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Title: 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.

1 **Introduction**

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

22

23 **Hypothesis**

24

25

26 Given the high prevalence of nocturnal desaturation in patients with COPD (17-19) and the
27 absence of cerebrovascular O₂ reactivity during NREM sleep stages (12-14), we hypothesize
28 that nocturnal desaturation during NREM sleep may act as a trigger for neuronal damage and
29 dysfunction in COPD (Figure 1).

30

31 **Arguments to support the hypothesis**

32 *Anatomical brain impairment in COPD*

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

48

49 *Functional repercussions of brain impairment*

50 The structural brain damage have several functional repercussions, although most studies
51 have focused on cognitive dysfunction (see Dodd et al. (25) for review). The results of
52 generic questionnaires such as the mini-mental state assessment (MMSE) or the Montreal
53 cognitive assessment (MoCA) have shown globally impaired cognitive function in patients
54 with COPD (23, 26). The P300 component of the event-related brain potential is a useful,
55 objective clinical tool to assess cognitive function. Two studies reported longer P300 latency
56 and lower P300 amplitude in patients with COPD compared with healthy controls, and both
57 these measures are known to reflect attention deficits and impaired decision-making processes
58 (7, 27). Another recent study found impairments in processing speed, working and episodic
59 memory, and executive functions (2), with memory and attention capacities being most
60 impaired (28). It should be noted that brain impairment is not systematic in COPD. Borson et
61 al. (29) found no differences in hippocampal volume or white matter lesions between patients
62 with COPD and healthy controls. Similarly, other studies have observed no significant
63 differences in MMSE scores between patients with COPD and healthy controls (30). Recent
64 studies have estimated the prevalence of cognitive dysfunction as being in the range of 27 to
65 36% (26, 31).

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

74

75 *Mechanisms responsible for brain impairment in COPD: an incomplete view*

76 Although evidence of a major brain impairment in COPD has steadily accumulated since the
77 first study by Fix et al. (36), the trigger for these cerebral alterations remains unknown (37). A
78 model including vascular disease, inflammation, smoking and hypoxia was proposed to
79 explain COPD neuronal damage and dysfunction (25), yet Dodd et al. (2) reported the
80 persistence of neuronal damage and cognitive dysfunction in COPD even after controlling for
81 smoking and stroke risks. Another study found higher cognitive dysfunction in O₂-dependent
82 patients with COPD than in non-dependent patients, with comparable level of systemic
83 inflammation in the two groups (29). This indicates that chronic inflammation, although
84 probably implicated (38), is not the main mechanism of the brain impairment. It also raises
85 doubt about the effectiveness of long-term O₂ supplementation in preventing or correcting
86 cerebral alterations, perhaps because hypoxemia per se is not fully responsible for COPD
87 brain impairment. Indeed, while most studies have blamed chronic hypoxemia and
88 hypercapnia (6, 28), neither direct evidence nor explanatory mechanisms could be clearly
89 provided. Moreover, several studies have reported brain impairment and cognitive
90 dysfunction in non-hypoxemic patients with COPD, raising further doubt about the credibility
91 of this hypothesis (2, 7, 8). Although the evidence that hypoxia in vitro induces cellular
92 necrosis is indisputable, it has long been established that hypoxia exposure alone is not able to
93 induce neuronal damage in vivo. Indeed, a fall in arterial oxygen tension (PaO₂) without
94 ischemia or a drop in blood pressure (which may cause ischemia) does not induce neuronal
95 death/necrosis (39-41). In this sense, it appears that abnormal perfusion is an essential
96 condition for neuronal damage in vivo. The exact mechanisms are examined in detail below.

97

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

100 Cerebral autoregulation is the physiological mechanism that maintains constant cerebral
101 perfusion despite blood pressure changes within the normal range (42). However, during
102 changes in arterial blood gases, cerebral autoregulation mechanisms adjust cerebral blood
103 flow (CBF) through CBF velocity and regulate artery caliber to ensure adequate blood gas
104 delivery to the brain (43). When PaO_2 decreases, CBF increases, and when arterial carbon
105 dioxide tension (PaCO_2) increases, CBF increases. These responses are called cerebrovascular
106 O_2 reactivity and cerebrovascular CO_2 reactivity, respectively. This close coupling between
107 CBF and arterial blood gases was first described by Kety et al. (44). When PaO_2 is decreased
108 in isocapnic conditions, the increase in global and regional CBF can reach up to 200% (9-11).
109 It is assumed that the adaptation of CBF during acute hypoxic exposure is protective,
110 maintaining the stable cerebral oxygen delivery that is a prerequisite for normal brain function
111 (9, 45-47). In contrast, it has been suggested that the increase in CBF in response to a PaCO_2
112 increase causes CO_2 washout from brain tissue in order to attenuate the level of central CO_2
113 (10), thereby preventing the deleterious effects of excessive PaCO_2 levels on brain tissue (48,
114 49). However, it is noteworthy that the deleterious effects were reported for PaCO_2 levels
115 above 100 mmHg (49), values rarely reached in humans.

116

117 Effects of hypoxic exposure on CBF in healthy individuals

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

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

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

137

138 Effects of hypoxemia on CBF in patients with COPD

139 Patients with COPD can experience acute hypoxemia (e.g., during exercise-induced oxygen
140 desaturation) and the most severe patients may even experience chronic hypoxemia. In
141 patients with COPD acute and chronic hypoxemia are generally accompanied by normocapnia
142 or hypercapnia, rather than hypocapnia compared to healthy individuals. This is due to
143 ventilation-perfusion mismatch and impaired ventilatory muscle function (57). The
144 combination of hypoxemia and hypercapnia increases CBF much more than hypoxemia or
145 hypercapnia alone, since these two phenomena have cumulative vasodilator effects (56). It is
146 thus possible to speculate that the COPD brain is normally much more protected from
147 cerebral hypoxia than the healthy human brain, on condition that both acute and chronic
148 cerebrovascular reactivity are preserved in COPD. Many studies have provided evidence of
149 cerebrovascular CO₂ reactivity in COPD (58-62), although this response seems mitigated

150 compared with that in healthy controls (59, 60). Regarding acute cerebrovascular O₂
151 reactivity, one study reported a similar CBF increase in patients with COPD and healthy
152 controls in response to arterial oxygen saturation (SaO₂) changes, supporting a preserved
153 response (58). In addition, another study reported higher CBF velocity and an increase in
154 cerebral artery diameter in recently exacerbated patients with COPD (63). More recently,
155 comparable levels of cerebral oxygen delivery during exercise-induced oxygen desaturation
156 were reported when the patients breathed room air and when they breathed oxygen to prevent
157 desaturation (64). This confirms the brain protection against acute hypoxemia in COPD.

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

169 To conclude, acute and chronic cerebrovascular O₂ reactivity is preserved in COPD,
170 indicating that cerebral oxygen delivery is adequate during hypoxemia in patients with COPD
171 (64). Hence, hypoxemia per se does not induce cerebral hypoxia in COPD and this may
172 explain why the involvement of hypoxemia in triggering neuronal damage in COPD has never
173 been demonstrated.

175 *Cerebrovascular reactivity during sleep compromises brain integrity in chronic respiratory*
176 *disorders*

177 As the studies cited above have shown, changes in diurnal blood gases are well tolerated by
178 the brain through CBF adaptations. However, this mechanism may be hampered during sleep.
179 Contrary to the adaptations that occur in the waking state, the oxygen desaturation during
180 non-rapid eye movement (NREM) sleep is not accompanied by an increase in CBF (Figure 2).
181 Meadows et al. (13) reduced SaO₂ from five to ten percent during slow-wave sleep in humans
182 and found an unexpected decrease in CBF during hypoxemia. This decoupling of CBF and
183 PaO₂ has also been reported in patients with obstructive sleep apnea (OSA) (12, 70, 71).
184 While decreasing PaO₂ by voluntary breath-holding increases CBF during the waking state
185 (72, 73), CBF tends to decrease during NREM sleep when PaO₂ is decreased by sleep apnea,
186 increasing the risk of inadequate cerebral O₂ delivery (70).

187 The absence of cerebrovascular O₂ reactivity during NREM sleep makes it more difficult to
188 prevent cerebral hypoxia in patients with cardiorespiratory disorders who experience oxygen
189 desaturation during NREM sleep. Cerebral hypoxia has been reported during sleep in patients
190 with OSA (15, 16). It should be noted that this response seems very specific to the NREM
191 sleep stages, as cerebrovascular reactivity is not impaired during rapid eye movement (REM)
192 sleep (12).

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

198

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

200 Patients with COPD who are hypoxemic in the waking state usually become more hypoxemic
201 during sleep (74), but nocturnal desaturation can also occur in patients with COPD who are
202 normoxic while awake (17). The prevalence of patients with COPD who are normoxic while
203 awake and who spend at least 30% of the total sleep time (TST) with a mean pulsed oxygen
204 saturation (SpO₂) below 90% ranges from 38 to 70% (17-19). Based on the same criteria, it is
205 also notable that nocturnal desaturation in COPD is observed in approximately half of the
206 patients undergoing long-term oxygen therapy because the diurnal flow rate is often
207 insufficient to prevent nocturnal desaturation (75). However, it is quite difficult to determine
208 the percentage of patients with COPD who desaturate during the NREM sleep stages because
209 all the studies to date have considered the total sleep time, thus including REM sleep. Indeed,
210 as the deepest desaturations occur during REM sleep, this sleep stage has logically been taken
211 as the main marker of COPD sleep abnormalities (74, 76, 77). Nevertheless, it is reasonable to
212 assume that desaturation during NREM sleep occurs in patients with nocturnal desaturation in
213 COPD, even though this has never been specifically assessed. The usual criterion to diagnose
214 sleep desaturation is oxygen desaturation for at least 30% of the total sleep time. As REM
215 sleep represents only approximately 13% of the total sleep time in COPD (78), more than half
216 of the desaturation time is likely to occur during NREM sleep in patients with COPD and
217 significant sleep desaturation.

218

219 **Future studies to test the hypothesis**

220 The abolition of cerebrovascular O₂ reactivity during NREM sleep was demonstrated in
221 humans (13) and then specifically in patients who experience nocturnal desaturation (11).
222 Transcranial Doppler (58) or near-infrared spectroscopy (64) could be used to assess the
223 extent to which CBF decreases during NREM sleep desaturation in patients with COPD.

224 Moreover, a follow-up study with correction of NREM sleep desaturation in the desaturating
225 patients, for example by oxygen therapy, would be of great interest. A few studies assessed
226 the effects of oxygen therapy on cognitive function in COPD but the results were inconclusive
227 (79-82). In these studies, the oxygen flow rate was not adapted to the specific needs during
228 sleep which are often higher than during the waking state (75). Therefore, manually or
229 automated oxygen flow titration should be considered to accurately adjust oxygen delivery
230 during NREM sleep (83). Beyond hypothesis testing, the demonstration that preventing
231 NREM sleep desaturation improves cerebral function (or at least stops the decline in function)
232 would constitute a first step in developing new treatments for the neuronal damage and
233 dysfunction of COPD.

234

235 **Conclusion**

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

244

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247

248 **Conflict of interest statement**

249 No conflict of interest, financial or otherwise, is declared by the authors.

250

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253

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Figures

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

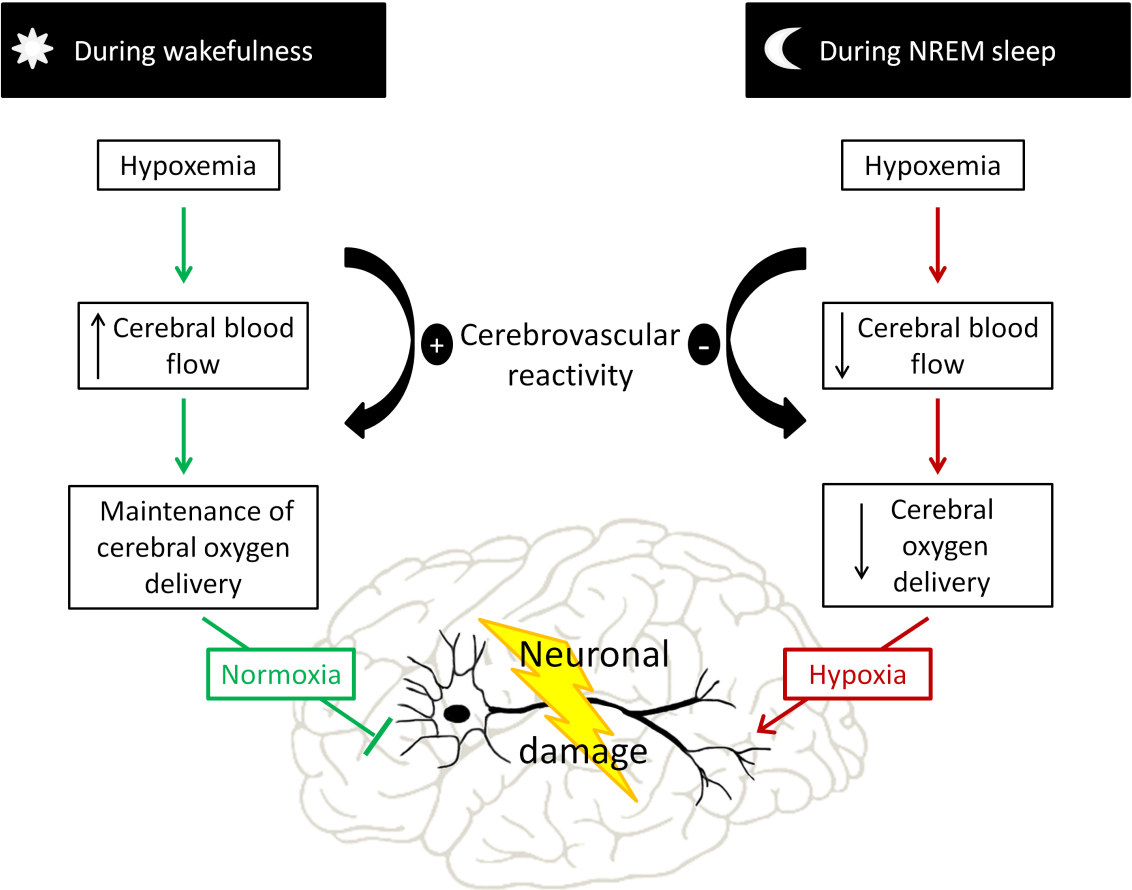


Figure 2: Mean flow velocity (MFV) in the right medial cerebral artery in healthy controls and patients with obstructive sleep apnea during wakefulness and sleep during which hypoxemia occurred: non-rapid eye movement sleep (NREM; stage 2) and rapid eye movement sleep (REM) of the second sleep cycle [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' MFV kinetics. * $p < 0.05$ between groups.

