Eur Respir J
1992, 5, 301–307

Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients

P. Levi-Valensi, E. Weitzenblum, Z. Rida, P. Aubry, A. Braghiroli, C. Donner, M. Aprill, J. Zielinski, G. Würtemberger

Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients. P. Levi-Valensi, E. Weitzenblum, Z. Rida, P. Aubry, A. Braghiroli, C. Donner, M. Aprill, J. Zielinski, G. Würtemberger.

ABSTRACT: It has been hypothesized that in chronic obstructive pulmonary disease (COPD), sleep-related hypoxaemia could lead to pulmonary hypertension (PH) and cor pulmonale, even in patients with only mild daytime hypoxaemia. We investigated the relationships between sleep variables and daytime pulmonary haemodynamics in 40 COPD patients with daytime arterial oxygen tension (Pao_2) between 60–70 mmHg (8–9.3 kPa). Patients were considered as desaturators if they spent at least 30% of the sleep recording time with a transcutaneous O_2 saturation ($Stco_2$) <90%.

Daytime arterial blood gases and pulmonary volumes could not discriminate desaturators "D" (n=18) from non-desaturators "ND" (n=22), but awake baseline $Stco_2$, measured just prior to the onset of sleep, was lower in group D. Pulmonary artery mean pressure was significantly higher in group D (19.1±4.7 *vs* 16.8±1.9 mmHg, $p<0.05$) and all patients with PH (6 out of 40) belonged to group D. PH was observed in 6 of the 15 patients whose mean nocturnal $Stco_2$ was <90% but in none of the 25 with a mean nocturnal $Stco_2$ >90%. The PH patients (n=6), all desaturators, differed from the desaturators with no PH (n=12), and from ND (n=22) in having higher numbers of desaturation dips, longer durations of dips, and lower mean nocturnal arterial oxygen saturation (Sao_2).

We conclude that a causal relation between nocturnal desaturation and permanent PH is very likely. Further studies are needed to see whether oxygen therapy can prevent PH in these patients.

Eur Respir J., 1992, 5, 301–307.

Depts of pulmonology of Amiens (France), Strasbourg (France), Veruno (Italy), Freiburg (Germany).

Correspondence: P. Levi-Valensi,
Pneumologie
hôpital sud,
80054
Amiens cedex
France.

Keywords: Causes of pulmonary hypertension in COPD; chronic obstructive pulmonary disease (COPD); mild daytime hypoxaemia; pulmonary hypertension; sleep related hypoxaemia.

Received: December, 1990
accepted after revision October 16, 1991.

This study was conducted by the European multicentre group, Chairman - P. Levi-Valensi, (France) and initiated by the International Oxygen Club (IOC). Composition of the group: Z. Rida, P. Aubry, P. Levi-Valensi, V. Jounieaux, D. Rose; Amiens (France): H. Matthys, G. Würtemberger; Frieberg (W. Germany): J.M. Bedicam, P. Escourrou, C. Gaultier; Paris, (France): M. Aprill, J. Krieger, E. Weitzenblum; Strasbourg, (France): A. Braghiroli, C. Donner; Veruno, (Italy): J. Cieslicki; P. Sliwinski; J. Zielinski, Warsaw (Poland).

In patients with advanced chronic obstructive pulmonary disease (COPD) hypoxaemia generally worsens during sleep and particularly during rapid-eye-movement (REM) sleep [1–3]. Sleep-related O_2 desaturation occurs more frequently in the "blue and bloated" type of COPD patients, exhibiting daytime hypoxaemia and hypercapnia [3, 4], but it is not possible to predict with sufficient accuracy nocturnal hypoxaemia from daytime data [5]. A significant sleep-related desaturation may be observed in patients whose daytime arterial oxygen tension (Pao_2) is >60 mmHg (8 kPa) [6], but the prognostic value of a nocturnal desaturation in excess of that predicted from daytime arterial blood gases has been denied in a recent study [7].

A close relationship between desaturation dips and peaks of pulmonary hypertension (PH) has been observed by several groups [8–11] and administration of supplemental O_2 during sleep has been shown to decrease pulmonary artery mean pressure (PAP) [9, 11]. It has been hypothesized that nocturnal desaturation occurring in patients with mild (Pao_2 >60 mmHg; 8 kPa) or absent daytime hypoxaemia, could lead, with time, to permanent PH [12, 13], but studies in this field have been rather scarce [14, 15] and need further confirmation. This question is of more than theoretical interest, since nocturnal oxygen therapy could be justified if isolated nocturnal desaturation might by itself induce permanent PH.

We thus decided to investigate the relationship between sleep-related desaturation and daytime pulmonary haemodynamics in COPD patients exhibiting mild daytime hypoxaemia (Pao_2 in the range 60–70 mmHg; 8–9.3 kPa). This multicentre study involved six European centres, which allowed the inclusion of 40 patients.

Methods

Forty patients were included in this prospective multicentre study on the following criteria: history of chronic bronchitis and diagnosis of COPD assessed by the results of pulmonary function tests. A forced expiratory volume/vital capacity (FEV_1/VC ratio <75% of the predicted value as well as a total lung capacity (TLC)/predicted TLC ratio >75%.

Daytime Pao_2 between 60–70 mmHg (8–9.3 kPa). Recorded Pao_2 was the mean of three measurements performed at intervals of two weeks, in patients free of acute exacerbation, in a stable state of the disease. Arterial blood samples were drawn from the patient breathing ambient air, in the morning, after a 15 min resting period in the supine position. We excluded from the study patients with systemic hypertension (systemic diastolic pressure >100 mmHg), and those with left heart or congenital heart diseases. We also excluded patients with obstructive sleep apnoea, defined by an apnoea index >5, patients with any other associated chronic lung disease, and those receiving almitrine bismesylate or other respiratory analeptics.

Each patient spent one night in the sleep laboratory. Whole night sleep studies were performed using standard polysomnographic techniques including electroencephalogram (C4/A1; C3/A2), bitemporal electro-oculogram and submental electromyogram, with surface electrodes. Nasal and oral airflows were detected by thermistors. Respiratory rib cage and abdominal movements were detected using pneumobelts connected to pressure transducers. Transcutaneous saturation ($Stco_2$) was continuously recorded with an ear oximeter or a pulse oximeter. All variables were recorded simultaneously by means of a polygraph.

Sleep stages were scored using scoring epochs of 20 s according to usual criteria [16]. Time in bed (TIB) was defined as the total duration from the start of - to the end of - recording. Total sleep time (TST) was defined as TIB less sleep latency + intra-sleep wakefulness. The minimal TST required for a satisfactory analysis of sleep recordings was two hours.

The baseline blood oxygen saturation was measured with the subject in the supine position, and awake, during the half hour preceding the onset of sleep. A desaturation dip was defined as a fall of $Stco_2$ by >4% from the awake baseline value. Mean nocturnal $Stco_2$ was measured manually in some centres and by means of a computer program in others.

Right heart catheterization was separated by no more than one week from sleep recordings and was performed as reported previously [17]. Briefly, patients were investigated in the supine position, in the morning, without premedication, two hours after a light breakfast. Right atrial, right ventricular, pulmonary artery and pulmonary wedge pressures were measured using balloon-tipped catheters introduced percutaneously. Systolic, diastolic and mean pressures were averaged over five respiratory cycles. The zero reference was at mid-thoracic level. An indwelling catheter was introduced in the radial or brachial artery for measurement of blood gases. Cardiac output was calculated according to the Fick principle applied to oxygen. Measurements were obtained during the last minute of a 15 min resting period, and during the last minute of a 10 min steady-state exercise performed on an ergometric bicycle, the load being 30 W. Exercise data could be obtained in 35 out of 40 patients. An informed consent was obtained from all patients.

Statistical analysis

Student's t-test was used for the comparison between groups (desaturators *vs* non-desaturators); simple and multiple regression analysis. Computations were carried out using Stat-View 512 Software (Brainpower, Inc.).

Results

Patients were divided into two groups according to the presence or not of significant nocturnal desaturation which was defined as spending 30% or more of the time in bed (TIB) with a $Stco_2$ <90%. A percentage of TIB rather than TST was chosen because it appeared more clinically meaningful. There was a very high correlation between desaturation time/TIB and desaturation time/TST (r=0.9). Furthermore, 30% desaturation/TIB approximately corresponded to 40% desaturation/TST. Eighteen patients were desaturators (group D) and 22 were non-desaturators (group ND).

Pulmonary volumes and daytime arterial blood gases (table 1).

Airway obstruction was moderate to severe and was similar in both groups. By definition, daytime hypoxaemia was modest, Pao_2 ranging between 60–70 mmHg (8–9.3 kPa). The mean Pao_2 and arterial carbon dioxide tension ($Paco_2$) were identical in the two groups. Thus, daytime data could not discriminate D from ND patients.

Sleep variables (table 2)

Awake baseline $Stco_2$ was >90% in all patients; it was lower in group D ($p<0.0001$). As expected, mean and lowest nocturnal saturations were lower in group D ($p<0.0001$ and $p<0.01$, respectively). TIB with $Stco_2$ <90% was, by definition, higher in group D (60±20% of TIB) than in group ND (5±7%). The number of desaturation dips did not discriminate the two groups, whereas the total duration of desaturation dips was higher in group D ($p<0.01$). Total sleep time (TST), sleep efficiency and the time spent in each sleep stage were identical in groups D and ND.

Table 1. – Anthropometric and daytime functional data of the two groups: desaturation (D) and non-desaturation (ND)

	Group D (n=18)		Group ND (n=22)		D *vs* ND t-test
	n	mean±SD	n	mean±SD	p
Age yrs	18	63±6	22	63±5	NS
Weight % pred	18	107±14	22	107±17	NS
TLC % pred	13	103±12	14	100±15	NS
VC % pred	18	60±13	22	66±15	NS
FEV_1 % pred	18	31±10	22	33±8	NS
FEV_1/VC % pred	18	51±13	22	49±8	NS
Haemoglobin $g \cdot l^{-1}$	18	148±1.4	22	152±1.0	NS
Pao_2 mmHg	18	63.5±1.9	22	63.6±2.1	NS
$Paco_2$ mmHg	18	41.5±3.3	22	41.0±6.1	NS

Weight % pred: according to Lorenz formula; TLC: total lung capacity; VC: vital capacity; FEV_1: forced expiratory volume in one second; RV: residual volume; Pao_2, $Paco_2$: arterial oxygen and carbon dioxide tension, respectively, (mean of three daytime measurements) (see text).

Table 2. – Sleep variables of groups: desaturators (D) and non-desaturators (ND)

	Group D		Group ND		D *vs* ND t-test
	n	mean±SD	n	mean±SD	p
Baseline $Stco_2$ awake %	18	91.0±1.1	22	93.4±1.2	<0.0001
Mean nocturnal $Stco_2$ %	18	88.6±1.9	22	92.4±1.2	<0.0001
Lowest nocturnal $Stco_2$ %	18	77.6±7.0	21	83.0±5.7	<0.01
% of TIB with $Stco_2$ ≥90%	18	60±20	22	5±7	<0.0001
Number of desaturation dips	17	39±43	22	30±38	NS
Total duration of desaturation dips min	18	105±137	21	14±19	<0.01
Apnoea index apnoea·h^{-1}	18	0.8±1.4	22	1.6±2.5	NS
TIB min	18	382±73	22	423±96	NS
TST min	18	280±98	22	325±90	NS
Sleep efficiency TST/TIB %	18	74±19	22	77±13	NS
Stage 1/TST %	17	29±16	20	21±13	NS
Stage 2/TST %	17	49±13	19	49±11	NS
Stage 3/TST %	16	5±6	13	9±9	NS
Stage 4/TST %	12	2±5	9	4±6	NS
REM-sleep/TST %	17	14±13	19	16±6	NS

TIB: time in bed; TST: total sleep time; $Stco_2$: oximeter (transcutaneous) oxygen saturation (for definition of these variables see text); REM: rapid eye movement.

Prediction of nocturnal desaturation from daytime variables

The linear correlations between daytime (Pao_2, $Paco_2$, FEV_1, FEV_1/VC) and nocturnal variables (mean nocturnal $Stco_2$, lowest nocturnal $Stco_2$ and TIB <90%), were not statistically significant. However, baseline awake $Stco_2$ was correlated with mean nocturnal $Stco_2$ ($r=0.78$, $p<0.0001$) with lowest nocturnal $Stco_2$ ($r=0.49$, $p<0.001$) and with TIB <90% ($r=-0.73$, $p<0.0001$). Multiple regession analysis did not improve the prediction of TIB <90% or of mean nocturnal $Stco_2$.

Pulmonary haemodynamics (table 3)

Resting PH, defined by a PAP>20 mmHg, was only present in six patients, all belonging to group D. Pulmonary wedge pressures were normal at rest but rose markedly during exercise in group D patients. Cardiac index did not differ between the groups.

In group D, mean PAP was significantly higher than in group ND ($p<0.05$), but there was, infact, an important overlapping of individual values between the two groups (figure 1). Pulmonary artery diastolic pressure was higher in group D ($p<0.01$) but there was no difference between the two groups with regard to pulmonary artery systolic pressure or pulmonary vascular resistanece. Exercising PAP was nearly identical in D and ND patients.

Relationship between nocturnal desaturation and pulmonary hypertension

Resting PH was present in 6 out of 18 group D patients, but in none of group ND patients ($p<0.01$) (table 3 and fig. 1). The threshold value of 90% for mean nocturnal $Stco_2$ allowed a good discrimination between patients with and without PH in the 25 patients whose mean nocturnal $Stco_2$ was >90%, PAP was <20 mmHg, whereas in the 15 patients with a mean nocturnal $Stco_2$ <90%, PH was present in six and the difference between the proportions was highly

significant ($p<0.001$). The six PH patients were compared to the 12 non-PH desaturators and to the 22 non-desaturators (table 4). The lung volumes, daytime Pao_2, age, smoke between the three groups. Only $Paco_2$ was higher in PH as compared to that of non-PH desaturators ($p<0.05$). The nocturnal saturation profile, however, showed more differences (table 5).

Table 3. – Haemodynamic data of the PH-desaturators (D) as compared with the non-PH desaturators and with the non-desaturators (ND) (values of t-test in brackets)

	D		ND
	PH n=6	non-PH n=12	all non-PH n=22
Mean PAP rest mmHg	25±3.8	16±2 (0.0001)	17±2 (0.0001)
Systolic PAP mmHg	36±4.4	26±2.4 (0.0001)	28±4.2 (0.0001)
Diastolic PAP mmHg	17±5.2	12±2 (0.001)	11±2.4 (0.0002)
PWP rest mmHg	7±4.2	7±2.4 (NS)	6±2.6 (NS)
RAP mmHg	5±4.6	4±4.6 (NS)	2±2 (NS)
Cardiac index $l \cdot min^{-1} \cdot m^2$	3±0.7	3±1.0 (NS)	3±0.8 (NS)
Heart rate beats·min^{-1}	90±21	87±14 (NS)	79±9 (NS)
PVR dynes·s·cm^{-5}	251±130	141±33 (NS)	185±64 (NS)
Mean PAP exercise mmHg	46±9.3	32±8 (0.01)	34±9 (0.02)
Mean PWP exercise mmHg	16±10	18±9 (NS)	12±2.4 (NS)

PAP: pulmonary artery pressure; PWP: pulmonary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; PH: pulmonary hypertension.

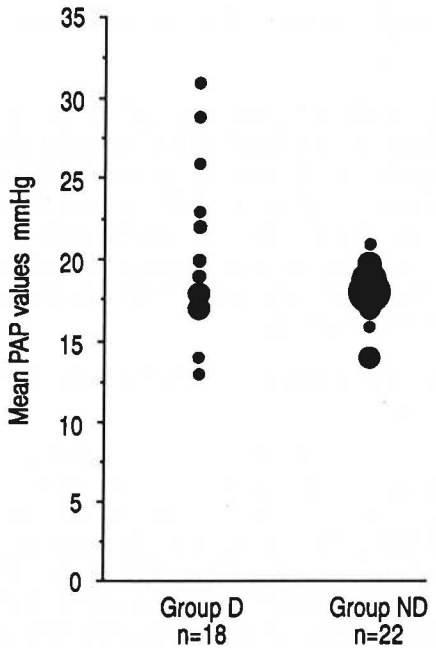

Fig. 1. – Distribution of the mean PAP values in desaturators (D) and non-desaturators (ND). PAP: pulmonary artery pressure.

Table 4. – Daytime functional and anthropometric data in the PH-desaturators (D) as compared with the non-PH desaturators and with the non-desaturators (ND) (values of t-test in brackets)

	D		ND
	PH n=6	non-PH n=12	all non-PH n=22
Pao_2 mmHg	64±1.9	63±1.9 (NS)	64±2.1 (NS)
$Paco_2$ mmHg	44±3.9	41±2.5 (p<0.05)	41±6.1 (NS)
FEV_1 % pred	33±12	31±9 (NS)	33±8 (NS)
FEV_1/VC % pred	54±17	50±12 (NS)	50±9 (NS)
VC % pred	52±13	64±12 (NS)	67±15 (NS)
TLC % pred	104±9	104±13 (NS)	100±15 (NS)
Age yrs	61±4	64±7 (NS)	63±5 (NS)
Weight % pred	107±19	106±11 (NS)	107±19 (NS)
Smoking pack-yrs	39±20	38±30 (NS)	37±20 (NS)

% pred: percentage predicted; PH: pulmonary hypertension. For further abbreviations see legend to table 1.

Table 5. – Nocturnal saturation parameters of the PH-desaturators (D) as compared with the non-PH desaturators and with the non-desaturators (NS) (value of t-test in brackets)

	D		ND
	PH n=6	non-PH n=12	all non-PH n=22
Baseline Sao_2 %	90.2±1.0	90.9±1.1 (NS)	93.4±1.2 (0.001)
Mean nocturnal Sao_2 %	87.7±2.2	89.0±1.8 (NS)	92.4±1.2 (0.0001)
Nadir Sao_2 %	75.5±2.2	78.8±6 (NS)	83.0±6 (0.02)
% TIB <90% of Sao_2	62±12	56±21 (NS)	5±7 (0.0001)
Number of dips/TIB <4%	71±60	26±26 (0.04)	30±38 (0.07)
Total duration of dips min	189±179	63±93 (0.06)	14±19 (0.0001)

Sao_2: arterial oxygen saturation; TIB: time in bed; PH: pulmonary hypertension

Mean nocturnal $Stco_2$ and nadir $Stco_2$ were significantly lower in the PH group when compared to the non-PH-ND group, but nonsignificantly when compared to the non-PH-D group. Two other parameters seemed to better distinguish PH-D from non-PH-D and from non-PH-ND: the total number of desaturation dips <4% and th total duration of dips. Significant correlation exists between mean PAP and the total duration of dips ($r=0.33$; $p<0.03$; 95% confidence interval of $r=0.06$–0.57) (fig. 2).

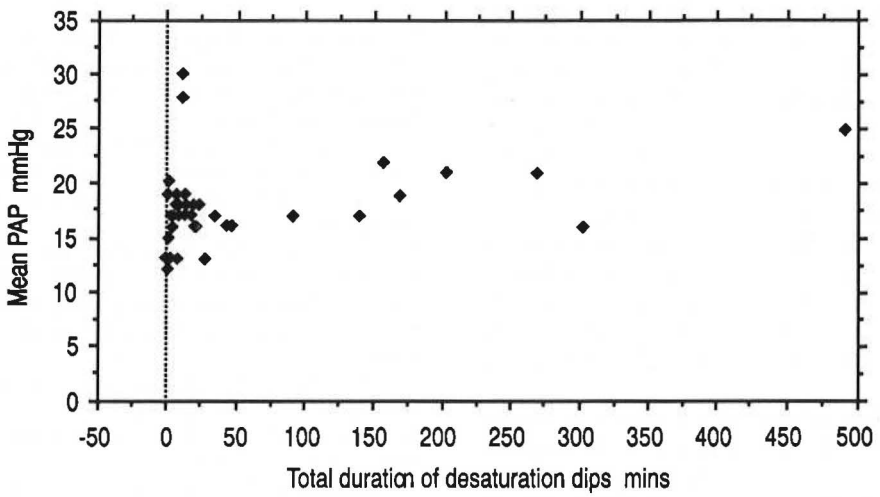

Fig. 2. – Mean PAP plotted against the total duration of desaturation dips r=0.33; p<0.03; 95% confidence interval of r=0.06–0.57. PAP: pulmonary artery pressure.

Discussion

In the present study, PH patients were exclusively found in the group of desaturators (6 out of 18 *vs* 0 out of 22). These six patients spent 62±12% of TIB with a $Stco_2$ <90%, whereas the 12 non-PH-D patients spent 56±21% and the 22 ND, by definition, spent <30% of TIB with a $Stco_2$ <90%. Furthermore, PH was found in 6 out of 15 patients whose mean nocturnal $Stco_2$ was <90%, but in none out of 25 of those with mean nocturnal $Stco_2$ >90%. The total number and duration of desaturation dips was higher in PH patients. Two PH patients curiously appear to have only few and short dips. This finding may be explained by the possible incipient exacerbation of their disease.

Thus, PH may be observed in COPD patients with slight daytime hypoxaemia (Pao_2 in the range 60–70 mmHg; 8–9.3 kPa) provided that they desaturate ($Stco_2$ <90%) during a sufficient time (>30%) while asleep. These findings are in good agreement with those of FLETCHER and co-workers [14], who found that PAP was significantly higher (p<0.05) in desaturators (n=36) than in non-desaturators (n=13). Infact, the difference between their average values was rather small (23.3±4.8 *vs* 20.4±4.2 mmHg, respectively) and there was overlapping of individual values of PAP from one group to another. There are at least two major differences between the studies of Fletcher and co-workers [6, 14, 15], which were the first in this field, and our own: the first is a methodological difference, since FLETCHER and co-workers defined a significant nocturnal desaturation as a five minute desaturation <90%, with a nadir desaturation level of at least 85%, whereas we required that 30% of TIB should be spent <90%. Furthermore, they included COPD patients with a Pao_2 >60 mmHg, which means that some patients had mild daytime hypoxaemia and others had no hypoxaemia at all. We restricted our study to patients with modest daytime hypoxaemia (Pao_2 60–70 mmHg; 8–9.3 kPa). The second difference concerns the results: as a mean the patients of FLETCHER and co-workers [14, 15] had higher resting PAP than ours, even among the non-desaturators, whose resting PAP could exceed 20 mmHg, whereas we have only observed pulmonary hypertension in patients with significant nocturnal desaturation. We have no explanation for this discrepancy, but, in our opinion, the fact that similar differences between D and ND patients could be observed in spite of these disparities in methodology and (possibly) in recruitment of patients, is an additional argument in favour of a relationship between the presence of nocturnal desaturation and the level of PAP in COPD patients with mild (or absent) daytime hypoxaemia.

Previous studies have indicated the presence of a relationship between nocturnal desaturation and right ventricular hypertrophy [18] and PAP [19] in COPD patients. The studies by FLETCHER and co-workers [14, 15] and the present one show that PH can develop in patients with slight daytime hypoxaemia insofar as they exhibit significant sleep-related desaturation, a finding which is consistent with the hypothesis of FLENLEY [13] and BLOCK *et al.* [12] on the possible causes of "incipient cor pulmonale".

Hypoxaemic episodes occurring during sleep, and particularly during REM sleep, have been shown to induce transient elevations of PAP and pulmonary vascular resistance in COPD patients [8–11]. These peaks of pulmonary hypertension may be severe [8, 10], but PAP generally returns to its baseline level after awakening [10]. We do not, at present, know how episodic (sleep-related) nocturnal PH can lead to permanent (daytime) PH, and we do not have a precise idea on the frequency of transient elevations of PAP due to hypoxaemic dips, since the rare studies in this field were obtained in patients with severe COPD, exhibiting marked daytime hypoxaemia and, generally, permanent PH. Other factors than sleep-related desaturation could play a role in the development of daytime PH, and a relationship between exercise desaturation and nocturnal desaturation has

been suggested [20]. If patients with nocturnal desaturation have higher levels of PH during exercise, this could contribute to the development of permanent PH. In the present study, the difference in exercising PAP between group D and group ND was small and nonsignificant (table 2). However, FLETCHER and co-workers [15] have recently observed a higher ($p<0.01$) PAP during exercise in nocturnal desaturators who also exhibited a lower Sao_2 during exercise ($p<0.01$), but exercise desaturation was not predictive of nocturnal desaturation. Thus, the mechanisms of daytime PH in nocturnal desaturators are not clearly understood and could be multifactorial, including the effects of O_2 desaturation and elevated PAP during exercise.

In our patients the presence of significant nocturnal desaturation could not be predicted from daytime pulmonary volumes and arterial blood gases, which were nearly identical in groups D and ND (table 1). Furthermore, the correlations between these data and the level of nocturnal desaturation were not significant. Awake baseline $Stco_2$, which was measured just prior to the onset of sleep, was the only variable statistically linked with mean nocturnal $Stco_2$, lowest nocturnal $Stco_2$ and TIB spent below 90% of $Stco_2$. It must be recalled that daytime Pao_2 was in fact the mean of three measurements performed at intervals of two weeks, and this probably explains why Pao_2 was not correlated with nocturnal variables, whereas awake baseline $Stco_2$ was. In this regard our results slightly differ from these of FLETCHER and co-workers [6] who found that daytime Pao_2 discriminated desaturators from non-desaturators but the range of daytime Pao_2 values was much larger in their series than in our own, as already mentioned. However, the prediction of nocturnal O_2 saturation from awake baseline $Stco_2$ is probably not reliable in individual cases since the correlation coefficients hardly exceeded 0.7, in good agreement with the previous results of MCKEON *et al.* [5] and CORMICK *et al.* [21].

In conclusion, we have observed that significant nocturnal desaturation was rather frequent in COPD patients exhibiting only slight daytime hypoxaemia (Pao_2 in the range 60–70 mmHg; 8–9.3 kPa) and that there was some link between the presence (and level) of nocturnal desaturation and the occurrence of permanent daytime pulmonary hypertension, even if the mechanism of this hypertension is probably multifactorial. Whether long-term nocturnal O_2 therapy could prevent the development and progression of pulmonary hypertension, in patients exhibiting significant nocturnal desaturation, is undoubtedly a question of high practical interest and adequate prospective longitudinal studies are needed in this field. There is no indication as yet to recommend nocturnal oxygen therapy for this type of patient.

Acknowledgements: The authors are indebted to VITAL-AIRE for their technical assistance, to B. Grandsire for group secretarial work and F. Fingar for technological contribution.

References

1. Wynne JW, Block AJ, Hemenway J, Hunt LA, Flick MR. – Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease. *Am J Med,* 1979; 66: 573–579.
2. Douglas NJ, Leggett RJE, Calverley PMA, Brash HM, Flenley DC, Brezinova V. – Transient hypoxaemia during sleep in chronic bronchitis and emphysema. *Lancet,* 1979; i: 1–4.
3. Catterall JR, Douglas HJ, Calverley PMA, Shapiro CM, Brezinova V, Brash HM, Flenley DC. – Transient hypoxaemia during sleep in chronic obstructive pulmonary disease is not a sleep apnea syndrome. *Am Rev Respir Dis,* 1983; 128: 24–29.
4. De Marco FJ, Wynne JW, Block AJ, Boysen PG, Taasan VC. – Oxygen desaturation during sleep as a determinant of the "blue and bloated" syndrome. *Chest,* 1981; 79 (6): 621–625.
5. McKeon JL, Murree-Allen K, Saunders NA. – Prediction of oxygenation during sleep in patients with chronic obstructive lung disease. *Thorax,* 1988; 43: 312–317.
6. Fletcher EC, Miller J, Divine GW, Fletcher JG, Miller T. – Nocturnal oxyhemoglobin desaturation in COPD patients with Pao_2 above 60 mmHg. *Chest,* 1987; 92: 604–608.
7. Connaughton JJ, Catterall JR, Elton RA, Stradling JR, Douglas NJ. – Do sleep studies contribute to the management of patients with severe chronic obstructive pulmonary disease? *Am Rev Respir Dis,* 1988; 138: 341–344.
8. Coccagna G, Lugaresi E. – Arterial blood gases and pulmonary and systemic arterial pressure during sleep in chronic obstructive pulmonary disease. *Sleep,* 1978; 1: 117–124.
9. Boysen PG, Block AJ, Wynne JW, Hunt LA, Flick MR. – Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Chest,* 1979; 76: 536–542.
10. Weitzenblum E, Muzet A, Ehrhart M, Ehrhart J, Sautegeau A, Weber L. – Variations nocturnes des gaz du sang et de la pression artérielle pulmonaire chez les bronchitiques chroniques insuffisants respiratoires. *Nouv Presse Méd,* 1982; 11: 1119–1122.
11. Fletcher EC, Levin DC. – Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. The effect of short and long term oxygen. *Chest,* 1984; 85: 6–14.
12. Block AJ, Boysen PG, Wynne JW. – The origin of cor pulmonale. A hypothesis (editorial). *Chest,* 1979; 75: 109–110.
13. Flenley DC. – Hypoxaemia during sleep. *Thorax,* 1980; 35: 81–84.
14. Fletcher EC, Luckett RA, Miller T, Costarangos C, Kutka N, Fletcher JG. – Pulmonary vascular hemodynamics in chronic lung disease patients with and without oxygen desaturation during sleep. *Chest,* 1989; 95: 757–763.
15. Fletcher EC, Luckett RA, Miller T, Fletcher JG. – Exercise hemodynamics and gas exchange in patients with chronic obstructive pulmonary disease, sleep desaturation and daytime PaO_2 above 60 mmHg. *Am Rev Respir Dis,* 1989; 140: 1237–1245.
16. Rechtschaffen A, Kales A. – *In*: A manual of standardized terminology, technique and scoring system for sleep stages of human sleep. Los Angeles: Brain Information Service. Brain Information Institute, UCLA, 1968.

17. Weitzenblum E, Schrijen F, Mohan-Kumar T, Colas des Francs V, Lockhart A. – Variability of the pulmonary vascular response to acute hypoxia in chronic bronchitis. *Chest,* 1988; 94: 772–778.
18. Midgren B, White T, Peterson T, Bryhn M, Airikala P, Elmkvist D. – Nocturnal hypoxaemia and cor pulmonale in severe chronic lung disease. *Bull Eur Physiopathol Respir,* 1985; 21: 527–533.
19. Sautegeau A, Hannhart B, Begin P, Polu JM, Schrijen F. – Pression artérielle pulmonaire basale diurne et niveau nocturne d'oxygénation chez les bronchitiques chroniques. *Bull Eur Physiopathol Respir,* 1984; 20: 541–545.
20. Kline LR, Goldszmidt AJ, Laufe MD, Pack AI. – Potential predictors of oxygen desaturation during REM sleep in patients with chronic obstructive lung diseases (Abstract). *Am Rev Respir Dis,* 1987; 135: 232A.
21. Cormick W, Olson LG, Hensley MJ, Saunders NA. – Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. *Thorax,* 1986; 41: 846–852.