Hypercapnia and hypocapnia in neonates

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Background: **The arterial partial pressure of carbon dioxide ($PaCO_2$) represents the balance between CO_2 production and consumption. Abnormal increase or decrease in $PaCO_2$ can affect the body's internal environment and function. Permissive hypercapnia has aroused more attention as a novel ventilatory therapy. The aim of this study was to elucidate the effects of hypercapnia and hypocapnia on the functions of such neonatal organs as the lung and brain.**

Data sources: **The PubMed database was searched with the keywords "hypocapnia", "hypercapnia" and "newborn".**

Results: **Hypocapnia is a risk factor for potential damage to the central nervous system, such as periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy, cognition developmental disorder, and auditory deficit. Hyperventilation can lessen pulmonary artery hypertension to certain extent, but hypocapnia can aggravate ischemia/reperfusion-induced acute lung injury. Severe hypercapnia can induce intracranial hemorrhage, even consciousness alterations, cataphora, and hyperspasmia. Permissive hypercapnia can improve lung injury caused by diseases of the respiratory system, lessen mechanical ventilation-associated lung injury, reduce the incidence of bronchopulmonary dysplasia and protect against ventilation-induced brain injury. In addition, permissive hypercapnia plays a role in expanding cerebral vessels and increasing cerebral blood flow.**

Conclusions: **Severe hypercapnia and hypocapnia can cause neonatal brain injury and lung injury. Permissive hypercapnia can increase the survival of neonates with brain injury or respiratory system disease, and lessen the brain injury and lung injury caused by mechanical ventilation. However, the mechanism of permissive hypercapnia needs further exploration to confirm its safety and therapeutic utility.**

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The arterial partial pressure of carbon dioxide ($PaCO_2$) reflects the balance between CO_2 production and consumption. $PaCO_2$ ranges from 4.7 to 6.0 kPa (35–45 mmHg) in healthy neonates.[1] Previous studies have demonstrated that hypercapnia caused by elevation of $PaCO_2$ can have an adverse effect on body internal environment and function. Recently, animal experimental studies and clinical trials show that neonatal hypocapnia (also known as hypocarbia) can increase the incidence of brain injury. Studies have demonstrated the protective role of permissive hypercapnia in neonates with respiratory tract disease and brain injury. This article reviews the current clinical status of hypocapnia and hypercapnia, discusses insights gained to date from basic scientific studies of permissive hypercapnia in neonates.

Hypocapnia

Influence of hypocapnia on the central nervous system

As early as the last century, it was noted that hyperventilation-induced hypocapnia does not decrease the size of the infarcted area after middle cerebral artery occlusion or increase cerebral blood flow at the ischemic site, but only increases the size of the ischemic area. Subsequent trials demonstrated that hypocapnia could aggravate the decrease in energy-rich phosphate, impair ischemic brain metabolism, and worsen cerebral ischemia.[2] The decrease in cerebral blood flow reduces oxygen transport, raises nervous excitation, and limits cerebral metabolism, which further limits oxygen transport. Ohyu et al[3] suggested that hypocapnia under hypotension might cause neuronal cell death in the hippocampus of the neonatal rabbit. Not only ischemia but also metabolic changes induced by hypocapnia might contribute to this damage to apoptotic neuronal cells.

Alkali poisoning of cerebrospinal fluid is the main adverse effect of hypocapnia on the nervous system.

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As an important component of the HCO_3^-/H_2CO_3 buffer system of extracellular fluid, CO_2 changes firstly alter pH, and initiate cerebral vessel contraction and reduce cerebral blood flow through NO, prostanoid, potassium channels, and intracellular Ca^{2+}. It has been reported[4] that during end tidal CO_2 changes, brain tissue oxygen tension ($PbrO_2$) is linearly correlated with intracranial blood flow, and $PbrO_2$ is correlated with end tidal CO_2 ($PbrO_2$ >60 or <20 mmHg). In addition, it was found that cerebral hypoxic events can be reduced significantly by increasing cerebral perfusion pressure as required.[5]

Hypocapnia is a potential risk factor for periventricular leukomalacia (PVL), cerebral palsy, cognition developmental disorder, and auditory deficits.[6,7] Erickson et al[8] found that the risk of severe intraventricular hemorrhage (IVH)/PVL was significantly increased when $PaCO_2$ was less than 30 mmHg within 48 hours after birth. There was also an association between the duration of hypocapnia and the risk of severe IVH/PVL. Fujimoto et al[9] retrospectively analyzed 167 survivors among very low birth weight infants with a gestational age of less than 35 weeks. The results showed that the incidence of cystic PVL in infants with and without hypocapnia was 23% and 5%, respectively. Okumura et al[10] also found that hypocapnia was associated with PVL because the time-averaged CO_2 index was larger and the time-averaged $PaCO_2$ lower in infants with PVL (n=26) than in those with normal development (n=26).

Recent studies suggested that hypocapnia during the first 2 hours of life adds to the risk of brain injury after intrapartum asphyxia.[11] In an observational study[12] performed in a large cohort of premature delivery with ischemia anoxic encephalopathy after asphyxia, born between 1985 and 1995, the mortality and incidence of severe cerebral palsy, blindness, deafness and hypoevolutism in infants were significantly increased. In addition, 34 infants who had a diagnosis of severe persistent pulmonary hypertension at birth were treated by hyperventilation or maintenance of $PaCO_2$ >50 mmHg.[13] The results showed that, among the infants treated by hyperventilation, physical development delay and severe neurologic abnormalities were highly correlated with the duration of hyperventilation, and the incidence of sensorineural hearing loss was the highest in severe neurologic abnormalities. In infants treated with maintenance of $PaCO_2$ >50 mmHg, however, none had sensorineural hearing loss, indicating that sensorineural hearing loss is associated with hypocapnia ($PaCO_2$ <25 mmHg). A retrospective study[7] has shown a strong association between $PaCO_2$ levels less than 30 mmHg and an increased incidence of cystic PVL and cerebral palsy in preterm infants. To examine the risk of disabling cerebral palsy (DCP) in mechanically ventilated very low birth weight (VLBW) infants in relation to hypocapnia and other ventilation-related variables, Collins et al[14] conducted a population-based prospective cohort study of 1105 newborns with birth weights of 500-2000 g. Among 902 survivors to age of 2 years, 657 had neurodevelopmental assessments at age of 2 years and records of blood gas measurements in the first week of life. DCP was subsequently diagnosed in 2.3% of the 257 unventilated newborns, in 9.4% of the 320 ventilated newborns without exposure to unusual levels of hypocapnia, and in 27.5% of the 80 ventilated infants with exposure to significant hypocapnia. The strong association with ventilation and hypocapnia persisted after adjustment of gestational age and other possible risk factors for cerebral palsy. Researchers recommend that neonatologists should avoid arterial PCO_2 levels being less than 35 mmHg and arterial PCO_2 levels greater than 60 mmHg whenever possible in ventilated low birth weight infants. There is extensive, albeit retrospective, evidence that hypocapnia in premature infants is associated with poor neurodevelopmental outcome, including PVL, IVH, and cerebral palsy,[14-16] possibly due to cerebral vasoconstriction, decreased cerebral blood flow (CBF), and decreased cerebral oxygen delivery. Therefore, prevention of hypocapnia must also be a primary objective in the management of these infants.

Effect of hypocapnia on the respiratory system

In the past, neonatal respiratory failure was thought to be associated with pulmonary artery hypertension, right-left shunt, and severe hypoxemia. In the treatment of infants with pulmonary artery hypertension by hyperventilation to maintain $PaCO_2$ levels at 25-30 mmHg, the pulmonary arterial pressure was significantly decreased and the right-left shunt was reversed, indicating that hyperventilation could lessen pulmonary artery hypertension. A breathing machine with high-frequency ventilation that can decrease pulmonary arterial resistance and improve general oxygenation of circulation was recommended to treat neonatal persistent pulmonary artery hypertension and congenital diaphragmatic hernia. An experimental study suggested that after a prolonged ventilation of neonatal rabbits for 3 hours, bronchial spasm, airway pressure, and microvascular permeability were elevated, but lung compliance was reduced. These results indicated that hypocapnia worsens the acute lung injury following ischemia-reperfusion. Moreover, the degree of lung injury was proportional to the degree of hypocapnic alkalosis.[17]

Hypercapnia

The influence of hypercapnia on neonates depends on the degree and speed of $PaCO_2$ elevation, hypoxia or ischemia condition, and intracranial disease or

other complications. Generally, the body has good compensation for and tolerance of acute hypercapnia or slowly elevated $PaCO_2$. Many studies have suggested that acute hypercapnia with $PaCO_2$ <10.67 kPa (80 mmHg) and pH >7.15 can hardly damage the body, and that the body has good compensation for and tolerance of respiratory acidosis. When saturation of blood oxygen is normal, slow elevation of $PaCO_2$ to 10.0–14.67 kPa (75-110 mmHg) does not result in noticeable clinical symptoms,[2] and even has some benefits, because this elevation increases gangliated nerve excitation, produces catecholamine, and expands peripheral vessels to improve blood circulation. Mild intracellular acidosis can even protect hypoxic cells.[18] However, continuous $PaCO_2$ elevation can lead to organ dysfunction. Hypoxia/ischemia and hypercapnia have an additive effect on body injury. Neonate and preterm infant cerebral vessels are more sensitive to $PaCO_2$ elevation (vessel expanding) than to $PaCO_2$ decrease (vessel contraction). Rapid elevation of $PaCO_2$ to 12.0–14.67 kPa (90–110 mmHg) can induce consciousness alterations, cataphora, and hyperspasmia.[19] Obvious $PaCO_2$ elevation leads to an increase in blood brain barrier permeability, cerebral interstitial edema, an increase in CBF, CBF autoregulation loss, and intracranial hypertension, sometimes even intracraninal hemorrhage. If the $PaCO_2$ elevation is complicated by tissue ischemia, intracellular acidosis can enhance brain cell metabolism. In particular, in the presence of reperfusion injury, it can stimulate oxygen free radical production and worsen tissue and cell damage.[18,20] Hypercapnia alters neuronal energy metabolism, increases phosphorylation of transcription factors, and increases the expression of apoptotic proteins in the cerebral cortex of newborn piglets; therefore, it may be deleterious to the newborn brain.[21] It is reported that hypercapnia in very low birth weight infants during the first 3 days of life is associated with severe IVH.[22] In addition, a retrospective review of clinical and blood gas data from 849 infants with birth weights of 401 to 1250 g, obtained during the first 4 postnatal days, also suggested both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe IVH in preterm infants, so it may be prudent to avoid extreme hypocapnia and hypercapnia during the period of risk for IVH.[23] When the cerebral vessels of neonates and preterm infants are dilated because of hypercapnia, deliberately reducing $PaCO_2$ by hyperventilation cannot relieve the vascular dilation.[2] Severe hypercapnia can inhibit the myocardial contractile force, expand vessels leading to blood pressure decrease, and stimulate gangliated nerve excitation, resulting in arrhythmia. Hypoxia and hypercapnia can induce pulmonary vasoconstriction and increase in pulmonary circulation resistance, thus leading to pulmonary arterial hypertension, cardiac ejection fraction reduction, and worsening of cerebral functional lesion.[24,25] Acute hypercapnia can reduce skeletal muscle contraction, especially diaphragmatic muscle contraction, and exhaust respiratory muscles. In contrast, chronic hypercapnia leads to an increase in adrenal medulla secretion and production of adrenocorticotrophic hormone, aldosterone and antidiuretic hormone.

Permissive hypercapnia

Recently, mechanical ventilation has been widely used as a new medical technique to improve newborn survival. However, ventilation is commonly used to inhibit hypercapnia by high ventilation and high frequency, which causes barotraumas such as over-distension of normally ventilated lung alveoli, lung interstitial emphysema, and systemic gas embolism. In addition, long-term complications, including bronchopulmonary dysplasia, chronic pulmonary disease and neurodevelopmental delay, affect the prognosis of infant patients. Considering the adverse effects of traditional ventilation and our current understanding of the pathology and physiology of the respiratory system, permissive hypercapnia is used clinically as a novel ventilatory therapy. The term "permissive hypercapnia" defines a ventilatory strategy for acute respiratory failure, in which the lungs are ventilated with a low inspiratory volume and pressure.[26] The aim of permissive hypercapnia is to minimize lung damage during mechanical ventilation. The small tidal volume ventilation reduces peak inspiratory pressure and mean airway pressure, and minimizes the incidence of air leaks and the effect of mechanical ventilation on returned blood volume and cardiac output.

Permissive hypercapnia and diseases of the respiratory system

Darioli and Perret[27] reported in 1984 that controlled mechanical ventilation was performed to maintain $PaCO_2$ at 90 mmHg to treat severe acute asthma and the effect was favorable. Subsequent studies also suggested that, in the treatment of some respiratory tract diseases, for instance, acute respiratory distress syndrome, CO_2 elevation to a certain extent can decrease complications and improve survival rate. Researchers treated newborns with persistent pulmonary hypertension or congenital septation by elevating $PaCO_2$ to 60 mmHg, and found that the newborns were tolerant of the treatment, with no adverse effects.[28] A recent study has demonstrated that CO_2 elevation to some extent can protect the lung from ischemia/reperfusion injury.[28] Trials of animals with acute lung injury showed that lung interstitial edema and cardiac load in a hypercapnic group were

significantly relieved compared with a high ventilation group, indicating that hypercapnia could improve acute pulmonary hemorrhage.[29] Also the measurements of lung mechanical, blood gas and pathological changes in non-CO_2 ventilation, CO_2 ventilation, and control groups indicated that hypercapnia improved index of lung mechanics, elevation of attenuated peak airway pressure, decrease of dynamic compliance, and protein content in bronchoalveolar lavage fluid, a lung permeability index.[30] All of the above-mentioned results suggest that permissive hypercapnia can improve the lung injury caused by diseases of the respiratory system.

Traditional mechanical ventilation often causes ventilator-related lung injury, and prolongs the course of disease and oxygen therapy. In VLBW and ultralow birth weight infants, the incidence of ventilator-related lung injury is 13%–35%.[31] Permissive hypercapnia may help reduce mechanical ventilation-induced lung injury and possibly reduce bronchopulmonary dysplasia.[32] In two trials involving 269 newborn infants,[33] there was no evidence that permissive hypercapnia reduced the incidence of death or chronic lung disease at 36 weeks, intraventricular hemorrhage grade 3 or 4 or periventricular leukomalacia, and one trial reported that permissive hypercapnia reduced the incidence of chronic lung disease in the 501-750 g subgroups. The potential for hypercapnia to contribute to the beneficial effects of protective lung ventilatory strategies is clear from experimental studies. However, the optimal ventilatory strategy and the precise contribution of hypercapnia to this strategy remain unclear. A clearer understanding of its effects and mechanisms of action is essential for determining the safety and therapeutic utility of hypercapnia in protective lung ventilatory strategies.[25]

Permissive hypercapnia and diseases of the central nervous system

Permissive hypercapnia can reduce assisted ventilation-induced lung injury and protect against ventilation-induced brain injury. A clinical study[34] suggested that hypoxemia and acute hypercapnia ($PaCO_2$ 68 mmHg) allows a 30% reduction of cerebral oxygen consumption to occur, and that neuronal nitric oxide synthase (nNOS)-derived nitric oxide plays a permissive role in the regulation of CBF and cerebral vasodilation response to hypercapnia.

$PaCO_2$ rapid changes have a great influence on CBF. At moderate hypercapnia, a 1 mmHg increase in $PaCO_2$ will induce a 6% increase in CBF,[35] and this change may reach the peak within 5–15 minutes. Monitoring of mean cerebral blood flow velocity (mCBFv), $PaCO_2$, and mean arterial blood pressure (MABP) from 43 ventilated VLBW infants during the first week of life showed that when $PaCO_2$ >45 mmHg, mCBFv is increased with increasing $PaCO_2$, suggesting that the progressive loss of cerebral autoregulation and impaired autoregulation during this period may be associated with increased vulnerability to brain injury.[20]

Although traditional hyperventilation is common, about 36% of board-certified neurosurgeons and almost 50% of emergency physicians routinely use prophylactic hyperventilation in patients with severe traumatic brain injury in the Unitied States.[2] However, more surveys and experimental studies show that permissive hypercapnia is a more scientific and efficient therapy, because it can avoid airway hypertension-induced barotraumas and circulatory disorders, while ensuring proper gas exchange to maintain body tolerance.

By targeting mild to moderate hypercapnia during ventilation of premature infants, permissive hypercapnia may be neuroprotective by avoidance of accidental hypocapnia,[36] and it should be noted that the pursuit of permissive hypercapnia should not be at the expense of decreased lung expansion, i.e., an adequate positive end-expiratory pressure is essential. On the other hand, inadvertent hypercapnia may result from this method, and hypercapnia has been associated with IVH.[37-39] In fact, in the initial pilot trial of permissive hypercapnia in premature infants, many infants in the hypercapnic group had maximum $PaCO_2$>55 mmHg, perhaps out of the traditional "safe" range of hypercapnia.[40,41]

In conclusion, permissive hypercapnia as a novel protective ventilation therapy may improve the survival rate of neonates with brain injury or respiratory tract diseases to some extent. However, a large sample study needs to be conducted to assess its clinical application. During permissive hypercapnia treatment, how to select the appropriate ventilatory index, and whether or not permissive hypercapnia can worsen cerebral edema and the potential risk of intracranial hypertension still need further investigation.

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