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Review

Physiological responses to hypothermia

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SUMMARY

Therapeutic hypothermia is the only treatment currently recommended for moderate or severe encephalopathy of hypoxic–ischaemic origin in term neonates. Though the effects of hypothermia on human physiology have been explored for many decades, much of the data comes from animal or adult studies; the latter originally after accidental hypothermia, followed by application of controlled hypothermia after cardiac arrest or trauma, or during cardiopulmonary bypass. Though this work is informative, the effects of hypothermia on neonatal physiology after perinatal asphyxia must be considered in the context of a prolonged hypoxic insult that has already induced a number of significant physiological sequelae. This article reviews the effects of therapeutic hypothermia on respiratory, cardiovascular, and metabolic parameters, including glycaemic control and feeding requirements. The potential pitfalls of blood–gas analysis and overtreatment of physiological changes in cardiovascular parameters are also discussed. Finally, the effects of hypothermia on drug metabolism are covered, focusing on how the pharmacokinetics, pharmacodynamics, and dosing requirements of drugs frequently used in neonatal intensive care may change during therapeutic hypothermia.

1. Introduction

Despite continuing improvements in obstetric care, perinatal asphyxia still affects two to four out of every 1000 live births, with 25–50% of those developing encephalopathy of presumed hypoxic–ischaemic (HI) origin. For infants with moderate or severe encephalopathy, the only treatment that has been shown to reduce death and long-term disability is therapeutic hypothermia (TH), which involves reducing core temperature to 33–34.5°C for 72 h [1]. Since the introduction of TH to resuscitation guidelines in 2010 [2], the number of centers offering TH for HI encephalopathy is increasing, with infants no longer only being cooled as part of controlled trials within tertiary centers. This may lead to less-expert administration of TH, potentially decreasing the efficacy of the treatment. Therefore, it is increasingly important that physicians treating encephalopathic infants understand the physiological changes that may occur during TH. Some data suggest that babies receiving TH within a controlled trial have more stable physiology than those who are cooled as part of standard therapy, even within the same center [3].

As the kinetics and chemistry of most processes in the body are largely optimised around 37°C and pH 7.4, reducing core temperature by just a few degrees can alter the physiology of almost every system and organ. Hypothermia causes a linear reduction in both heart rate and cardiac output in line with metabolic rate, and these should be considered physiological rather than pathological. In fact, hypothermia may blunt the effect of inotropic therapies [4], as well as shift the response away from a β-adrenergic (inotropic) effect towards a peripheral α-adrenergic (vasoconstrictive) effect. As temperature drops, reduced metabolism leads to a decrease in CO_2 production. This, alongside the increased solubility of CO_2 in the blood, results in a fall in pCO_2, with downstream effects on cerebral blood flow. Additionally, the fall in pCO_2 may result in an alkalosis, increasing the risk of seizures. At the same time, the risk of immunoparesis, deranged haemostasis, and altered glucose metabolism may be increased by hypothermia, but these will be largely influenced by the severity of the hypoxic insult [5–7], which is often not known. The metabolism and clearance of a large number of regularly administered drugs is also slowed during hypothermia [4]. The physiological picture during hypothermia therefore provides a number of potential pitfalls for the attending clinician. The purpose of this review is to discuss physiological changes during hypothermia, as well as areas that require further study, with a focus on data relevant to the asphyxiated neonate.

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2. Cardiovascular effects

Mild hypothermia has a number of diverse and opposing effects on the cardiovascular system. As metabolic demand decreases during TH, heart rate (HR) is reduced by around 10 bpm/°C reduction in core body temperature [8,9]. During TH, cardiac output (CO) also decreases linearly with temperature, with more variable effects on stroke volume (SV) and mean arterial blood pressure (MABP), which depend largely on the use of inotropic drugs.

Hypothermia reduces HR by slowing diastolic repolarisation in the sino-atrial node [10], and increasing both myocardial conduction time and absolute refractory period [11], as well depressing sympathetic autonomic nervous system contribution to HR. In the adult, this effect of hypothermia on myocardial conduction manifests as ECG changes including prolonged PR, QRS and QT intervals, as well as the classic positive deflection between the QRS and ST segments known as the Osborne (or "J" wave). However, the latter has not been described in neonates undergoing mild hypothermia [12]. Additionally, though an increase in QTc is often seen during neonatal TH [12,13], this is not associated with an increased risk of arrhythmias [1]. As the reduction in HR is physiologically linked to metabolic rate, it is rarely pathological. In fact, cardiac stability may be increased during mild hypothermia [9].

Additionally, as the structure of the cardiomyocyte remains immature until after the cardiovascular pressure changes associated with birth, both normal transverse tubule structure and the excitation–contraction coupling (release of Ca^{2+} from the sarcoplasmic reticulum as a result of L-type Ca^{2+}-channel activation) associated with adult myocyte activation are not fully developed in the newborn heart [14]. Thus, the developing heart may rely on reversed action of the Na^{+}/Ca^{2+}-exchanger to increase intracellular calcium in response to the cardiac action potential [14]. This means that adult data are unlikely to reflect the response of the neonatal heart to hypothermia, especially in the context of post-hypoxic cardiac dysfunction. In the asphyxiated neonate, increased cardiac injury (assessed by cardiac troponin release), presumably due to a more severe hypoxic insult, is associated with greater reductions in CO, independent of temperature [15].

In adults, CO decreases by ~7% per °C [16], and a similar effect is seen in neonatal TH, where CO in cooled neonates (33–34°C) is 60–70% of that at normothermia [17–19]. Experimentally, mild hypothermia (3–5°C reduction in core temperature) also increases cardiac contractility due to increased myofibrillar sensitivity to intracellular calcium. However, a concomitant increase in duration of the cardiac action potential and time to maximal contraction, with increased left ventricular stiffness and prolonged relaxation time [20], may result in a reduced overall ability of the heart to perform work during mild hypothermia. This is particularly noticeable when HR is artificially increased during TH, which results in a decrease in contractility [21]. Indeed, it appears that the hypothermia-induced increase in myocardial contractility can only occur if HR is allowed to fall [21]. Thus, studies suggest that left ventricular contractility and SV during mild hypothermia may be increased, unaffected or reduced, and this is likely to be due to a combination of the degree of hypothermia, anaesthetic regimen, and use of additional inotropic agents during TH. For instance, cooling pigs by 5°C resulted in a spontaneous reduction in HR and maintenance of SV, unless HR was artificially increased by pacing, when SV fell [20].

With respect to blood pressure (BP), small studies examining the effects of TH on BP parameters in neonates describe either no change, or an increase of up to 10 mmHg in MABP during cooling [13,22]. Cooled asphyxiated neonates are also not at increased overall risk of hypotension requiring inotropic support [1]. As BP is traditionally defined as the product of CO and total peripheral resistance (TPR), the decrease in CO seen during TH must be compensated for by an increase in TPR, which largely occurs via peripheral vasoconstriction. However, some studies suggest that more prolonged inotropic support is used in cooled infants, despite no difference in requirement for inotropes (assessed by MABP) between cooled and normothermic infants [23]. Hence it is important to stress that unless pathological hypotension is seen clinically, the physiological reduction in HR should be allowed to occur in order to maximise cardiac efficiency and SV during hypothermia. This can be done by ensuring adequate sedation, with judicious use of inotropes. Indeed, in one study of haemodynamics in seven cooled asphyxiated newborns, a 23% reduction in SV was seen during cooling, but this may well be because average HR was higher than would be expected (129 bpm), for the reasons listed above [17]. Overall, it seems that the fall in CO in neonates undergoing TH is mainly attributable to the physiological fall in HR [19,20].

During TH, constriction of the venous system and sedation (leading to reduced spontaneous movement) results in reduced venous return and cardiac preload. However, as CO falls during TH, it also appears that the increase in TPR (as well as hypoxia-induced loss of cerebral autoregulation) results in maintenance of cerebral perfusion [19]. Though the upshot of this redistribution remains to be determined, changing pressures within the cardiovascular system also increase the risk of fluid shifts and peripheral oedema during TH. Fluid movement within the peripheral (micro)vasculature is determined by the balance of oncotic and hydrostatic pressures, as well as by the permeability of the capillary wall. Ischaemia–reperfusion injury is likely to increase the permeability of the peripheral microvasculature, though this effect may be ameliorated by TH [24]. However, the combination of increased intravascular hydrostatic pressure (as a result of vasoconstriction), increased permeability of the capillary bed, and reduced venous return and lymphatic return results in fluid moving out of the vascular compartment and into the extracellular space [16]. These fluid shifts result in a potential haemoconcentration, which, alongside a decreased deformability of red blood cells within the microcirculation during hypothermia, leads to an experimental increase in blood viscosity of 4–6% per 1°C [25]. Unlike adults, however, asphyxiated neonates do not appear to undergo "cold diuresis" [16]. In fact, reduced urine output due to asphyxia-induced acute kidney injury [26], as well as reduced insensible losses resulting from vasoconstriction during TH, may lead to intravascular overload. This, alongside the relatively large volume of blood taken for monitoring during TH, may prevent the rise in haematocrit and risk of microembolisation that may otherwise occur.

As well as fluid shifts, there is also the potential for solute loss from the vascular compartment as potassium moves into the intracellular or extravascular compartment during TH [16]. Importantly, however, there does not seem to be an increased risk of hypokalaemia during TH [1], though an increase in intravascular volume may lead to an increased risk of hyponatraemia [27]. Details for other electrolytes are less well documented, though one study of 25 infants noted low magnesium levels and increased need for magnesium supplementation (with no changes in potassium, phosphate, or calcium) in neonates receiving parenteral nutrition during TH [28], and protocols suggest maintaining serum magnesium levels >1.0 mmol/L [29].

Hypothermia also produces an altered response to adrenergic stimulation (also see Section 8.3.1). Though α-adrenergic sensitivity appears to increase (resulting in increased TPR) during hypothermia, β_1 (cardiac)-adrenergic responses have been seen to increase, remain constant, or decrease during hypothermia, depending on the experimental model and temperatures investigated [4]. It is likely that hypothermia alters cAMP and Ca^{2+} signaling such that an increased response to β_1-adrenergic stimulation (increased Ca^{2+}