Neonatal thermoregulation

Since the first use of mercury in glass thermometers in 1798[1], the importance of thermoregulation in clinical care has been appreciated. In no discipline is this more acute than in the management of premature neonates. Hypothermia at birth is a worldwide problem[2-4]. The EPICure study highlighted that for neonates less than 26 weeks' gestation a temperature of <35 °C on admission to a neonatal unit was independently associated with death[5]. Heat loss is a particular problem at resuscitation[6]. Hypothermia can also occur during transfer of infants to neonatal units, during routine care[7] and in operating theatres[8]. Similarly, hyperthermia can have severe adverse consequences and should be avoided[6]. Current routine neonatal practice is founded upon preventing significant temperature changes.

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Key points

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1. Newborn infants are acutely vulnerable to the harmful effects of thermal stress.
2. Preventing damaging heat loss from premature neonates at delivery remains a significant challenge.
3. More research is required to develop an evidence base for heat loss prevention at neonatal resuscitation.
4. Hyperthermia has been associated with poor neurological outcome, and has stimulated research into therapeutic hypothermia.

Hypothermia at birth

Immediately after delivery if no action is taken, the core and skin temperatures of a term neonate can decrease at a rate of approximately 0.1°C and 0.3°C per minute respectively[9]. The World Health Organisation defines mild hypothermia as a core body temperature of 36°C-36.4°C, moderate hypothermia as 35.9°C-32°C and severe hypothermia as less than 32°C[10]. The rapid decline in temperature is mainly due to physical characteristics of the newborn and environmental factors of the delivery area. Typically a wet newborn with a high surface area to volume ratio moves from a warm aqueous uterine environment into a cooler, dry delivery room[9,11]. The newborn immediately loses heat by evaporation, convection, conduction and radiation, dependent on the ambient air pressure, temperature and humidity and the temperature of surrounding surfaces[12,13].

As the temperature falls between 36°C to 35°C, newborn infants peripherally vasoconstrict and initiate non-shivering thermogenesis (NST) of brown adipose tissue[14,15]. Non-shivering and shivering thermogenesis from immature skeletal musculature is insignificant[16]. Brown fat constitutes approximately 1.4 percent of the body mass of newborns greater than 2 kilograms in weight and is prominent in nuchal subcutaneous tissue, around the kidneys, the mediastinium and intra-scapular regions[17]. Brown fat contains high levels of triglycerides, is rich in capillaries and is innervated by sympathetic nerve fibres. NST is triggered by a surge in catecholamines, released from the sympathetic nervous system during times of cold stress. Noradrenaline combines with beta 3 adrenoreceptors on brown adipocytes and activates adenylate cyclase which increases cytosolic cyclic adenosine monophosphate, phosphorylates protein kinase, and activates hormone-sensitive lipase. Uncoupling of oxidative phosphorylation by the protein thermogenin results in marked heat production[18], and a significant increase in metabolic rate[19,20]. With continued cold stress the stores of brown fat become depleted resulting in hypoxia and hypoglycaemia[21].

Brown adipose tissue can be identified after 26 weeks' gestation[22]. Post delivery brown adipose tissue does not continue to develop, as it would have done in the intra-uterine environment, so preterm neonates remain at a disadvantage. The preterm infant has the additional disadvantages of decreased fat for insulation, decreased glycogen stores, immature skin which increases water loss, poor vascular control, a lower maximal metabolism and a narrower range of thermal control[11,20,22].

Heat loss on NICU

Reducing heat losses in the first few days of life, particularly in preterm neonates has been known to be associated with improved survival since the early 1960s[23]. High transepidermal water loss and consequential evaporative heat loss due to structurally and functionally immature skin is a major problem for extremely premature neonates[24]. Transepidermal water loss decreases with increasing postnatal age (**FIGURE 1**), however at four to five weeks' postnatal age, 25-27 week gestational age infants still have losses twice those of their term counter parts[25]. A

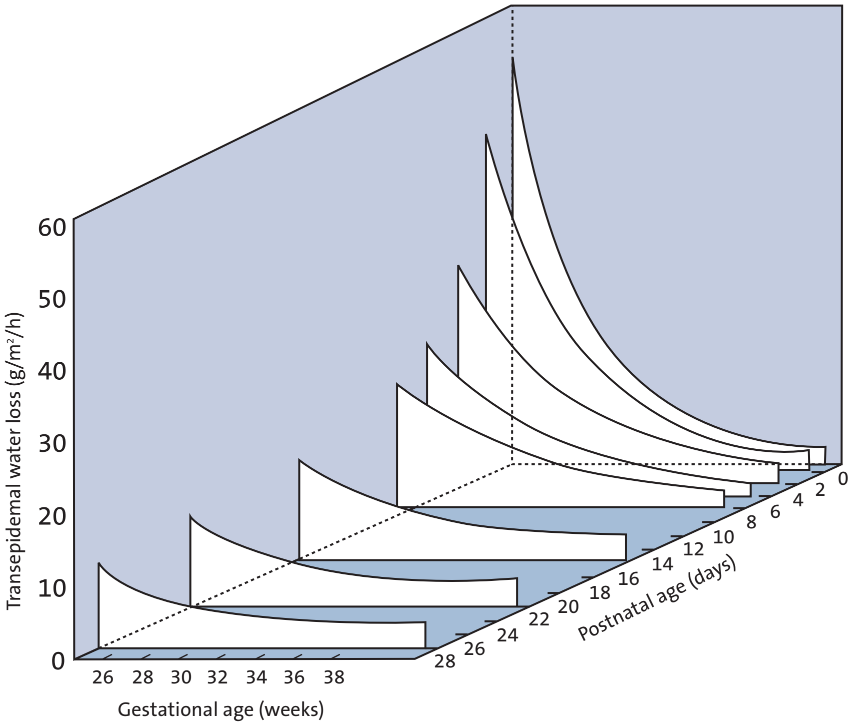

FIGURE 1 The relationship between transepidermal water loss and the age (gestational and postnatal) of newborns[25].

prospective study of modern standardised hygiene care regimes of extremely low birthweight neonates highlighted sharp peripheral and core temperature falls, despite procedures to minimise this[7].

Heat loss during neonatal operations

The transfer of neonates out of incubators for investigations or operative procedures unquestionably increases the risk of heat loss. A recent study highlighted that ten minutes after induction of anaesthesia in a series of neonates, the core temperatures began to fall. If the operating room was below 23°C the losses continued to the end of the procedures[8]. The reason for the decrease in body temperature during anesthesia is not that anaesthesia itself is associated with a loss of thermoregulation, but rather that a broadening of the tolerated core temperatures occurs[26,27]. It is postulated that because of their high amounts of brown adipose tissue and thus their high potential for nonshivering thermogenesis, neonates should be able to produce more heat to compensate for heat loss. However unlike other small mammals who can and do perform nonshivering thermogenesis under anaesthesia, neonates do not[26,27]. Neonates like adults are unable to respond to mild intraoperative hypothermia, despite maintaining other thermoregulatory responses[26,27].

Clinical signs of cold stress

During development of hyperthermia, a neonate may become cold to the touch, restless, irritable or lethargic, hypotonic, a poor feeder with gastric distension or increased aspirates, and bradycardic. As the condition worsens the neonate can become tachypnoeic or apnoeic, hypoglycaemic[28], hypoxic and metabolically acidotic[29], develop coagulation defects, acute renal failure and necrotizing enterocolitis[30] and ultimately die[28].

Risk factors

All neonates are at risk of hypothermia within the first twelve hours of life, particularly the extremely premature and growth retarded infants. Other risk factors include abnormal skin integrity including gastroschisis, exomphalos and neural tube defects and neonates with neurological impairment – global or to the hypothalamus in particular. Hypoglycaemic infants or those already significantly metabolically stressed are also at risk[30-32].

Preventative measures – temperature control at resuscitation

Traditional techniques for decreasing heat loss include the provision of a warm delivery room. A temperature of 25°C is suggested though this is not always achievable[10]. The immediate drying of the infant under radiant heat, discarding the wet towel and replacing it with a warm towel, in a warm draught-free area is recommended[33-35]. However very low birthweight (<1500 g) preterm babies are likely to become hypothermic despite all these measures[5]. As a consequence, recommendations to place newborns inside plastic wrapping or bags with their heads protruding, have been developed[36-38]. The recent Heat Loss Prevention (HeLP) randomised controlled trial found that polyethylene occlusive skin wrapping prevented heat loss at the delivery of infants less than 28 weeks' gestational age[36]. Resuscitation should continue unhindered by the heat loss preventative measures.

A number of other methods to maintain temperature have been described, these include swaddling close to mother with a special blanket[39]. These measures have not been evaluated in any randomised controlled trials. A recent Cochrane review was not able to provide any firm recommendations due to small sample sizes and lack of follow-up data[40]. It is important to closely measure temperature as hyperthermia associated with polyethylene bags and a third degree burn with a thermal heat pack have been reported[41-42].

Thermoregulation on NICU

The mainstay of care is to maintain the newborn in a neutral thermal environment which ensures minimal metabolic activity and oxygen consumption are required to conserve body temperature[43]. Incubators are now specifically designed to minimise losses by radiation, convection, conduction and evaporation whilst allowing clear visibility and access to the patient (**FIGURE 2**). Ambient temperature and humidity are easily controlled. A skin temperature probe is placed away from regions where brown fat metabolism occurs and should be reflective if under a radiant warmer. All newborns should have a hat to prevent excessive heat loss from the head. Plastic wrapping and increased vigilance regarding maintaining temperature control should be instigated for any transfers.

Re-warming after a period of hypothermia should be a well controlled, closely observed treatment, monitoring for hypoxaemia and metabolic acidosis, cardiovascular instability, hydration status, hypoglycaemia and hyperbilirubinaemia.

Rapid rewarming has been advocated[44] but may be associated with vasodilatation and seizures[43].

Clinical implications of hyperthermia

Neonatal hyperthermia is defined as a body temperature above 37.5 °C[10]. There have been reports of neonatal seizures in newborns of febrile mothers[45,46]. It has been postulated from animal studies that hyperthermia during or after hypoxic-ischaemic events may cause neonatal brain injury[47,48]. The current considerable focus on therapeutic hypothermia as a treatment modality is out of the scope of this review.

Clinical signs of hyperthermia

Hyperthermia is usually secondary to overheating due to an external source; however it can be secondary to other factors including sepsis, hypermetabolism, neonatal abstinence syndrome, and maternal hyperthermia at delivery. Clinically hyperthermia may present with irritability, poor feeding, flushing, hypotension, tachypnoea or apnoea, lethargy and abnormal posturing, in addition to an elevated peripheral or core temperature. If untreated then seizures, coma, neurological damage and ultimately death may occur[42]. The treatment of hyperthermia requires the same close monitoring and observation for signs of deterioration as described for the management of neonatal hypothermia. Rapid reduction in temperature is associated with the potential for cold stress shock[49].

The future

Our basic understanding of how neonatal temperature control occurs at the molecular level remains relatively limited. Non-thermal factors such as hydration status[50,51] and hypoglycaemia, which have been shown to lower the core threshold for the onset of shivering[52], require further investigation. There is a need for larger, high quality randomised controlled trials to develop an evidence base for heat loss-preventing interventions at resuscitations. A focus particularly on longer term follow-up and economic considerations to ensure a worldwide benefit would be desirable. The current focus on therapeutic hypothermia will increase further our understanding of thermoregulation and may lead to further novel interventions.

FIGURE 2 A preterm baby being nursed in an incubator which maintains the baby in a neutral thermal environment. *Photo courtesy of GE Healthcare.*

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