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. Partial pressure of carbon dioxide (PaCO₂) represents the balance between carbon dioxide production and elimination. Hypercapnia (partial pressure of carbon dioxide > 45 mmHg) by physiological mechanisms. PaCO₂ represents the balance between carbon dioxide production and elimination. 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; hypocapnia; hypercapnia; intracranial pressure; nervous system; neuroprotection; stroke; traumatic brain injury

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INTRODUCTION
Carbon dioxide (CO₂) 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. 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. CO₂ is widely used in various aspects of life due to its unique physicochemical properties. CO₂ is abundant in nature and forms part of the atmosphere. CO₂ 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 × 10¹² tons. It is mainly caused by the burning of carbonaceous material and animal metabolism. CO₂ is a waste product of aerobic cellular. In healthy people, carbon dioxide is maintained within a narrow range (35–45 mmHg) by physiological mechanisms. Partial pressure of carbon dioxide (PaCO₂) represents the balance between carbon dioxide production and elimination.

ACUTE BRAIN INJURY
Stroke is an acute cerebrovascular disease including ischemic stroke and hemorrhagic stroke. The incidence of ischemic stroke is higher than hemorrhagic stroke, accounting for 60% to 70% of the total number of stroke patients. Stroke is characterized by fast progression, high mortality and high morbidity. 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.

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.

CARBON DIOXIDE IN STROKE
CO₂ is a waste product of aerobic cellular. In healthy people, carbon dioxide is maintained within a narrow range (35–45 mmHg) by physiological mechanisms. PaCO₂ represents the balance between carbon dioxide production and elimination. CO₂ 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 PaCO₂ and changes in pH can alter cerebral blood flow (CBF) by affecting arterial vascular tone. Disorder of PaCO₂ are thought to aggravate clinical outcomes after multiple forms of brain injury by altering cerebral blood flow (CBF) and increasing cerebral ischemia. 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.

HYPOCAPNIA
CO₂ is a vasodilator, and low carbon dioxide is thought to cause cerebral vasoconstriction. 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.13 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 vasodilatation, 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 neurochemistry, structural histology, neuronal apoptosis and cerebral edema. Mild and moderate increases in carbon dioxide levels (PaCO2, 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 PaCO2 management on the clinical efficacy of patients with brain injury requiring mechanical ventilation is not clear. The regulation of PaCO2 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 PaCO2 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 PaCO2 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.26 Inhalation of 6% CO2 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.26 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.27 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 proteinases. It has been demonstrated that caspase-3 activation is associated with neuronal apoptosis after multiple types of injury.28 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.29 After acute brain injury, cytochrome C, which is associated with apoptotic protease activation factor, is released from the mitochondrial membrane to the
cytoplasm to degrade caspase-3 precursors. 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. 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. Excitatory amino acid increases obviously during cerebral ischemia and hypoxia, and glutamate is the main excitatory amino acid in the brain. 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. 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. 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.

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.

REFERENCES

1. Sakurai A, Ihara S, Tagami R, et al. Parameters influencing brain oxygen measurement by regional oxygen saturation in postcardiac arrest patients with targeted temperature management. Ther Hypothermia Temp Manag. 2019. doi:10.1089/ther.2019.0032.
2. Akça O. Optimizing the intraoperative management of carbon dioxide concentration. Curr Opin Anaesthesiol. 2006;19:19-25.
3. Chang QY, Lin YW, Hsieh CL. Acupuncture and neuroregeneration in ischemic stroke. Neural Regen Res. 2018;13:573-583.
4. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. Circulation. 2011;123:e18-209.
5. Rolfs A, Fazekas F, Grittner U, et al. Acute cerebrovascular disease in the young: the stroke in young fabry patients study. Stroke. 2013;44:340-349.
6. Pucciarelli G, Vellone E, Savini S, et al. Roles of changing physical function and caregiver burden on quality of life in stroke: a longitudinal dyadic analysis. Stroke. 2017;48:733-739.
7. Wu J, He J, Tian X, Zhong J, Li H, Sun X. Activation of the hedgehog pathway promotes recovery of neurological function after traumatic brain injury by protecting the neurovascular unit. *Transl Stroke Res.* 2020. doi:10.1007/s12975-019-00771-2.

8. Harrington BA, Thrall SF, Mann LM, Tymko MM, Day TA. The effect of steady-state CO₂ on regional brain blood flow responses to increases in blood pressure via the cold pressor test. *Auton Neurosci.* 2019;222:102581.

9. Akhondi-Asl A, Vonberg FW, Au CC, Tasker RC. Meaning of intracranial pressure-to-blood pressure fisher-transformed Pearson correlation-derived optimal cerebral perfusion pressure: testing empiric utility in a mechanistic model. *Crit Care Med.* 2018;46:e1160-e1166.

10. Lafave HC, Zouboulou SM, James MA, et al. Steady-state cerebral blood flow regulation at altitude: interaction between oxygen and carbon dioxide. *Eur J Appl Physiol.* 2019;119:2529-2544.

11. Aly S, El-Dib M, Lu Z, El Tatawy S, Mohamed M, Aly H. Factors affecting cerebrovascular reactivity to CO₂ in premature infants. *J Perinat Med.* 2019;47:979-985.

12. Bequiri E, Czaszynka M, Lalou AD, et al. Influence of mild-moderate hypocapnia on intracranial pressure slow waves activity in TBI. *Acta Neurochir (Wien).* 2019. doi:10.1007/s00701-019-04118-6.

13. Brandi G, Stocchetti N, Pagunmenta A, Stretti F, Steiger P, Klinzing S. Cerebral metabolism is not affected by moderate hyperventilation in patients with traumatic brain injury. *Crit Care.* 2019;23:45.

14. Mas A, Saura P, Joseph D, et al. Effect of acute moderate changes in PaCO₂ on global hemodynamics and gastric perfusion. *Crit Care Med.* 2000;28:360-365.

15. Howarth C, Sutherland B, Choi HB, et al. A critical role for astrocytes in hypercapnic vasodilation in brain. *J Neurosci.* 2017;37:2403-2411.

16. Jarvis JM, Fink EL. A note on comfort in pediatric critical care: music and mechanical ventilation. *Pediatr Crit Care Med.* 2020;21:105-106.

17. Asai T. History of resuscitation: 3. Development of resuscitation in the mid-18 century-3: artificial respiration. *Masui.* 2017;66:449-455.

18. Somerson SJ, Sicilia MR. Historical perspectives on the development and use of mechanical ventilation. *AANA J.* 1992;60:83-94.

19. Ciotti R, Bouras M, Roquilly A, Asehnouve K, Management and weaning from mechanical ventilation in neurologic patients. *Ann Trans Med.* 2018;6:381.

20. Vannucci RC, Brucklacher RM, Vannucci SJ. Effect of carbon dioxide on cerebral metabolism during hypoxia-ischemia in the immature rat. *Pediatr Res.* 1997;42:24-29.

21. Putzer G, Braun P, Martini J, et al. Effects of head-up vs. supine CPR on cerebral oxygenation and cerebral metabolisation - a prospective, randomized porcine study. *Resuscitation.* 2018;128:51-55.

22. Nyholm L, Howells T, Lewin A, Hilleder L, Enblad P. The influence of hyperthermia on intracranial pressure, cerebral oximetry and cerebral metabolism in traumatic brain injury. *Ups J Med Sci.* 2017;122:177-184.

23. Svedung Wettervik T, Howells T, Hilleder L, et al. Mild hyperventilation in traumatic brain injury-relation to cerebral energy metabolism, pressure autoregulation, and clinical outcome. *World Neurosurg.* 2020;133:e567-e575.

24. Ensault P, Roubin J, Cardinales M, et al. Spontaneous hyperventilation in severe traumatic brain injury: incidence and association with poor neurological outcome. *Neurocrit Care.* 2019;30:405-413.

25. Soliz J, Tam R, Kinkead R. Neonatal maternal separation augments carotid body response to hypoxia in adult males but not female rats. *Front Physiol.* 2016;7:432.

26. Yokoyama S, Hifumi T, Okazaki T, et al. Association of abnormal carbon dioxide levels with poor neurological outcomes in aneurysmal subarachnoid hemorrhage: a retrospective observational study. *J Intensive Care.* 2018;6:83.

27. Miller CL, Alexander K, Lampard DG, Brown WA, Griffiths R. Local cerebral blood flow following transient cerebral ischemia. II. Effect of arterial PCO2 on reperfusion following global ischemia. *Stroke.* 1980;11:542-548.

28. Nakagawa Y, Ohitsuka K, Tsuru M, Nakamura N. Effects of mild hypercapnia on somatosensory evoked potentials in experimental cerebral ischemia. *Stroke.* 1984;15:275-278.

29. Vannucci RC, Towfighi J, Brucklacher RM, Vannucci SJ. Effect of extreme hypercapnia on hypoxic-ischemic brain damage in the immature rat. *Pediatr Res.* 2001;49:799-803.

30. Katsura K, Kristián T, Smith ML, Siesjö BK. Acidosis induced by hypercapnia exaggerates ischemic brain damage. *J Cereb Blood Flow Metab.* 1994;14:243-250.

31. Ekholm A, Kristián T, Siesjö BK. Influence of hyperglycemia and of hypercapnia on cellular calcium transients during reversible brain ischemia. *Exp Brain Res.* 1995;104:462-466.

32. Paljärvi L, Söderfeldt B, Kalimo H, Olsson Y, Siesjö BK. The brain in extreme respiratory acidosis. A light- and electron-microscopic study in the rat. *Acta Neurophysiol.* 1982;58:87-94.

33. Xu YJ, Elimban V, Dhalia NS. Suppression of phosphorylated MAPK and caspase 3 by carbon dioxide. *Mol Cell Biochem.* 2017;436:23-28.

34. D’Amelio M, Cavallucci V, Cecconi F. Neuronal caspase-3 signaling: not only cell death. *Cell Death Differ.* 2010;17:1104-1114.

35. Ischiropoulos H. Living and dying with reactive species. Focus on “peroxynitrite induces apoptosis of HL-60 cells by activation of a caspase-3 family protease”. *Am J Physiol.* 1998;274:C853-C854.

36. Xu H, Cao J, Xu J, et al. GATA-4 regulates neuronal apoptosis after intracerebral hemorrhage via the NF-kB/Bax/Caspase-3 pathway both in vivo and in vitro. *Exp Neuro.* 2019;315:21-31.

37. Xie YL, Zhang B, Jing L. MiR-125b blocks Bax/Cytochrome C/Caspase-3 apoptotic signaling pathway in rat models of cerebral ischemia-reperfusion injury by targeting p53. *Neuro Res.* 2018;40:828-837.

38. Van Leuven F, Weyne J, Leusen I. Glutamate and glutamine in the brain of the neonatal rat during hypercapnia. *Arch Int Physiol Biochem.* 1977;85:295-304.

39. Silva NT, Nalivaike E, da Silva LG, Haibara AS. Excitatory amino acid receptors in the dorsomedial hypothalamic area contribute to the chemoreflex tachypneic response. *Respir Physiol Neurobiol.* 2015;212-214:1-8.

40. Nuñez-Figueroed Y, Ramirez-Sánchez J, Hansel G, et al. A novel multi-target ligand (JM-20) protects mitochondrial integrity, inhibits brain excitatory amino acid release and reduces cerebral ischemia injury in vitro and in vivo. *Neuropharmacology.* 2014;85:517-527.

41. Brogi S, Campigiani G, Brindisi M, Butini S. AllostERIC modulation of ionotropic glutamate receptors: an outlook on new therapeutic approaches to treat central nervous system disorders. *ACS Med Chem Lett.* 2019;10:228-236.

42. O’Neill N, McLaughlin C, Komiyama N, Sylantyev S. Biphasic modulation of NMDA receptor function by metabotropic glutamate receptors. *J Neurosci.* 2018;38:9840-9855.

43. Zhang L, Wang H, Zhou X, Mao L, Ding K, Hu Z. Role of mitochondrial calcium uniporter-mediated Ca(2+)- and iron accumulation in traumatic brain injury. *J Cell Mol Med.* 2019;23:2995-3009.

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