REVIEW

The role of carbon dioxide in acute brain injury

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Abstract

Carbon dioxide is a common gas in the air which has been widely used in medical treatment. A carbon dioxide molecule consists of two oxygen atoms and one carbon atom through a covalent bond. In the body, carbon dioxide reacts with water to produce carbonic acid. In healthy people, carbon dioxide is maintained within a narrow range (35–45 mmHg) by physiological mechanisms. The role of hypocapnia (partial pressure of carbon dioxide < 35 mmHg) and hypercapnia (partial pressure of carbon dioxide > 45 mmHg) in the nervous system is intricate. Past researches mainly focus on the effect of hypocapnia to nerve protection. Nevertheless, Hypercapnia seems to play an important role in neuroprotection. The mechanisms of hypocapnia and hypercapnia in the nervous system deserve our attention. The purpose of this review is to summarize the effect of hypocapnia and hypercapnia in stroke and traumatic brain injury.

Key words: carbon dioxide; hypercapnia; hypocapnia; intracranial pressure; nervous system; neuroprotection; stroke; traumatic brain injury

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Introduction

Carbon dioxide (CO_2) is a common greenhouse gas in the air. A carbon dioxide molecule consists of two oxygen atoms and one carbon atom through a covalent bond. It is a colorless, odorless, non-flammable gas at room temperature. It is denser than air, slightly soluble in water, and reacts with water to form carbonic acid.[1] At the beginning of the 17th century, Belgian chemist Van Helmont discovered carbon dioxide when he was testing by-products of charcoal combustion and fermentation. CO_2 is widely used in various aspects of life due to its unique physicochemical properties. CO_2 is abundant in nature and forms part of the atmosphere. CO_2 is also contained in some natural gas or oilfield associated gas and in ore formed by carbonates. The carbon dioxide content in the atmosphere is 0.03–0.04% (volume ratio), and the total volume is about 2.75×10^{12} tons. It is mainly caused by the burning of carbonaceous material and animal metabolism. CO_2 is a waste product of aerobic cellular. In healthy people, carbon dioxide is maintained within a narrow range (35–45 mmHg) by physiological mechanisms.[2] Partial pressure of carbon dioxide ($PaCO_2$) represents the balance between carbon dioxide production and elimination.[2]

Acute Brain Injury

Stroke is an acute cerebrovascular disease including ischemic stroke and hemorrhagic stroke.[3] The incidence of ischemic stroke is higher than hemorrhagic stroke, accounting for 60% to 70% of the total number of stroke patients.[4] Stroke is characterized by fast progression, high mortality and high morbidity.[5] As there has been a lack of effective treatments, prevention is currently the best measure, and hypertension is an important and controllable risk factor for stroke. The most common symptom of stroke is sudden weakness on one side of the face, arms, or legs, faintly faint, unconscious.[6]

Traumatic brain injury (TBI) is a complex pathophysiological process, often resulting in death or long-term disability. TBI has become a major public health problem worldwide. Brain damage is the most common cause of death in patients with out-of-hospital cardiac arrest.[7]

Carbon Dioxide in Stroke

CO_2 is a waste product of aerobic cellular. In healthy people, carbon dioxide is maintained within a narrow range (35–45 mmHg) by physiological mechanisms. $PaCO_2$ represents the balance between carbon dioxide production and elimination. CO_2 is a fat-soluble small molecular gas that has a strong diffusion capacity and can cross the blood-brain barrier. Whether carbon dioxide has a neuroprotective effect is still a question worth discussing. Regulation of $PaCO_2$ and changes in pH can alter cerebral blood flow (CBF) by affecting arterial vascular tone. Disorder of $PaCO_2$ are thought to aggravate clinical outcomes after multiple forms of brain injury by altering cerebral blood flow (CBF) and increasing cerebral ischemia.[8] It is generally believed that the brain tissue cannot be compressed and its volume is hardly changed, and the regulation effect on intracranial pressure (ICP) is very small. Variation of ICP mainly depends on the regulation of cerebrospinal fluid and CBF. Hypocapnia reduces CBF and cerebral blood vessel volume by contracting intracranial arteries, which results in reduction of ICP. However, hypocapnia does not directly reduce ICP by reducing blood vessel volume but indirectly reduces blood vessel volume by decreasing CBF.[9]

Hypocapnia

CO_2 is a vasodilator, and low carbon dioxide is thought to cause cerebral vasoconstriction.[10] Historically, inducible hypocapnia has been used to treat elevated ICP frequently seen in patients with brain injury. Despite these findings, hypocapnia is still

associated with adverse clinical outcomes in various forms of brain injury. CBF inhibition may exacerbate ischemia during acute brain injury and may even cause irreversible infarction of brain tissue. In patients with TBI, hypocapnia is often used to control ICP.[11] But this effect cannot be sustained and chronic hypocapnia increases the risk of mortality and severe disability in TBI patients.[12] The oxyhemoglobin dissociation curve shifts to the left due to respiratory alkalosis associated with hypocapnia, reducing oxygen delivery to the brain. The imbalance of supply and demand of oxygen in hypocapnia eventually increases the risk of cerebral ischemia. In TBI patients, elevated ICP is usually caused by bleeding and edema of brain tissue. Induced hypocapnia can cause further damage to damaged brain.[13] In neurosurgery, hypocapnia is generally achieved by hyperventilation when elevated ICP is expected.

Hypercapnia

Increased cerebral blood volume due to hypercapnia may have an adverse effect on ICP in patients with TBI. Hypercapnia may improve CBF through cerebral vasodilation, but it may also lead to brain edema and increased ICP. Hypercapnia causes the oxyhemoglobin dissociation curve to shift to the right, reducing systemic vascular resistance and increasing tissue oxygen availability.[14] Increased ICP not only leads to a decrease of CBF in the ischemic region, but also causes an increased risk of cerebral hemorrhage in stroke. Permissive hypercapnia has an effect on neuroethology, structural histology, neuronal apoptosis and cerebral edema. Mild and moderate increases in carbon dioxide levels ($PaCO_2$ 60–100 mmHg) have neuroprotective effects against cerebral ischemia/reperfusion injury and this protective effect may be related to the influence of apoptosis-regulating proteins.[15]

Mechanical Ventilation

Mechanical ventilation is based on the help of a ventilator to maintain airway patency, improve ventilation and oxygenation, and prevent hypoxia and carbon dioxide accumulation in the body, so that the body can avoid respiratory failure due to the underlying disease.[16] Mechanical ventilation is a type of ventilation that uses mechanical devices to replace, control, or change autonomous breathing movements. In the days of the Roman Empire, the famous doctor Galen had made such records: If you blow through the trachea through the reeds of the dead animal's throat, you will find that the animal's lungs can reach maximum expansion. In 1774, Tossach successfully used mouth-to-mouth breathing to successfully resuscitate a patient.[17] Sprinter Dalziel first produced a negative pressure breathing machine in 1832.[18] Brain injury is one of the most common causes of mechanical ventilation in critically ill patients. The effect of $PaCO_2$ management on the clinical efficacy of patients with brain injury requiring mechanical ventilation is not clear. The regulation of $PaCO_2$ by mechanical ventilation is a routine method of treating various forms of brain injury.[19] No study suggests that there is an exact functional relationship between $PaCO_2$ and ICP. In the case of persistent hypocapnia, the cerebrospinal fluid will act as a buffer which makes CBF to be normal.[20] Blood lactate and lactate/pyruvate levels were positively correlated with ICP, and ICP reduction was more pronounced at 24 to 36 hours after severe head trauma than at 3 to 4 days.[21,22] With prolonged ventilation, hyperventilation does not reduce mortality and morbidity in patients with TBI.[23] On the one hand, hyperventilation causes a decrease in CBF while reducing ICP, which may lead to ischemic cerebral infarction.[24] On the other hand, if the primary disease is not cleared in time, cerebral edema will gradually increase, and ICP will rise further.[13] Although the role of hyperventilation in reducing ICP is clear, its timeliness is not yet clear. Hyperventilation can only be used as an aid to reduce ICP for a short period of time. Clinical and basic research on the relationship between mechanical ventilation and ICP is in the ascendant, but the relationship between them is intricate. Only by fully understanding the dialectical relationship between mechanical ventilation and brain function can we avoid the misconduct in the clinical work.

Experiment Research

Hypercapnia increases the grave of hypoxic brain damage in neonatal rats.[25] Hyperbaric artery carbon dioxide pressure aggravates cerebral ischemia injury. Mild hypercapnia due to carbon dioxide inhalation can reduce brain injury, while $PaCO_2$ over 65 mmHg increases the risk of cerebral hemorrhage. In cerebral ischemia, moderate hypercapnia improves neurological dysfunction and severe hypercapnia increases brain edema and aggravated brain damage.[25] Inhalation of 6% CO_2 results in persistent neuroprotection in neonatal hypoxic rats. There is evidence that mild-to-moderate hypercapnia may have a neuroprotective effect following cerebral ischemia, whereas severe hypercapnia may exacerbate neuronal damage.[2] We analyze several recent experimental studies related to this gas for stroke treatment in this paper (**Table 1**), and summarize the outcomes.

Mechanisms of the Neuroprotection of Carbon Dioxide

First, hypercapnia can inhibit the activation of caspase-3 and promote the survival of neurons.[33] Caspase-3 plays an irreplaceable role in apoptosis, which is a key step in the development of apoptosis and a common pathway for all apoptotic signaling.[34] People already know that there are at least two ways of cell death, namely, cell necrosis and apoptosis. Apoptosis is autonomously ordered death of cells controlled by genes. Apoptosis plays a role in many pathological and physiological processes of the adult organism's nervous system, which has important biological significance. Unlike cell necrosis, apoptosis is not a passive process but an active process. In the process of apoptosis, activation of the caspase cascade is a critical phenomenon. Caspase-3, which is an important protease in the process of apoptosis, is the only way for the cascade of apoptosis proteases. It has been demonstrated that caspase-3 activation is associated with neuronal apoptosis after multiple types of injury.[35] There is almost no activated caspase-3 in the normal human brain, and caspase-3 is activated in a short time after acute injury and maintained for a while.[36] After acute brain injury, cytochrome C, which is associated with apoptotic protease activation factor, is released from the mitochondrial membrane to the

Table 1: The neuroprotective effects of carbon dioxide (CO_2) in stroke

Study	Model	Main results	Species
Yokoyama et al.[26]	SAH	Both the maximum and minimum $PaCO_2$ levels during intensive care unit management in patients with SAH were significantly associated with unfavorable neurological outcomes.	Human
Vannucci et al.[20]	MCAO	Mild hypercapnia (~54 mmHg induced by 6% CO_2 inhalation in immature rats) preserved cerebral blood flow during hypoxia-ischemia, improved oxidative metabolism and inhibited glutamate secretion.	Rats
Miller et al.[27] Nakagawa et al.[28]	MCAO	Mild hypercapnia ($PaCO_2$ of 45–70 mmHg) hastens the post-ischemia recovery of cortical electrical activity.	Rats
Vannucci et al.[29]	MCAO	In immature hypoxic-ischemic rats, exposure to 15% CO_2 (mean $PaCO_2$ of 100 mmHg) induced more brain damage than did exposure to lower CO_2 concentrations.	Rats
Katsura et al.[30] Ekholm et al.[31]	MCAO	Severe hypercapnia may aggravate neuronal injury by inducing marked extra- and intra-cellular acidosis and/or impaired cell calcium hemostasis.	Rats
Paljärvi et al.[32]	MCAO	Short-term, moderate hypercapnia ($PaCO_2$ of 150 mmHg for 45 min) has no effect on neuronal ultrastructures in anesthetized rats, severe hypercapnia ($PaCO_2$ of 300 mmHg) results in the coarsening of nuclear chromatin, mitochondrial swelling and disruption of polyribosomes.	Rats

Note: MCAO: Middle cerebral artery occlusion; $PaCO_2$: partial pressure of carbon dioxide; SAH: subarachnoid hemorrhage.

cytoplasm to degrade caspase-3 precursors.[37] Increased expression of caspase-3 after brain injury causes neuronal apoptosis. Inhibition of caspase-3 can reduce neuronal apoptosis. In the current research, permissive hypercapnia can reduce terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling-positive neurons and have a favorable modulatory effect on apoptosis-regulating proteins.

Second, hypercapnia reduces glutamate expression after brain injury.[38] N-methyl-D-aspartic acid (NMDA) receptors are highly excitatory amino acid receptors currently under study. The NMDA receptor consists of NR1, NR2, and NR3 subunits, and different subunits constitute different functions of the NMDA receptor.[39] Excitatory amino acid increases obviously during cerebral ischemia and hypoxia, and glutamate is the main excitatory amino acid in the brain.[40] Glutamate is the most abundant and important amino acid in the central nervous system which participates both in synaptic transmission and maintains normal physiological functions of nerve cells, under normal conditions, glutamate release, uptake, and reabsorption maintain a dynamic equilibrium.[41] Large accumulation of glutamate after brain injury aggravates brain damage. Glutamate plays a key role in neuronal damage caused by brain injury through NMDA receptors. When the NMDA receptor is activated, a large number of calcium influx. Moreover, increased calcium influx can further promote glutamate release.[42] The increase of Ca^{2+} influx is considered to be the main cause of neuronal damage. Ca^{2+} overload is a major factor in brain injury.[43]

Conclusion

Hypocapnia, often used to control ICP, is thought to cause cerebral vasoconstriction. But this effect cannot be sustained and chronic hypocapnia increases the risk of mortality and severe disability in TBI patients. Hypercapnia may improve CBF through cerebral vasodilation. Specifically, hypocapnia and severe hypercapnia exacerbate brain injury, while mild hypercapnia has a protective effect. Current research shows that permissive hypercapnia has a good therapeutic effect in cerebral ischemia. However, the exact mechanism by which hypercapnia reduces brain injury is not yet clear. There is a lot of work to be done before fully understanding the different effects of hypercapnia and acidosis. Further experimental and clinical studies are needed to elucidate the neuroprotective effects of hypercapnia.

Author contributions
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Conflicts of interest
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