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Chapter 5

The Impact of Ventilation on the Development of Brain Injury in Asphyxiated Newborns Treated with Hypothermia

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Abstract

Birth asphyxia and the resulting neonatal encephalopathy are a significant cause of mortality and long-term morbidity in children. Hypothermia is currently the only neuroprotective treatment to have been clinically tested in large trials to prevent the development of brain injury in some term asphyxiated newborns. Most of the asphyxiated newborns treated with hypothermia are intubated at birth as per resuscitation measures and remain on mechanical ventilation during some part of the hypothermia treatment or during the whole length of the treatment. They also may present with oxygenation problems. Very often, they present with hypocapnia that can be worsened with the use of mechanical ventilation during the first days of life. When taking care of these newborns, a few important points should be remembered about the impact of asphyxia and therapeutic hypothermia on oxygenation and ventilation. In this article, we review some of the physiopathology behind neonatal encephalopathy and the implications of brain cooling from a respiratory point of view. Strategies to optimize oxygenation and ventilation for these newborns, as well as to prevent further brain injury, are also discussed based on a current literature review.

Keywords: brain, hypocapnia, neonatal encephalopathy, persistent pulmonary hypertension, ventilation

1. Introduction

Birth asphyxia and the resulting neonatal encephalopathy are significant causes of infant morbidity and mortality. Every year, three to five newborns per 1000 live births suffer from birth asphyxia and have an increased risk to die or to develop long-term neurodevelopmental sequelae [1, 2]. The sequelae may range from mild traits such as language impairments, attention deficits, and hyperactivity to more severe traits such as cerebral palsy, global developmental delay, and epilepsy [3].

Brain injury secondary to birth asphyxia and neonatal encephalopathy is a dynamic two-step process. Initially, the asphyxial insult leads to decreased blood flow to the brain (primary lesions), and this oxygen and blood deprivation around the time of birth may cause direct neuronal cell injury and cell death (necrosis) within minutes [4]. Then, as the blood flow is restored in an injured brain, a cascade of secondary pathways is initiated within the first hours and days of life that can lead to further worsening of neuronal cell injury and cell death (apoptosis) ("reperfusion injury"). Several mechanisms have been involved in these reperfusion injuries, that is, excitotoxicity from glutamate and aspartate release, disruption of calcium homeostasis, generation of oxygen-free radicals, and inflammation [2].

In the past, asphyxiated newborns were managed with supportive care only (avoidance of hypotension, avoidance of hypoglycemia, correction of blood gas parameters, and seizure control), with the goal to maintain homeostasis to limit brain injury [5]. In recent years, a number of large trials have demonstrated the efficacy of therapeutic hypothermia for the treatment of neonatal encephalopathy [6–12]. Therapeutic hypothermia is currently the only neuroprotective treatment demonstrated to be effective for preventing the development of brain injury in some term asphyxiated newborns by preventing reperfusion injuries [8] and for decreasing the risk of death and disability [1, 13, 14]. Therapeutic hypothermia involves systemic or selective head cooling of the asphyxiated newborns to an esophageal temperature of 33.5°C. Based on animal studies, the treatment has been shown to be efficient when started within 6 hours of life and continued for 72 hours, followed by progressive rewarming [6–12]. The exact therapeutic window in humans is yet to be determined.

Despite hypothermia treatment, a significant number of asphyxiated newborns still develop brain injury, and maintenance of homeostasis within the first hours and days of life is of the utmost importance.

2. Impact of birth asphyxia on oxygenation and ventilation

Brain oxygenation occurs normally through the glycolytic pathway where glucose is converted to pyruvate. This step produces the formation of the acetyl coenzyme, which enters the Krebs cycle to generate energy in the form of adenosine triphosphate through mitochondrial oxidative phosphorylation [15]. Thus, oxygen delivery to the brain cells is critical for oxidative phosphorylation to occur and for the cell to produce energy. In contrast, excessive oxygen

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delivery to this powerful cellular machinery will result in the generation of oxygen-free radicals leading to hyperoxia-related brain and lung injury [16]. The delivery of oxygen to the different organs, especially the brain, requires several key steps. First, oxygen is delivered from the air to the lungs. The second step occurs in the lungs at the alveolar level where the delivered oxygen is exchanged with tissue-produced carbon dioxide; this step requires adequately functioning alveoli and pulmonary vessels around these alveoli. The third step requires an adequate circulating blood flow generated by the heart to deliver the oxygen to the tissues, but also an adequate cerebral perfusion for oxygen delivery to occur in the brain. The fourth step is the extraction of the hemoglobin-bound oxygen by the tissues and its delivery to the cells.

Birth asphyxia affects the oxygenation process through several mechanisms. At the cellular level, the asphyxial event deprives cells from oxygen, and thus, pyruvate is converted to lactate through the lactate dehydrogenase enzyme. In addition, this anaerobic condition blocks the oxidative phosphorylation in the mitochondria, which leads to energy production failure, since adenosine triphosphate production is reduced [15]. In the lungs, asphyxia increases pulmonary vascular resistance, and thus the risk of persistent pulmonary hypertension, and therefore contributes to oxygenation failure, since persistent pulmonary hypertension often leads to a right-to-left shunting of deoxygenated blood, and thus a decreased delivery of oxygen to the brain [17]. This right-to-left shunting could be either intracardiac through the patent foramen ovale or through the ductus arteriosus, or intrapulmonary shunting. Also, high pulmonary vascular resistance may impair oxygenation in the absence of shunting by causing right ventricular dysfunction. Asphyxia also has a direct negative impact on cardiac function [18], and this cardiac dysfunction may contribute to oxygenation failure, since an adequate cardiac output is important for oxygen delivery to all tissues, particularly the brain. An impairment of the oxygen process has the potential to worsen brain injury in asphyxiated newborns.

Birth asphyxia leads to metabolic acidosis, mainly because the cells switch to an anaerobic metabolism as oxygen gets depleted, which leads to lactate accumulation [19]. This metabolic acidosis may lead to hyperventilation, hypocapnia, and the development of a respiratory alkalosis. Hypocapnia has been shown to exacerbate brain injury and lead to negative outcomes. Hypocapnia alters pH, reduces cerebral blood flow (through vasoconstriction and a release of vasoactive factors), alters potassium channels, and affects calcium homeostasis, all of which contribute to further damaging the brain. Hypocapnia has been associated with periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy, cognition developmental disorder, and auditory deficits [20]. Thus, it may also worsen brain injury in asphyxiated newborns.

Clinical manifestations of neonatal encephalopathy include an initially altered level of consciousness, tone and reflexes, and seizures may happen [9, 21]. Respiratory difficulties are very often associated with the initial neonatal encephalopathy [21]. Most asphyxiated newborns are intubated at birth as per resuscitation measures and remain on mechanical ventilation during some part of the hypothermia treatment or during the whole length of the treatment [22].

3. Impact of hypothermia on oxygenation and ventilation

Mild hypothermia achieves neuroprotection mainly by decreasing metabolic demand and minimizing secondary energy failure. A reduction of 2–4°C of the body temperature of asphyxiated newborns can decrease their rate of cell death, delay metabolic changes, and even delay secondary brain injury [23]. The metabolic rate decreases by 5–8% with every 1°C reduction in core temperature, which in turn reduces glucose and oxygen utilization, and therefore mitigates energy failure following the initial asphyxial event [24].

Overall, hypothermia has a direct and favorable effect on oxygenation parameters (**Table 1**). Hypothermia shifts the oxygen-dissociation curve to the left, and thus, a lower partial pressure of oxygen is needed to achieve the same level of hemoglobin saturation. This left shift prevents some of the oxygen release to the tissues, which should be considered an appropriate physiological adaptation, since hypothermia also decreases the demand for oxygen. Although hypothermia has been suspected to worsen the existing pulmonary hypertension caused by asphyxia [25], larger randomized studies of asphyxiated newborns that have tested hypothermia as a treatment did not report an increased incidence of persistent pulmonary hypertension [1, 26]. In addition, hypothermia also may have an impact on lung mechanisms [27]. Asphyxiated newborns treated with hypothermia tend to have an increased compliance and a decreased mean airway pressure, and these changes tend to reverse during the rewarming process [27], and may thus predispose the newborn to a worsening of the underlying persistent pulmonary hypertension during that phase of treatment [27]. Further impairment of persistent pulmonary hypertension, and thus of oxygenation, has the potential to worsen the brain injury of asphyxiated newborns treated with hypothermia.

Parameters	Changes during hypothermia treatment	Management Strategies
Oxygen (FiO_2 and pO_2)	Lower temperature shifts the oxygen-dissociation curve to the left. Lower pO_2 are thus needed to achieve same level of hemoglobin saturation	Avoid hyperoxia (lower PO_2 may be needed to achieve same saturation)
Mean airway pressure (MAP)	Lower temperature increases lung compliance and decreases mean airway pressure	Optimize lung recruitment and avoid overdistension (lower MAP may be needed). Carefully monitor changes in lung compliance during rewarming
Ventilatory rate	Lower temperature decreases metabolic rate, and thus CO_2 production	Avoid hyperventilation by adjusting ventilatory settings
Pulmonary pressure	Lower temperature may worsen persistent pulmonary hypertension (?)	Use O_2 and NO as needed to avoid further hypoxia. Maintain adequate systemic blood pressure. ECMO to be considered when optimized treatment fails. Avoid hyperoxia
Blood gas analysis	Lower temperature decreases pCO_2 and increases pH	"pH-stat" strategy (correction of pH and pCO_2 to the body temperature) suggested as the most cautious approach

Abbreviations: ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; NO, nitric oxide; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

Table 1. Ventilation in asphyxiated newborns treated with hypothermia.

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Another important factor to take into account is the variations in oxygen utilization and demand that occur during hypothermia treatment, in particular during the first few hours of life. In a previous study on asphyxiated newborns treated with hypothermia, the regional cerebral oxygen saturation measured by near-infrared spectroscopy (NIRS) increased from day 1 to 2 of life in all newborns regardless of whether they did or did not develop brain injury. However, newborns who later develop brain injury had higher regional cerebral oxygen saturation, which may reflect either more severe neuronal injury, and thus less utilization of oxygen by dead tissues, or the phenomenon of luxury perfusion that occurs when increased brain perfusion exceeds the metabolic demand [28].

As previously mentioned, hypothermia decreases metabolic rate and therefore leads to a decrease in carbon dioxide production. With respect to an asphyxiated newborn treated with hypothermia, who is breathing spontaneously, this means that any drop in the partial pressure of carbon dioxide (by a decrease in carbon dioxide production) will correlate with decreased ventilation via chemoreceptor inhibitory input into the respiratory center, in an effort to maintain a stable partial pressure of carbon dioxide. However, regarding an asphyxiated newborn treated with hypothermia, who is intubated, a risk of hyperventilation and respiratory alkalosis exits if the ventilator parameters are not adjusted to the decreased carbon dioxide production [22]. Further worsening of the hypocapnia by hypothermia may further worsen brain injury in asphyxiated newborns treated with hypothermia.

4. Evidence for best practices for ventilation in asphyxiated newborns treated with hypothermia

Most asphyxiated newborns are intubated at birth as per resuscitation measures and remain on mechanical ventilation during some part of the hypothermia treatment or during the whole length of the treatment. Past studies have reported that the ventilatory management of asphyxiated newborns treated with hypothermia is very complex [29], since it has to take into account all the previously discussed issues. The adjustment of ventilator settings should be closely fine-tuned to optimize oxygenation and limit hypocapnia in asphyxiated newborns treated with hypothermia (**Table 1**).

Mechanical ventilation in asphyxiated newborns treated with hypothermia should aim for optimal lung recruitment and avoidance of overdistension. Optimal lung recruitment should decrease atelectasis, which may reduce the effective gas exchange area in the lungs and contribute to the hypoxic pulmonary vasoconstriction [25]. In contrast, overdistension should be avoided, since it may lead to systemic hypotension by decreasing venous return, exacerbate persistent pulmonary hypertension, worsen the oxygen delivery, and thus decrease the organs' perfusion, particularly the brain [30]. No evidence from randomized controlled trials has suggested the superiority of high-frequency oscillatory ventilation over conventional mechanical ventilation in near-term and term newborns [31]. In addition, no available studies have explored which mode is the most suitable among the different possible modes of mechanical ventilation for these newborns.

After optimal lung recruitment, optimizing oxygenation consists mainly in limiting persistent pulmonary hypertension. Wide variations in the management of persistent pulmonary hypertension persist among neonatologists, which probably reflect the lack of an evidence-based approach for the treatment of neonatal persistent pulmonary hypertension [32]. In addition, the most optimal values for oxygenation parameters for asphyxiated newborns during hypothermia treatment are currently not known and probably vary according to the day of life, as has been demonstrated by the previously discussed variations in oxygen utilization and demand that occur during hypothermia treatment. Increasing the fraction of inspired oxygen has a known pulmonary vasodilator effect and should thus improve oxygen delivery and decrease the risk of further brain injury. However, this increase in the fraction of inspired oxygen should be carefully monitored, since hyperoxia or an excessive delivery of oxygen relative to the demand may lead to a worsening of brain injury through the formation of oxygen-free radicals that could at the same time worsen pulmonary hypertension [33]. Although current evidence does not support the early use of inhaled nitric oxide in preterm infants, it has been shown to decrease the need for extracorporeal membrane oxygenation in near-term and term infants with hypoxic respiratory failure [34]. Given the potential-added beneficial effect on neuroprotection and the possible impact of persistent pulmonary hypertension on brain injury, the use of nitric oxide should be considered early in the course of treatment [35]. In addition, it is important to consider cardiopulmonary interactions and optimize blood pressure in these newborns to limit the right-to-left shunting. As a last treatment resort, extracorporeal membrane oxygenation should be considered to optimize oxygenation and has been demonstrated to be feasible for asphyxiated newborns treated with hypothermia [17]. Further studies are needed to determine the most optimal values for oxygenation parameters and the best methods to reach them with respect to asphyxiated newborns treated with hypothermia.

Limiting hypocapnia is the next important step. Several studies have highlighted the importance of preventing hypocapnia in ventilated asphyxiated newborns during hypothermia [29, 36]. It remains to be established what has the worst impact on brain perfusion—a single hypocapnic episode, cumulative hypocapnia, and/or fluctuations in the partial pressure of carbon dioxide [29]. Moreover, it may be the combination of hypocapnia with hyperoxia that could lead to more adverse outcomes [36]. Alternatively, hypercapnia also should be avoided, since it has been shown to alter cerebral blood flow by causing cerebral vasodilatation and impairing cerebral autoregulation [37]. Currently, conflicting evidence exists with respect to the efficacy of permissive hypercapnia on brain protection. Although some studies have argued that it helps to avoid ventilation-induced brain injury [20], a recent study on extremely low-birth weight infants has found no significant decrease in lung injury nor mortality in newborns managed with permissive hypercapnia [38]. Permissive hypercapnia has yet to be further studied in asphyxiated newborns receiving therapeutic hypothermia. Further studies that continuously monitor the partial pressure of carbon dioxide levels and quickly adjust the ventilator settings would be necessary to improve the ventilatory management of these newborns.

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To monitor the changes in the partial pressure of carbon dioxide and pH during hypothermia treatment and the adjustment of ventilatory settings, two strategies are available, depending on whether the partial pressure of carbon dioxide and pH are corrected or not for temperature. The "α-stat" strategy does not correct the partial pressure of carbon dioxide and pH for body temperature; rather, it measures them at normal body temperature (37°C) as is usually done for lab measurements of blood gas parameters if not specified otherwise. Alternatively, the "pH-stat" strategy adjusts the partial pressure of carbon dioxide and pH values to the actual body temperature of the newborn. At hypothermia temperature (33.5°C), the partial pressure of carbon dioxide will decrease and pH will increase compared to normal body temperature (37°C) [22, 39], since the solubility of a gas within a liquid (such as blood) decreases with lower temperature due to physical laws. A review of 16 studies comparing the efficacy of these two strategies in managing acid-base disturbances in the context of deep hypothermic circulatory arrest have suggested that the pH-stat strategy should be preferred for the pediatric population [40–44]. Such a study has not yet been performed in asphyxiated newborns treated with cooling. In the large randomized controlled trials of therapeutic hypothermia following asphyxia [9, 10], the pH-stat strategy was used, since it was considered to be the most cautious approach for maintaining the physiologic partial pressure of carbon dioxide and pH levels. With this strategy, ventilator settings need to be decreased more aggressively.

5. Conclusions

The respiratory management of asphyxiated newborns treated with hypothermia is complex. Many factors specifically related to asphyxia and hypothermia must be considered when dealing with the ventilatory management of these newborns, so to offer them the best possible level of care. Evidence is currently lacking regarding the best practices to use to optimize oxygenation and ventilation in these newborns and prevent the development of further brain injury. Further studies should be performed to determine what is the optimal mode of ventilation and what are the most optimal values for oxygenation parameters for these newborns during hypothermia treatment. Until then, the treating team should keep a very close eye on them to maintain, as much as possible, homeostasis, and to avoid hypoxemia, hyperventilation, and hypocapnia.

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