Innate Hypothermia after Hypoxic Ischaemic Delivery

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Key Words

Acidosis · Adaptation at birth · Asphyxia · Body temperature · Hypothermia · Hypoxia · Ischaemia · Thermogenesis

Abstract

The focus of this review is to collate the literature on the phenomenon of impaired thermal adaptation after hypoxic ischaemic (HI) delivery often culminating in hypothermia. This phenomenon appears different in severity and duration to a spontaneous postnatal fall in temperature observed after normal delivery. The original observation and contemporary descriptions of the temperature response to HI are described and a mechanism of action is proposed that may be utilised as a novel biomarker for HI.

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We are born naked, wet and hungry. Without intervention, the inevitable consequence of this state is newborn hypothermia. Historically, infants who have experienced hypoxic ischaemia (HI) during delivery frequently experienced hypothermia [1]. Whilst there is a large body of literature describing the evidence base supporting therapeutic hypothermia after HI encephalopathy, there is scant literature on how antenatal HI impairs human newborn thermal adaptation. The purpose of this review is to collate the evidence around impaired thermal adaptation after HI delivery – a maladaptation sometimes sufficient to result in hypothermia.

Prior to birth, the fetus is typically 0.5°C warmer than the mother [2, 3] and rapidly cools [1] unless dried and wrapped. Heat is lost to the environment by evaporation, convection, conduction, and radiation, culminating in up to 10% of infants [4, 5] experiencing transient hypothermia soon after birth [6]. The fall in temperature seen after normal delivery can be minimised by appropriate care practices such as drying and wrapping [1].

The normal adaptive response to cold air exposure after birth is associated with a rise in oxygen consumption [7] from the activation of brown adipose tissue [8, 9]. Brown adipose tissue is rich in mitochondria which consume oxygen, generating metabolic heat through uncoupled aerobic respiration – non-shivering thermogenesis. When exposed to a heat-losing environment, normal term infants are able to double their oxygen consumption to mount a metabolic thermogenic response [10, 11]. Hypothermia occurs when heat loss to the environment exceeds non-shivering thermogenesis. At particular risk of impaired thermal adaptation are infants who have experienced HI during labour and delivery. This deficit in thermogenesis may be related to the effects of HI delivery and require external heating to compensate. Hence, even with adequate attempts to minimise heat loss, in the absence of external heating hypothermia may result.

Hypothermia following delivery has been observed and documented in the early literature [12]. In 1958 Burnard and Cross [13] systematically studied the temperature profile of asphyxiated infants, using ‘a failure to achieve spontaneous respiration by 3 min’ as a definition

Fig. 1. Mean rectal temperatures after normal birth and after birth asphyxia (defined as failure to establish respiration within 3 min). The vertical lines are the 95% confidence limits of the means. Continuous line: $n = 53$ babies (normal delivery); broken line: $n = 15$ babies (asphyxia, no pethidine). Redrawn from Burnard [13] with permission.

of asphyxia. They observed that under the same environmental conditions as non-asphyxiated infants, the asphyxiated infants had lower rectal temperatures, taking 18 h to achieve similar temperatures to the normal infants (fig. 1). They speculated that the observed fall in temperature was related to reduced oxygen consumption and heat generation following the asphyxial insult [14]. No details were documented on the care procedures and some of the asphyxiated infants may have received supplemental unheated and unhumidified ambient oxygen, contributing to their fall in temperature. Over the subsequent 50 years disparate studies have reiterated this observation in human newborn infants [15], and recently in low-resource settings [16, 17]. The studies are difficult to compare and, crucially, they differ in the different definitions of asphyxia or perinatal HI. The original definition of asphyxia used by Burnard and Cross [13] would not now be deemed evidence of perinatal hypoxia [18], but contemporary studies have used definitions that

are consistent with cooling trial inclusion criteria. Despite these differences in case definition similar patterns emerge.

A significant, widely cited paper on thermal adaptation, published in *Biology of the Neonate*, was the work of Brück et al. [19]. The authors described infants born by difficult delivery who, on exposure to cold, were unable to achieve the doubling of heat production seen in neonates after uncomplicated delivery [20]. Other authors found that the oxygen consumption of a group of asphyxiated infants (Apgar scores 1–7 at 1 and 5 min) was lower than that of non-asphyxiated infants when examined at room temperature (24°C) and remained lower for at least 72 h [21]. When challenged with a 1-hour fall in environmental temperature there was a rise in oxygen consumption in most asphyxiated infants, but not to the magnitude seen in normal infants exposed to the same challenge, suggesting that oxygen consumption was lower than expected in the asphyxiated infants and possibly explaining a persistently low temperature in the first 24 h. Similarly, Schubring [22] showed that when the oxygen consumption and temperatures of 13 resuscitated infants (with Apgar scores <7) were compared with 31 term infants with normal Apgar scores, a significant difference in the oxygen consumption was noted until 130 min and in rectal temperature until 75 min.

It is also interesting to note that impaired heat generation may also precede delivery. The following studies suggest that heat loss from infants who have experienced a period of acidosis or hypoxia during labour have reduced heat generation and hence heat loss. In the 30 min prior to delivery, scalp heat loss was correlated with umbilical artery pH, suggesting that heat production may be lower in those who were acidotic [23]. A difference in heat loss was also noted in infants who were not acidotic or required resuscitation [24] and heat loss from the back of newborn infants, overlying one site of brown adipose tissue, was correlated with umbilical artery PaO_2 .

The most recent illustrations of impaired thermal adaptation are from neuroprotective hypothermia trials. One study [16] noted a fall in rectal temperature in the control group, attaining normothermia at a mean age of 15 h (fig. 2), and a recent study [17] reported hypothermia for 8 h in control infants [Thayyil, pers. commun.]. During a randomised hypothermia trial it was noted by one cooling centre that the cooling blanket was being used to warm the baby for the majority of the 72 h [25]. Another centre offering therapeutic hypothermia noted that infants with more severe encephalopathy had a low-

Fig. 2. Mean rectal temperature in standard care (n = 15) and therapeutic hypothermia (n = 21) groups during the first 80 h after randomisation. Infants were randomised when the Apgar score at 5 min had been less than 6 and the Thomson score at 30 min to 3 h after birth was higher than 5. Mean age at randomization was 112 min. Error bars = SD. Reproduced from Robertson [16] with permission.

er temperature prior to the induction of active cooling [26].

In contradistinction, there is evidence that temperature instability and pyrexia is associated with the development of cerebral palsy in symptomatic [27] and asymptomatic infants [28]. HI that goes unrecognised prior to birth may lead to a failure in heat generation after birth and consequent labile temperature, later manifesting as cerebral palsy. Similarly, hyperthermia after perinatal HI encephalopathy is recognised as a predictor of poor outcome in the large cooling trials [29, 30], suggesting that a period of low temperature after HI may be a protective physiological response.

The failure of the normal thermal adaptive response has been employed in the delivery of therapeutic neuroprotective hypothermia. The neuroprotective trials have been conducted using active cooling. However, passive cooling is used in the peri-transfer period [31–33] and to initiate and maintain mild hypothermia [34], exploiting the transient hypothermia experienced by infants after HI delivery. Impaired heat production may not be universal in all infants after HI delivery but is a component of multi-organ injury seen in the majority [35, 36] of babies with HI encephalopathy. Infants experiencing endogenous cooling due to reduced heat production capability in the control arm of trials [16] might also dilute the expected trial effect of active neuroprotective hypothermia.

The evidence substantiating the original finding of Burnard and Cross [13] of impaired thermal adaptation is compelling but not conclusive. The challenge is to replicate the original findings in a population of infants after HI delivery, using contemporary definitions of HI deliv-

ery [18]. A full characterisation of the phenomenon would require the use of calorimetry to quantify the heat transfer to the environment. The greatest challenge is to identify a relationship between thermal maladaptation and encephalopathy following HI delivery [37].

A fall in temperature after birth has been described in the early literature and can be minimised with simple interventions. Studies over the last 50 years have described temperature profile or heat production after HI delivery that differs from that after uncomplicated delivery, despite different definitions of HI, many of which would not be considered valid today. The term innate hypothermia is used speculatively to describe hypothermia that is not a consequence of environmental conditions or inadequate care practices but an obligate, evolved protective response to HI delivery. Hypothermia following hypoxia is seen in other immature and mature newborn mammals [38] and may provide an adaptive survival benefit [39] after mild or moderate HI delivery. Neuroprotective hypothermia may not date back to the late 1940s [40] but to a common mammalian ancestor [41] 96 million years ago.

In summary, impaired heat production and consequent lower body temperature after HI delivery appears to be a measurable phenomenon with a plausible mechanism of action that warrants further investigation and may serve as a biomarker for the severity of insult.

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