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

François Alexandre, Nelly Heraud, Alain Varray

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Francois Alexandre[1,2], Nelly Heraud[2], Alain Varray[1]

[1]Movement To Health Laboratory, Euromov, University of Montpellier 1, Montpellier, France. [2]Clinique du Souffle La Vallonie, Fontalvie, Lodève, France

Corresponding author:

Francois Alexandre, Movement To Health (M2H), Euromov, University of Montpellier 1, 700 avenue du Pic Saint Loup, 34090 Montpellier, France. Phone: (+33) 434 432 632; Fax: (+33) 434 432 644; E-mail: francois.alexandre@5-sante.fr

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

26   Given the high prevalence of nocturnal desaturation in patients with COPD (17-19) and the

27   absence of cerebrovascular O_2 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 O_2-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 O_2 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 (PaO_2) 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 CO_2 reactivity in COPD (58-62), although this response seems mitigated

150 compared with that in healthy controls (59, 60). Regarding acute cerebrovascular O_2

151 reactivity, one study reported a similar CBF increase in patients with COPD and healthy

152 controls in response to arterial oxygen saturation (SaO_2) 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 O_2 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.

174

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 SaO_2 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   PaO_2 has also been reported in patients with obstructive sleep apnea (OSA) (12, 70, 71).

184   While decreasing PaO_2 by voluntary breath-holding increases CBF during the waking state

185   (72, 73), CBF tends to decrease during NREM sleep when PaO_2 is decreased by sleep apnea,

186   increasing the risk of inadequate cerebral O_2 delivery (70).

187   The absence of cerebrovascular O_2 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 (SpO_2) 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 O_2 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

247

248   **Conflict of interest statement**

253

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Figures

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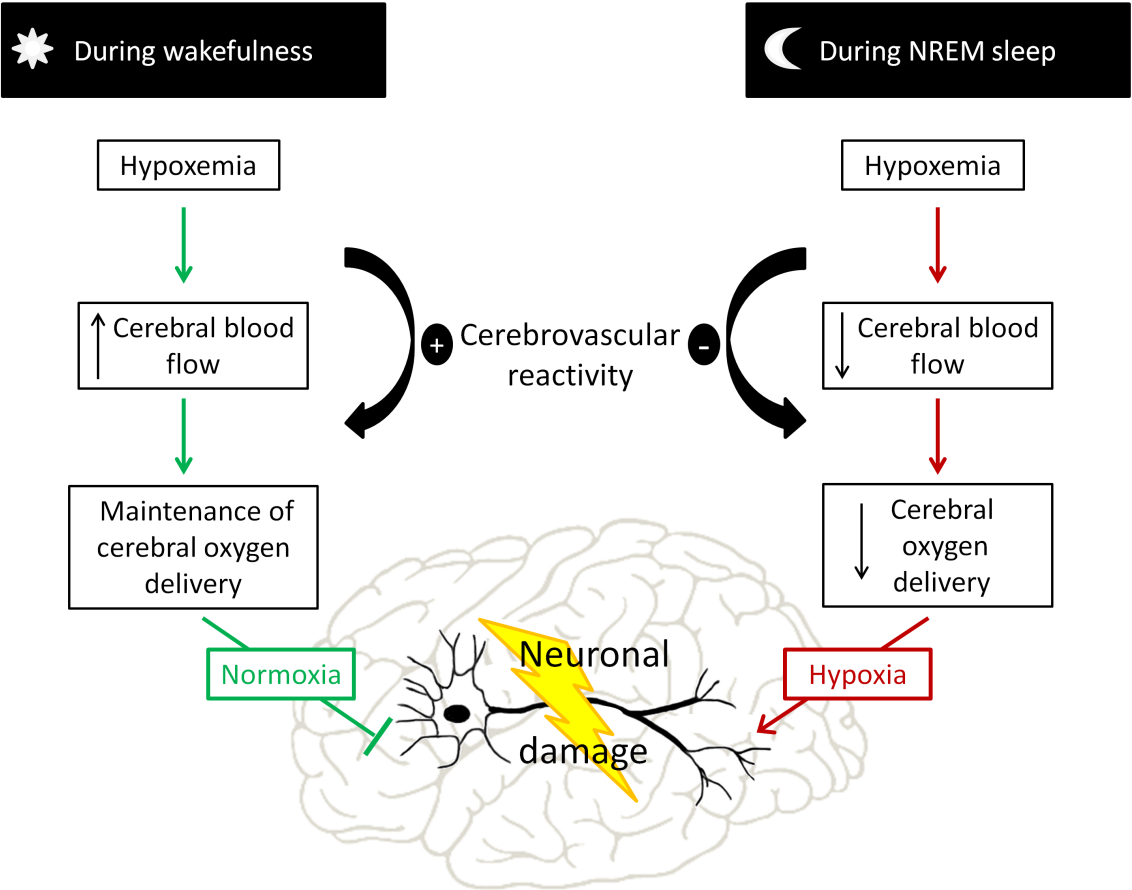and potentially damages brain tissue

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' MVF kinetics. * $p < 0.05$ between groups.