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REVIEW ARTICLE

Respiratory management during therapeutic hypothermia for hypoxic-ischemic encephalopathy

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Abstract

Therapeutic hypothermia (TH) has become the standard of care treatment to improve morbidity and mortality in infants with hypoxic-ischemic encephalopathy (HIE). Although TH has clearly proven to be beneficial, recent studies suggest optimization of respiratory management as an approach to prevent further damage and improve neurodevelopmental outcome. The ventilatory management of asphyxiated neonates presents a challenge because both the hypoxic insult and TH have an impact on respiratory functions. Although the danger of recurrence of hypocapnia is well recognized, a brief period of severe hyperoxia also can be detrimental to the previously compromised brain and have been shown to increase the risk of adverse neurodevelopmental outcomes. Therefore, judicious ventilatory management with rigorous monitoring is of particular importance in patients with HIE. In the present review, we provide an overview of the currently available evidence on pulmonary function, respiratory morbidities, and ventilation strategies in HIE and we highlight possible future research directions.

Introduction

Perinatal asphyxia is a serious condition which can lead to hypoxic-ischemic encephalopathy (HIE) in newborns and subsequent permanent neurological deficits. Despite advances in obstetric care, the incidence of HIE has remained approximately 1–2 cases per 1000 full-term live births in developed countries, thereby placing a huge burden on families and healthcare systems [1]. Therapeutic hypothermia (TH) in infants with moderate to severe HIE has been associated with decreased risk of death and neurodevelopmental impairment [2]. This protective effect has been maintained through childhood [3]. However, even with hypothermia, nearly half of the infants with moderate to severe encephalopathy are at risk of death or severe disability [2, 4]. Optimization of intensive care of these neonates might have the potential to prevent injury progression and further improve neurodevelopmental outcomes.

Respiratory management of asphyxiated infants is challenging because both the hypoxic-ischemic (HI) insult and hypothermia have an impact on respiratory functions (Fig. 1). Perinatal hypoxia is often associated with elevated pulmonary vascular resistance or meconium aspiration syndrome (MAS). In addition, HI injury is typically followed by cerebral reperfusion and excessive oxidative stress [5, 6]. Hypothermia causes a decrease in metabolic rate with a parallel reduction in oxygen (O_2) consumption and carbon dioxide (CO_2) production [7]. Many infants remain intubated and ventilated throughout the treatment period, although a relatively high percentage of the asphyxiated infants have a strong respiratory drive to compensate for metabolic acidosis [8]. In spite of increasing evidence of the harmful effects of hypocapnia [9–12], it is difficult to achieve normocapnia in these patients.

Even though TH has become the standard of care for neonatal HIE, little is known about optimal ventilation strategies for an infant undergoing TH. Our knowledge is currently based on retrospective studies or secondary analyses of the landmark hypothermia trials, as prospective, randomized respiratory management studies are lacking. Indeed, respiratory management and its effect on pulmonary and neurological function may impact the long-term neurological outcome of the survivors. The aims of this work

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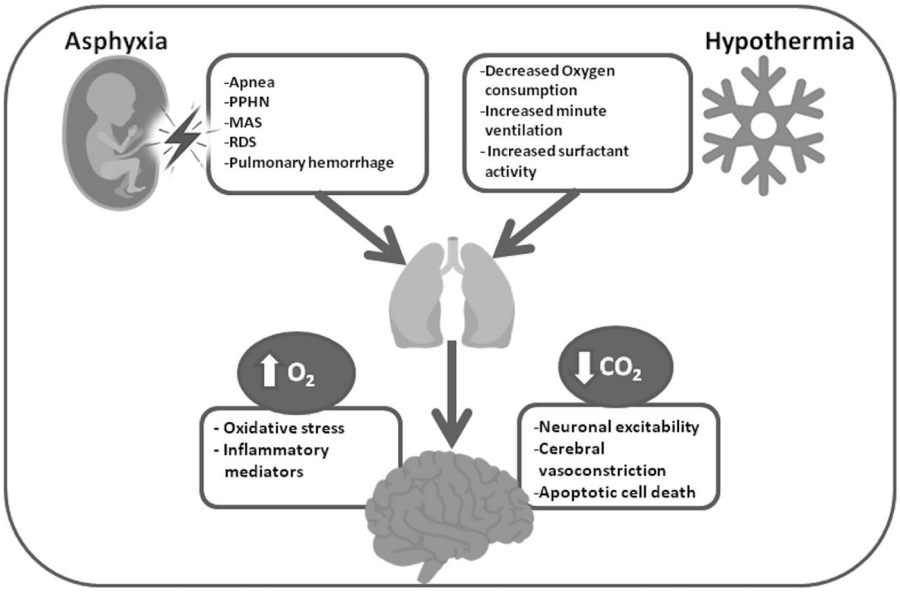

Fig. 1 The effects of asphyxia and hypothermia on respiratory function. Perinatal asphyxia is often complicated by apnea, pulmonary hypertension (PPHN), meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), and pulmonary hemorrhage. On the other hand, hypothermia causes a physiological decrease in metabolic rate with a parallel reduction in oxygen (O_2) consumption and carbon dioxide (CO_2) production. During therapeutic hypothermia, increased minute ventilation and improved surfactant activity have been described. The altered respiratory function can lead to hyperoxia and hypocapnia, which in turn have the potential to exacerbate brain injury. Hypocapnia causes increased cerebral vasoconstriction, reduced CBF, neuronal excitability, thereby initiating apoptotic cell death, while hyperoxia may lead to increased oxidative stress, potentiate inflammatory mediators, and neuronal death

are to review the currently available evidence on pulmonary function and respiratory management in HIE patients, especially those receiving TH, and to describe future potentially fruitful research directions.

Respiratory function in infants with perinatal asphyxia

Effect of perinatal asphyxia on the respiratory system

Perinatal asphyxia may have a deleterious effect on the lungs and respiratory function. The presence of hypoxia at birth alters the physiology of transition to extrauterine life. Hypoxia increases the pulmonary vascular resistance further, resulting in decreased pulmonary blood flow and right to left shunting across the foramen ovale. Severe hypoxia abolishes the initiation of spontaneous breathing leading to apnea and bradycardia [13, 14].

HI can directly affect brainstem especially in severe prolonged insults [15]. Direct injury to respiratory centers can lead to respiratory depression. Moreover, patients with status epilepticus secondary to HIE are also at risk for inability to maintain normal ventilation. These factors contribute to increased incidence of mechanical ventilation in these neonates [16].

Perinatal asphyxia is a significant risk for pulmonary hypertension via multiple mechanisms [17]. Hypoxia acts through the endothelin/nitric oxide (NO) axis leading to increased vasoconstriction due to elevated endogenous endothelin production followed by impaired NO synthesis [18]. Furthermore, chronic fetal hypoxia, especially with meconium aspiration, is associated with pulmonary vasoconstriction as well as vascular remodeling [19]. Meconium aspiration is associated with the immediate release of inflammatory cytokines in addition to direct lung injury [17]. In addition, some asphyxiated infants present with signs of respiratory distress syndrome (RDS). The underlying mechanism of the RDS-like clinical presentation appears to be related to metabolic acidosis and increased pulmonary capillary permeability of plasma proteins which lead to inactivation of surfactant [20–22]. Finally, perinatal asphyxia has been reported to increase the risk for pulmonary hemorrhage [23]. Pulmonary hemorrhage can also inactivate surfactant and cause respiratory deterioration [24].

Effect of hypothermia on pulmonary functions

Hypothermia can affect pulmonary functions via different mechanisms. Increased pulmonary vascular resistance, decreased oxygen release due to the leftward shift of hemoglobin dissociation curve, and reduced oxygen consumption affect pulmonary functions [25, 26]. Furthermore,

low temperature decreases chest wall compliance [27] and respiratory muscle function [28].

Interestingly, none of the three landmark randomized hypothermia trials provided detailed information on the severity of the pulmonary dysfunction, except for the occurrence of respiratory distress or persistent pulmonary hypertension (PPHN) [29–31]. An observational study on the association between TH and pulmonary dysfunction reported a minimal need for positive pressure and supplemental oxygen requirement in asphyxiated infants, irrespective of the method of cooling (selective head cooling or mild total body hypothermia). In addition, the authors described a slightly higher alveolar–arterial oxygen gradient that reflected mild pulmonary dysfunction in infants without PPHN [32]. In a retrospective study on the effects of hypothermia on ventilatory parameters, Dassios et al. reported increased minute ventilation and tidal volume during hypothermia compared to the pre-cooling and rewarming phases of the treatment. The ventilation efficacy index, calculated from the respiratory rate, peak inflating pressure, and the partial pressure of carbon dioxide (PCO_2), increased consistently with an improvement in the overall ventilation performance. In this study, oxygenation was also favorably affected by hypothermia [33]. The increased minute ventilation and tidal volume are consistent with the findings of an Italian research group who compared the effect of mild (33–34 °C) and deep (30–33 °C) whole body hypothermia on respiratory function. Thus, in the deeply hypothermic infants, respiratory rate was significantly lower, whereas minute ventilation and tidal volume were slightly higher (tidal volume 17.7 vs. 15.8 ml/min; minute volume 683 vs. 654 L/min) [34]. Based on these findings, hypothermia appears to have a beneficial effect on lung mechanics and has potential to enhance vention, but further trials with more participants are warranted to elucidate pathophysiological changes in lung mechanics during hypothermia.

Respiratory management during neonatal therapeutic hypothermia

Mechanical ventilation and TH

Approximately 50–70% of asphyxiated infants without pulmonary disease have been reported to require mechanical ventilation during TH due to the poor respiratory drive, altered level of consciousness, or seizure burden secondary to encephalopathy [10, 12, 35]. Data from the Vermont Oxford Network Neonatal Encephalopathy Registry 2006–2010 showed that 64% of eligible infants received mechanical ventilation [36]. While in some centers all infants are intubated and sedated through the course of hypothermia, centers that expanded their cooling protocol to include mild encephalopathy have reported only 30% of babies receiving hypothermia needed mechanical ventilation [37].

Blood gas management during TH

The partial tension of blood gases (PCO_2 and PO_2) and pH are temperature dependent. At a lower temperature, the solubility of gases increases within the blood or other fluids. For example, in a healthy newborn infant, a pH of 7.4 will rise to 7.5 and a PCO_2 of 40 mmHg will decrease to 34 mmHg, if the actual body temperature is reduced to 33 °C by the hypothermia treatment [38]. To address this problem during intensive care, two acid–base management strategies are available, the alpha-stat or pH-stat strategy. Currently, it is unclear which strategy should be preferred in neonates receiving TH.

With the alpha-stat method, the uncorrected values of PCO_2, PO_2, and pH are maintained close to the reference values at 37 °C. The principle of the alpha-stat hypothesis is that intracellular pH remains close to the pH of neutrality due to proteins (imidazole group of histidine), bicarbonate, and phosphate buffering. This approach maintains the net charge on all proteins constant despite the changes in temperature. Essentially, the alpha-stat method is not temperature corrected. This method overestimates the partial tension of gases in the blood and underestimates the pH, leading to relative hypocapnia and alkalosis in patients with lower body temperature. In contrast, during pH-stat management, the blood gas values represent the true acid–base status of the patients under TH because the blood gas values are corrected to the actual body temperature of the patients [38, 39]. Over moderate ranges, the changing of PCO_2, PO_2, and pH can be treated as linear. The actual PO_2 and PCO_2 values can be estimated by subtracting 5 and 2 mmHg, respectively, per each 1 °C below 37 °C. The reduction in PCO_2 is associated with a 0.012 units decrease in pH for each 1 °C under 37 °C [40, 41]. Most modern blood gas analyzers can calculate and present the temperature-corrected blood gas values.

To date, there are four prospective randomized clinical trials assessing whether pH-stat or alpha-stat is the better protocol in terms of morbidity and mortality in pediatric patients undergoing deep hypothermic circulatory arrest [42–45]. Three out of four studies demonstrated the pH-stat method to be more beneficial during heart surgery and in the postoperative period, by resulting in better cerebral oxygenation, less inotropic support, and shorter period of intensive care [42, 43, 45]. Importantly, the pH-stat method also reduced the seizure burden and shortened the recovery time of the EEG activity [42, 43]. However, concerning the long-term neurodevelopmental outcome at 1 and 2–4 years of age, there were no differences between the management

strategies [44]. Furthermore, in the adult population, a better outcome was reported with the alpha-stat method [46]. Thus far, insufficient evidence exists to support one protocol over the other in hypothermic infants after perinatal asphyxia. The National Institute of Child Health and Human Development (NICHD) and CoolCap hypothermia trials recommended using pH-stat in the management of the newborns [38].

In summary, currently the pH-stat method appears to be more likely to optimize the acid–base status of asphyxiated infants, but further systematic studies are needed to address whether this treatment strategy leads to improved neurodevelopmental outcome, e.g., by lowering the risk of hypocapnic episodes and extracellular alkalosis.

Carbon dioxide management and HIE

The partial pressure of carbon dioxide can change over a wide range in infants with perinatal asphyxia, and recent studies have highlighted the possible role of carbon dioxide management in neurodevelopmental outcomes. During the sentinel asphyxial event hypercapnia is common, but subsequently, hypocapnia is frequently observed (5.8–88.7%) in the early hours of postnatal life [10, 35]. Several physiologically plausible explanations for the low carbon dioxide levels in this patient population may be posited. First, impaired energy metabolism of the injured brain can lead to a reduction in CO_2 production. Second, TH can be an independent risk factor for the development of hypocapnia because of a reduction in metabolic rate [7, 47]. Third, severe metabolic acidosis can lead to compensatory hyperventilation and result in hypocapnia [48]. Interestingly, case reports have suggested that hypothermia could be utilized as a rescue therapy for refractory hypercapnia in cases of severe respiratory failure [49, 50].

The intensity and duration of resuscitation, as well as the parameters of mechanical ventilation, have a great impact on the clearance of carbon dioxide. As noted earlier, 50–70% of babies who received TH have been supported by mechanical ventilation. However, in a small study of asphyxiated newborns with mild encephalopathy, and less ventilatory support, Nadeem et al. reported that only 6 out of 52 maintained normal PCO_2 throughout the first 72 h after birth and that the rate of moderate hypocapnia (<3.3 kPa = 24.7 mmHg) was 31% in the self-ventilated infants and 69% in those with mechanical ventilator support [35].

Hypocapnia has the potential to exacerbate brain injury by causing cerebral vasoconstriction with reduced cerebral blood flow (CBF), and by further decreasing oxygen supply due to the leftward shift of oxyhemoglobin curve [48]. Carbon dioxide is one of the most potent regulators of CBF. The relationship between PCO_2 and CBF is nearly exponential. Under normal conditions, a 1 mmHg change in the PCO_2 causes a 4% change in CBF [51]. In healthy newborns or adults, the decreased cerebral perfusion due to hypocapnia is transient and well tolerated. However, the decreased perfusion could be deleterious to the previously injured brain if oxygen transport and extraction are diminished, and the removal of potentially toxic metabolites is reduced.

In addition to the cerebral vasoconstriction, hypocarbia is associated with neuronal excitability through increasing glutamate transmission and suppressing GABA inhibition [52]. Moreover, hypocapnia initiates nuclear DNA fragmentation in the cerebral cortex, membrane lipid peroxidation, and apoptotic cell death [53, 54].

Brain alkalosis after recovery from asphyxia plays a role in neuronal excitability as well as modulation of cell death and seizure burden [55]. Observations from animal studies suggest that a graded restoration of normocapnia could reduce seizure burden and improve neurological outcome [56]. Robertson et al. utilized phosphorus magnetic resonance spectroscopy to show that neonates with severely abnormal outcomes had higher pH as long as 20 weeks after birth [57]. This finding may support the notion that manipulation of intracellular brain pH could enhance neuroprotection after perinatal asphyxia.

It has been established that hypocapnia is one of the risk factors for the development of periventricular leukomalacia and cerebral palsy in preterm infants [58]. A similar relationship between brain injury and hypocapnia has been shown in term infants with HIE (Table 1). In term infants with HIE, Klinger et al. demonstrated that patients who were hypocapnic within the first 2 h of life had a 2.34-fold increased likelihood to develop adverse neurological outcome than infants without hypocapnic episodes [9]. According to the secondary analysis of NICHD hypothermia trial, both minimum and cumulative exposure to PCO_2 less than 35 mmHg within the first 12 h of life increased the risk of death and adverse neurodevelopmental outcome [10]. Consistent with this observation, a post-hoc analysis of the CoolCap study showed that the probability of unfavorable outcome was raised dose-dependently with decreasing PCO_2 in infants with moderate and severe HIE [11]. Moreover, a recent retrospective study also reported an association between hypocapnia over the first 4 days of life and brain injury on MRI [12].

Despite the consistent reports of an association of hypocapnia and unfavorable outcomes, it remains unclear whether hypocapnia is a biomarker or a modifiable risk factor. Furthermore, it is important to note that the definitions of hypocapnia and hyperoxia were different in the above-discussed studies. See details in Table 1. A prospective clinical trial of controlled normocapnia is warranted to determine the nature of the relationship between hypocapnia and long-term outcome. Nevertheless, the

Table 1 Articles published on the association between carbon-dioxide levels and neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy

Author, date, and journal Study type	Outcomes	Definitions of hyperoxia and hypocapnia	Key results
Klinger et al. (2005), Arch Dis Child Fetal Neonatal Ed *Retrospective cohort study* 218 infants with intrapartum asphyxia before the era of hypothermia included in the multivariate analysis	Death or severe neurodevelopmental disability at 12 months of age	Arterial blood gases during the first 20–120 min of life Severe hyperoxia: $PaO_2 \geq 200$ mmHg Severe hypocapnia: $PaCO_2 < 20$ mmHg	Multivariate analysis Severe hyperoxia **and** hypocapnia OR 3.07 (1.31–7.18); $p = 0.001$ Severe hyperoxia **or** hypocapnia OR 4.56 (1.4–14.9); $p = 0.012$
Nadeem et al. (2010), Am J Perinatol *Retrospective cohort study* 52 term infants with HIE who completed follow up before the era hypothermia	Death or Griffith's quotient < 87 or significant motor disability	Blood gases collected between 9 min and 72 h from birth: arterial, capillary, and venous Severe hypocapnia: $PCO_2 < 2.6$ kPa (19.5 mmHg) Moderate hypocapnia: $PCO_2 < 3.6$ kPa (27 mmHg) Hypercapnia: $PCO_2 > 6.6$ kPa (49.5 mmHg)	Univariate and multivariate logistic regression No association between PCO_2 and adverse outcome
Pappas et al. (2011), J Pediatr *Secondary observational study to NICHD randomized trial* 204 term infants with moderate to severe HIE A mixed population of cooled and non-cooled infants	Death or severe/moderate disability at 18–22 months of age	Temperature corrected arterial blood gases before randomization, at randomization, and 4, 8, 12 h of intervention Minimum $PaCO_2$ and cumulative exposure to $PaCO_2$< 35 mmHg (calculated as the difference between 35 mmHg and the sampled $PaCO_2$ multiplied by the duration of time spent below 35 mmHg)	Multiple logistic regression Minimum $PaCO_2$ to 12 h OR 2.0 (1.1–3.4); $p = 0.0151$ Cumulative exposure of hypocapnia OR 6.9 (1.5–31.9); $p = 0.0490$
Sabir et al. (2012), J Pediatr *Retrospective cohort study* 61 term infants with moderate to severe HIE who underwent whole-body hypothermia	Death or severe neurodevelopmental disability at 18–22 months of age	Temperature corrected blood gases from birth to 6 h of life: capillary, venous, arterial Hypocapnia: $PCO_2 < 30$ mmHg Hyperoxia: $PaO_2 > 100$ mmHg	Linear regression analysis No association between any measurements of hypocapnia or hyperoxia and adverse outcome
Lingappan et al. (2016), Pediatr Res *Secondary observational study to CoolCap randomized trial* 196 of 234 patients with moderate to severe HIE with p_aCO_2 and follow up data	Death or severe disability at 18 months of age	Temperature-corrected arterial blood gases 0, 4, 8, 14, 24, and 72 h from study randomization	Minimal adequate regression model to predict probability Point estimate ± SE $PaCO_2$ of 40 mmHg 0.20 ± 0.1 $PaCO_2$ of 30 mmHg 0.53 ± 0.23 $PaCO_2$ of 20 mmHg 0.89 ± 0.16
Lopez Laporte et al. (2017), J Matern Fetal Neonatal Med *Retrospective cohort study* 198 term infants with moderate to severe HIE underwent who whole-body hypothermia	Brain MRI findings according to the scoring system of Barkovich et al. Brain injury on MRI: yes vs. no	Temperature corrected blood gases during 1–4 days of life: arterial, capillary, and venous The lowest PCO_2 averaged over days of 1–4 of life	Multivariate logistic regression OR 1.07 (1.00–1.14); $p = 0.040$

The numbers in brackets indicate the 95% confidence interval in the key results column

consistent findings of an association between hypocapnia and poor outcomes suggest that avoidance of hypocapnia is a reasonable approach to achieve optimal neuroprotection in these patients.

Oxygen management and HIE

Perinatal asphyxia is characterized by a transient period of hypoxia-ischemia followed by a reperfusion phase with the production of oxidative stress. Reactive oxygen species cause endothelial cell injury, astrocyte dysfunction, and lead to necrotic cell death and neuronal loss. Even a brief period of hyperoxia, another inducer of oxidative stress through the upregulation of glutathione-related enzymes may increase the risk of a secondary neural injury after HI episodes [6, 59, 60].

Evaluation of oxygen management in asphyxiated newborns can be divided into two distinct phases of care: (1) resuscitation in the delivery room, which has been studied extensively; and (2) a return of spontaneous circulation (ROSC) phase followed by TH, a period that has been studied less.

The aim of ventilation management during resuscitation of a newborn is to establish the functional residual capacity of the lungs, decrease pulmonary vascular resistance, and increase pulmonary blood flow, thereby enabling the ROSC. In the past decades, resuscitation after HI injury was routinely performed with 100% oxygen; however, experimental studies identified the deleterious effects of hyperoxia due to increased oxidative stress, free radical production, and inflammatory mediators acting on an already compromised brain [61, 62]. Consistent with these studies, several randomized control clinical studies showed that resuscitation with room air is as effective as resuscitation with 100% oxygen and resulted in less acute tissue damage to the heart and kidney [63]. According to the recent meta-analysis of Saugstad et al., resuscitation with room air showed a 31% reduction in neonatal mortality (RR 0.69, 95% CI 0.54–0.88) among term newborns when compared to 100% oxygen. Based on the analysis of 6 randomized and 4 quasi-randomized trials, for every 25 infants resuscitated with room air, there will be one more surviving infant (number needed to treat is 25). They also found a strong trend toward a reduction in the presence of stage 2 or 3 HIE according to the Sarnat score [64]. On the other hand, long-term follow-up at 18–24 months of age showed no significant differences between the 2 groups in somatic growth and neurodevelopmental outcome, although the follow up rate was only 66% [65]. The current Neonatal Resuscitation Guidelines recommend that the resuscitation of term infants be initiated with room air and if there is no increase in heart rate and peripheral oxygen saturation, the oxygen concentration should be titrated to achieve an adequate saturation and heart rate [66, 67]. In addition, pulse oximetry is recommended to monitor preductal transcutaneous oxygen saturation and heart rate, as its use can help avoid the excessive use of oxygen.

Regarding the ROSC period, Sabir et al. conducted a retrospective data analysis to evaluate the association between hyperoxia during the first 6 h of postnatal life and neurodevelopmental outcome at 18 months of age in a small group of newborns with HIE who were treated with TH. They found an association between increased inspired oxygen concentration (both >0.4 and 0.3) during the first 6 h of postnatal life and poor outcome. However, there was no association between high arterial PO_2 (>100 mmHg) and poor outcome [68]. Before the TH era, Klinger et al. reported an independent association between severe hyperoxia ($PO_2 > 200$ mmHg) during the first 20–120 min of postnatal life and adverse outcome. Moreover, their adjusted model showed that infants with the combination of severe hyperoxia and hypocapnia (<20 mmHg) were 3 times more likely to develop poor outcome at 18–20 months of age (OR 3.07; 95% CI 1.31–7.18; $p = 0.001$) [9].

Respiratory morbidities of perinatal asphyxia

PPHN

PPHN of the newborn is defined as a failure of normal pulmonary vascular relaxation shortly after birth, leading to elevated pulmonary vascular resistance, and right-to-left shunting across the foramen ovale and ductus arteriosus. Hypoxia plays an important role in the pathophysiology of PPHN due to the impairment of NO synthase [18]. Furthermore, lower body temperature can induce pulmonary vasoconstriction mainly through neuronal mechanisms [32, 69, 70]. Thus, TH theoretically could increase the risk of development of PPHN in asphyxiated infants. However, meta-analysis of hypothermia trials did not report a higher incidence of PPHN or increased use of inhaled nitrogen monoxide (iNO) among cooled infants compared to controls [2]. The occurrence of PPHN is reported to be between 13% and 25% in asphyxiated hypothermic infants [71, 72], which is clearly higher than the incidence in the general population (~2/1000 live births) [73]. Factors associated with PPHN include hypoxia-induced vasoconstriction, MAS, pulmonary hemorrhage, maternal age, and outborn status rather than the hypothermia treatment [72].

PPHN itself could be an additional risk factor in infants with HIE for the development of an unfavorable neurological outcome. However, a single center observational trial showed that short-term outcomes, such as amplitude-integrated electroencephalography (aEEG) and MRI findings, did not differ significantly between cooled asphyxiated

infants with varying PPHN status [72]. It is noteworthy that the mortality of PPHN, when combined with moderate and severe HIE, is approximately 27%, a value is considerably higher than the mortality rate of 7.6–8.5% in PPHN infants without HIE [74]. The management of PPHN during TH should follow the same local guidelines for infants not receiving TH, including proper cardiorespiratory support and if needed, NO and extracorporeal membrane oxygenation (ECMO).

MAS

Fetal distress can lead to in utero passage of meconium, and irregular respiration or gasping associated with hypoxia can lead to the aspiration of meconium-stained amniotic fluid during labor. The presence of meconium in the lung causes an inflammatory response and an impairment of pulmonary surfactant activity. Small case series showed that hypothermia may improve surfactant activity time-dependently at 33.5 °C [75, 76] and reduce some proinflammatory mediators as interleukin-6 and 8 in lung epithelial lining fluid [77]. Consistent with this finding, a multicenter retrospective observational trial compared cooled and uncooled neonates with MAS and found an improved oxygenation index in the cooled group of infants, especially in the most severe cases [78]. These possible benefits of hypothermia in MAS may be explained by the enhanced surfactant function and the reduction in inflammatory response.

A beneficial role for TH and ECMO in the management of severely affected infants with a history of perinatal distress and MAS is suggested by the report of five infants by Massaro et al. All infants met the criteria for whole body cooling, and after the failure of mechanical ventilation and iNO therapy, they were placed on ECMO while hypothermia was continued and maintained at 33.5 °C for 72 h. Based on this report, total body hypothermia seems feasible during ECMO [79]. To date, the safety and feasibility of hypothermia during ECMO have been investigated in only a limited number of pilot studies [80, 81]. Although the preliminary results are promising, further trials are warranted to test the combined effects.

Respiratory monitoring during TH

Carbon dioxide monitoring

Since there is increasing evidence that an association exists between hypocapnia and long-term neurodevelopmental outcome, a close monitoring of carbon dioxide exchange seems to be highly important in asphyxiated infants. Arterial blood gas analysis, the gold standard for monitoring the respiratory components of acid–base homeostasis, has obvious limitations that preclude its continuous use to follow the dynamically changing level of PCO_2.

Transcutaneous CO_2 monitoring ($tcPCO_2$) is the most commonly used non-invasive CO_2 monitoring system in neonatal intensive care and has been correlated to PCO_2 in premature infants [82]. Total body hypothermia causes peripheral vasoconstriction which can affect the accuracy of this technology. However, to this date, the feasibility of $tcPCO_2$ under controlled hypothermia treatment has not been evaluated systematically. In critically ill adult patients, Rodriguez et al. conducted a study to evaluate the accuracy of $tcPCO_2$ and they found a trend for a larger $tcPCO_2$ bias under hypothermic conditions (<36 °C) compared to normothermia [83]. While the results of neonatal studies are needed, it can be hypothesized that $tcPCO_2$ monitoring for PCO_2 trends might be a useful addition to the critical care of asphyxiated neonates.

End-tidal CO_2 ($ET\text{-}CO_2$) monitoring became an available option to monitor carbon dioxide exchange continuously in mechanically ventilated infants due to recent technical advances, such as the microstream technique that requires both a smaller sample volume and instrumental dead space. Some authors recommend $ET\text{-}CO_2$ as an acceptable method to estimate arterial carbon dioxide level [84, 85]. However, this technique still has several limitations and should be used with caution in neonatal intensive care. Ventilation-perfusion mismatch, failure to reach an expiratory plateau due to rapid respiratory rate and other technical limitations of monitoring (humidity, temperature) should be taken into consideration before interpreting $ET\text{-}CO_2$ values. Tingay et al. reported that the degree of bias between $ET\text{-}CO_2$ and arterial PCO_2 was 1.04 kPa (=7.8 mmHg) and only 48% of $ET\text{-}CO_2$ recordings were within 1.0 kPa (=7.5 mmHg) of the paired arterial PCO_2 samples [86].

Although continuous CO_2 monitoring would be desirable in asphyxiated infants, to date neither of the non-invasive CO_2 monitoring techniques have been evaluated systematically or used routinely in the intensive care of asphyxiated hypothermic infants.

Oxygen monitoring

Close observation of systemic oxygen saturation is an important component of the intensive care of newborns receiving TH. Oxygen saturation is affected not only by O_2 delivery to tissues but also by O_2 consumption. This complex relationship is dynamic and can change during the process of cooling and rewarming.

Cerebral oxygen saturation monitoring determined by near infrared spectroscopy (NIRS) in infants with HIE provide insights into cerebral oxygenation. Earlier studies have shown that newborns with severe HIE have decreased cerebral oxygen extraction and increased cerebral oxygen

saturation [87]. Although TH has the potential to decrease cerebral perfusion, oxygen metabolism, and extraction, the overall higher cerebral saturation is associated with worse outcome [88]. The predictive value of cerebral oxygen saturation for predicting brain injury and outcome is increased when combined with aEEG [88, 89]. While commercially available NIRS cannot separate changes in CBF and oxygen metabolism (cerebral metabolic rate of oxygen—$CMRO_2$), more advanced optical methods, such as frequency domain NIRS (FDNIRS) and diffusion correlation spectroscopy (DCS) can provide such separation. In one study, while cerebral saturation did not change from the time of cooling to rewarming, both $CMRO_2$ and CBF decreased during TH when compared to post-hypothermia or healthy controls [90].

Conclusions and future directions

Respiratory management of asphyxiated infants receiving TH presents a challenge. The impact of hypothermia on respiratory function has not been studied extensively; furthermore, it is still unclear whether the alpha-stat or pH-stat strategy is the ideal to optimize acid–base status in asphyxiated, cooled infants. However, the avoidance of extreme oxygen and carbon dioxide levels has become a central feature of current management.

Hypocapnia and extreme hyperoxia, which are both detrimental to the previously compromised brain and increase the risk of adverse neurodevelopmental outcome, should be avoided. Although the definitions of dangerous levels of hypocapnia and hyperoxia are not standardized in literature, common neonatal standards should be used. A minimum FiO_2 is recommended to maintain a normal PO_2 level of 50–100 mmHg and peripheral saturation above 92% [8, 9, 91]. To obtain optimal PCO_2 levels of 40–50 $mmHg^9$, frequency and tidal volume should be kept at a minimum during mechanical ventilation [8]. Currently, there are no treatment options to avoid hypocapnia in spontaneously breathing infants. With deep sedation or muscle relaxation, control of ventilation is feasible; however, these approaches add the adverse effects of paralytics, sedatives, and analgesics which can easily accumulate during hypothermia and reach a potentially toxic level [92, 93]. Clearly, further randomized trials are warranted to test the effect of controlled normocapnia on short and long-term outcomes. At present, there is an ongoing randomized clinical trial which investigates the safety and feasibility of therapeutic hypercapnia (50–55 mmHg) in the adult population after cardiac arrest by reduction of minute ventilation on the ventilator (ACTRN12612000690853). In asphyxiated cooled neonates, the feasibility and safety of 5% CO_2 inhalation to avoid hypocapnia and maintain desired levels of carbon dioxide in the early hours of

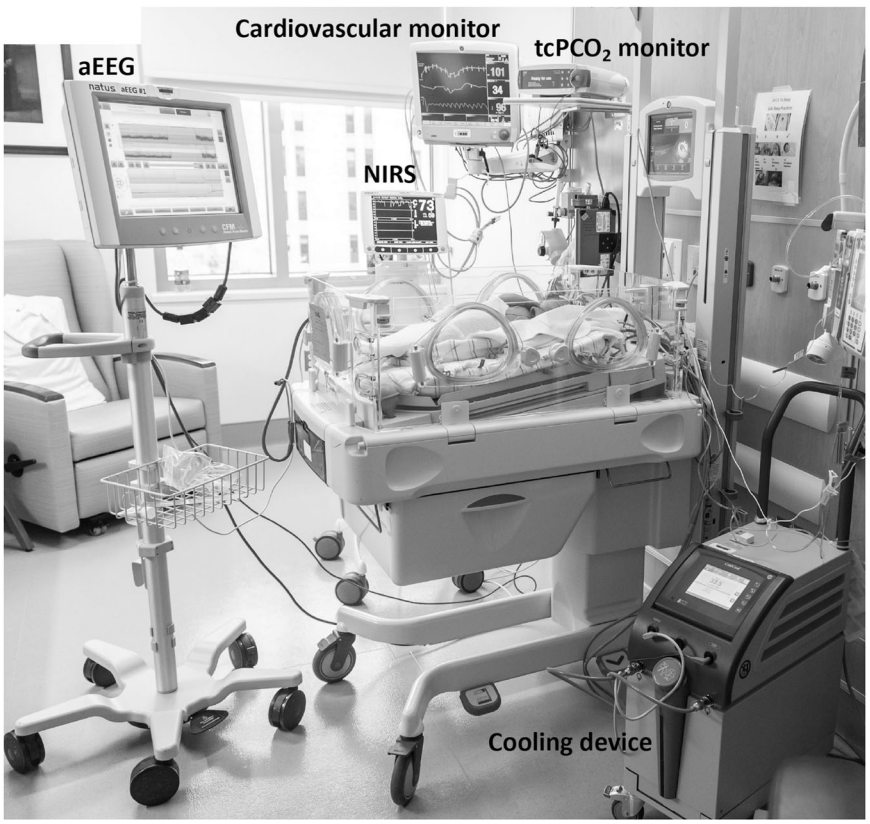

Fig. 2 Complex monitoring strategies in the intensive care of asphyxiated infants. Beside conventional patient monitors, several other monitoring systems may aid clinicians to provide personalized ventilatory management to HIE patients. Transcutaneous CO_2 ($tcPCO_2$) monitoring might be a useful addition to follow the dynamically changing level of PCO_2. Close observation of systemic oxygen saturation is important as part of the intensive monitoring. Near infrared spectroscopy (NIRS) in babies with HIE can provide insights into cerebral oxygenation and brain perfusion. Amplitude-integrated electroencephalography (aEEG) monitoring shows a response to interventions instantly and correlates well with potential outcomes. (Courtesy of Department of Pediatric Newborn Medicine, Brigham and Women's Hospital.)

postnatal life (NCT02700854) are also currently being tested. Finally, continuous, non-invasive monitoring of PCO_2 and oxygen saturation are strongly suggested in the early hours of life and during hypothermia treatment in asphyxiated infants.

In summary, the optimization of respiratory management with the currently available techniques (Fig. 2) may be an important approach to enhance the neuroprotective effect of hypothermia, and could be proven to be more cost-effective when compared to recently tested adjunctive pharmacological agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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