol 35 (2008) 749–763
doi:10.1016/j.clp.2008.07.018 **perinatology.theclinics.com**
0095-5108/08/$ – see front matter

outcome data are available. It is important, however, to note that the current published data support cooling with a relative risk (RR) of 0.76 (95% confidence interval [CI]: 0.54–0.86) and a number needed to treat number to treat (NTT) to prevent 1 case of death or severe disability of 6. In a recent commentary, the point was made that even if the three trials named previously with 650 infants did not show any positive effect, the RR would still have a CI less than 1.0 and the NNT would increase to 15.[4,6]

In the United Kingdom, infants who currently undergo therapeutic hypothermia are registered to an anonymized data set, the "TOBY register".[8] The TOBY register protocol and data sheets are freely available linked to the Web site.

DELAY AND DURATION OF COOLING: DIFFERENT METHODS IN USE

It is strongly recommended to follow the trial protocols[2,3] with regard to the selection of infants, the therapeutic window for initiation of treatment, and the duration of hypothermia. There are limited safety data available for infants that do not fit these entry criteria; that is, infants who were younger than 36 weeks of age, were more than 6 hours old when cooling was initiated, or had a core temperature less than 33.5°C during cooling. Eicher and colleagues[1] cooled infants to 33.0°C and included infants as premature as 35 weeks of gestation. These investigators reported more adverse effects than the CoolCap or NICHD trial. An Italian feasibility study cooled infants to 32°C or 34°C and reported no increase in adverse effects[9] in the 32°C group.

MANAGEMENT OF THE ASPHYXIATED INFANT IN THE DELIVERY ROOM

If severe, clinical asphyxia is apparent and the child fulfils the entry criteria, cooling therapy should be considered. The overhead heater should be turned off during resuscitation as soon as adequate ventilation and heart rate are obtained. The decision to turn off external heating is made by the medical staff as a treatment decision. Active heating is also turned off in the transport incubator. A rectal probe should be inserted to 6 cm to monitor core temperature within 20 minutes after birth, whether this occurs during transport or in the NICU. **Fig. 1** shows the relationship between the deep brain (basal ganglia), superficial brain, scalp skin temperature, and rectal temperature

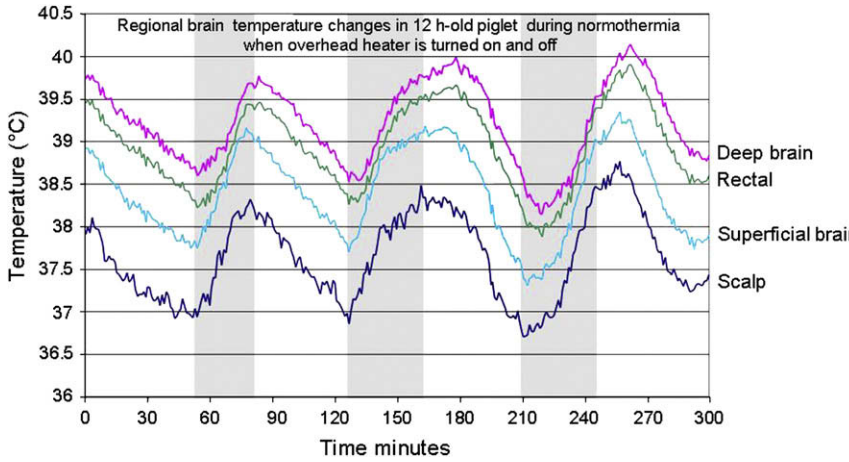

Fig. 1. Continuous temperature recordings from different areas within the brain in addition to skin and rectal temperature at normothermia (which is 39°C for piglets). The shaded boxes indicate when the overhead heater is turned on.

in a 12-hour-old piglet when the overhead heater is turned on and off at regular intervals. There is a parallel increase in all temperatures within minutes after the heater is turned on.

COOLING AND MONITORING DURING TRANSPORT

It is not a simple matter to predict how fast a baby 's temperature is going to drop once the external heating is turned off. The classic study by Dahm and James[10] shows that a healthy baby who is dried and wrapped drops from a rectal temperature of 37.5°C (at birth, newborns are approximately 0.5°C warmer than their mother) to 36.0°C by 30 minutes after birth. If the baby is mildly asphyxiated and self-ventilating, the temperature drops to 34.5°C by 30 minutes.[11] Therefore, "active cooling" is rarely indicated after birth, because the reduced metabolism and heat production in an asphyxiated infant reduce core temperature. Adding active cooling may inadvertently lead to "overcooling." This illustrates the importance of rectal temperature monitoring.

Fig. 2 illustrates serious overcooling. A term newborn was resuscitated for 30 minutes after placental abruption. The active heating was turned off, and cooling was initiated without continuous rectal temperature monitoring; only intermittent axillary temperature measurements were done. The arriving transport team recorded a core temperature of 30°C, and, although rewarming was started during transport to the cooling center, the temperature continued to drop to 27.7°C. The heart rate dropped to approximately 70 beats per minute (however, there was no cardiac arrhythmia), and moderate hypotension to a mean arterial blood pressure (MABP) of 30 mm Hg and significant hypocapnia to 2.4 kPa occurred. These changes are as expected and reflect the low metabolism and low temperature. The ventilator settings used were typical for

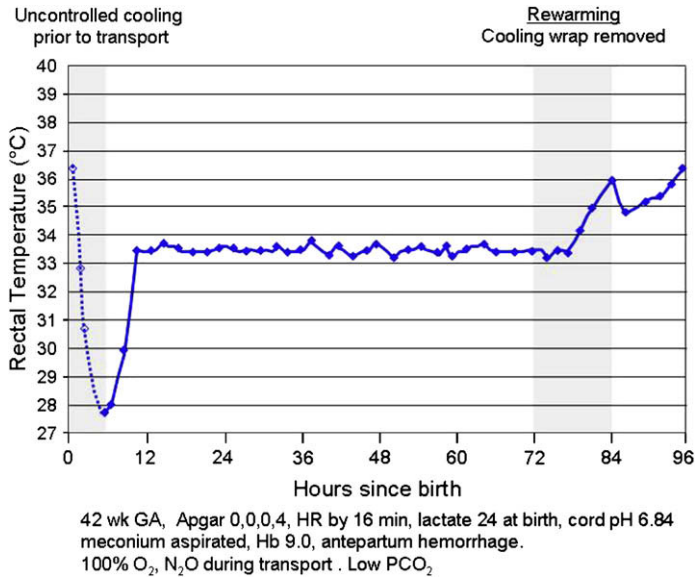

Fig. 2. Overcooling of a term newborn when a rectal probe was not used until arrival in the cooling center, at which time the temperature was found to be 27.7°C. The open symbols represent axillary temperature. After rewarming to 36°C at 84 hours, the cooling wrap was removed. The temperature dropped 1°C because the infant could not maintain the core temperature in a bed preheated to 29°C. GA, gestational age; HR, heart rate; Hb, hemoglobin.

a term normothermic newborn; however, hypothermia reduced metabolism and carbon dioxide (CO_2) production and severe hypocapnia occurred.

Fig. 2 also shows a common problem at the end of rewarming: when the cooling equipment is removed, the newborn often becomes hypothermic, because it is difficult to anticipate a baby's individual, external heating needs.

METHODS OF COOLING AND STABILITY OF TEMPERATURES

In 1998, the Thoresen and Whitelaw[12] placed gloves filled with cold water around the infant as a method of cooling. This approach was followed by the CoolCap procedure, which was developed in New Zealand.[5] A cap circulating with cold water is fitted onto the head to make cooling "selective" (ie, cooling the head more than the rest of the body). The body is simultaneously heated using an overhead heater to "balance" the cooling so that the rectal temperature is only moderately hypothermic (34.5°C). The CoolCap equipment is now approved by the US Food and Drug Administration (FDA) for neuroprotective therapy.[13]

For many years while recruiting to the TOBY trial, the author and her colleagues used a cooling blanket circulated with a coolant fluid for manual temperature regulation. For the past year, however, a servo-controlled system for cooling with a "body wrap" around the trunk and legs circulating with cold water has been used. This device records rectal and skin (forehead)[14] temperature to run an algorithm that automatically adjusts the water temperature to maintain a steady rectal temperature. Since

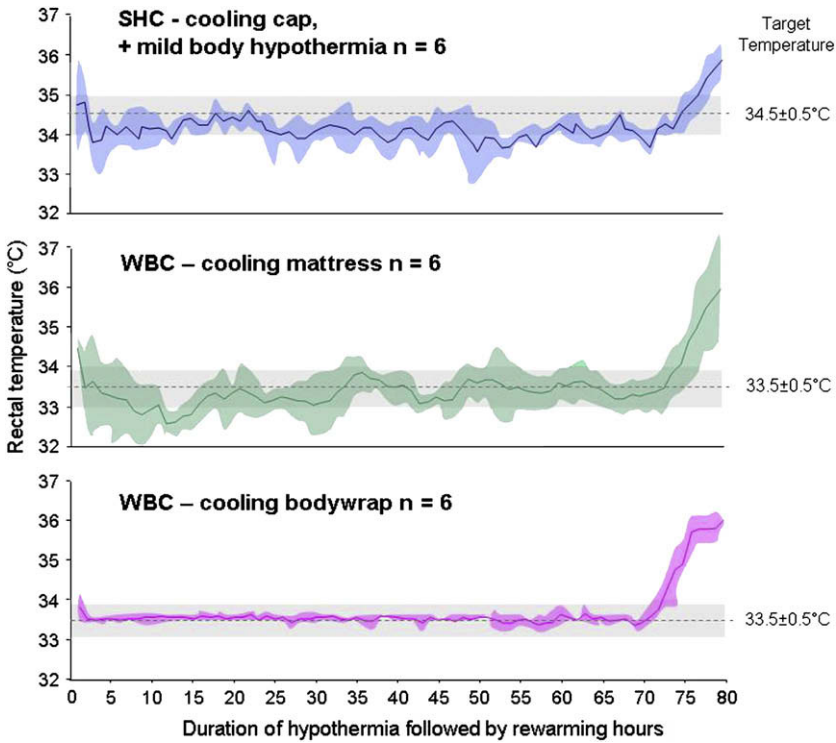

Fig. 3. Mean temperature with SD (shaded) during hypothermia treatment in three groups of term newborns cooled with different methods. SHC, selective head cooling; WBC, whole-body cooling.

using this equipment, no manual temperature adjustment has been necessary. **Fig. 3** shows mean temperatures from six randomly chosen infants cooled with these three methods. It is not known whether large swings in temperature are damaging in themselves or whether a gradient of temperatures throughout the brain, as is likely to occur with SHC, is beneficial. What we do know is that SHC and total body cooling gave significant and similar neuroprotection in the two large trials.

In a piglet cooling study, the animals were randomized between 24 hours of SHC, blanket cooling, or normothermia starting 3 hours after the insult. There was no difference in neuroprotection obtained between the cooling methods, and, in fact, no protective effect of cooling was observed when the cooling was started with a 3-hour delay.[15]

In experimental models, one is able to cool the brain, particularly the cortex, more than the core (rectal) temperature.[16] For obvious reasons, invasive brain temperature data are not available in infants, and it has been suggested that it is not possible to cool the deep brain in a large infant head more than the body core temperature. There is some observational evidence that the cortex may be better protected by SHC.[17]

TOO HOT OR TOO COLD: CLINICAL EXAMPLES OF DIFFICULTIES IN CONTROLLING CORE TEMPERATURE

Fig. 4 shows a case in which the rectal temperature was grossly hyperthermic to 39.5°C before transport to a cooling center could take place. Active, manually controlled cooling resulted in ''overcooling'' to 30.5°C during treatment. **Fig. 5** shows stable temperature during cooling (body wrap with servo-control) until the wrap was removed before transport to the MRI scanner. Without rectal temperature monitoring during transport and in the scanner, the temperature had dropped to 29.6°C on return to the neonatal intensive care unit (NICU). The corresponding physiological data on return were a heart rate of 76 beats per minute and blood pressure of 62 mm Hg.

Another example where temperature instability may arise is when seizures are stopped with anticonvulsants. **Fig. 6** shows that when phenobarbital is given, the rectal temperature drops. When seizures stop, heat production is reduced. Phenobarbital also reduces metabolism per se.

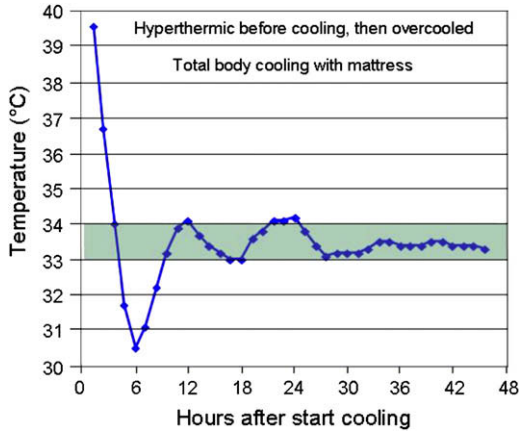

Fig. 4. Newborn who was hyperthermic after resuscitation followed by overcooling. With large temperature swings, it is difficult to obtain steady temperatures with manual control of the cooling device.

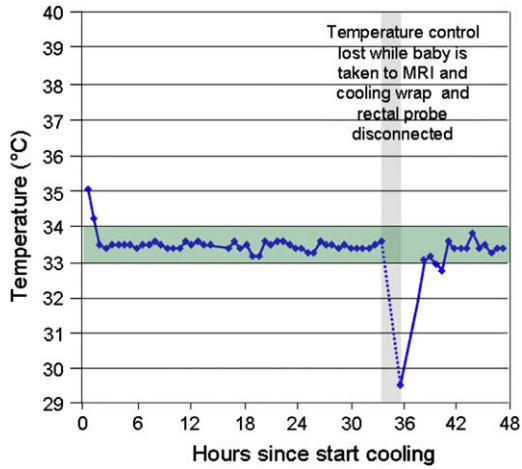

Fig. 5. Stable rectal temperature with servo-controlled total body cooling. During the trip to the MRI scanner, the rectal cooling probe was removed and active temperature control was halted. On return, the temperature was 29.6°C.

REWARMING AFTER RESUSCITATION AND REWARMING AFTER 72 HOURS OF HYPOTHERMIA

Fig. 7 shows rewarming of an infant brought in cold and in poor condition after a home delivery. Rapid rewarming in a preheated incubator after resuscitation brought the temperature from 32°C to 37°C within 1.5 hours, followed by a rapid overshoot to 39°C. The temperature was difficult to maintain within the normal range by changing incubator temperature, and long hyperthermic periods occurred coinciding with seizure activity. There is ample evidence, experimentally[18–21] and clinically,[22,23] that hyperthermia increases injury after hypoxia-ischemia. The children randomized to normothermia within the trials have had a rectal temperature tightly controlled to 37.0°C ± 0.2°C. The asphyxiated children who the author and her colleagues treated during a 12-month period between the CoolCap and TOBY trials had significantly worse temperature control, with an average temperature of 37.4°C ± 0.8°C. Analysis of temperatures in the noncooled infants in their CoolCap trial showed that even one measurement of rectal temperature greater than 38.0°C increased the risk of a poor outcome.[23]

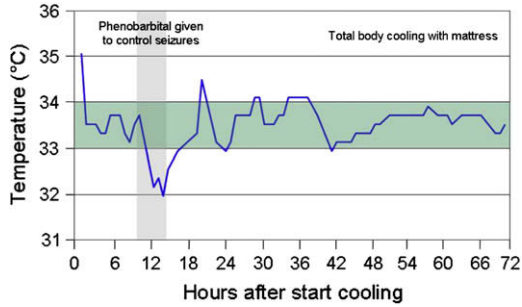

Fig. 6. Effect on core temperature when seizures are stopped with phenobarbital. Heat production is reduced and the temperature drops.

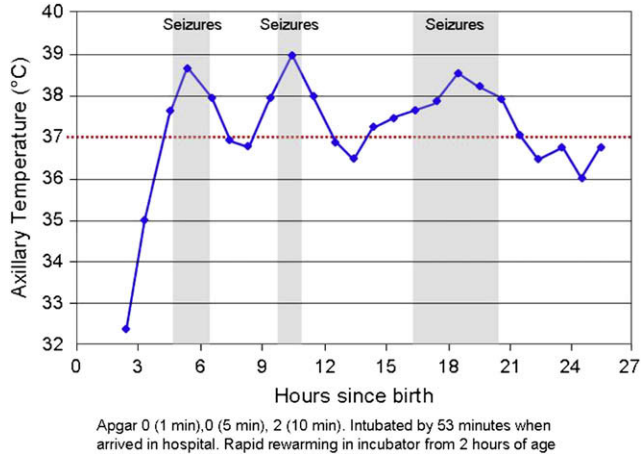

Fig. 7. Newborn had seizures during the periods of background shading on the trace, which coincided with high temperature. Rectal temperature would be expected to be 0.5°C higher than axillary temperature.

PARTICULAR PROBLEMS DURING REWARMING

Seizures are more likely to occur during rewarming.[24] Recently, in 17 infants rewarmed after 72 hours of hypothermia in the author's center, seizures occurred in 4; in 3 infants, the seizures were nonconvulsive only (diagnosed on amplitude-integrated electroencephalograpy [aEEG]), an example of which is shown in shown in **Fig. 8**. This child had a grade 3 encephalopathy with early seizures that responded to phenobarbital at a dose of 20 mg/kg administered twice and was seizure free until 3 hours into rewarming at 0.5°C per hour. The nonconvulsive seizures were first recognized after 3 hours and stopped by clonazepam at a dose of 100 μg/kg; rewarming was stopped and resumed slowly after a delay with no further seizures. Continuous aEEG monitoring allows detection of nonconvulsive seizures and the effect of anticonvulsive treatment. Evidence is lacking as to whether these seizures are damaging in themselves, although experimental data suggest that postinsult seizures increase brain injury.[25]

During rewarming, the vasoconstricted skin dilates and intravascular blood volume increases. If the vascular bed is underfilled, hypotension may occur. Echocardiography

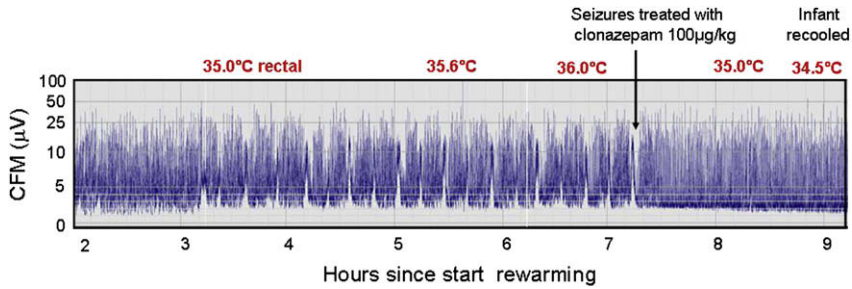

Fig. 8. aEEG trace during rewarming and the occurrence of nonconvulsive seizures that stopped after treatment (clonazepam). The core temperature was reduced again, and rewarming was halted for 3 hours. There were no further seizures, and the total rewarming time was 11 hours in this baby. CFM, cerebral function monitor.

is the definitive way of answering this question. The author and her colleagues give volume of 0.9% NaCl, or albumin at a dose of 10 mL/kg if the albumin value is low (<28 g per 100 mL) at the discretion of the attending physician as soon as there is a drop of 5 mm Hg in MABP. Experimentally, there is some evidence that there may be a mismatch between oxygen delivery and consumption during rewarming.[26,27] A proxy marker for this observation is an increase in plasma lactate value, which should normally not increase during rewarming. In two newborns who were self-ventilating at the start of rewarming, the author and her colleagues have experienced intermittent apnea during the beginning of rewarming. Continuous positive airway pressure (CPAP) during the rest of the rewarming period was necessary, and within a few hours of normal temperature, these neonates were again self-ventilating.

AMPLITUDE-INTEGRATED ELECTROENCEPHALOGRAPHY AND TEMPERATURE DURING SELECTIVE HEAD COOLING OR TOTAL BODY COOLING

There is a linear relation between temperature and electroencephalography (EEG) amplitude. Cooling healthy halothane-anesthetized piglets from 39°C to 35°C reduces the background voltage of approximately 30 μV by 2.3 μV[28] (raw EEG); 0.6 μV/°C.

Because the temperature difference between normothermia and hypothermia in clinical cooling is 3.5°C, one would not expect a significant change in voltage in the temperature range of 37°C to 33.5°C. Horan found that cooling term newborns from 37°C to 34°C during extracorporeal membrane oxygenation (ECMO) did not significantly reduce aEEG.[29] **Fig. 9** shows aEEG in a 7-day-old rat pup that was cooled to 20°C and rewarmed.[30] The aEEG pattern does not change visually until the temperature has dropped to 30°C. Because SHC cools the cortex more than core temperature, one would be more likely to see a change in aEEG voltage when the cap is taken off the head as the cortex quickly rewarms to core temperature. In **Fig. 10**, the upper trace shows an aEEG when rewarming was begun by stopping SHC. There is a 1- to 1.5-μV increase in the lower margin voltage. The scalp (skin) temperature increased from 22.6°C to 33.4°C during the first 20 minutes, and the rectal temperature was unchanged. The lower panel indicates when cooling stops and rewarming starts after whole-body cooling. The rectal temperature increases from 33.5°C to 34.5°C, but there is no change in the aEEG.

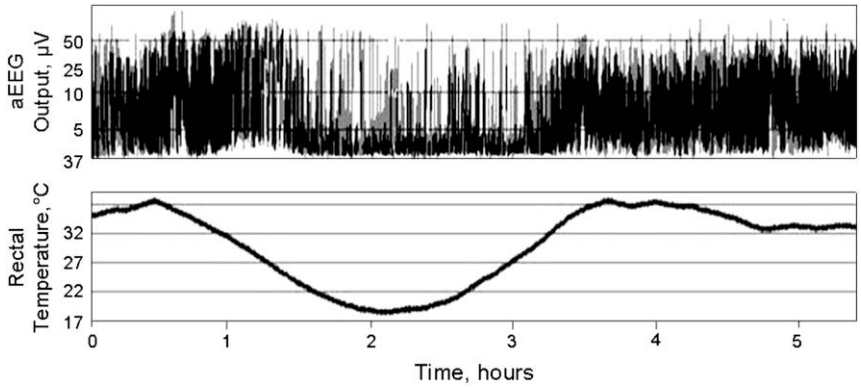

Fig. 9. aEEG trace in a 7-day-old rat pup that underwent rapid cooling to 20°C, followed by rewarming. The aEEG trace was visually unaffected by the low temperature until the rectal temperature was lower than 30°C.[30]

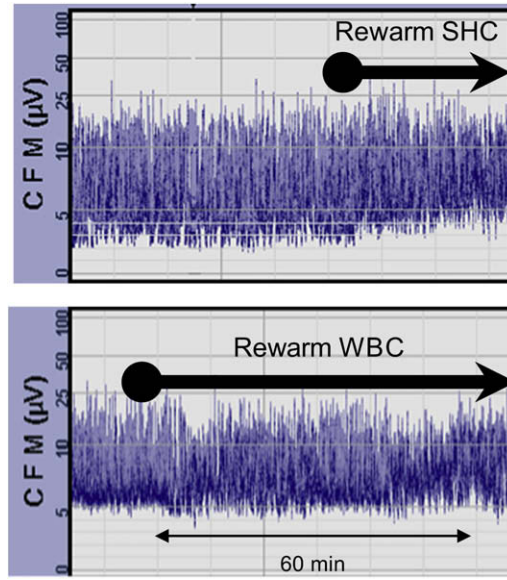

Fig. 10. aEEG trace at the start of rewarming in two infants. The upper trace shows rewarming after stopping SHC, and an accompanying small increase in the lower margin of the aEEG trace. When whole-body cooling (WBC) stops (*lower trace*), there is no change in aEEG voltage. CFM, cerebral function monitor.

BLOOD GASES AND COOLING

The partial pressure of gases depends on temperature. As such, all blood gas machines have the option of analyzing the blood at ''actual'' temperature. Because this is cumbersome, most clinicians have chosen not to correct for temperature. The author and her colleagues have changed the ''normal'' range for cooled infants, taking into account the temperature effect on P_{CO_2}. The partial pressure of CO_2 is reduced by approximately 4% per degree Centigrade reduction in core temperature[31] (and as more CO_2 is dissolved in the blood). It is the partial pressure of CO_2 that affects cerebral blood flow (CO_2 reactivity; with higher CO_2, there is higher cerebral blood flow). In ventilated infants who are cooled to a rectal temperature of 33.5°C, the author and her colleagues therefore adjust the normal P_{CO_2} range, which at 37°C is 36 to 44 mm Hg to 41 to 51 mm Hg. Interestingly, it has been suggested that the seizure threshold is lower with alkalosis attributable to hypocapnia.[32] This finding is yet another reason to keep CO_2 within the corrected normal range.

VENTILATION

A reduction in metabolism (5%–8% per degree Centigrade reduction in temperature) is the expected and desired effect of low temperature[33] and results in a decrease in CO_2 production is decreased. To keep CO_2 within the suggested normal range during cooling, the ventilator frequency or tidal volume must therefore be turned down to reduce minute ventilation. Often, it is not possible to achieve normocapnia, because the infant is driving his or her own ventilation, compensating for a metabolic acidosis. It is not known whether it would be better to paralyze and take control of the ventilation and maintain a higher CO_2 or to allow the low P_{CO_2} to occur. The evidence for

a damaging effect of low CO_2 is mainly from ventilated premature infants,[34,35] but it also comes from term infants who were kept ventilated on extra corporeal membrane oxygenation (ECMO) with different CO_2 levels.[36]

From a practical point of view, secretions are stickier during hypothermia, and cooled infants therefore benefit from frequent turning, suctioning, and instillation of saline as needed.

In previous cooling guidelines, it was recommended not to cool if there was persistent pulmonary hypertension and a need for a high fraction of inspired oxygen (F_{IO_2}). In published trials so far, however, the incidence of persistent pulmonary hypertension has been the same in the cooled and noncooled groups. When needed, the author and her colleagues administer inhaled nitric oxide (NO) using the standard protocol, and cooling does not seem to be contraindicated.

The author and her colleagues also think it is important that the infant does not become hyperoxic after asphyxia. They therefore follow F_{IO_2} and saturation closely to keep values within the normal range. The effect of temperature on P_{O_2} is different and smaller than for P_{CO_2} during hypothermia, such that the author and her colleagues do not use different P_{O_2} ranges.[37] The same applies for pH.

Most infants have been ventilated throughout the treatment period, although 20% breathe spontaneously the whole or part of the cooling period. **Fig. 11** shows simultaneous measurements of nasopharyngeal and rectal temperature during SHC. The two temperatures are identical as long as the infant is ventilated; however, after extubation, the nasopharyngeal temperature measures 1.5°C to 2.0°C lower than the rectal temperature.

CLOTTING AND COOLING

Blood flows mores slowly and is ''stickier'' during hypothermia, with a potentially increased risk for microembolism.[38] Human newborns have a relatively high hemoglobin level, which may result in poor microcirculation, but there is no evidence that infants undergoing therapeutic hypothermia suffer more emboli than during normothermic

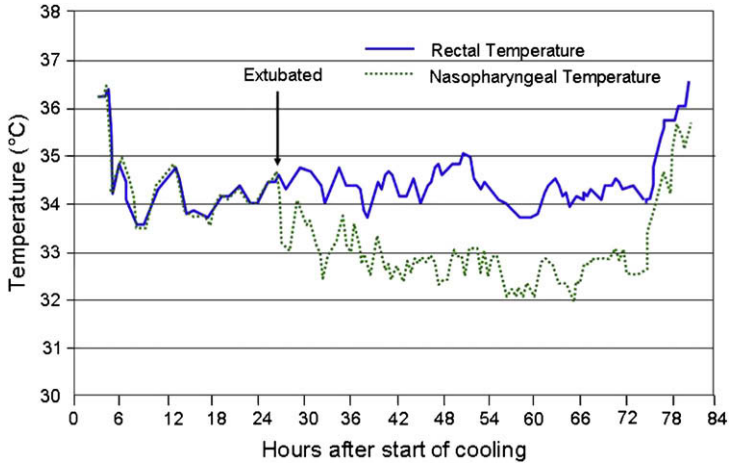

Fig. 11. Simultaneous recordings of nasopharyngeal and rectal temperature during SHC. While intubated, these core temperatures are identical. After extubation, the nasopharyngeal temperature drops nearly 2° because the sensor is influenced by the air temperature in the pharynx. Hence, nasopharyngeal temperature is only valid while the patient is intubated.

care or that hypothermia, per se, increases the hematocrit (hct). The author and her colleagues therefore maintain the same intervention level for normothermic and hypothermic children with regard to hemodilution.

It is physiologic that coagulation is prolonged during hypothermia, and animals that hibernate have a vastly prolonged bleeding time.[39] If coagulation is normal to start with, there are no problems with clotting attributable to therapeutic hypothermia per se. Sick asphyxiated newborns often have deranged clotting at birth, however, and it is not known whether cooling them may further derange their clotting function.

The most concerning infants are those with traumatic deliveries and ongoing bleeding, such as subgaleal hemorrhages. The author and her colleagues have treated three such cases with total body cooling and have been aggressive with fresh-frozen plasma, blood, cryoprecipitate, and volume infusion on clinical indication. They do not use SHC when there is trauma to the head, because one could fear deranged clotting attributable to low cortex/scalp temperature.

In piglets, the author and her colleagues examined activated partial thromboplastin time (APPT) at two temperatures: 39°C, which is normothermia for piglets, and 29°C, which is a typical brain cortex temperature during SHC. APPT increased from [mean (SD)] 20.8 (8.3) seconds to 26.7 (10.6) seconds ($P < .01$), a 10% prolongation, which is not clinically significant.[40] In infants and pigs, a 10% to 39% lower platelet count has been found,[41,42] although the author and her colleagues have not observed that this change has any clinical significance. They have not seen hemorrhagic lesions in the brain on pathologic examination of term piglets' brains instrumented with invasive probes, in which the cortex temperature has been as low as 26°C for 24 hours.[43]

HEART RATE AND HYPOTHERMIA: IS A LOW HEART RATE DANGEROUS?

As with ventilation, reduced metabolic rate reduces cardiac output and heart rate. The author and her colleagues have found that heart rate is reduced by 14 beats per degree Centigrade reduction in body temperature in the range of 39°C to 32°C for piglets and 37°C to 33°C for infants (given that they are not stressed, hypovolemic, anemic, or in pain). Despite many occasions with overcooling, the author and her colleagues have never experienced arrhythmias, only sinus bradycardia with heart rate, on one occasion, as low as 64 beats per minute in overcooled infants. In adults, it has been shown that the heart is more stable against arrhythmias at low temperatures.[44]

DRUG TREATMENT IN HYPOTHERMIC INFANTS

Currently, there is no general recommendation to treat hypothermic infants differently from normothermic infants with regard to the choice of drug or dose.

There are several groups of drugs that most infants receive: antibiotics, inotropic support, anticonvulsive treatment, and sedative treatment, and some are paralyzed.

Drugs that are excreted unchanged by way of the kidneys are less affected by temperature. Routine antibiotic treatment is often penicillin or ampicillin combined with an aminoglycoside. In piglets, gentamicin levels are the same in cooled and noncooled animals.[45] Recently, the author and her colleagues presented clinical data from 54 patients showing that there was no difference in gentamicin serum levels among 30 infants who were cooled as compared with those maintained at normothermia.[46]

Drugs that are metabolized by the liver, such as morphine and phenobarbital, have been shown to have higher levels in the cooled group.[47,48] Vecuronium, which is metabolized in the liver, has been shown in adults to have a prolonged half-life during hypothermia.[49] In practice, when hypothermic infants are started on continuous infusions, the author and her colleagues run the "normothermic" dose for 6 to 12 hours

and then reduce the dose until clinical signs of less drug effect appear, such as lack of sedation (increased heart rate) or paralysis (movement). In their piglet studies, the author and her colleagues did not find that piglets needed less pancuronium to maintain paralysis (M. Thoresen, unpublished data, 2007).

The author and her colleagues have used the same drug regimen to treat hypotension in normothermic and hypothermic infants, and they have not experienced a difference in response to inotropic support in hypothermic infants compared with normothermic infants, although there could be differences in receptor activation at different temperatures.

NUTRITION AND FLUID MANAGEMENT

Large cooling trials,[2,3] as a part of the protocol, withheld enteral feeding during hypothermia. The rationale was to relieve the burden on a gastrointestinal tract made vulnerable by hypoxia-ischemia and the additional risk for hypothermia. There has been a low incidence of necrotizing enterocolitis in the trials, and this complication is similar in both groups (1%–2%).

The Scandinavian hypothermia protocols are different; they allow nonnutritive feeding (breast milk, 1 mL/kg given every 4 hours throughout the hypothermia period), and researchers report no cases of necrotizing enterocolitis (M. Blennow, personal communication, 2007).

The author and her colleagues start with clear fluids at 60 mL/kg/d, followed by total parenteral nutrition. Volume is increased as clinically indicated (cardiac and renal function). Often, asphyxiated infants receive volume in response to hypotension, and the average actual volume on day 1 has been 90 mL/kg. None of the 70 children in the author 's cohort who were cooled over the past 10 years developed permanent kidney failure or needed transient dialysis. In randomized piglet experiments, the author and her colleagues found that 24 hours of hypothermia delayed the postinsult increase in creatinine until after the cooling period.[50] In the same study, they also found that the need for glucose was slightly higher in the cooled group. In the clinical data set, however, the author and her colleagues do not have enough detail to be able to address this question.

LEVELS OF PLASMA ELECTROLYTES

Electrolytes should be kept within the normal range. There is conflicting experimental evidence as to whether magnesium is neuroprotective[51] on its own or only in combination with hypothermia.[52] In adults, increased magnesium levels reduce shivering (if only modestly)[53] and are advocated in cooled patients. The recommendation of the author and her colleagues is to maintain magnesium at a level greater than 1.0 mmol/L during hypothermic treatment (ie, within the high normal range).

INOTROPIC SUPPORT

The published trials did not find that hypothermic infants are more hypotensive than normothermic infants with the same severity of asphyxia.[2,3] The author and her colleagues use the same treatment principles for all asphyxiated infants: if hypotensive, first correct hypovolemia (best examined with echocardiography). If reduced myocardial contractility is found, they use dobutamine; if the infant is hypotensive and not hypovolemic or having poor contractility, they use dopamine or noradrenaline.

SUMMARY

Hypothermia as a neuroprotective treatment requires significant knowledge of how temperature affects all organ systems and interventions used in intensive care. The incidence of moderate and severe perinatal asphyxia is low, and such treatment is best undertaken in a large unit that would treat at least eight cases per year for staff to have the necessary experience and confidence. Education and training in resuscitation, including avoidance of hyperthermia, early diagnosis of eligible infants, and initiation of early cooling followed by safe transport of cooled infants to the cooling center is the way forward.

ACKNOWLEDGMENTS

The author is grateful to Dr. Catherine Hobbs for making the figures and commenting on the manuscript; to her clinical colleagues for their support in recruiting patients since 1998; to Olympic Medical (Seattle, Washington) for making available the CoolCap; to Inspiration (United Kingdom) for the cooling mattress; and to MTRE Medical (Israel) for the cooling wrap. The clinical trials were funded by Olympic Medical, United States (CoolCap trial) and the Medical Research Council, United Kingdom (TOBY trial); and equipment was provided by SPARKS (United Kingdom), Laerdal Foundation for Acute Medicine (Norway), and donations from parents.

REFERENCES

1. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. Pediatr Neurol 2005;32(1):11–7.
2. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 2005;365(9460):663–70.
3. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353(15): 1574–84.
4. Hoehn T, Hansmann G, Bührer C, et al. Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. Resuscitation 2008;78(1):7–12.
5. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. Pediatrics 1998;102(4 Pt 1):885–92.
6. Thoresen M, Whitelaw A. Therapeutic hypothermia for hypoxic-ischaemic encephalopathy in the newborn infant: review. Curr Opin Neurol 2005;18(2):111–6.
7. Azzopardi D, Brocklehurst P, Edwards D, et al. The TOBY study: whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial. BMC Pediatr 2008;8:17.
8. Available at: http://www.npeu.ox.ac.uk/tobyregister/contact.
9. Compagnoni G, Bottura C, Cavallaro G, et al. Safety of deep hypothermia in treating neonatal asphyxia. Neonatology 2008;93(4):230–5.
10. Dahm LS, James LS. Newborn temperature and calculated heat loss in the delivery room. Pediatrics 1972;49:504–13.
11. Burnard EE, Cross KW. Rectal temperature in the newborn after birth asphyxia. BMJ 1958;ii:1197–9.
12. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics 2000;106(1 Pt 1):92–9.

13. Available at: http://www.natus.com/index.cfm?page=products_1&crid=115.
14. Hertzman AB, Roth LW. The absence of vasoconstriction reflexes in the forehead circulation. Effects of cold. J Physiol 1949;149:692–7.
15. Karlsson M TJ, Satas S, H, et al. Delayed hypothermia as selective head cooling or whole body cooling does not protect brain or body in newborn piglets. Pediatr Res 2008;64:74–8.
16. Thoresen M, Simmonds M, Satas S, et al. Effective selective head cooling during posthypoxic hypothermia in newborn piglets. Pediatr Res 2001;49(4):594–9.
17. Rutherford MA, Azzopardi D, Whitelaw A, et al. Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy. Pediatrics 2005;116(4):1001–6.
18. Hobbs C, Brun C, Eagle R, et al. Post insult hyperthermia exacerbates hypoxic-ischaemic brain damage in the neonatal rat. Crit Care Med, Submitted for publication.
19. Kim Y, Busto R, Dietrich WD, et al. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. Stroke 1996;27(12):2274–80 [discussion: 81].
20. Kim Y, Truettner J, Zhao W, et al. The influence of delayed postischemic hyperthermia following transient focal ischemia: alterations of gene expression. J Neurol Sci 1998;159(1):1–10.
21. Yager JY, Armstrong EA, Jaharus C, et al. Preventing hyperthermia decreases brain damage following neonatal hypoxic-ischemic seizures. Brain Res 2004;1011(1):48–57.
22. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet 1996; 347(8999):422–5.
23. Wyatt JS, Gluckman PD, Liu PY, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics 2007;119(5):912–21.
24. Battin M, Bennet L, Gunn AJ. Rebound seizures during rewarming. Pediatrics 2004;114(5):1369.
25. Wirrell EC, Armstrong EA, Osman LD, et al. Prolonged seizures exacerbate perinatal hypoxic-ischemic brain damage. Pediatr Res 2001;50(4):445–54.
26. Morray JP, Pavlin EG. Oxygen delivery and consumption during hypothermia and rewarming in the dog. Anesthesiology 1990;72(3):510–6.
27. van der Linden J, Ekroth R, Lincoln C, et al. Is cerebral blood flow/metabolic mismatch during rewarming a risk factor after profound hypothermic procedures in small children? Eur J Cardiothorac Surg 1989;3(3):209–15.
28. Haaland K, Loberg EM, Steen PA, et al. Posthypoxic hypothermia in newborn piglets. Pediatr Res 1997;41(4 Pt 1):505–12.
29. Horan M, Azzopardi D, Edwards AD, et al. Lack of influence of mild hypothermia on amplitude integrated-electroencephalography in neonates receiving extracorporeal membrane oxygenation. Early Hum Dev 2007;83(2):69–75.
30. Tucker A, Ferguson J, Thoresen M. The effect of core temperature on aEEG in 7-day-old rat pups. Pediatr Res 2006; PAS2006.59.3726.8.
31. Dill D. Respiratory and metabolic effects of hypothermia. Am J Physiol 1941;132:685.
32. Schuchmann S, Schmitz D, Rivera C, et al. Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. Nat Med 2006;12(7):817–23.
33. Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in mammalian central nervous system. J Cereb Blood Flow Metab 2003;23(5):513–30.
34. Greisen G, Trojaborg W. Cerebral blood flow, $Paco_2$ changes, and visual evoked potentials in mechanically ventilated, preterm infants. Acta Paediatr Scand 1987; 76(3):394–400.

35. Pryds O, Greisen G. Effect of $Paco_2$ and haemoglobin concentration on day to day variation of CBF in preterm neonates. Acta Paediatr Scand Suppl 1989;360:33–6.
36. Bennett CC, Johnson A, Field DJ, et al. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. Lancet 2001;357(9262):1094–6.
37. Ashwood ER, Kost G, Kenny M. Temperature correction of blood-gas and pH measurements. Clin Chem 1983;29(11):1877–85.
38. Schreiner RS, Rider AR, Myers JW, et al. Microemboli detection and classification by innovative ultrasound technology during simulated neonatal cardiopulmonary bypass at different flow rates, perfusion modes, and perfusate temperatures. ASAIO J 2008;54(3):316–24.
39. Svihla A, Bowman HR, Ritenour R. Prolongation of clotting time in dormant estivating mammals. Science 1951;114(2960):298–9.
40. Ferguson J, Britton F, Simmonds M, et al. Selective head cooling is safe, cooling by 10°C only mildly prolongs coagulation time in the newborn pig. Early Hum Dev 2006;82:613.
41. Faustini M, Bronzo V, Maffeo G, et al. Reference intervals and age-related changes for platelet count, mean platelet volume and plateletcrit in healthy preweaning piglets in Italy. J Vet Med A Physiol Pathol Clin Med 2003;50(9):466–9.
42. McPherson RJ, Juul S. Patterns of thrombocytosis and thrombocytopenia in hospitalized neonates. J Perinatol 2005;25(3):166–72.
43. Tooley JR, Satas S, Porter H, et al. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. Ann Neurol 2003;53(1):65–72.
44. Johansson BW. The hibernator heart—nature 's model of resistance to ventricular fibrillation. Cardiovasc Res 1994;31:826–32.
45. Satas S, Hoem NO, Melby K, et al. Influence of mild hypothermia after hypoxia-ischemia on the pharmacokinetics of gentamicin in newborn pigs. Biol Neonate 2000;77(1):50–7.
46. Liu X, Borooah M, Hoque N, et al. Does 72-hours of therapeutic hypothermia in encephalopathic infants affect plasma gentamicin levels? [abstract]. Pediatr Res 2008; E-PAS2008.63.3761.2.
47. Thoresen M SJ, Hoem NO, Brun C, et al. Hypothermia after perinatal asphyxia more than doubles the plasma half-life of Phenobarbitone. Ped Res 2003; [abstract].
48. Roka A, Melinda KT, Vasarhelyi B, et al. Elevated morphine concentrations in neonates treated with morphine and prolonged hypothermia for hypoxic ischemic encephalopathy. Pediatrics 2008;121(4):e844–9.
49. Withington D, Menard G, Harris J, et al. Vecuronium pharmacokinetics and pharmacodynamics during hypothermic cardiopulmonary bypass in infants and children. Can J Anaesth 2000;47(12):1188–95.
50. Satas S, Loberg EM, Porter H, et al. Effect of global hypoxia-ischaemia followed by 24 h of mild hypothermia on organ pathology and biochemistry in a newborn pig survival model. Biol Neonate 2003;83(2):146–56.
51. Penrice J, Amess PN, Punwani S, et al. Magnesium sulfate after transient hypoxia-ischemia fails to prevent delayed cerebral energy failure in the newborn piglet. Pediatr Res 1997;41(3):443–7.
52. Zhu H, Meloni BP, Moore SR, et al. Intravenous administration of magnesium is only neuroprotective following transient global ischemia when present with post-ischemic mild hypothermia. Brain Res 2004;1014(1–2):53–60.
53. Wadhwa A, Sengupta P, Durrani J, et al. Magnesium sulphate only slightly reduces the shivering threshold in humans. Br J Anaesth 2005;94(6):756–62.