

## **EDITORIAL**

# **Supplemental oxygen for COPD patients with nocturnal desaturations?**

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The degree of agreement is high regarding the criteria for prescribing supplemental oxygen for chronic obstructive pulmonary disease (COPD) patients with a daytime arterial oxygen tension ( $P_{a,O_2}$ ) of  $<7.3$  kPa, or ranging 7.4–8.6 kPa with signs of polycythaemia (haematocrit  $>55\%$ ) or of cor pulmonale. The classical Medical Research Council and Nocturnal Oxygen Therapy Trial studies in the early 1980s showed that the standard treatment of 15 h of supplemental oxygen improves survival in these severe COPD patients [1, 2]. In a group of 135 COPD patients with less severe hypoxia (daytime  $P_{a,O_2} >7.3$  kPa), long term oxygen treatment (LTOT) apparently did not improve survival [3]. This was confirmed in a study from the French Association Nationale pour le Traitement à Domicile de L'Insuffisance Respiratoire chronique group on 7,700 COPD patients with a forced expiratory volume in one second (FEV1) of  $\sim 30\%$  of the predicted value [4].

There is another subgroup of patients with COPD who have desaturations only during sleep. In rapid eye movement (REM) sleep, there is hardly any activity in the intercostal and accessory respiratory muscles, due to "gamma-paralysis". Consequently, the diaphragm is virtually the only respiratory muscle that is active during REM sleep. This leads to paradoxical breathing and further hypoventilation. During tonic REM, the breathing pattern is fairly regular, and predominantly diaphragmatic.

In most COPD patients, the diaphragm is chronically flattened, and consequently at a disadvantageous position on its length/tension curve. Furthermore, the diaphragm is frequently weakened in COPD patients, in proportion to the level of hyperinflation [5]. The mean nocturnal saturation in COPD is positively correlated with maximal inspiratory mouth pressure ( $r=0.65$ ) and maximal trans-diaphragmatic pressure ( $r=0.53$ ) [6]. The rapid shallow type of breathing that occurs in many COPD patients and the ensuing alveolar hypoventilation is one of the most important mechanisms of nocturnal hypoxaemia in COPD [7]. All this contributes to hypoxaemia and oxygen desaturations, especially during REM sleep, in COPD patients.

The prevalence of these isolated nocturnal desaturations differs in various studies. FLETCHER *et al.* [8] studied a group of patients with a daytime  $P_{a,O_2}$  of  $>8$  kPa and found desaturations in 27% of them. In a group of 60 patients with a mean FEV1 of 43% pred, episodes of noc-

turnal desaturation were found in 47 (78%) [9]. FLEETHAM *et al.* [10] found nocturnal desaturations in all COPD patients with an FEV1 of  $<26\%$  pred. This was confirmed in the studies of DEMARCO *et al.* [11] (FEV1 0.9 L) and of TATSUMI *et al.* [12] (FEV1/forced vital capacity 50% pred). In a recent multicentre study on 94 COPD patients ( $P_{a,O_2}$  7.4–9.2 kPa, FEV1  $\sim 1.0$  L), CHAOUAT *et al.* [13] found 77% were desaturators.

These differences in prevalence of nocturnal desaturation highly depend on the definition used. FLETCHER *et al.* [8] defined a nocturnal desaturation as a decrease in arterial oxygen saturation ( $S_{a,O_2}$ ) to  $<90\%$  for  $\geq 5$  min, with a lowest value  $\leq 85\%$ . In Europe, another criterion of  $\geq 30\%$  of the recording time at an  $S_{a,O_2} <90\%$ , is mostly used. Owing to these different criteria, the prevalences of nocturnal desaturations given by the various authors can differ substantially.

The diagnosis of nocturnal desaturations in an individual patient can only be made on the basis of sleep studies. Daytime blood gas levels are related to nocturnal hypoxaemia in groups of patients [14]. The blue and bloating type of COPD patient seems especially to desaturate during the night [15]. The correlations between daytime  $P_{a,O_2}$  and mean nocturnal  $S_{a,O_2}$  in groups of patients ranged from  $r=0.56$  [16], to  $r=0.81$  [17]. Consequently, in the individual patient, the predictive value of daytime blood gas analysis is hardly relevant, due to the wide scatter of the individual points around the regression line. Using daytime blood gas levels to predict nocturnal desaturation would wrongly deny this phenomenon in 20% of COPD patients, and 22% would be falsely diagnosed as nocturnal desaturators. Additional measurement of the ventilatory responses to  $CO_2$  in these patients improves the negative predictive value for nocturnal hypoxaemia to 91%, the positive predictive value remaining low at 50% [16].

FLEETHAM *et al.* [10] were among the first to correlate the ventilatory response to hypercapnia with nocturnal desaturation in COPD patients with a mean FEV1 of 26% pred. They found a range of hypercapnic responses (expressed in  $dP_{0.1}/dP_{A,CO_2}$ , where  $P_{0.1}$  is the mouth occlusion pressure and  $P_{A,CO_2}$  the alveolar carbon dioxide tension) of  $0.41 \pm 0.06$   $cmH_2O \cdot mmHg^{-1}$ , mean nocturnal desaturation ranging 4–40% and a negative correlation between the hypercapnic response and the degree of desaturation. In this study, the hypoxic ventilatory response was not correlated with the degree of nocturnal desaturation. However, TATSUMI *et al.* [12] have shown that a diminished ventilatory response to hypoxia will also predispose to nocturnal hypoxaemia in COPD.

The consequences of isolated nocturnal hypoxaemia in patients with COPD are not really clear. It is not yet established that nocturnal desaturations increase their red cell mass, though some indications in the literature are suggestive of this [18]. Cardiac arrhythmias such as ectopic contraction seem to be more frequent in desaturating COPD patients. No firm evidence is available as to the clinical relevance of these arrhythmias.

Some animal experiments suggest that 2 in 24 h of desaturation to  $P_{a,O_2}$  of  $\sim 7.5$  kPa suffice for the development of pulmonary hypertension [19]. This seems to be partially supported by the findings of FLETCHER *et al.* [20], suggesting that nocturnal saturations might shorten life expectancy in patients with COPD. In the acute situation during nocturnal desaturations ranging 94–77%, in various patients, there were indeed transient rises in pulmonary artery pressure (PAP) [21]. Also, systemic arterial blood pressure increased considerably by 35 mmHg during nocturnal hypoventilation. SHEPARD *et al.* [22] calculated that the myocardial demand for oxygen increased to levels that were comparable to those found during maximal exercise in these patients with COPD (FEV<sub>1</sub>  $40 \pm 16\%$  pred). These authors suggested that "the hypoxaemic stress placed on the coronary blood flow reserves to maintain myocardial  $O_2$ -delivery during sleep may contribute to nocturnal mortality in patients with COPD". Indeed, other investigators have found that approximately half of the patients who die in hospital with a diagnosis of bronchitis or emphysema do so during the night. Patients whose  $P_{a,O_2}$  was maintained at  $>8$  kPa, by means of supplemental oxygen, showed no increase in nocturnal mortality [23].

The recent cross-sectional study of CHAOUAT *et al.* [13] in 94 COPD patients, 66 with hypoxaemia only during sleep and 28 who were nondesaturators, showed that PAP was not different between the groups. They concluded that isolated nocturnal hypoventilation and hypoxaemia did not favour the development of pulmonary hypertension. Thus, nocturnal oxygen supplementation could not be expected to have a great impact on the development of pulmonary hypertension. A similar suggestion had been made earlier by CONNAUGHTON *et al.* [24] who did not find any justification for monitoring nocturnal oxygen saturation in patients with COPD and giving some of them oxygen during the night. COPD patients with more nocturnal hypoxaemia than predicted from arterial blood gas measurements had similar survival rate to patients who were less hypoxaemic than predicted. They argued that giving supplemental oxygen during sleep is not warranted, and that sleep studies do not contribute to the clinical management of patients with COPD. However, CONNAUGHTON *et al.* [24] did not establish whether their hypoxaemic patients (mean  $P_{a,O_2}$  7.3 kPa) had pulmonary hypertension nor whether this possible hypertension would have been reversible by giving supplemental oxygen. DOUGLAS [18] supports the notion that clinical polysomnography in COPD patients should be carried out only "when [sleep apnoea/hypopnoea syndrome] SAHS is suspected, because of symptoms, or the development of hypoxaemic complications such as cor pulmonale and polycythaemia in patients whose daytime arterial oxygen tension is greater than 60 mmHg". Pulmonary hypertension can be reversible in the acute situation by supplementing oxygen, as was shown by ASHUTOSH and DUNSKY

[25]. In a group of 43 COPD patients, they found that 28 had a PAP lowered by  $\sim 10$  mmHg, when breathing 28% oxygen. The survival of these "responders" was significantly better than that of the nonresponders.

Following a previous abstract [26], new data are presented in full, in this issue of the *European Respiratory Journal* [27] concerning a randomized trial of nocturnal oxygen for 8–10 h in 71 COPD patients with mild-to-moderate daytime hypoxia (7.5–9.2 kPa), thus not qualifying for LTOT. These patients had a mean nocturnal  $S_{a,O_2}$  of 88%. Forty-one patients were allocated to nocturnal oxygen treatment, 35 were controls. After 2 yrs, 12 patients on nocturnal oxygen and 10 controls had deteriorated in such a way that LTOT was necessary. Nine patients in the nocturnal oxygen group and seven in the control group had died. In both groups of survivors there was a small nonsignificant increase in PAP. The authors explain the differences between the results of their study and those of FLETCHER *et al.* [20] by the size of the group, and by the fact that some of the patients in the latter study had signs of left ventricular dysfunction and a somewhat higher starting value of the PAP.

The new data from this multicentre trial suggest that there might be no reason for prescribing nocturnal oxygen treatment for COPD patients with isolated nocturnal desaturations with the aim of increasing life expectancy or delaying the development of pulmonary hypertension, and neither does it seem that nocturnal oxygen treatment can delay the initiation of LTOT.

Considerations concerning life expectancy in COPD patients have focused mainly on hypoxia, its severity and the subsequent development of cor pulmonale. The other blood gas parameter,  $P_{a,CO_2}$ , which is an expression of the adequacy of alveolar ventilation has hardly been studied in this respect. COOPER and HOWARD [28] performed a retrospective study from the time of death, on a group of COPD patients on LTOT. They showed that  $\sim 3$  yrs before death, these patients developed hypercapnia. Of course, it is impossible to establish causal relationships from such a retrospective study; is the hypercapnia one of the signs of the deterioration caused by the disease, or does hypercapnia contribute to this deterioration? It is well known that hypercapnia has a negative effect on (respiratory) muscle contractility, and increases the retention of fluids. In this perspective, it would be of interest to know the  $P_{a,CO_2}$  of the patients who died in the present study of CHAOUAT *et al.* [27]. There were certainly a substantial number of patients with hypercapnia in their population; the mean  $\pm$  SD  $P_{a,CO_2}$  was  $\sim 6 \pm 0.7$  kPa. Furthermore, it was shown that chronic hypercapnic patients had a worse prognosis than those who were normocapnic before and after an exacerbation of their COPD, or than those who were only transiently hypercapnic during the exacerbation [29].

Thus further studies on respiratory insufficiency and the possible effects of ventilatory support are required, and should shed more light on the possible detrimental effects of hypercapnia.

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