Is nocturnal desaturation a trigger for neuronal damage in chronic obstructive pulmonary disease?

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Summary

Patients with chronic obstructive pulmonary disease (COPD) present many neurological disorders of unknown origin. Although hypoxemia has long been thought to be responsible, several studies have shown evidence of neuronal damage and dysfunction even in non-hypoxemic patients with COPD. Adaptive mechanisms protect the brain from hypoxia: when arterial oxygen tension (PaO_2) decreases, the cerebral blood flow (CBF) increases, ensuring continuously adequate oxygen delivery to the brain. However, this mechanism is abolished during non-rapid eye movement (NREM) sleep. Any drop in PaO_2 during NREM sleep is therefore not compensated by increased CBF, causing decreased cerebral oxygen delivery with subsequent brain hypoxia. Patients with may therefore be exposed to neuronal damage during this critical time. This mechanism is of vital importance for patients with COPD because of the potentially deleterious cortical effects. Nocturnal desaturation is quite frequent in COPD and affects approximately one out of two patients who are not hypoxemic during wakefulness. Although the prevalence of NREM sleep desaturation has never been specifically assessed in COPD, current data suggest that at least half of the nocturnal desaturation in desaturating patients occurs during NREM sleep. This review presents the rationale for the hypothesis that nocturnal desaturation during NREM sleep promotes neuronal damage and dysfunction in COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide. COPD is not restricted to the lung but instead has major systemic repercussions, and it is now considered to be a multi-component syndrome. Accordingly, the predictors of COPD survival include not only the degree of airflow obstruction, but also body mass index, dyspnea, exercise capacity, peripheral muscle size and strength, and the level of hypoxemia. Brain impairment is a well-documented secondary outcome of the disease, but surprisingly this is often forgotten (1). Yet recent reports have irrefutably confirmed severe anatomical brain impairment in COPD (2, 3) with significant functional repercussions that are not limited to cognitive disorders; for example, both peripheral muscle strength (4) and driving abilities (5) can be affected. The mechanisms of brain impairment are still not well understood, however, and it is therefore essential to determine their origins so that they can be better anticipated, with the ultimate goal being to prevent their deleterious effects. Although hypoxemia has long been thought to be responsible for brain impairment (6), several studies have shown evidence of neuronal damage and dysfunction even in non-hypoxemic patients with COPD (2, 7, 8). Adaptive mechanisms protect the brain from hypoxia: when arterial oxygen tension (PaO_2) decreases, the cerebral blood flow (CBF) increases, ensuring continuously adequate oxygen delivery to the brain (9-11). However, this mechanism is abolished during non-rapid eye movement (NREM) sleep (12-14). Therefore, any drop in PaO_2 during NREM sleep is not compensated by increased CBF, causing decreased cerebral oxygen delivery with subsequent brain hypoxia (15, 16).

Hypothesis

Given the high prevalence of nocturnal desaturation in patients with COPD (17-19) and the absence of cerebrovascular O_2 reactivity during NREM sleep stages (12-14), we hypothesize that nocturnal desaturation during NREM sleep may act as a trigger for neuronal damage and dysfunction in COPD (Figure 1).

Arguments to support the hypothesis

Anatomical brain impairment in COPD

Patients with COPD present many anatomical brain alterations. The neuronal damage in COPD was first characterized as periventricular white matter lesions (20) and cerebral metabolic abnormalities (21). Levels of N-acetyl aspartate, a marker of neuronal density, were also reported to be lower in patients with COPD compared with healthy controls (21). More recently, improvements in magnetic resonance imaging analyses through diffusion tensor imaging and voxel-based morphometry have provided better descriptions of the structural brain damage in COPD (2, 3, 22). Zhang et al. (22) found that gray matter volume was reduced bilaterally in the frontal cortex, the cingulate cortex and the left insular cortex in patients with COPD. They also identified gray matter deficits in many subcortical areas such as the right thalamus and left amygdala (22). Hippocampal atrophy was observed and associated with an increased level of serum S100b, a peripheral marker of glial cell impairment (23). In addition, a high prevalence of cerebral microbleeds and small cerebral vessel disease was found in patients with COPD (24), which is consistent with reports of both the decrease in microstructural integrity and the increase in white matter ultrastructural damage in several cortical and subcortical areas (2, 3).

Functional repercussions of brain impairment

The structural brain damage have several functional repercussions, although most studies have focused on cognitive dysfunction (see Dodd et al. (25) for review). The results of generic questionnaires such as the mini-mental state assessment (MMSE) or the Montreal cognitive assessment (MoCA) have shown globally impaired cognitive function in patients with COPD (23, 26). The P300 component of the event-related brain potential is a useful, objective clinical tool to assess cognitive function. Two studies reported longer P300 latency and lower P300 amplitude in patients with COPD compared with healthy controls, and both these measures are known to reflect attention deficits and impaired decision-making processes (7, 27). Another recent study found impairments in processing speed, working and episodic memory, and executive functions (2), with memory and attention capacities being most impaired (28). It should be noted that brain impairment is not systematic in COPD. Borson et al. (29) found no differences in hippocampal volume or white matter lesions between patients with COPD and healthy controls. Similarly, other studies have observed no significant differences in MMSE scores between patients with COPD and healthy controls (30). Recent studies have estimated the prevalence of cognitive dysfunction as being in the range of 27 to 36% (26, 31).

As noted above, the functional repercussions of neuronal damage are not restricted to cognitive functioning. For instance, driving ability may be severely impaired in patients with COPD (5, 32). Some studies have reported alterations in resting motor cortex excitability in these patients (33, 34), and another found a lower level of voluntary activation of the knee extensor muscles (35). In a recent study from our laboratory, we assessed the neural activity of the motor cortex during maximal voluntary contractions of the knee extensors and recorded lower motor cortical output in the patients with COPD (4). Taken together, these data support the hypothesis that cerebral processes are involved in COPD muscle weakness.

Mechanisms responsible for brain impairment in COPD: an incomplete view

Although evidence of a major brain impairment in COPD has steadily accumulated since the first study by Fix et al. (36), the trigger for these cerebral alterations remains unknown (37). A model including vascular disease, inflammation, smoking and hypoxia was proposed to explain COPD neuronal damage and dysfunction (25), yet Dodd et al. (2) reported the persistence of neuronal damage and cognitive dysfunction in COPD even after controlling for smoking and stroke risks. Another study found higher cognitive dysfunction in O_2-dependent patients with COPD than in non-dependent patients, with comparable level of systemic inflammation in the two groups (29). This indicates that chronic inflammation, although probably implicated (38), is not the main mechanism of the brain impairment. It also raises doubt about the effectiveness of long-term O_2 supplementation in preventing or correcting cerebral alterations, perhaps because hypoxemia per se is not fully responsible for COPD brain impairment. Indeed, while most studies have blamed chronic hypoxemia and hypercapnia (6, 28), neither direct evidence nor explanatory mechanisms could be clearly provided. Moreover, several studies have reported brain impairment and cognitive dysfunction in non-hypoxemic patients with COPD, raising further doubt about the credibility of this hypothesis (2, 7, 8). Although the evidence that hypoxia in vitro induces cellular necrosis is indisputable, it has long been established that hypoxia exposure alone is not able to induce neuronal damage in vivo. Indeed, a fall in arterial oxygen tension (PaO_2) without ischemia or a drop in blood pressure (which may cause ischemia) does not induce neuronal death/necrosis (39-41). In this sense, it appears that abnormal perfusion is an essential condition for neuronal damage in vivo. The exact mechanisms are examined in detail below.

Brain protection against hypoxemia during wakefulness: mechanisms and differences between patients with COPD and healthy individuals

Cerebral autoregulation is the physiological mechanism that maintains constant cerebral perfusion despite blood pressure changes within the normal range (42). However, during changes in arterial blood gases, cerebral autoregulation mechanisms adjust cerebral blood flow (CBF) through CBF velocity and regulate artery caliber to ensure adequate blood gas delivery to the brain (43). When PaO_2 decreases, CBF increases, and when arterial carbon dioxide tension ($PaCO_2$) increases, CBF increases. These responses are called cerebrovascular O_2 reactivity and cerebrovascular CO_2 reactivity, respectively. This close coupling between CBF and arterial blood gases was first described by Kety et al. (44). When PaO_2 is decreased in isocapnic conditions, the increase in global and regional CBF can reach up to 200% (9-11). It is assumed that the adaptation of CBF during acute hypoxic exposure is protective, maintaining the stable cerebral oxygen delivery that is a prerequisite for normal brain function (9, 45-47). In contrast, it has been suggested that the increase in CBF in response to a $PaCO_2$ increase causes CO_2 washout from brain tissue in order to attenuate the level of central CO_2 (10), thereby preventing the deleterious effects of excessive $PaCO_2$ levels on brain tissue (48, 49). However, it is noteworthy that the deleterious effects were reported for $PaCO_2$ levels above 100 mmHg (49), values rarely reached in humans.

Effects of hypoxic exposure on CBF in healthy individuals

Isocapnia during acute hypoxic exposure is a very rare phenomenon in healthy humans. Acute hypoxemia normally induces an increase in ventilation, which in turn leads to hypocapnia to improve blood oxygenation (47, 50, 51). This occurrence of hypocapnia during hypoxic exposure subsequently hampers the increase of CBF velocity caused by lower PaO_2, as hypoxemia and hypocapnia have opposite effects on CBF (52, 53). In addition, as CBF is more sensitive to changes in $PaCO_2$ than in PaO_2, this heightens the risk of inadequate oxygen delivery to the brain during acute hypoxemia-hypocapnia (53). Nevertheless, more recent

studies have shown that the modest increase in CBF velocity during acute hypoxemia-hypocapnia is compensated by a greater increase in the caliber of cerebral arteries to ensure normal oxygen delivery to the brain (46, 50).

During chronic hypoxia in healthy humans, cerebral oxygen delivery also remains preserved compared to sea-level values (47, 50, 54, 55). The mechanisms suggest that the adaptations differ from those that occur during acute hypoxic exposure, since a progressive return of CBF toward sea-level values has been observed after several days of hypoxic exposure (54-56). This fall in CBF is nevertheless compensated by an increase in arterial oxygen content, mainly due to respiratory acclimatization and a slight rise in hemoglobin concentration (55), resulting in adequate cerebral oxygen delivery (47, 50, 54, 55). Thus, taken together, the aforementioned findings do not support the occurrence of cerebral hypoxia under either acute or chronic hypoxic exposure.

Effects of hypoxemia on CBF in patients with COPD

Patients with COPD can experience acute hypoxemia (e.g., during exercise-induced oxygen desaturation) and the most severe patients may even experience chronic hypoxemia. In patients with COPD acute and chronic hypoxemia are generally accompanied by normocapnia or hypercapnia, rather than hypocapnia compared to healthy individuals. This is due to ventilation-perfusion mismatch and impaired ventilatory muscle function (57). The combination of hypoxemia and hypercapnia increases CBF much more than hypoxemia or hypercapnia alone, since these two phenomena have cumulative vasodilator effects (56). It is thus possible to speculate that the COPD brain is normally much more protected from cerebral hypoxia than the healthy human brain, on condition that both acute and chronic cerebrovascular reactivity are preserved in COPD. Many studies have provided evidence of cerebrovascular CO_2 reactivity in COPD (58-62), although this response seems mitigated

compared with that in healthy controls (59, 60). Regarding acute cerebrovascular O_2 reactivity, one study reported a similar CBF increase in patients with COPD and healthy controls in response to arterial oxygen saturation (SaO_2) changes, supporting a preserved response (58). In addition, another study reported higher CBF velocity and an increase in cerebral artery diameter in recently exacerbated patients with COPD (63). More recently, comparable levels of cerebral oxygen delivery during exercise-induced oxygen desaturation were reported when the patients breathed room air and when they breathed oxygen to prevent desaturation (64). This confirms the brain protection against acute hypoxemia in COPD.

Regarding the effect of chronic hypoxemia on CBF, a study reported higher CBF velocity and larger cerebral artery diameter using transcranial Doppler in chronic hypoxemic patients with COPD compared with healthy controls (65). This study showed that the mechanisms of cerebral vasodilation persist in patients with COPD during chronic blood gas changes. In addition, the highest CBF levels were found in the hypoxemic-hypercapnic patients, indicating a possible cumulative effect of chronic hypoxemia-hypercapnia on the cerebrovascular vasodilative response (65). Nevertheless, this response is sometimes difficult to observe because of confounding factors (66, 67). For example, CBF is closely coupled with cerebral metabolism: the lower the cerebral metabolism, the lower the CBF is. As patients with COPD exhibit lower resting cerebral metabolism (21, 68, 69), the resting CBF can be lowered in both hypoxemic (66, 67) and non-hypoxemic (62) patients.

To conclude, acute and chronic cerebrovascular O_2 reactivity is preserved in COPD, indicating that cerebral oxygen delivery is adequate during hypoxemia in patients with COPD (64). Hence, hypoxemia per se does not induce cerebral hypoxia in COPD and this may explain why the involvement of hypoxemia in triggering neuronal damage in COPD has never been demonstrated.

Cerebrovascular reactivity during sleep compromises brain integrity in chronic respiratory disorders

As the studies cited above have shown, changes in diurnal blood gases are well tolerated by the brain through CBF adaptations. However, this mechanism may be hampered during sleep. Contrary to the adaptations that occur in the waking state, the oxygen desaturation during non-rapid eye movement (NREM) sleep is not accompanied by an increase in CBF (Figure 2). Meadows et al. (13) reduced SaO_2 from five to ten percent during slow-wave sleep in humans and found an unexpected decrease in CBF during hypoxemia. This decoupling of CBF and PaO_2 has also been reported in patients with obstructive sleep apnea (OSA) (12, 70, 71). While decreasing PaO_2 by voluntary breath-holding increases CBF during the waking state (72, 73), CBF tends to decrease during NREM sleep when PaO_2 is decreased by sleep apnea, increasing the risk of inadequate cerebral O_2 delivery (70).

The absence of cerebrovascular O_2 reactivity during NREM sleep makes it more difficult to prevent cerebral hypoxia in patients with cardiorespiratory disorders who experience oxygen desaturation during NREM sleep. Cerebral hypoxia has been reported during sleep in patients with OSA (15, 16). It should be noted that this response seems very specific to the NREM sleep stages, as cerebrovascular reactivity is not impaired during rapid eye movement (REM) sleep (12).

In summary, cerebrovascular reactivity is impaired and even abolished during NREM sleep in humans (13). In patients who experience hypoxemia or desaturation during NREM sleep, cerebral hypoxia can occur and may induce neuronal damage (14). We thus propose that nocturnal desaturation during NREM sleep can act as a trigger for neuronal damage and cerebral dysfunction in patients with COPD (Figure 1).

Desaturation during NREM sleep in COPD: does it exist and, if so, does it matter?

Patients with COPD who are hypoxemic in the waking state usually become more hypoxemic during sleep (74), but nocturnal desaturation can also occur in patients with COPD who are normoxic while awake (17). The prevalence of patients with COPD who are normoxic while awake and who spend at least 30% of the total sleep time (TST) with a mean pulsed oxygen saturation (SpO_2) below 90% ranges from 38 to 70% (17-19). Based on the same criteria, it is also notable that nocturnal desaturation in COPD is observed in approximately half of the patients undergoing long-term oxygen therapy because the diurnal flow rate is often insufficient to prevent nocturnal desaturation (75). However, it is quite difficult to determine the percentage of patients with COPD who desaturate during the NREM sleep stages because all the studies to date have considered the total sleep time, thus including REM sleep. Indeed, as the deepest desaturations occur during REM sleep, this sleep stage has logically been taken as the main marker of COPD sleep abnormalities (74, 76, 77). Nevertheless, it is reasonable to assume that desaturation during NREM sleep occurs in patients with nocturnal desaturation in COPD, even though this has never been specifically assessed. The usual criterion to diagnose sleep desaturation is oxygen desaturation for at least 30% of the total sleep time. As REM sleep represents only approximately 13% of the total sleep time in COPD (78), more than half of the desaturation time is likely to occur during NREM sleep in patients with COPD and significant sleep desaturation.

Future studies to test the hypothesis

The abolition of cerebrovascular O_2 reactivity during NREM sleep was demonstrated in humans (13) and then specifically in patients who experience nocturnal desaturation (11). Transcranial Doppler (58) or near-infrared spectroscopy (64) could be used to assess the extent to which CBF decreases during NREM sleep desaturation in patients with COPD.

Moreover, a follow-up study with correction of NREM sleep desaturation in the desaturating patients, for example by oxygen therapy, would be of great interest. A few studies assessed the effects of oxygen therapy on cognitive function in COPD but the results were inconclusive (79-82). In these studies, the oxygen flow rate was not adapted to the specific needs during sleep which are often higher than during the waking state (75). Therefore, manually or automated oxygen flow titration should be considered to accurately adjust oxygen delivery during NREM sleep (83). Beyond hypothesis testing, the demonstration that preventing NREM sleep desaturation improves cerebral function (or at least stops the decline in function) would constitute a first step in developing new treatments for the neuronal damage and dysfunction of COPD.

Conclusion

In summary, cerebrovascular reactivity to blood gas changes is a mechanism that prevents brain hypoxia in awake humans. During NREM sleep, however, this reactivity is reduced or even totally abolished. Consequently, any oxygen desaturation during this sleep stage will favor neuronal damage. As abnormal blood oxygenation during NREM sleep is a common feature in COPD and a decreased oxygen supply might not be compensated by an increase in cerebral blood flow, the patient's brain is potentially exposed to hypoxic stress. The hypothesis developed above considers NREM sleep desaturation as a potential trigger for neuronal damage and dysfunction in COPD.

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Conflict of interest statement

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Figures

Figure 1: Hypoxemia during non-rapid eye movement (NREM) sleep promotes brain hypoxia and potentially damages brain tissue

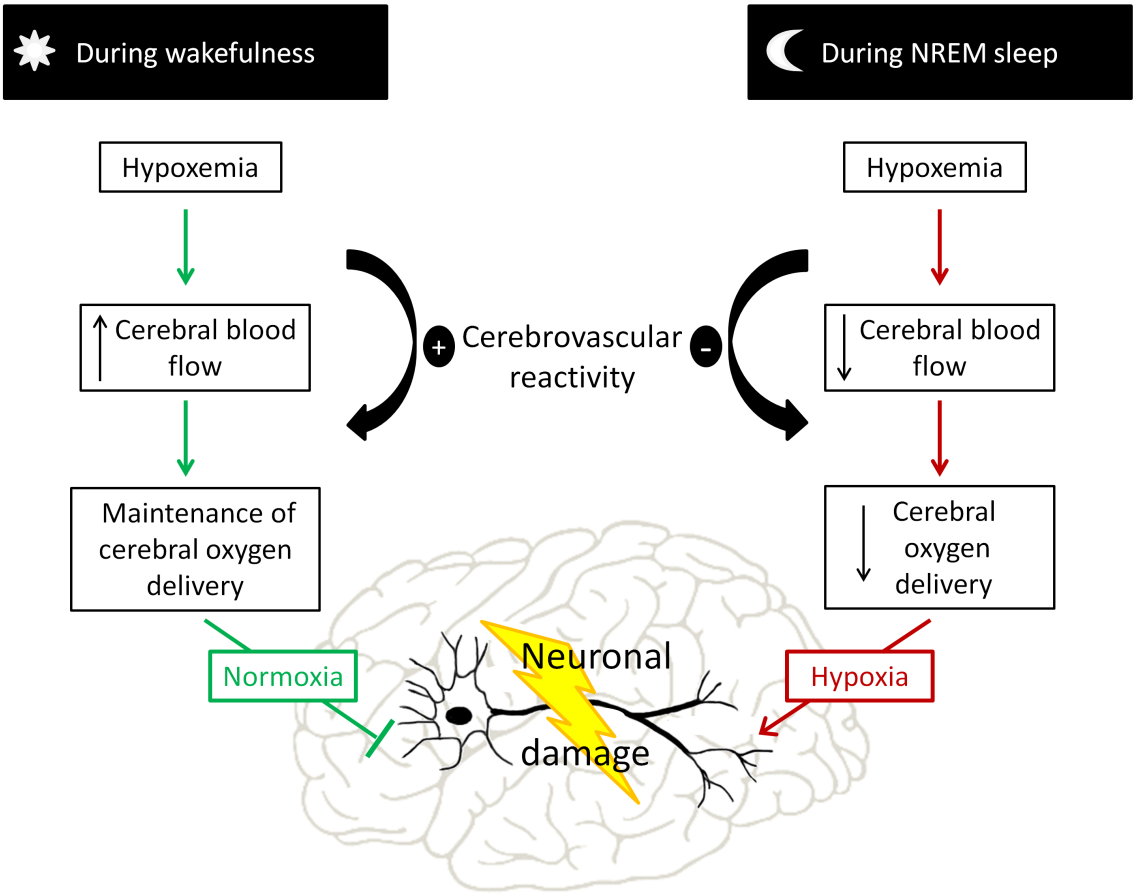

Figure 2: Mean flow velocity (MFV) in the right medial cerebral artery in healthy controls and patients with obstructive sleep apnea during wakefulness and sleep during which hypoxemia occurred: non-rapid eye movement sleep (NREM; stage 2) and rapid eye movement sleep (REM) of the second sleep cycle [Adapted from the data of Hajak et al. (12)]. Apnea-induced hypoxemia is compensated during REM sleep by an MFV increase, but this adjustment is totally abolished during NREM sleep, where MFV tends to decrease, mimicking the healthy controls' MVF kinetics. * $p<0.05$ between groups.