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The effect of permissive hypercapnia on cerebral oxygen metabolism and brain function in patients with craniocerebral trauma surgery.

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Abstract

The aim of this study was to evaluate the effects of permissive hypercapnia on Cerebral Oxygen Metabolism (COM) and brain function in patients with craniocerebral trauma surgery. Sixty patients with severe traumatic brain injury were randomly divided into three groups (n=20), hypocapnia (group L, $PaCO_2$ 25-30 mmHg), hypercapnia (group H, $PaCO_2$ 50-55 mmHg), and control (group C, $PaCO_2$ 35-45 mmHg) groups. All patients underwent retrograde jugular vein and radial artery puncturing. The inducing drugs used were midazolam 0.1 mg/kg, sufentanil 0.5 μg/kg, vecuronium 0.1 mg/kg, and propofol 1.5 mg/kg. Blood samples from an artery and vein were extracted to measure the oxygen content at three time points, during cutting of the endocranium (T1), 1 h after the cutting (T2), suturing of the endocranium (T3). We measured the vein ball oxygen content difference ($Ca\text{-}vDO_2$) to observe COM. Glasgow scores were recorded at preoperation and postoperative 24 h and 10 d. Compared with group C, the $Ca\text{-}vDO_2$ of group L and H decreased at T2 and T3 ($P<0.05$); compared with T1, $Ca\text{-}vDO_2$ decreased at T2 and T3 for all patients ($P<0.05$). Glasgow scores of the three groups were not statistically different at preoperation and postoperative 24 h ($P>0.05$). After 10 d, compared with group L, patients with a 3-point score decreased significantly and the 3-8 point patients increased significantly in group H ($P<0.05$); compared with group C, the 3-point score patients decreased significantly in group H ($P<0.05$). Permissive hypercapnia may improve Glasgow scores and prognosis of patients of severe traumatic brain injury without affecting oxygen uptake of brain.

Keywords: Permissive hypercapnia, Craniocerebral trauma, Cerebral oxygen metabolism, Brain function.

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Introduction

Craniocerebral trauma surgery is a major component of the neurosurgical emergency surgeries. For anesthesia of patients with traumatic brain injury or intraoperative encephalocele, generally the partial pressure of carbon dioxide ($PaCO_2$) is reduced using hyperventilation to decrease intracranial pressure to eliminate the acute increase of pressure [1]. Studies have shown that proper hyperventilation can relax the brain during selective operations and improve the outcome [2].

Studies have shown that for patients with brain injury, excessive ventilation is not advisable, as hypocapnia may cause the shrinking of the blood vessels, decrease of Cerebral Blood Flow (CBF), reduction of cerebral perfusion pressure and thus the aggravation of brain tissue damage. It is generally believed that when the $PaCO_2$ is lower than 20 mmHg, the CBF is reduced to a level that can cause ischemia. Thus, oxygen uptake while reducing intracranial pressure during brain surgery requires attention [3].

Recent research has shown that moderate hypercapnia is a more scientific and effective treatment. Numerous studies have shown that acute hypercapnia with $PaCO_2$ less than 80 mmHg and pH value greater than 7.15 is not harmful to the body, due to the compensatory and buffering capacity of the human body for respiratory acidosis. With normal oxygen saturation, a slow rise of 10.0~14.6 kPa (75~110 mmHg) in $PaCO_2$ will not cause obvious clinical symptoms, in fact may be beneficial because it can increase the sympathetic activity, causing a release of catecholamine's, and a direct expansion of peripheral blood vessels to improve blood circulation. Moreover, permissive intracellular acidosis can protect hypoxic cells. During cardiopulmonary bypass, hypoxemia accompanied with mild acute hypercapnia ($PaCO_2$ 68 mmHg) can reduce cerebral oxygen consumption by 30%, while during hypercapnia, the production of nitric oxide induced by neuronal nitric oxide synthase plays an important role in improving the cerebral vasodilation and blood flow [4].

In this study, the impact of $PaCO_2$ on the cerebral metabolic rate for oxygen ($CMRO_2$) in patients with brain injury during surgery was investigated. The hypercapnia approach applied for these patients is completely different from the previous anesthesia ventilation method, which decreases the intracranial pressure through hypocapnia. Instead of low intracranial pressure, the hypercapnia approach focuses on oxygen uptake in the brain. The numerical range of moderate hypercapnia to maintain the desired cerebral oxygen metabolism and brain

function, without increasing surgical difficulties and risks, was observed, in an attempt to provide theoretical support for anesthesia management, thereby improving the level of anesthesia management for patients with craniocerebral injury.

Materials and Methods

General information

Patients with severe craniocerebral injuries (n=60) (Glasgow Coma Score of 3-8 points, as shown in Table 1), with ratings on ASA II-III, aged 40-65 y, weight 50-80 kg, with an expected operation time of 3-4 h were included. Using the random number table method, patients were divided into three groups (n=20) as follows: a hypocapnia (Group L, $PaCO_2$ 25-30 mmHg), hypercapnia (Group H, $PaCO_2$ 50-55 mmHg), and control group (Group C, $PaCO_2$ 35-45 mmHg). This study was approved by the Ethics Committee of Weifang People's Hospital, and all patients and their families signed the informed consent.

Table 1. Glasgow coma scale.

Items	Responses	Scores
Eye opening response	Eyes opening spontaneously	4
	Eye opening to speech	3
	Eye opening in response to pain stimuli	2
	No eye opening	1
Verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
Motor response	Obeys commands	6
	Localizes to pain	5
	Withdrawal to painful stimuli	4
	Abnormal flexion to painful stimuli	3
	Extension to painful stimuli	2
	No motor response	1

Monitoring index

The pressure of the patients was measured through retrograde jugular vein catheterization and radial artery catheterization in the operating room. Mindray T8 monitor (Mindray Company, Shenzhen, China) was employed to monitor invasive blood pressure, heart rate, electrocardiogram, arterial oxygen saturation, end-tidal CO_2 pressure ($PetCO_2$) and bispectral index.

Drugs

Inducing drugs, midazolam 0.1 mg/kg, sufentanil 0.5 mg/kg, vecuronium 0.1 mg/kg, and propofol 1.5 mg/kg were used. After intubation, the anesthesia ventilator was connected for mechanical ventilation, and inhalation of sevoflurane was initiated, with an inhalation concentration of 3% and an oxygen flow rate of 1.5 L/min. Sufentanil and vecuronium were supplied during the surgery to maintain circulatory stability.

Cerebral oxygen metabolism

For the analysis of gases, blood samples were extracted from the radial artery and internal jugular vein at three time points as follows: during the cutting of endocranium (T1), 1 h after the cutting (T2) and during the suturing of endocranium (T3). The oxygen content was measured using the blood gas analyzer. Cerebral arteriovenous oxygen differences ($Ca\text{-}vDO_2$) in patients with craniocerebral injury at each time point was calculated using the Fick formula, to observe the conditions of cerebral oxygen metabolism.

Glasgow scores

Glasgow Coma scores of the patients before surgery, after 24 h of surgery, and 10 d after surgery were recorded.

Statistical analysis

The SPSS 17.0 statistical software was adopted for analysis. All measurement data were represented as mean ± standard deviation ($\bar{x} \pm s$). Analysis of variance was used to compare the different time points in the same group, while analysis of variance and t-tests were used to compare between different groups, and $P<0.05$ was considered as statistically significant.

Results

No statistically significant differences were observed in the general data and surgical features between the patients in the three groups ($P>0.05$, Table 2).

Compared with Group C, the $Ca\text{-}vDO_2$ at T2 and T3 in Groups L and H was significantly reduced ($P<0.05$); compared with T1, $Ca\text{-}vDO_2$ in the three groups were significantly reduced at T2 and T3 ($P<0.05$, Table 3).

There were no statistically significant differences in the scores before surgery and 24 h after surgery between patients in the three groups ($P>0.05$). 10 d after surgery, compared with Group L, patients scoring 3 points were significantly decreased in Group H, while those scoring 3 to 8 points were significantly increased ($P<0.05$); compared with Group C, patients scoring 3 points were significantly decreased in Group H ($P<0.05$, Table 4).

Table 2. *Comparison of general data and surgical features of patients in 3 groups (n=20, $\bar{x} \pm s$).*

Groups	Age (y)	Height (cm)	Weight (kg)	Anesthesia time (min)	Operative time (min)	Bleeding volume (ml)	Infusion volume (ml)
L	55 ± 8	165 ± 6	63 ± 8	200 ± 20	165 ± 24	554 ± 112	3612 ± 122
H	52 ± 12	163 ± 10	65 ± 6	198 ± 28	158 ± 20	542 ± 132	3158 ±1 01
C	56 ± 6	166 ± 8	64 ± 8	202 ± 24	160 ± 18	550 ± 108	3632 ± 110

Note: There was no statistically significant difference in the general data and surgical features between patients in the three groups.

Table 3. *Comparison of Ca-vDO_2 of patients in 3 groups (n=20, $\bar{x} \pm s$).*

Groups	T1 (ml/L)	T2 (ml/L)	T3 (ml/L)
L	50.5 ± 5.4	33.6 ± 4.8*	34.8 ± 4.5*
H	53.6 ± 5.0	34.5 ± 5.0*	32.8 ± 4.6*
C	54.5 ± 5.8	43.5 ± 5.3	42.6 ± 6.0

Note: Compared with Group C, at T2 and T3, Ca-vDO_2 in Groups L and H was significantly reduced (*P<0.05); Compared with T1, Ca-vDO_2 in the three groups were significantly reduced at T2 and T3 (P<0.05).

Table 4. *Glasgow coma scores of patients in 3 groups before surgery, 24 h after surgery and 10 d after surgery.*

	Group L	Group H	Group C
Before surgery			
3 points	9 (45%)	8 (40%)	7 (35%)
3-8 points	10 (50%)	11 (55%)	11 (55%)
8-15 points	1 (5%)	1 (5%)	2 (10%)
24 h after surgery			
3 points	6 (30%)	5 (25%)	6 (30%)
3-8 points	12 (60%)	14 (70%)	12 (60%)
8-15 points	2 (10%)	1 (5%)	2 (10%)
10 d after surgery			
3 points	4 (20%)	2 (10%)*	4 (20%)
3-8 points	13 (65%)	16 (80%)*	14 (70%)
8-15 points	3 (15%)	2 (10%)	2 (10%)

Note: There was no statistically significant difference in the scores before surgery and 24 h after surgery between patients in the three groups (P>0.05). 10 d after surgery, compared with Group L, patients scoring 3 points were significantly decreased in Group H, while patients scoring 3 to 8 points were significantly increased (*P<0.05); Compared with Group C, patients scoring 3 points were significantly decreased in Group H (P<0.05).

Discussion

High blood flow perfusion, a prominent feature of brain tissue, is mainly associated with cerebral perfusion pressure, intracranial pressure, and chemical regulation. In particular, an increase in hypoxia and $PaCO_2$ can lead to increased CBF, and $PaCO_2$ in the range of 25~80 mmHg is most sensitive to the regulation of CBF [5,6]. $PaCO_2$ has important regulatory effects on the CBF. Obrist et al. found that, when $PaCO_2$ changes by 1 mmHg in the abnormal range, CBF can be changed by 3%~4% [7]. Defined as $PaCO_2$<35 mmHg, hyperventilation can decrease $PaCO_2$, shrink cerebral vessels, and decrease intracranial pressure, resulting in a reduced CBF. Cruz et al. demonstrated that hyperventilation maintained at $PaCO_2$ of 21 ± 1.6 mmHg can decrease the intracranial pressure in patients with brain injury, improve cerebral perfusion, and thus promote the uptake of carbohydrate and oxygen and cerebral metabolic balance in the brain tissues [8].

In neurosurgical anesthesia, the intracranial pressure is primarily decreased by reducing $PaCO_2$, *via* the following mechanism: reduced CO_2 causes hypocapnia, increasing the pH value in the surroundings of the cerebral blood vessels; since the small resistance vessels are sensitive to pH changes in the cerebrospinal fluid, the resulting cerebrovascular contraction will reduce CBF and cerebral blood volume, thereby decreasing the intracranial pressure [9].

Randomized clinical trials have shown possible short and long-term side effects of hyperventilation on neurological function. Pilot research using a cortical damage model has indicated that hyperventilation for 5 h after traumatic brain injury could increase apoptosis in the hippocampus CA3 neurons [10]. Another study showed that chronic hyperventilation could increase the concentrations of anaerobic respiration markers (pyruvic acid and lactic acid) and excitotoxic substances (glutamic acid) in the extracellular fluid of brain tissues. Therefore, hypocapnia induced by hyperventilation can lead to cerebrovascular contraction, reduce CBF and cerebral blood volume, and thus lower the intracranial pressure. Intermittent hyperventilation may contribute to temporary increase in intracranial pressure, in the cases of craniocerebral injury, acute nerve damage, and cerebral ischemic stroke, and hence can be used as a life-saving measure for the treatment of cerebral edema and increased intracranial pressure [11]. In selective neurosurgery, proper hyperventilation helps to prevent the rise in intracranial pressure and to improve surgical conditions, although a short-term, appropriate hyperventilation can also cope with the intraoperative acute encephalocele, such lowering effect on the intracranial pressure is only temporary and may rebound after resuming normal ventilation. Prophylactic hyperventilation is currently not recommended for long-term treatment, because it may aggravate brain ischemia, which can be especially crucial in known cases of low CBF conditions, such as severe traumatic brain injury or vascular spasm [12,13].

Current studies show that permissive hypercapnia is a protective strategy recognized and confirmed in recent years and a more scientific and effective treatment. Studies have shown that in animal experiments, maintaining an appropriate arterial hypercapnia will decrease the hypoxia injury of the brain tissue. In this study, therefore, experimental groups with different $PaCO_2$ were designed to observe its influences on the cerebral oxygen metabolism and brain function after surgery.

For anesthesia of patients with severe craniocerebral trauma, $CMRO_2$ of the brain tissue is an important parameter [14]. By monitoring the jugular venous oxygen saturation ($SjvO_2$), the cerebral oxygen supply and demand balance can be comprehensively evaluated, and this method is mainly adopted in early detection of decreased $SjvO_2$ during brain tissue ischemia, hypoxia, decreased intracranial pressure, or increased brain oxygen consumption [15]. After leaving the skull, 80%-90% of the venous return from the brain tissue first collects in the jugular bulb, where there is almost no mixed venous blood from outside the brain. For this reason, the detection and calculation of the radial artery and jugular bulb can reflect the metabolic changes in the brain tissue [16]. The $SjvO_2$ can effectively reflect the global cerebral oxygen supply and demand balance, with 50% of the $SjvO_2$ as the threshold [17]. Studies on patients with brain tumor reported that $SjvO_2$ decreases after hyperventilation, and if low temperature occurs simultaneously, then the $SjvO_2$ of 50% of the patients is less than 50%. A $SjvO_2$ less than 50% can cause transient neurological disorder, disturbance of consciousness, and a slowed down EEG frequency [18,19]. Different $PetCO_2$ can change the $SjvO_2$ by affecting the CBF [20]. As $PetCO_2$ rises, CBF increases, and $SjvO_2$ significantly increases. When $PetCO_2$ is 25 mmHg, $SjvO_2$ drops to 53.7 ± 2.5%, which introduces a risk of ischemia and hypoxia. However, only reflecting the overall metabolism of the ipsilateral hemisphere, $SjvO_2$ cannot exclude ischemia and hypoxia of the contralateral hemisphere ischemia [21]. According to the Fick formula, the cerebral metabolic rate for oxygen can be calculated through the $Ca\text{-}vDO_2$ and CBF, but CBF can be difficult to measure, as it requires fairly complicated equipment. In this study, without measuring CBF, the estimated cerebral metabolic rate for oxygen can be reliably obtained through a cerebral metabolic parameter, that is, $Ca\text{-}vDO_2$. In this study, compared with $Ca\text{-}vDO_2$ at T1, $Ca\text{-}vDO_2$ in the hypercapnia and hypocapnia groups at T2 and T3 was significantly reduced ($P<0.05$), and the difference was statistically significant.

Glasgow Outcome Scale (GOS) is a criterion for neurological function and efficacy evaluation in the acute phase, and can be used for prognosis and treatment effect analysis. In this study, the before and 24 h after surgery GOS scores showed no significant difference ($P>0.05$) between the groups. 10 d after surgery, compared with the control group, the proportion of GOS scores of 3 points was significantly decreased ($P<0.05$) in the hypercapnia group, and the difference was statistically significant. Compared with the hypocapnia group, in the hypercapnia group, the proportion of patients with GOS scores of 3 points was significantly decreased ($P<0.05$), the proportion with 3 to 8 points was significantly increased ($P<0.05$), and the difference was statistically significant. It's possible mechanism may be as follows: Under normal circumstances of oxygen saturation, a slow rise of 75~110 mmHg in $PaCO_2$ will not cause obvious clinical symptoms, in fact may be beneficial, because it can increase sympathetic activity, causing the release of catecholamine's, and a direct expansion of peripheral blood vessels to improve blood circulation. Permissive intracellular acidosis can protect hypoxic cells; the production of nitric oxide induced by neuronal nitric oxide synthase plays an important role in improving the cerebral vasodilation and blood flow [22].

Conclusion

In anesthesia for neurosurgical patients with severe craniocerebral trauma, in the premise of not affecting the oxygen uptake in the brain, a moderate hypercapnia can improve the Glasgow scores and enhance the prognosis of the patients after surgery.

Conflicts of Interest

We have no conflicts of interest.

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