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Role of hypercapnia in brain oxygenation in sleep-disordered breathing

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Review

Abstract. Adaptive mechanisms may diminish the detrimental effects of recurrent nocturnal hypoxia in obstructive sleep apnea (OSA). The potential role of elevated carbon dioxide (CO_2) in improving brain oxygenation in the patients with severe OSA syndrome is discussed. CO_2 increases oxygen uptake by its influence on the regulation of alveolar ventilation and ventilation-perfusion matching, facilitates oxygen delivery to the tissues by changing the affinity of oxygen to hemoglobin, and increases cerebral blood flow by effects on arterial blood pressure and on cerebral vessels. Recent clinical studies show improved brain oxygenation when hypoxia is combined with hypercapnia. Anti-inflammatory and protective against organ injury properties of CO_2 may also have therapeutic importance. These biological effects of hypercapnia may improve brain oxygenation under hypoxic conditions. This may be especially important in patients with severe OSA syndrome.

Key words: adaptation, cerebral blood flow, hypercapnia, hypoxia, neuroprotection, sleep apnea

INTRODUCTION

Patients with obstructive sleep apnea (OSA) syndrome experience recurrent episodes of upper airway obstruction during sleep. Such apneic events (up to several hundred per night) are associated with episodes of hypoxia, and terminate with arousal and strong inspiratory efforts. The arterial oxygen saturation (SaO_2) may intermittently drop by as little as few percent up to more than 50% (Brzecka and Davies 1993). The intermittent hypoxia in OSA syndrome closely mimics what is seen in ischemia-reperfusion injury, where there is restoration of oxygen delivery and/or blood flow to previously hypoxic and/or ischemic tissue. There is attenuated endothelium-dependent vasodilation of resistance vessels in patients with OSA compared with matched normal subjects, caused by an imbalance of endothelium-derived relaxing and contracting factors (Kato et al. 2000). That may contribute to the progression and complications of hypertension and atherosclerosis (Kato et al. 2000). Multiple clinical studies confirm that OSA syndrome exacerbates or leads to numerous adverse cardiovascular consequences, including chronic heart failure and stroke, especially in the patients with severe OSA syndrome (Kiely and McNicholas 2000).

In OSA patients nocturnal increases in arterial carbon dioxide partial pressure ($PaCO_2$) occur as a consequence of sleep disordered breathing (Resta et al. 2000). In some of the OSA patients, especially with coexisting chronic obstructive pulmonary disease (COPD) and/or morbid obesity, chronic alveolar hypoventilation develops, leading to chronic CO_2 retention (Resta et al. 2000). Extremely low levels of SaO_2 during sleep can be observed especially in those OSA patients who developed concomitant chronic alveolar hypoventilation (Brzecka and Davies 1993).

Usually the sleep-related episodes of arterial oxygen desaturation are well tolerated, suggesting that adaptive mechanisms help patients survive even profound episodes of hypoxemia during sleep. One of the mechanisms enabling survival of severe nocturnal hypoxemia in OSA patients is preconditioning, an important phenomenon of increasing tolerance to repetitive hypoxic stimuli (Brzecka 2005). An important question is whether chronic hypercapnia in some patients with OSA syndrome is only an undesirable complication of sleep apnea, or rather is it another mechanism that facilitates survival of severe hypoxic episodes during sleep?

Chronic alveolar hypoventilation resulting in daytime and nocturnal hypercapnia is frequently observed clinically in patients with severe COPD. In general, hypercapnia in patients with COPD is considered as an indicator of poor prognosis compared to normocapnic patients (Costello et al. 1997). However, recent somewhat controversial published data suggest that this might not always be true. Saryal and coauthors (1999) found that COPD patients with chronic hypercapnia had similar 10-year survival rate as patients without chronic hypercapnia. Nizet and others (2005) did not find statistically significant, negative influence of the $PaCO_2$ on the survival rate in the COPD patients. Oswald-Mammosser and others (1995) found that hypercapnia had no prognostic value in the COPD patients receiving long-term oxygen therapy; these authors showed that pulmonary hypertension was the single best predictor of mortality in this group of patients. Park and colleagues (2006) found that hypercapnia at admission is an independent predictor of better survival of COPD patients admitted to the intensive care unit and requiring mechanical ventilation. However, in some patients with COPD the development of hypercapnia – as for example induced by supplemental oxygen administration – constitutes an unintended deleterious effect.

Here, we review selected mechanisms of CO_2 actions that may have beneficial effects on brain oxygenation in OSA and other syndromes characterized by intermittently or chronically impaired breathing.

EFFECTS OF HYPERCAPNIA ON GAS EXCHANGE

Hypercapnia synergistically with hypoxia increases ventilatory drive. Increasing CO_2 level stimulates ventilation with the maximum increase occurring up to 100–150 mmHg after which there is a gradual reduction of ventilation (Potkin and Swenson 1992).

Hypercapnia may also help in improving ventilation/perfusion (V/Q) matching. In the lungs, there are potent mechanisms matching local alveolar ventilation and local blood flow (perfusion) that serve to optimize gas exchange. Hypoxia has a major vasoconstrictive influence. Constriction of pulmonary vasculature in response to hypercapnia is generally weaker (Kregenow and Swenson 2002). In fact CO_2 may act not only as a vasoconstrictor, but also as a vasodilator with the

direction of vasomotor effect of hypercapnia depending on pulmonary arterial pressure. In one study elevations in CO_2 acted as a mild constrictor at normal pulmonary artery pressure but was a vasodilator at increased pulmonary artery pressure (induced e.g. by hypoxia) (Baudouin and Evans 1993). CO_2 might modulate the pulmonary vascular tone secondarily *via* alterations in nitric oxide (NO) release (Yamamoto et al. 2001). NO is a diffusible gas, formed by the enzyme NO synthetase (NOS). In the lung, NOS immunoactivity is localized in airway epithelium and pulmonary vascular endothelium (Kobzik et al. 1993). Increased expression of NO synthetase – and in turn increased NO release -– are induced by the formation of prostaglandins, a process in which K^+ and Ca^{2+} channels are involved (Najarian et al. 2000). Levels of prostaglandins increase in response to hypercapnic acidosis (Willis and Leffler 1999) and the resultant increase in NO acts to attenuate acute hypoxic vasoconstriction. Hypercapnia diminishes the acute hypoxic vasoconstrictor response by increase in NO synthesis and possibly through the other, not fully elucidated mechanisms (Ooi et al. 2000).

In contrast in experiments on buffer-perfused lungs Yamamoto and colleagues (2001) have shown that alveolar hypercapnia, but not intravascular hypercarbia, markedly reduced the levels of the metabolites of NO with subsequent rise in pulmonary arterial pressure, whereas intravascular hypercapnia did not elicit these effects (Yamamoto et al. 2001). The combination of hypercapnia and hypoxia in poorly ventilated alveoli may lead to a decreased NO production, causing an enhancement of local hypoxic vasoconstriction and thereby an improvement of V/Q matching with resulting improvement in gas exchange (Yamamoto et al. 2001). Brogan and others (2004) have shown in animals that the admixture of low concentration (5%) of CO_2 to the inspired air improved the arterial blood oxygenation. Improved oxygenation caused by CO_2 inspired only during the latter half of inspiration was mainly related to improved V/Q matching; systemic respiratory acidosis induced by admitting 5% CO_2 throughout inspiration further improved arterial oxygenation (Brogan et al. 2004). Persisting hypercapnia during sleep (including short periods of increased ventilation between the apneas) may protect against bronchoconstriction caused by hypocapnic hyperventilation (van den Elshout et al. 1991); the elevated $PaCO_2$ also may relax airway smooth muscles (van den Elshout et al. 1991) and improve regional lung ventilation. Similarly, increased collateral ventilation in response to hypercapnia, found in many species (Traystman et al. 1978), might also increase regional ventilation. Elevated CO_2 also increases surface tension-lowering properties of alveolar surfactant leading to increased lung compliance (Wildeboer-Venema 1984). Thus, the effects of CO_2 on the pulmonary vessels, peripheral bronchi, and parenchymal compliance may all improve V/Q matching (Kregenow and Swenson 2002). Hypercapnia may also improve pulmonary gas exchange through its effects on the heart rate. Physiological changes in the heart rate (respiratory sinus arrhythmia) with inspiration and expiration are augmented by hypercapnia. Thus hypercapnia may enhance pulmonary gas exchange efficiency by improving matching pulmonary blood flow with lung volume within each respiratory cycle (Yasuma and Hayano 2004).

In the patients with OSA syndrome, hypercapnia may also influence upper airway muscle tone. CO_2 exposure leads to activation of monoaminergic cells, as well as noradrenaline-, serotonin-, and histamine-containing neurons, which all may modulate respiratory response to hypercapnia. Activation of monoaminergic neurons by an increase in CO_2/H^+ facilitates respiratory related motor discharge, particularly of upper airway dilating muscles (Haxhiu et al. 2001). Therefore breathing at increased CO_2 may prevent obstructive events or reduce their severity.

Increased CO_2 levels during sleep may also prevent the occurrence of central sleep apneas. Decreased levels of CO_2 decreasing respiratory drive may promote central apneas (Bradley and Phillipson 1992). This may be important in patients with coexisting overt or occult cardiac dysfunction, who frequently experience central sleep apneas or Cheyne-Stokes respiration (Nopmaneejumruslers et al. 2005). Any tendency toward central apnea is counteracted by hypercarbia. In fact, inhalation of CO_2 has been used in the treatment of apnea of prematurity. Al-Aif and others (2001) found that inhalation of CO_2 in low (0.5%–1.5%) concentrations in preterm infants with apnea decreased the number and time of apneas, improved oxygenation, and increased ventilation.

EFFECTS OF HYPERCAPNIA ON HEMOGLOBIN OXYGEN AFFINITY

A unique feature of the hemoglobin-oxygen dissociation curve influences the delivery of oxygen to the

tissues. CO_2 is an important regulator for the oxygen affinity of hemoglobin. Hypercapnic acidosis causes a rightward shift of the oxyhemoglobin dissociation curve that leads to improved oxygen delivery. The influence of increased CO_2 tension on facilitation of unloading oxygen to the tissues is known as Bohr effect.

The analogous phenomenon of facilitation of unloading CO_2 from hemoglobin caused by increased oxygen tension is known as Haldane effect. Due to Haldane effect, deoxygenated blood has a higher CO_2 content than oxygenated blood at the same CO_2 level. As a result the changes in pH and PCO_2 are minimized despite transport of large amounts of CO_2. In the brain, where there is a high oxygen uptake and CO_2 release per unit blood flow, the Haldane effect is especially important, as it increases the blood CO_2 combining capacity as a consequence of oxyhemoglobin desaturation. This phenomenon may be beneficial in cases of severe hypercapnia.

HYPERCAPNIA AND CEREBRAL BLOOD FLOW

The autoregulatory mechanisms of the cerebral blood flow (CBF) are extremely important when there is decreased oxygen supply. Hypoxemia combined with hypoperfusion strongly exacerbates ischemic brain damage (Miyamoto and Auer 2000). In humans, as in all mammals, CBF increases in response to acute hypoxia (Severinghaus 2001). The magnitude of the CBF response to hypoxia is dependent on the balance between the hypoxemia-induced cerebral vasodilation and the cerebral vasoconstriction secondary to hypocapnia associated with the increased ventilation (Severinghaus 2001). In case of isocapnia the rise in CBF is in proportion to hypoxia (Ainslie and Poulin 2004). CO_2 is an important vasodilator of cerebral blood vessels (Severinghaus 2001). Concomitant hypoxia and hypercapnia exert an additive effect on CBF. Ainslie and Poulin (2004) have shown that isocapnic hypoxia, reflected by SaO_2 as low as 80% caused a 24% increase in CBF from baseline and hypercapnic hypoxia of the similar level caused 34% increase in CBF.

The mechanisms of the cerebral blood vessels dilation caused by hypercapnia are not fully elucidated and encompass both the direct effects of a high concentrations of molecular CO_2 on vascular smooth muscle cells as well as the effects of endothelial NO production elicited by CO_2 (Iadecola 1992). NO exhibits also a potent antioxidative and neuroprotective action that terminates oxidant stress in the brain by suppressing iron-induced generation of hydroxyl radicals, interrupting the chain reaction of lipid peroxidation, augmenting the antioxidative potency of reduced glutathione and inhibiting cysteine proteases (Chiueh 1999).

Both hypoxia and hypercapnia lead to sympathetic activation. Hypoxia stimulates mainly the peripheral chemoreceptors (located in the carotid and aortic bodies) and hypercapnia stimulates central chemoreceptors (located principally in the ventrolateral medulla and responding to changes in H^+ concentration). The augmentation of the sympathetic tone is important factor increasing arterial blood pressure. Hypercapnia is of greater importance than hypoxia in causing sympathetically induced increase in vascular resistance (Cooper et al. 2005). Thus hypercapnia may also influence CBF through its beneficial effect on arterial blood pressure.

Interestingly, during acute hypertension, hypercapnia protects the blood–brain barrier and decreases the risk of its disruption (Baumbach et al. 1986). Studies performed in cats with 125I-labeled serum albumin have shown that with severe hypertension there is markedly increased permeability of the blood-brain barrier during normocapnia, but not during hypercapnia (Baumbach et al. 1986). In an experiment performed by the same authors in anesthetized cats, measurement of the permeability of the blood-brain barrier using fluorescent dextran have shown that the disruption of the blood-brain barrier during hypertension is decreased by hypercapnia (Baumbach et al. 1986).

BRAIN OXYGENATION DURING HYPERCAPNIA

Oxygen tension in brain tissue ($PbrO_2$) can be measured directly and invasively with Clark-type polarographic probes inserted into the cerebral tissue (Hare et al. 2003, Hemphill et al. 2001, Manley et al. 2000, Poca et al. 2005, van Hulst et al. 2002). The direct measurements of $PbrO_2$ show increased brain oxygenation in hypoxemia with concomitant hypercapnia as compared with hypoxemia alone. In rats, a stepwise increase in cerebral $PbrO_2$ closely fol-

lowed increases in inspired CO_2 (Hare et al. 2003). The relative magnitude of the increase in $PbrO_2$ achieved during hypercapnia was 3-fold higher than that obtained when a comparable increase in arterial oxygen partial pressure (PaO_2) was induced by increasing the percentage of inspired oxygen (Hare et al. 2003). In anesthetized dogs, PbrO2 during hypercapnia ($PaCO_2$ 53 mmHg) increased 20% as compared with normocapnia (Hoffman et al. 2001). A similar influence of CO_2 on $PbrO_2$ was also observed in pigs (Hemphill et al. 2001, Manley et al. 2000, van Hulst et al. 2002). $PbrO_2$ increased proportionally to changes in end-tidal CO_2 concentrations (Hemphill et al. 2001). In the study of van Hulst and colleagues (2002), $PbrO_2$ increased during controlled hypoventilation, resulting in hypercapnia ($PaCO_2$ 90.4 ± 10.4 mmHg), while arterial blood pressure remained constant and intracranial pressure increased. Following a 50% loss of blood produced by controlled hemorrhage, $PbrO_2$ rapidly declined; at this point hyperventilation resulted in a further 56% mean decrease in PbrO2 whereas hypoventilation produced a 166% mean increase in $PbrO_2$ (Manley et al. 2000).

Oxyhemoglobin saturation in cerebral tissue can be measured non-invasively using near-infrared spectroscopy (Poca et al. 2005). This sensitive method allows measurement of the influence of CO_2 on the brain oxygenation (Smielewski et al. 1995). Transcranial cerebral oxygen saturation measurements performed during surgical procedures show higher values (68 ± 9% vs. 55 ± 4%) during hypercapnia than normocapnia without any change in cardiac index (Akca et al. 2003).

In the OSA patients a decrease in cerebral oxyhemoglobin correlates with apnea duration and can be predicted on the basis of mean and minimal SaO_2 at the end of apneas (Valipour et al. 2002). The results show that there might be only partial compensation for the reduction in arterial SaO_2 during apneic episodes (Valipour et al. 2002).

THE EFFECTS OF CO_2 AND THERAPEUTIC HYPERCAPNIA

Hypercapnia stimulates anti-inflammatory and protective pathways, e.g., superoxide formation, phospholipase A2 activity, cellular adhesion molecule expression, leukocyte and vascular endothelial cell cytokine release (IL-8, IL-6), inhibition of xanthine oxidase and oxygen radical formation (Kregenow and Swenson 2002, Laffey et al. 2000, Strand et al. 2003). Hypercapnia causes a decrease of such indicators of lung inflammation and injury as total amount of protein and the number of white blood cells in alveolar space, concentration of hydrogen peroxide produced by alveolar cells, and pro-inflammatory cytokine expression by alveolar cells (Strand et al. 2003).

Acidosis may protect against cell death during ischemia (Lemasters et al. 1996). However, the return from acidic to normal pH after reperfusion worsens the injury, what has been called "pH paradox" (Currin et al. 1991). This phenomenon has been found in the brain and in the other organs (Currin et al. 1991, Nomura et al. 1994). Gradual rather than rapid restoration of intracellular pH while cells become reoxygenated minimizes the cellular injury associated with ischemia-reperfusion (Kregenow and Swenson 2002). In multiple experimental models of ischemia-reperfusion, hypercapnic acidosis has been found to be protective against organ injury (Nomura et al. 1994, Strand et al. 2003).

Hypercapnia is commonly involved in current protective lung ventilation strategies in treatment of several types of patients. (O'Croinin et al. 2005). The original term "permissive hypercapnia" described the acceptance of increased concentrations of CO_2 in ventilated patients with severe asthma in order to reduce dynamic hyperinflation. It was later demonstrated that a low tidal volume strategy including permissive hypercapnia improved survival in patients with acute lung injury (Hickling et al. 1994). This approach has even been extended to "therapeutic hypercapnia" whereby $PaCO_2$ is deliberately elevated in order to attenuate end-organ injury (Laffey et al. 2000). Permissive/therapeutic hypercapnia has become more commonly accepted, tolerated, and practiced in patients supported with mechanical ventilation (Kregenow and Swenson 2002).

Despite multiple beneficial effects of CO_2 its clinical application is now very limited. Taking into consideration the positive effect of CO_2 on sympathetic tone one must be careful with hypercapnia in patients on β-adrenergic antagonists or those with heart failure or coronary artery disease (Kregenow and Swenson 2002). Hypercapnic acidosis, combined with arterial hypoxemia, can lead to intense renal vasoconstriction causing depressed glomerular filtration with subsequent fluid retention (DiBona and

Kopp 1997). Hypercapnia should also be avoided when cerebral vasodilation induced by CO_2 might aggravate a preexisting intracranial disorder (Perret and Feihl 1995). The deleterious effects of hypercapnia are in large part caused by decrease in intracellular and extracellular pH. Respiratory acidosis may have a suppressive effect on myocardium, but at the same time it may elicit strong neuroendocrine response with release of catecholamines and glucocorticoids which both have an opposite cardiostimulary action (Potkin and Swenson 1992).

CEREBRAL BLOOD FLOW DURING SLEEP AND IN OSA SYNDROME

The changes in cerebral vascular regulation during sleep may be indirectly estimated by measuring cerebral vascular reactivity early in the morning. In the study of Meadows and coauthors (2005) the cerebral vascular reactivity was lower in the morning as compared with evening hours. During hypoxia hypercapnic cerebral vascular reactivity decreased from 2.0 ± 0.4 cm/s/mmHg in the evening to 1.3 ± 0.2 cm/s/mmHg in the morning with intact cerebral vascular response to isocapnic hypoxia during this time period (Meadows et al. 2005). In the study of Qureshi and colleagues (1999) reduction in a morning cerebral blood flow velocity relative to values from the preceding evening persisted when the study was performed while breathing 5% CO_2; although hypercapnia was associated with increase in the velocity of CBF, CO_2 retention during sleep predicted a diminished hypercapnic vasomotor response in the morning (Qureshi et al. 1999). Thus chronic alveolar hypoventilation with high levels of CO_2 during sleep may cause less prominent fluctuations of CBF.

CBF is influenced by sleep stages. Studies performed with a computer-assisted Doppler ultrasonography system concomitantly with polysomnography show different CBF velocities during non-rapid eye movement (NREM) and REM sleep, corresponding to changes in brain function and metabolism (Diomedi et al. 1998, Hajak et al. 1994, Klingelhofer et al. 1995). Mean CBF velocity decreases steadily during deepening of NREM sleep and increases during REM sleep (Hajak et al. 1994). The lowest values of mean CBF velocity were found in stage 2 preceding the last REM sleep, reaching –19 ± 5.1% compared to the waking state (Klingelhofer et al. 1995). The increase in CBF varied from 8.9% during the first REM sleep cycle up to 18% during the last REM sleep cycle (Klingelhofer et al. 1995).

In OSA patients nocturnal profiles of CBF velocity are similar to those of normals, with decrease during NREM and increase during REM sleep, indicating preserved the general pattern of brain perfusion (Hajak et al. 1995). However, in OSA patients there is a major impact of sleep disordered breathing on the CBF. Balfors and Franklin (1994) found that CBF velocity increased by 15 ± 6% compared with baseline at 5.3 ± 2.6 s after apnea termination and decreased to a minimum of –23 ± 8% below baseline at 19.4 ± 4.5 s after apnea. Return to baseline occurred within 60 s except for apneas repeating with shorter interval; thus repetitive apneas were associated with prolonged periods of reduced CBF velocity. Fisher and others (1992) reported decreased CBF velocities in the OSA patients both in NREM and in REM sleep as compared with healthy controls. Klingelhofer and others (1992) observed increases in blood pressure of 12.5–83.1% and in mean CBF velocity of 19–219% during the apneic episodes, with maximum increases during REM sleep. Ci and coauthors (1998) found close negative correlation of the mean CBF velocity (measured by transcranial Doppler ultrasonography in the anterior, middle and posterior cerebral arteries) with apnea index and positive correlation of the mean CBF velocity with SaO_2.

OSA patients can have either normal (Klingelhofer et al. 1992) or decreased (Diomedi et al. 1998) cerebrovascular reactivity to hypercapnia in the waking state as compared with normal subjects. However, CO_2 reactivity in OSA patients is markedly increased during sleep compared with wakefulness (Klingelhofer et al. 1992). The greatest increase in CO_2 reactivity was found during REM sleep, with an increase of up to three times the waking value (Klingelhofer et al. 1992). Adequate CBF regulation is essential in OSA patients, especially in those OSA patients who experience severe arterial oxygen desaturation during sleep.

FINAL REMARKS

The data discussed show that hypercapnia occurring either repetitively or chronically during sleep, especially during obstructive sleep apneas, may exert

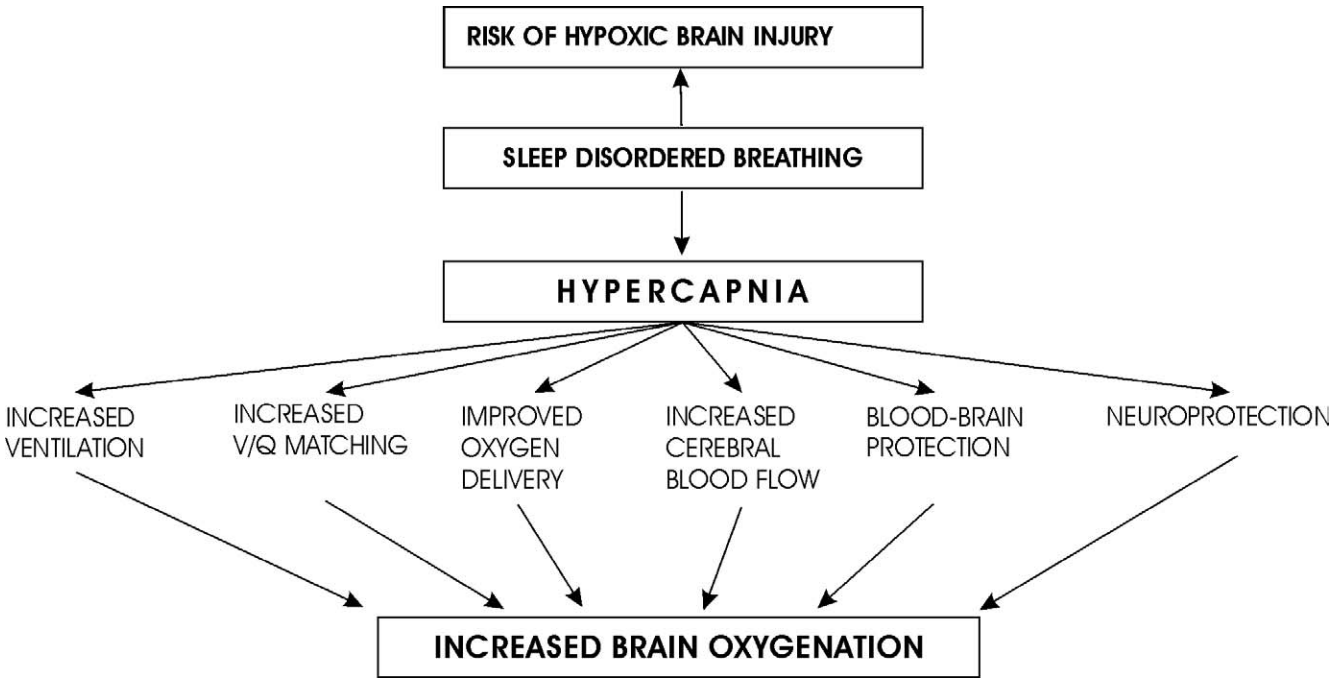

Fig. 1. The influence of hypercapnia on brain oxygenation in sleep disordered breathing

some beneficial effects and thus diminish deleterious effects of hypoxemia resulting from sleep disordered breathing. Some of these beneficial effects concern brain tissue (Fig. 1). Hypercapnia may improve the oxygenation of arterial blood by increasing ventilation and improving local V/Q matching through its effects on the pulmonary vessels, peripheral bronchi, parenchymal compliance, and respiratory related sinus arrhythmia. It may also – to some extent – diminish the severity of breathing disorders during sleep by facilitating motor discharge in the pharyngeal dilating muscles and preventing the occurrence of central sleep apneas. Hypercapnia may lead to improved oxygen delivery to the tissues (including brain tissue) acting as an important regulator of the oxygen affinity of hemoglobin and thus facilitating unloading of oxygen from the red blood cells. Hypercapnia may enhance CBF through its effects of the cerebral blood vessels (vasodilation) and through its influence on sympathetic activation (increased blood pressure). Increased CBF leads to augmented oxygen delivery to the brain. Hypercapnia acts protectively on the blood-brain barrier and decreases its risk of disruption in the situation of increased sympathetic activation and increased arterial blood pressure. Some of the molecular actions of hypercapnia exert anti-inflammatory and neuro-protective affect. All those effects of hypercapnia may improve brain oxygenation in patients exposed to severe repetitive hypoxemia during sleep disordered breathing.

OSA syndrome constitutes the clinical model of chronic intermittent hypoxia that is much influenced by the effects of hypercapnia. Intermittent hypoxia occurring in the consequence of sleep apneas may evoke the effects of preconditioning (enabling survival of severe arterial oxygen desaturations after frequent exposes to profound hypoxemia of short duration). Additionally increased CO_2 levels may enhance the effects of preconditioning. Hypercapnia developing in some OSA patients may lead to improved oxygen uptake and delivery through its ventilatory, cardiac, vasoactive, and molecular effects. Both processes – preconditioning and hypercapnia – exert neuroprotective action and may have beneficial effects in case of chronic intermittent hypoxia occurring in OSA patients.

Frequent occurrence of the episodes of extremely profound hypoxemia in OSA patients that are usually quite well tolerated implicate the need for further search for the mechanisms that enable brain protection against severe arterial deoxygenation during sleep.

CONCLUSION

Presented review of some biological effects of hypercapnia indicates that increased levels of $PaCO_2$ may contribute to improved oxygen uptake and delivery. Hypercapnia, acting together with the other pathophysiological mechanisms may protect the brain against hypoxic injury during obstructive sleep apneas. Chronic hypercapnia developing in some patients with OSA syndrome, especially in the cases of normal or only slightly impaired lung function, might be regarded as a sign of adaptation to severe, chronic intermittent sleep hypoxia.

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