Systemic complications and hypothermia

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SUMMARY

Cooling for neonatal hypoxic–ischemic encephalopathy is a novel and promising neuroprotective therapy that requires significant understanding of how cooling affects all organ systems and interventions used to treat systemic complications of cooling in an intensive care setting. As cooling is used more widely and has been newly introduced in neonatal units, continued surveillance of its use in clinical practice is mandatory. Units offering cooling should strongly consider joining a registry (e.g., the Vermont–Oxford Neonatal Encephalopathy Registry in the USA or the TOBY Register in the UK) that facilitates benchmarking of short-term adverse effects and long-term outcomes of cooling and that supports local quality improvement efforts.

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1. Introduction

Therapeutic hypothermia is an emerging therapy for hypoxic–ischemic encephalopathy (HIE) in the term or late preterm infant. Many clinicians are now sufficiently convinced of safety and efficacy of therapeutic hypothermia for HIE by the available evidence from recently published randomized clinical trials and several published meta-analyses (e.g., such as the meta-analysis by P.S. Shah in this issue, pp. 000–000), as well as a plethora of generally supportive review articles, and presentations at scientific conferences. This prompted many former clinical trial sites to continue to offer this therapy, and a growing number of neonatal intensive care units (NICUs) that did not participate in the original trials are either currently offering cooling or actively considering ‘trying it out’ without realizing the potential danger associated with ‘overcooling’. For example, recent data from a phase IV study of infants registered with the UK TOBY Cooling Register which was established on completion of enrollment to the TOBY trial shows that, in the UK, cooling of infants with neonatal HIE is increasingly being provided outside the setting of a clinical trial, as part of routine clinical care in the centers that originally participated in the TOBY trial and were familiar with the cooling protocol.

However, it remains uncertain if cooling can be applied safely and effectively in centers that are newly considering undertaking implementation of a cooling protocol outside of a regional program in neonatal hypothermia. Our experience, and that of others, suggest that it takes months of preparation, training, and a multidisciplinary approach before a cooling program is implemented successfully, and thus, wherever possible such a program should be regional. This article reviews the potential systemic complications of cooling and emphasizes the need to understand what to expect, in order to better handle the full range of multi-organ system complications typically presented by asphyxiated infants during cooling treatment.

2. Systemic complications of ‘overcooling’ in the less-resourced setting

Excessive cooling or ‘overcooling’ commonly is associated with ‘inadequately controlled’ cooling, as happens during transport of very ill asphyxiated infants when cooling is initiated by relatively inexperienced staff3 during ‘uncontrolled’ cooling in a low-resourced setting in absence of sufficient numbers of well-trained staff, or during administration of cooling with a non-servo-controlled cooling system. Asphyxiated newborns with HIE are well known to have impaired thermoregulation. Episodes of hypothermia overshoot during transport do occur in the absence of adequate monitoring by inexperienced staff, and one study reported at least one recorded temperature of <30 °C in 14% and <32 °C in 34% of patients from active cooling during transport.5 In this and another report that looked at the risk of overcooling during transport, many of the overcooled patients had only intermittent rather than continuous core temperature monitoring during transport.5,6

We and others have also observed episodes of hypothermia overshoot in some of our infants during administration of therapeutic hypothermia induced with the non-servo-controlled

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selective head cooling system. Indeed, we have seen hypothermia overshoot with a servo-controlled whole body cooling system (Blanketrol II) when infants could not be kept in the target range despite the maximum blanket water temperature of 42 °C. These occurrences can lead to inadvertent cycles of ‘overcooling’, followed by rapid rewarming with overshoot. Potentially this could lead to cardiovascular instability and emergence or re-emergence of seizures, as has been reported both in infants and in experimental animal models.7–9 Systemic adverse effects of hypothermia in general appear to be proportional to the degree of cooling, with most occurring at core temperatures <34 °C.10 As the minimum depth of hypothermia that is required for effective neuronal rescue in infants with HIE seems typically to be at a brain temperature ≤34 °C, there might be a trade-off between the potential neurological benefits and risk of adverse systemic effects of cooling,11 which could increase mark-
edly if the temperature drops too low during ‘inadequately controlled’ cooling. The potential systemic complications of such ‘overcooling’ or hypothermia overshoot in newborn infants, the so-called ‘cold-injury syndrome’, include increased mortality, particu-
larly in preterm infants; development of sclera, skin erythema, and acrocyanosis; pulmonary hemorrhage: renal failure; increased blood viscosity and disseminated intravascular coagulation; hypo-
glycemia; acid–base and electrolyte disturbances; increased risk of infections; and significant cardiovascular disturbances.12–15 Sudden cardiac arrest and ventricular tachyarythmia including fibrillation have been reported in infants who were hypothermic with rectal temperatures of ≤34.5 °C during exchange transfusion with cold blood.16 Even mild hypothermia of 34–35 °C has been reported to cause a marked decrease in myocardial contractility17 and cardiac output in experimental animal models,18 and can lead to conduction disturbances, hypotension and cardiac arrhythmia as seen in adults and newborn infants.19,20 Hypothermia can cause hemoconcentration, hyperviscosity,21 pulmonary vasoconstric-
tion.22 Although the net effect of hypothermia on ventilation is unclear, all these factors have been reported to increase pulmonary vascular resistance and the development of pulmonary hyperten-
sion with ventilation–perfusion mismatch in experimental animal models.22 Finally, hypothermia may result in decreased leukocyte mobility and phagocytosis, and increased risk of infection, espe-
cially pneumonia, as has been reported in adults.23,24 It is important to recognize that multi-organ dysfunction in the form of renal, cardiovascular, pulmonary, or hepatic involvement is frequent in post-asphyxial infants with HIE,25 and has been reported in one study to be present in 70%, 62%, 86%, and 85% of infants with HIE, respectively.26 The effects of excessive cooling, specifically pulmonary and cardiac dysfunction, might be expected to be more serious in asphyxiated infants who already have multi-
organ system dysfunction,27,28 or the multi-organ dysfunction initially triggered by the hypoxic–ischemic event itself may be magnified by superimposed cold-injury syndrome. In an experi-
mental adult dog model, deep hypothermia (15 °C) after cardiac arrest produced worse cerebral and cardiac outcomes,29 whereas controlled mild hypothermia (34–36 °C) provided consistent neu-
roprotection.30 The mechanism of the detrimental effect of deep hypothermia or ‘overcooling’ on cerebral outcome is not clear but might be related to myocardial dysfunction leading to decreased cardiac output, systemic hypotension, and compromised cerebral perfusion.18 Hypothermia has also been reported to be strongly associated with mortality, even in term infants with a rectal temperature <36 °C.31 A recent study correlating severity of hypothermia clas-
sified as per World Health Organization recommendations32 in sick extramural neonates with fatality and physiological derangements reported mortality rates of 39%, 52%, and 80%, respectively with mild, moderate, and severe hypothermia at presentation to hospital. When hypothermia was associated with perinatal asphyxia, the case fatality was much higher, and was >50% even with mild hypothermia.33 Although this association is unlikely to be causal, nevertheless, these data raise the possibility that there may be dangers from ‘overcooling’ asphyxiated infants in any setting, and specifically in an under-resourced setting. Indeed, as discussed next, advances in intensive care including continuous cardio-respiratory monitoring, mechanical ventilation, and better understanding of pathophysiology of hypothermia in the newborns have reduced, if not eliminated, many of these adverse effects previously reported with cooling.3

3. Systemic complications of therapeutic hypothermia in the intensive care environment

Systemic complications of cooling in a ‘controlled’ NICU setting have been addressed in both pilot safety trials and the randomized controlled clinical trials, and more comprehensively in some preliminary studies whose primary aim was to assess the safety of cooling in asphyxiated newborns.34–36 Sinus bradycardia and thrombocytopenia have been reported to be the only significant adverse effects of hypothermia in all of the current meta-analyses of the cooling trials.34–36 Although these studies suggest that therapeutic cooling is generally safe, it is important to appreciate that these reported safety data are based on administration of cooling in NICUs, within strict cooling protocols and often at centers with considerable experience with cooling.

3.1. Cardiovascular and pulmonary complications of hypothermia

Current meta-analyses of all the neonatal cooling trials document that the only consistent cardiovascular effect of cooling is clinically benign physiological sinus bradycardia.14 Hypothermia is consistently associated with sinus bradycardia as it slows the atrial pacemaker and intracardiac conduction.41,42 The QT interval also can be prolonged, and hypotension can occur during hypothermia. Cardiovascular complications in adult cooling trials include sinus bradycardia, cardiac arrhythmia, hyperviscosity, and pulmonary vasoconstriction with development of pulmonary hyperten-
sion.7,23,24 A recent small neonatal case series reported lower cardiac output and stroke volume (without hypotension) during the period of cooling with slow increase of both during the re-warming phase.47 However, the maintenance of normal blood pressure in this study raises the possibility that the reduction in cardiac output may have simply matched the reduction in oxygen metabolism during cooling.

In a recent meta-analysis, there was an increase in hypotension treated with inotropes in hypothermia groups that was of border-
line significance; the same meta-analysis failed to demonstrate a significant effect of hypothermia on the incidence of arrhythmia requiring medical treatment and/or cessation of cooling.44 Further, Battin et al. recently reported that the requirement of inotropes for blood pressure support during cooling was more related to an apparent change in physician behavior, with slower withdrawal of inotrope therapy in cooled infants.45 Eicher et al.30 reported an increase in persistent pulmonary hypertension that required inhaled nitric-oxide treatment in the cooled infants. However, the number of infants with persistent pulmonary hypertension was similar between the cooled and the non–cooled infants in the three large cooling trials, including the recently reported TOBY trial.41,43

3.2. Haematological adverse effects

Hypothermia-induced coagulation abnormalities include platelet dysfunction, increased fibrinolytic activity, and inhibition
of enzymatic reactions of the coagulation cascade with substantial prolongation of prothrombin time and partial thromboplastin time tests. \(^4^9\)

Thrombocytopenia has also been reported with hypothermia. Meta-analysis of the four trials\(^3^4,3^9,4^1,4^2\) which reported the effect of hypothermia on platelet count showed a statistically significant increase in thrombocytopenia in the hypothermic groups.\(^4^4\)

However, no increase in bleeding complications was reported in any of the three large randomized cooling trials.\(^5^1–5^4\) In a smaller safety study, Eicher et al.\(^4^6\) reported an increase in coagulopathy with prolongation of prothrombin time and partial thromboplastin time but the coagulopathy was easily manageable with fresh frozen plasma and platelet transfusions and no increase in intracranial bleed was reported. Because of the smaller sample size and relatively high loss to follow-up in the study of Eicher et al.,\(^4^6\) it is difficult to ascertain whether the increased coagulopathy in the cooled infants was a chance finding or was related to a lower target core temperature of 33 °C in that trial. Deep hypothermia did not cause intracranial hemorrhage in an experimental animal study,\(^5^0\) and in a recent pilot study in newborn term infants, deep whole body hypothermia even down to a target rectal temperature of 30 °C was reported to be safe.\(^5^1\)

3.3. Renal impairment with cooling

Hypothermia is known to suppress antidiuretic hormone, and in experimental animal models cooling was associated with a decrease in renal perfusion and glomerular filtration rate.\(^5^2\) However, meta-analysis of the five trials that reported the effect of hypothermia on urine output showed no statistically significant difference in the rate of oliguria in cooled infants.\(^4^4\)

3.4. Immunologic adverse effects of cooling

Studies in adults have shown cooling to have profound immunosuppressive and anti-inflammatory effects.\(^2^3,2^4\) However, meta-analysis of the five trials that reported the effect of hypothermia on sepsis did not show any increased risk of infection. It is possible that any risk was masked by the routine use of antibiotics in asphyxiated infants during hypothermia treatment.\(^4^4\)

4. Is there any difference in systemic complications with current selective head cooling and whole body cooling protocols?

The relative systemic adverse effects from whole body versus selective head cooling in HIE can be determined by comparing the adverse outcomes from the TOBY trial\(^4^3\) with those of the Cool Cap trial.\(^4^1\) Trial design features and entry criteria for the TOBY trial are similar to the Cool Cap trial, as both required qualifying amplitude-integrated electroencephalogram for entry. The only major difference between these two trials was the method used to achieve therapeutic cooling. These two trials, which constitute the largest cohorts of infants studied under an identical enrollment protocol, showed that cardiac arrhythmia and coagulopathy (TOBY 5% vs Cool Cap 9%, \(P = 0.22\), OR: 0.53, 95% CI: 0.2–1.4; and TOBY 41% vs Cool Cap 50%, \(P = 0.17\), OR: 0.69, 95% CI: 0.43–1.1, respectively) were not different between cooled infants in these trials. Hypotension, defined as a mean blood pressure of \(\leq 40\) mmHg, was more common in the cooled infants from the TOBY trial compared to the cooled infants from the Cool Cap trial (TOBY 77% vs Cool Cap 55%, \(P < 0.001\), OR: 2.75, 95% CI: 1.63–4.6). However, the TOBY trial did not provide data regarding patients with clinically significant hypotension requiring fluid boluses or inotropes.

The risk of thrombocytopenia in cooled infants could not be compared between the TOBY and Cool Cap trials, as different definitions were used for diagnosis of thrombocytopenia. In a smaller non-randomized study,\(^5^5\) the authors and their colleagues have recently reported that the important components of multi-organ system dysfunction in asphyxiated newborns during cooling, including clinically significant respiratory distress needing ventilatory support, use of fresh frozen plasma and platelet transfusion to treat coagulopathy and thrombocytopenia, need for vasopressors for >24 h to treat hypotension, incidence of oliguria (urine output <0.5 mL/kg/h for >24 h after birth), and rising serum creatinine (with maximum serum creatinine >0.9 mg/dL) was similar for both whole body cooling (WBC) and selective head cooling (SHC). Similar findings have recently been reported in an animal study, which found no difference between the two cooling methods in any of the systemic biochemical or histopathological variables investigated.\(^5^4\) Speculatively, it may well be that the target core temperatures (rectal temperatures of 34.5 °C for SHC and esophageal temperatures of 33.5 °C for WBC) maintained during currently available cooling protocols\(^4^1,4^2\) are not sufficiently different to produce clinically significant differential adverse effects.

5. Does hypothermia treatment protect systemic organs other than the brain?

As the main pathogenetic processes of HIE and dysfunction of other organs are presumably similar after a hypoxic–ischemic insult, one might anticipate that therapeutic hypothermia which is beneficial for HIE should also protect systemic organs other than the brain. The Cool Cap trial\(^4^1\) reported an apparent reduction in elevated liver enzymes in the cooled infants (38% of cooled vs 53% non-cooled infants, \(P = 0.02\)), raising the possibility that cooling may be beneficial for other systemic organs outside the brain. In a small study (a single center’s experience as a part of the TOBY trial), cooling was reported to improve multi-organ system dysfunction in asphyxiated newborns.\(^5^5\) However, further evidence of hypothermia treatment protecting organ systems other than the brain in infants with HIE has not been reported.

6. Effects of cooling on drug therapy during hypothermia

Several groups of drugs including anticonvulsants, sedatives, neuromuscular paralyzing agents, antibiotics, and inotropic agents are commonly used in asphyxiated infants while receiving therapeutic cooling. Metabolism and excretion of these drugs and their metabolites might be modified by cooling, as well as by the frequent presence of hypoxic–ischemic hepato cellular and renal injury complicating HIE. However, the current recommendation is not to treat infants receiving hypothermic neuroprotection differently from normothermic asphyxiated infants.

The metabolism of drugs such as phenobarbital, morphine, and vecuronium in the liver is reportedly slowed by effects of hypothermia treatment on the temperature-dependent cytochrome P450 enzyme system. In preliminary data by Thoresen et al.,\(^5^6\) the half-life of phenobarbital in asphyxiated infants receiving therapeutic hypothermia was double that of normothermic controls, but another preliminary study indicated no effects of hypothermia on phenobarbital half-life.\(^5^7\) In a study where morphine infusion rates were determined by clinical state, moderate induced hypothermia was associated with reduced morphine clearance and elevated serum morphine concentrations, sometimes to potentially toxic levels.\(^5^8\) Neuromuscular paralyzing agents such as vecuronium have also been shown in infants and children to have a prolonged half-life during hypothermia treatment.\(^5^9\) These findings, and the frequent association of initial hypoxia–ischemia-induced hepatic
dysfunction in infants with HIE, suggest that clinicians wishing to treat infants with HIE should be aware of the possibility of elevated serum concentrations to potentially toxic levels of these commonly used drugs during therapeutic hypothermia. Close monitoring of anticonvulsant levels during treatment of seizures, and of clinical level of sedation and paralysis while morphine and paralyzing agents are being used, is merited during treatment with hypothermia.

Drugs that are excreted unchanged through the kidneys appear to be less affected by hypothermia treatment. Gentamicin combined with penicillin or ampicillin are usually the initial antibiotics of choice for treatment of suspected sepsis in infants with HIE. A recent study comparing the serum gentamicin concentrations during once-daily gentamicin treatment in cooled and non-cooled encephalopathic infants showed that clearance of gentamicin is affected by the impaired renal function complicating HIE and not by the reduced body temperatures.60 Thus, typical adjustment of gentamicin dosing for impaired renal function based on trough serum concentrations is recommended when treating actual or suspected infection during therapeutic hypothermia.

Use of inotropic agents to treat hypotension is also common in very ill infants with HIE. To date, no difference in response to inotropic support has been experienced among cooled and non-cooled infants with HIE, or in animal studies.74

7. Effects of cooling on laboratory values during hypothermia

7.1. Ventilation, blood gases and cooling

Decreasing body temperature lowers metabolic rate by about 5–8% per degree Celsius and results in a decrease in CO₂ production.61 Furthermore, partial pressure of blood gases and pH are also affected because of altered gas solubilities during hypothermia. With each degree Celsius decrease in core temperature, pH increases by 0.015, PCO₂ and PO₂ decrease by 4% and 7% respectively.62 Excessively low PCO₂ during therapeutic hypothermia may result in altered cerebral blood flow autoregulation, and reduced cerebral perfusion,63 and may lower the seizure threshold.94 Hence, blood gas values should be corrected for core body temperature, and ventilatory adjustments should keep the corrected blood gas values within the normal range, as has been the case in two larger clinical trials.41,42

7.2. Serum electrolytes and cooling

Disturbances in electrolytes and glucose homeostasis are common in infants with HIE, including those receiving therapeutic hypothermia. It is recommended that serum electrolytes and plasma glucose should be kept within the normal range during hypothermia treatment.4 Changes in electrolytes and glucose homeostasis with cooling are detailed below.

7.2.1. Serum potassium

Hypothermia causes an intracellular shift of potassium and has been shown to predispose post-surgical adult patients to hypokalemia with related cardiac complications.65 Aggressive correction of hypokalemia during hypothermia has also been shown to result in ‘overshoot’ hyperkalemia on rewarming.66 Reassuringly, meta-analysis of the three trials40,41,42 that reported the effect of hypothermia on serum potassium showed no statistically significant difference in the incidence of hypokalemia (serum potassium < 3.5 mmol/L) in cooled infants [typical relative risk (RR): 1.03 (95% CI: 0.85, 1.25); typical risk difference (RD): 0.02 (95% CI: −0.09, 0.12)].44

7.2.2. Serum calcium, magnesium and plasma glucose

Hypocalcemia, hypomagnesemia, and hypoglycemia are common in asphyxiated newborn infants. Larger drops in serum calcium and lower cord blood serum magnesium are more frequently present in infants with severe HIE and poor outcome.67,68 In a piglet model subjected to hypoxia–ischemia, hypothermic animals normalized their plasma calcium and magnesium significantly faster than normothermic controls.54 However, the incidence of hypocalcemia in cooled and non-cooled infants was not different in two larger cooling trials,41,42 and meta-analysis of the four cooling trials34,41,42,69 reported no significant hypoglycaemia in hypothermic groups [typical RR: 0.83 (95% CI: 0.54, 1.27); typical RD: −0.03 (95% CI: −0.09, 0.03)].44

7.3. Serum lactate

Reduced tissue perfusion during therapeutic hypothermia has the potential to cause lactic acidosis. Hypothermia also shifts the hemoglobin–oxygen dissociation curve to the left, thus reduces oxygen availability to tissues, and thus could contribute to metabolic acidosis.65 However, if, as suggested by experimental studies, perfusion is reduced proportionately with reduced demand, then in principle there would be no increase in anerobic metabolism. Strongly supporting this concept, in an experimental piglet model the post-hypoxic–ischemic insult decline in lactate was noted to be temperature independent and it was only the severity of the insult that influenced the lactate levels.54

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**Practice points**

- Adequate knowledge of how cooling affects all organ systems of the asphyxiated infants who are already sick from multi-organ ischemia–reperfusion injury is necessary to avoid systemic complications of overcooling.
- Overcooling mostly occurs during transport when cooling is initiated by relatively inexperienced staff, or during ‘uncontrolled’ cooling in an under-resourced setting.
- The potential danger of overcooling is the development of ‘cold-injury syndrome’ and the key to safety (and avoiding over-cooling) is continuous core temperature monitoring.
- Cooling also affects the blood gas values, and glucose homeostasis, and can alter the metabolism and excretion of various drugs that are commonly used in asphyxiated infants.
- Adequate resources including the diagnostic and well-trained multidisciplinary staff to monitor and manage multi-organ system complications in asphyxiated infants during therapeutic cooling are mandatory during implementation of a cooling protocol, and thus wherever possible therapeutic hypothermia should be offered as a regional service.

**Research directions**

- The safety and efficacy of cooling using novel technology in a low-resourced setting, and specifically during transport, needs to be confirmed.
- Further clinical trials to determine the depth of systemic cooling that provides most optimal neuroprotection without significantly increasing the adverse systemic effects of cooling are necessary.