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A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients

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A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. A. Chaouat, E. Weitzenblum, R. Kessler, C. Charpentier, M. Ehrhart, R. Schott, P. Levi-Valensi, J. Zielinski, L. Delaunois, R. Cornudella, J. Moutinho dos Santos. © ERS Journals Ltd 1999.

ABSTRACT: The beneficial effects of nocturnal oxygen therapy (NOT) in chronic obstructive pulmonary disease (COPD) patients with mild-to-moderate daytime hypoxaemia (arterial oxygen tension (P_{a,O_2}) in the range 7.4–9.2 kPa (56–69 mmHg)) and exhibiting sleep-related oxygen desaturation remains controversial. The effectiveness of NOT in that category of COPD patients was studied. The end points included pulmonary haemodynamic effects after 2 yrs of follow-up, survival and requirement for long-term oxygen therapy (LTOT).

Seventy-six patients could be randomized, 41 were allocated to NOT and 35 to no NOT (control). The goal of NOT was to achieve an arterial oxygen saturation of >90% throughout the night. All these patients underwent polysomnography to exclude an associated obstructive sleep apnoea syndrome. The two groups exhibited an identical means$_D$ daytime P_{a,O_2} of 8.4±0.4 kPa (63±3 mmHg) at baseline.

Twenty-two patients (12 in the NOT group and 10 in the control group, p=0.98) required LTOT during the whole follow-up (35±14 months). Sixteen patients died, nine in the NOT group and seven in the control group (p=0.84). Forty-six patients were able to undergo pulmonary haemodynamic re-evaluation after 2 yrs, 24 in the NOT and 22 in the control group. In the control group, mean resting pulmonary artery pressure increased from 19.8±5.6 to 20.5±6.5 mmHg, which was not different from the change in mean pulmonary artery pressure in the NOT group, from 18.3±4.7 to 19.5±5.3 mmHg (p= 0.79).

Nocturnal oxygen therapy did not modify the evolution of pulmonary haemodynamics and did not allow delay in the prescription of long-term oxygen therapy. No effect of NOT on survival was observed, but the small number of deaths precluded any firm conclusion. These results suggest that the prescription of nocturnal oxygen therapy in isolation is probably not justified in chronic obstructive pulmonary disease patients.

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The beneficial effects of long-term oxygen therapy (LTOT) have been demonstrated in chronic obstructive pulmonary disease (COPD) patients with marked daytime hypoxaemia, *i.e.* in patients with an arterial oxygen tension (P_{a,O_2}) measured in the stable state of the disease, of <7.3 kPa (<55 mmHg) or in the range 7.4–7.8 kPa (56–59 mmHg), and exhibiting "cor pulmonale" or polycythaemia [1, 2]. These beneficial effects include improved survival [1, 2], but also an amelioration of pulmonary haemodynamics [3, 4]. The beneficial effects of LTOT on survival have not been observed in COPD patients with moderate hypoxaemia (P_{a,O_2} in the range 7.4–8.6 kPa (56–65 mmHg)), as indicated by a very recent Polish study [5].

The worsening of hypoxaemia during sleep, and particularly during rapid eye movement sleep, has been well established in patients with advanced COPD [6–10]. It must be underlined, however, that most of these studies have included patients with severe COPD, exhibiting marked daytime hypoxaemia. Conventional LTOT, given for >15–18 h·day^{-1}, compulsorily includes sleep time and, accordingly, sleep-related hypoxaemia is corrected by oxygen therapy. However, sleep-related oxygen desaturation may also be present in patients not qualifying for conventional LTOT, *i.e.* in patients with a diurnal P_{a,O_2} of >7.3–8.0 kPa (>55–60 mmHg) [11], which naturally raises the question: does this hypoxaemia, limited to sleep, deserve treatment with nocturnal oxygen?

Nocturnal oxygen therapy (NOT) could be justified if isolated nocturnal hypoxaemia had deleterious effects on life expectancy, which has not been convincingly demonstrated [12]; and on pulmonary haemodynamics, which is rather controversial. The results of two initial studies [13, 14], suggesting an increased risk of developing pulmonary hypertension in nocturnal desaturators, without

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marked daytime hypoxaemia (P_{a,O_2} 8.0 kPa (≥60 mmHg)), have not been confirmed in a more recent study [15] including a larger group of patients.

On the other hand, NOT could have favourable effects on pulmonary haemodynamic evolution, as suggested by the study of FLETCHER *et al.* [16], which included 38 nocturnal desaturators randomly allocated to NOT or room air; however, control haemodynamic investigations, after 3 yrs, could only be performed in seven patients treated with nocturnal oxygen and in nine patients in the control group. There was some haemodynamic improvement in the treated group ($p<0.02$) but undoubtedly the limited number of patients weakened the bearing of the results. There was no difference in mortality between the two groups.

Probably due to the fact that the recommendations of scientific societies [17] regarding indications for and use of NOT in COPD patients not qualifying for conventional LTOT are presently imprecise, a number of patients are currently treated with NOT although the beneficial effects of this therapy have not yet been firmly established.

Thus, a controlled, multicentric study was undertaken on the long-term effects of NOT, in COPD patients not qualifying for conventional oxygen therapy but exhibiting significant nocturnal desaturation. Seventy-six patients were included and 46 were able to undergo two pulmonary haemodynamic investigations, the first at the onset of the study and the second after 2 yrs. The criteria used for estimating the efficiency of NOT were: its pulmonary haemodynamic effects; its effects on survival; and, finally, its effects on the worsening of respiratory insufficiency (number of patients who required LTOT during follow-up).

Patients and methods

Patients were included in this prospective, multicentric study if they fulfilled the following criteria. 1) A diagnosis of COPD based on the usual clinical and functional grounds. The forced expiratory volume in one second (FEV_1)/vital capacity ratio had to be <60% and the total lung capacity (TLC) >80% of the predicted value [18], in order to exclude restrictive diseases. 2) The presence of mild-to-moderate daytime hypoxaemia, with a daytime P_{a,O_2} in the range 7.4–9.2 kPa (56–69 mmHg) on two measurements separated by 4 weeks, in patients free of acute exacerbation and in a stable state of the disease. Arterial carbon dioxide tension P_{a,CO_2} could be high (≥6.0 kPa (≥45 mmHg) normal or low ≤4.8 kPa (≤36 mmHg). Arterial blood for blood gases analysis was drawn from the patient whilst breathing ambient air in the morning, after a 15-min resting period in the supine position. 3) The presence of a significant nocturnal desaturation, which was defined, as in the authors' previous studies [14, 15] as spending ≥30% of the recording time (time in bed) with a transcutaneous arterial oxygen saturation (S_{a,O_2}) of <90%. A previous study [14] showed that time in bed is strongly correlated with total sleep time, and that 30% of time in bed spent with an S_{a,O_2} of <90% corresponds to ~40% of total sleep time spent with an S_{a,O_2} of <90%.

The great majority of the patients were exsmokers. Current smokers were strongly advised to stop smoking. Patients who did not feel able to stop smoking were not included.

Patients were excluded from the study if they had left heart or congenital heart diseases, interstitial lung diseases, bronchiectasis, lung carcinoma or other severe diseases that could influence survival (hepatic cirrhosis and chronic renal failure). In addition, patients were excluded if they had obstructive sleep apnoea syndrome, defined by an apnoea/hypopnoea index of ≥10 events·h^{-1}. Patients were also excluded if they were receiving almitrine bismesylate or other respiratory analeptics.

Since the presence of obstructive sleep apnoea was an exclusion criterion, patients had to undergo conventional polysomnography in a sleep laboratory. Polysomnography was performed as reported previously [14, 15]. Standard techniques, including electroencephalography (C4/A1; C3/A2), electro-oculography and submental electromyography were used. Nasal and oral airflows were detected *via* thermistors. Ribcage and abdominal movements were detected using pneumobelts. Transcutaneous S_{a,O_2} was continuously recorded using a pulse oximeter. The baseline S_{a,O_2} was measured with the subject awake, in the supine position during the 30 min preceding the onset of sleep. The mean nocturnal S_{a,O_2} and the percentage of recording time with an S_{a,O_2} of <90% were calculated using computer software.

Thus, patients underwent two oximetric studies; the first involved simple all-night oximetry. The second, separated from the first study by ≤2 weeks, was combined with polysomnography. The percentage of the recording time (time in bed) with an S_{a,O_2} of <90% had to be ≥30% in both instances. The results given in tables 1 and 2 are those of the second oximetry.

Table 1. – Initial anthropometric, functional, gasometric and haemodynamic data

Variable	NOT group	Control group	p-value
Patients n	41	35	NS
Age yrs	63±8	64±6	NS
BMI kg·m^{-2}	26.4±4.9	27.8±4.9	NS
VC mL	2680±980	2849±910	NS
% pred	72±19	76±17	NS
FEV_1 mL	1080±500	980±310	NS
% pred	39±16	35±11	NS
FEV_1/VC (%)	41±13	36±10	NS
TLC mL	6320±1760	6910±1625	NS
% pred	103±22	110±19	NS
P_{a,O_2} mmHg	62.6±3.0	62.8±3.0	NS
P_{a,CO_2} mmHg	44.4±5.6	44.9±4.9	NS
PAP, rest mmHg	19.7±5.3	19.5±5.3	NS
PAP, exercise mmHg	37.1±7.4	38.4±9.8	NS
PCWP mmHg	7.4±3.0	8.4±3.7	NS
Cardiac output L·min^{-1}·m^{-2}	2.9±6.4	3.0±8.3	NS
Nocturnal S_{a,O_2} %	88±2	88±3	NS
tS_{a,O_2} <90% %	65±24	69±23	NS

Data are presented as mean±SD. NOT: nocturnal oxygen therapy; BMI: body mass index; VC: vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; PAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; S_{a,O_2}: arterial oxygen saturation; tS_{a,O_2} <90%: recording time spent with an S_{a,O_2} <90% ; NS: nonsignificant.

Table 2. – Gasometric and pulmonary haemodynamic variables at *t*0 to *t*2 in the nocturnal oxygen therapy (NOT) and control group

Variables	NOT group		Control group		p-value*
	*t*0	*t*2	*t*0	*t*2	
Patients n	24		22		
BMI kg·m^{-2}	26.7±3.6	26.7±3.6	29.1±3.9	29.4±4.2	NS
VC mL	2660±880	2550±720	2800±1040	2770±930	NS
% pred	72.9±15.9	71.0±13.6	79.0±19	81.0±20.2	NS
FEV1 mL	1070±480	1010±420	940±220	1020±330	NS
% pred	38.5±15.0	37.0±13.1	35.9±8.7	39.7±12.3	NS
FEV1/VC (%)	41.1±12.3	39.7±11.5	36.6±9.9	38.1±10.2	NS
TLC mL	5950±1750	6050±1800	6570±1890	6310±1440	NS
% pred	97.0±21.5	98.9±23.8	108.0±20.6	103.3±12.0	NS
P_{a,O_2} mmHg	63.0±3.3	62.2±7.4	63.1±2.8	64.5±5.7	NS
P_{a,CO_2} mmHg	45.0±5.6	46.3±5.9	44.3±4.2	44.9±5.6	NS
PAP,rest mmHg	18.3±4.7	19.5±5.3	19.8±5.6	20.5±6.5	NS
PAP, exercise mmHg	35.2±7.2	38.3±10.3	36.2±11.7	37.1±11.3	NS
PCWP mmHg	7.8±3.1	8.8±4.5	10.1±4.0	9.5±4.2	NS
Cardiac output L·min^{-1}·m^{-2}	2.86±0.51	3.16±0.51	3.01±0.74	3.14±0.64	NS
Nocturnal S_{a,O_2} %	87.9±2.7	87.9±4.2	88.6±2.0	89.3±2.9	NS
tS_{a,O_2} <90% %	62.5±25.3	57.9±31.9	64.7±24.8	51.2±36.2	NS

Data are presented as mean±SD. *: within-group at 2 yrs (*t*2) *versus* at onset of study (*t*0) (paired t-test) or (*t*2-*t*0) between the two groups (t-test for impaired data). NOT: nocturnal oxygen therapy; BMI: body mass index; VC: vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; PAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; S_{a,O_2}: arterial oxygen saturation; tS_{a,O_2} <90%: recording time spent with an S_{a,O_2} <90% ; NS: nonsignificant.

Pulmonary volumes were measured by means of conventional spirometry. Static volumes were measured *via* the helium-dilution method. The reference values were those of the European Respiratory Society [18].

Right heart catheterization was separated from polysomnography by ≤1 week, and was performed as reported previously [19]. Patients were investigated in the supine position, in the morning, after a light breakfast. Either balloon-tipped Swan-Ganz catheters or small Grandjean floating catheters [20] were introduced percutaneously. Systolic, diastolic and mean pressures were averaged over five respiratory cycles. The zero reference was at mid-thoracic level. A catheter was introduced into the radial artery for measurement of arterial blood gas tensions. Cardiac output was calculated according to the Fick principle applied to oxygen, measurements being obtained during the last minute of a 15-min resting period. In most of the patients, measurements could also be obtained during the last minute of a 7-min steady-state exercise performed on an ergometric bicycle, in the supine position; the load being 40 W, or less in patients who were too breathless.

From November 1992 to January 1996, 118 patients were recruited from six hospital outpatient clinics of four European countries. These COPD patients were in a stable state of their disease, with a P_{a,O_2} in the range 7.4–9.2 kPa (56–69 mmHg). Of these 118 patients, 11 refused to undergo right heart catheterization, two had associated obstructive sleep apnoea syndrome and 29 did not exhibit sleep-related hypoxaemia as defined above. Subsequently, 76 patients (fig. 1) fulfilled the above criteria and were randomly allocated to NOT or no NOT (control group). Each centre was provided with a different table of random sampling numbers with the instruction to allocate prospectively, in well-determined order, NOT to even numbers and no NOT to odd numbers. In the NOT group, oxygen therapy was given for 8–10 h·night^{-1}. The flow of oxygen used was that that allowed the nocturnal S_{a,O_2} to be constantly >90%. This was assessed by means of pulse oximetry during a full-night recording. In most cases, the oxygen flow was 2 L·min^{-1}. Oxygen was provided from a concentrator and was given *via* nasal prongs. The compliance with the treatment was checked by reading the oxygen meter built into the oxygen concentrator.

Patients were regularly followed-up, once every 3 months, with the measurement of ambient air arterial blood gas levels. Patients whose daytime P_{a,O_2} persistently fell below 7.3 kPa (55 mmHg) during the follow-up (at least two arterial blood gas measurements separated by 1 month and not performed during an acute exacerbation of the disease) were given conventional LTOT (≥18 h·day^{-1}). The survival of and requirement for LTOT of the 76 randomized patients were monitored until January 1, 1998, which corresponded to a delay of 2 yrs after the last inclusion. In order to determine the pulmonary haemodynamic effect of NOT, all the investigations listed above, except polysomnography, but including pulmonary haemodynamic measurements, were repeated after 2 yrs. In keeping with the aim of the study, pulmonary haemodynamic measurements were not re-evaluated in the patients who required LTOT during the first 2 years of follow-up.

Informed consent was obtained from each patient and the study protocol was approved by the Ethics Committee of the University Hospital of Strasbourg (France).

Statistical analysis

SPSS computer software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. All data were expressed as meansd. The group of NOT patients and the control group were compared using Student's t-test for

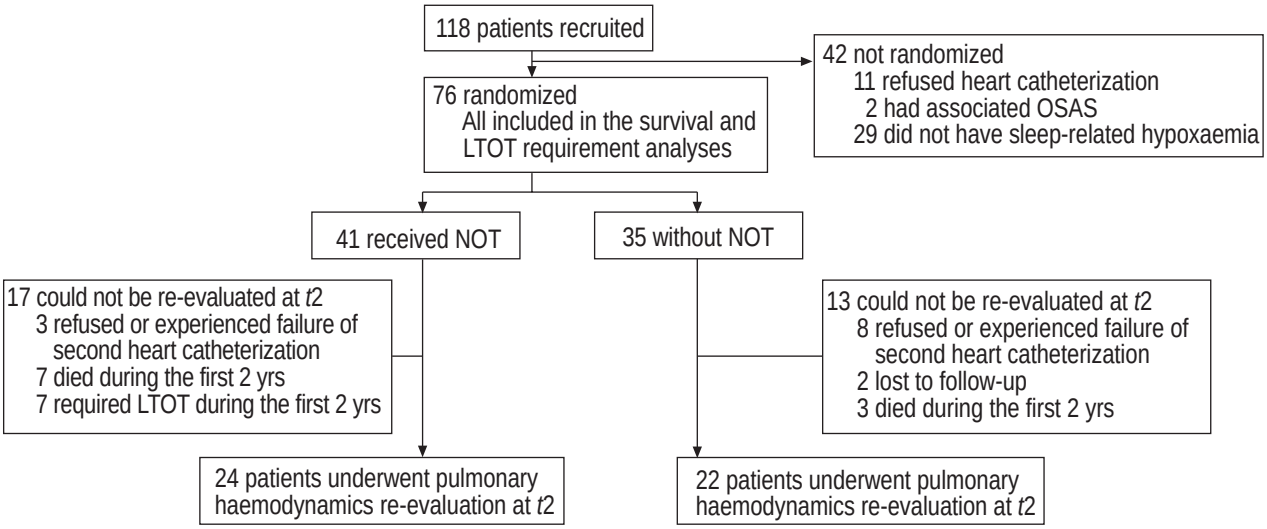

Fig. 1. – Trial profile. OSAS: obstructive sleep apnoea syndrome; LTOT: long term oxygen therapy; NOT: nocturnal oxygen therapy; *t*2: 2-yrs follow-up time point.

unpaired data. Student's t-test was also used when comparing other subgroups (defined below). The evolution of the main anthropometric, spirometric, gasometric and pulmonary haemodynamic variables from *t*0 to *t*2, in NOT and control patients, was compared using Student's t-test for paired samples. Survival rates and requirement for LTOT rates were calculated according to the Kaplan-Meier method. To test the equality of the survival distributions of the two randomized groups a log rank test was used. This was performed according to intention-to-treat. In all statistical tests, a p-value of 0.05 was accepted as significant.

If it is assumed that a favourable effect of NOT in terms of change in mean pulmonary artery pressure (PAP) corresponds to a increase of 2 mmHg from *t*0 to *t*2 in the control group, and to a decrease of 2 mmHg in the NOT group (according to the results of FLETCHER *et al.* [16] who observed mean changes of +3 and -3 mmHg over a 3-yr follow-up period), it has been calculated, taking into account the SD of PAP in the patients (4–5 mmHg), that the inclusion of 20 patients in each group (control and NOT) allows the achievement of a power of 80% at the significance level of 0.05.

Results

Follow-up, survival rates and prescription of conventional long-term oxygen therapy during the follow-up

Seventy-six patients could be included in the study. Forty-one were randomly allocated to NOT and 35 to no NOT (control group). The initial anthropometrical functional, gasometric and haemodynamic data of the two groups are compared in table 1: the two groups were identical with regard to all variables. As could be expected, taking into account the inclusion criteria, hypoxaemia was generally mild with a mean±SD P_{a,O_2} of 8.4±0.4 kPa (63±3 mmHg) in both groups. The P_{a,CO_2} and mean pulmonary artery pressure (PAP) were at the upper limit of the normal range (6.0 and 2.7 kPa (45 and 20 mmHg) respectively). The nocturnal S_{a,O_2} was 88% in both groups. Airway obstruction was moderate to severe.

Forty-two patients were included from the co-ordinating centre. When these latter patients were compared with the other 34 patients, no differences were observed for all variables listed in table 1 (data not shown).

The follow-up period ranged 2.5–60 months with a mean±SD of 35.1±14.3 months. During this follow-up, the daily compliance with oxygen therapy of the 41 patients allocated to NOT, excluding all periods of LTOT treatment, was 8.9±1.9 h·day^{-1} (range 6.0–14.2). In 11 patients, the follow-up period was ≤1 yr (five patients died within 1 yr and six were given conventional LTOT). There were nine deaths in the NOT group (of 41) and seven deaths in the control group (of 35) (fig. 2a); this difference was not statistically significant (p=0.84) using the log rank test). As indicated above (*Statistical analysis*), all the 76 randomized patients were analysed on an intention-to-treat even if conventional LTOT was required during the follow-up. Five patients died during LTOT, two in the NOT group and three in the control group. When survival analysis was adjusted to LTOT exposure, similar results to those obtained in the intention-to-treat analysis were reached.

The patients whose P_{a,O_2} persistently fell below 7.3 kPa (55 mmHg) during the follow-up did not continue with the treatment (NOT or not NOT) initially allocated and were prescribed conventional LTOT (≥18 h·day^{-1}). An almost identical number of patients in each group were given conventional LTOT during the whole follow-up (fig. 2b), 12 in the NOT group and 10 in the control group (the difference was not statistically significant; p=0.98 using the log rank test). When both events were analysed, death or requirement for LTOT, disease-free survival rates were also similar (p=0.68 using the log rank test) in the two randomized groups. These events occurred in 19 of the 41 patients allocated to NOT *versus* 14 of the 35 patients of the control group.

Evolution of pulmonary haemodynamics

Of the 76 patients who were included at the onset of the study (*t*0), only 46 underwent the second pulmonary

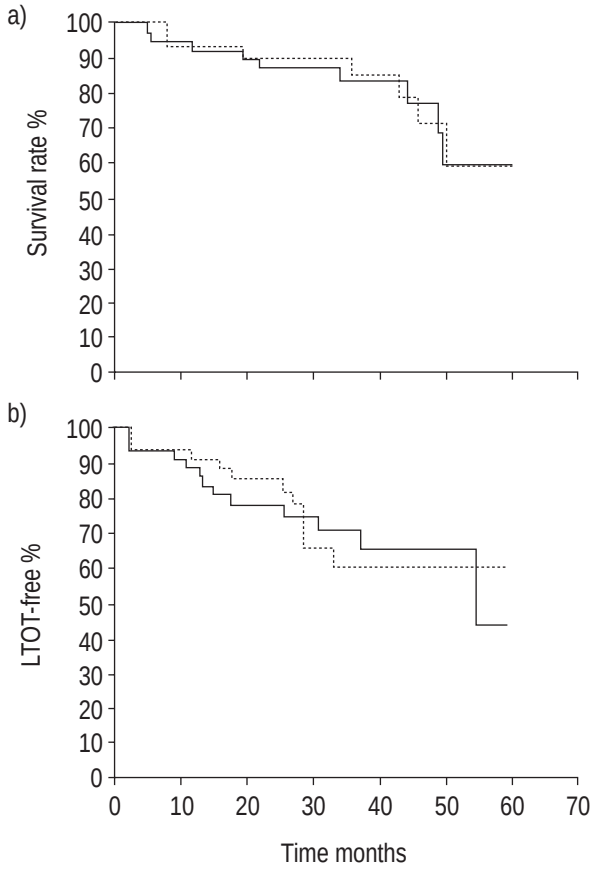

Fig. 2. – Kaplan-Meier curves for: a) survival; and b) requirement for long term oxygen therapy (LTOT). The risk of death was not significantly different (p=0.84 using the log rank test) in the 41 patients randomized to nocturnal oxygen therapy (NOT; ——) compared with the 35 patients without NOT (control group; - - -). Similarly, the risk of worsening of respiratory failure was not significantly different (p=0.98 using the log rank test) in the two groups.

haemodynamic investigation that took place after 2 years (*t*2). Right heart catheterization could not be performed at *t*2 in 11 patients (refusal or failure), three in the NOT group and eight in the control group. Two patients, both from the control group, were lost to follow-up. Ten patients died within 2 yrs, seven in the NOT group and three in the control group. Finally, seven additional patients were prescribed conventional LTOT during the first 2 yrs of follow-up, all in the NOT group. The second right heart catheterization after 2 yrs (*t*2) could be performed in 24 NOT and 22 control patients (fig. 1).

The 46 patients who completed the study did not differ from the 30 who could not with regard to initial (*t*0) anthropometric, spirometric, gasometric, oximetric and pulmonary haemodynamic data (data not shown).

Table 2 gives the initial (*t*0) and follow-up (*t*2) data from the two groups of patients who could complete the study. Again, it can be observed that there was no difference at *t*0 between the NOT (n=24) and the control group (n=22) with regard to pulmonary volumes, arterial blood gas tensions, nocturnal desaturation and pulmonary haemodynamic data. By definition, the percentage of the recording time with a nocturnal S_{a,O_2} <90% was high (>30%) in both groups. The initial PAP was 18.3±4.7 mmHg in NOT patients, and 19.8±5.6 mmHg in control patients. Pulmonary hypertension, defined by a resting PAP of ≥20 mmHg, was observed in nine of 24 NOT patients and in 10 of 22 control patients. As could be expected in these patients with advanced COPD, exercising PAP was abnormally high in patients receiving NOT (35.2±7.2 mmHg) as well as in control patients (36.2±11.7 mmHg).

The evolution of the main variables from *t*0 to *t*2 is shown in table 2. In NOT as well as in control patients, there was no significant change in pulmonary volumes, P_{a,O_2}, P_{a,CO_2} and resting and exercising PAP. There was no difference between the two groups with regard to the change in any variable from *t*0 to *t*2. In the control group, resting PAP varied from 19.8±5.6 to 20.5±6.5 mmHg, which was not different from the change in PAP in the NOT group, from 18.3±4.7 to 19.5±5.3 mmHg (p=0.79). When considering only the small subgroups of patients with pulmonary hypertension at the onset (*t*0), PAP varied from 23.6±2.5 to 21.8±5.5 mmHg in the nine NOT patients (p=0.21) and from 25.0±3.6 to 24.4±6.2 mmHg in the 10 control patients (p=0.74). The chronological changes in exercising PAP were also not significant, from 36.2±11.7 to 37.1±11.3 mmHg in the control group (n=10, p=0.78) and from 35.2±7.2 to 38.3±10.3 mmHg in the NOT group (n=14, p=0.37).

Discussion

This study has shown that NOT given to COPD patients not justifying conventional LTOT, but exhibiting sleep-related oxygen desaturation, did not alter the evolution of pulmonary haemodynamics. Furthermore, NOT did not allow delay in the initiation of conventional LTOT since similar numbers of patients in the NOT group and in the control group required this treatment during the follow-up, due to the worsening of arterial hypoxaemia. The analysis of survival must be interpreted with caution taking into account the small number of deaths in each group: nine deaths in the NOT group (of 41) and seven in the control group (of 35). Indeed the difference was not statistically significant, however, different result had the numbers of patients (and accordingly the numbers of deaths) been markedly higher cannot be excluded.

To the best of the authors' knowledge, only one controlled study, that of FLETCHER *et al.* [16], has investigated the influence of NOT on survival in COPD patients with a daytime P_{a,O_2} of >8.0 kPa (>60 mmHg) exhibiting nocturnal hypoxaemia. This 3-yr trial included 38 patients, 19 receiving NOT (3 $L \cdot min^{-1}$) and 19 receiving room air (3 $L \cdot min^{-1}$) from defective oxygen concentrators. As in the present study, there was no difference in mortality between the two groups (five deaths in the NOT group *versus* six in the control group), but the very high attrition rate of the study, with 11 of 38 patients being dropped, precluded any firm conclusion.

Indeed, the mortality results of FLETCHER *et al.* [16] and the present ones were obtained from relatively small numbers of patients (38 and 76 patients, respectively, were randomized and allocated to either NOT or no NOT) and are probably insufficient for comparing survival rates. Of interest, these results are rather similar and suggest that NOT does not alter survival of COPD patients without marked daytime hypoxaemia. This is not completely

unexpected given the following. 1) It has not been convincingly demonstrated that isolated nocturnal desaturation had deleterious effects on survival in COPD patients compared to patients with a similar degree of airway obstruction not exhibiting sleep-related oxygen desaturation. The only study which has attempted to answer this question, that of FLETCHER *et al.* [12], was a retrospective noncontrolled one and included subjects treated or not treated with oxygen. As the authors themselves stated, this kind of retrospective study carries with it sources of potential bias. 2) The beneficial effects of oxygen therapy on survival have only been observed in COPD patients with severe daytime hypoxaemia [1, 2]. The very recent study by GÓRECKA *et al.* [5] showed that, in a large series (n=135) of COPD patients with moderate-to-mild hypoxaemia, P_{a,O_2} being in the range 7.4±8.6 kPa (56–65 mmHg), with a mean±SD value of 8.0±0.4 kPa (60.4±2.8 mmHg), LTOT, >15 h·day^{-1}, did not improve survival. Indeed, the presence of sleep-related hypoxaemia was not investigated in these patients, but nocturnal hypoxaemia was probably present in ~40–50% of them, taking into account the results of an earlier study [14] in which COPD patients of a comparable degree of severity were included. Of interest, the functional impairment (P_{a,O_2}, P_{a,CO_2}, and FEV1) in the 135 patients followed-up by GÓRECKA *et al.* [5] was comparable to that observed in the 76 patients included in the present study.

The major aim of oxygen therapy is indeed to increase life expectancy, but another important purpose of NOT could be to delay the onset of conventional LTOT in advanced COPD. Conventional LTOT is generally prescribed when P_{a,O_2} persistently falls below 7.3 kPa (55 mmHg) [1, 17]. The P_{a,O_2} of the patients included in the present study was 8.4±0.4 kPa (63±3 mmHg) at t0 and, not unexpectedly, P_{a,O_2} worsened during the follow-up in some patients who could no longer stay in their allocated group of treatment. These patients were given LTOT. They were equally distributed between the two groups: 12 in the NOT group and 10 in the control group. Thus, it does not seem that NOT can delay the initiation of conventional home oxygen therapy, which could be explained by the progression of airway obstruction, observed in most advanced COPD patients. This progression is not altered by conventional LTOT [21] and should not be influenced by NOT. The worsening of bronchial obstruction leads with time to more severe diurnal hypoxaemia. Indeed, if table 2 is considered, FEV1 was relatively stable in those patients who could be recatheterized at *t*2, but in fact 17 patients worsened within the first 2 yrs of follow-up (10 deaths, seven prescriptions of LTOT) and these patients, by definition, could not be recatheterized after 2 yrs.

The most relevant result of the present study was the absence of significant changes in pulmonary haemodynamics in either group. This means that during a 2-yr follow-up PAP neither worsened in patients not receiving nocturnal oxygen nor improved in patients given NOT. Negative results must indeed be interpreted with caution, but it was calculated (see *Statistical analysis*) that the number of patients in each group was sufficient to achieve a power of 80% at a significance level of 0.05.

In COPD patients not receiving oxygen therapy, the yearly changes in PAP have been shown to be relatively small, of ~+0.5 mmHg·yr^{-1} [22]. Thus, the present results in the control group are in rather good agreement with earlier data in the literature, since PAP varied (not significantly) from 19.8±5.6 to 20.5±6.5 mmHg. Conversely, PAP could have been expected to improve in COPD patients given noc-turnal oxygen, and in this regard the present results differ from those of FLETCHER *et al.* [16]: in their nine control subjects PAP increased after 3 yrs, from 22.5±1.8 to 26.4±1.9 mmHg, whereas it decreased in their seven NOT subjects from 26.7±2.2 to 23.0±2.1 mmHg, and the difference was statistically significant ($p<0.02$). Curiously, these changes were not due to a decreased pulmonary vascular resistance (PVR) in the treated group but to a decreased pulmonary capillary wedge pressure (PCWP) from 14.4±2.2 to 11.1±1.4 mmHg, whereas PCWP increased in the control group. FLETCHER *et al.* [16] concluded that improved cardiac (*i.e.* left heart) performance might account for the improved pulmonary haemodynamics although earlier studies [3, 4] had demonstrated that the beneficial effects of oxygen therapy on the evolution of PAP were due to a significant fall in PVR.

The marked difference between the results of FLETCHER *et al.* [16] and those of the present study could be explained by: 1) the smaller number of patients in their study (16 patients could be recatheterized *versus* 46 in the present multicentric trial); 2) the presence of some degree of left ventricular dysfunction in the patients of FLETCHER *et al.* [16], at least in the NOT group, whereas PCWP was normal in the present patients; 3) a somewhat higher PAP at *t*0 in their patients. The present group as a whole had at the onset a PAP of 19.6±5.3 mmHg, *i.e.* at the upper limit of the normal range. Only 36 of 76 patients had pulmonary hypertension defined by a resting PAP ≥20 mmHg. However, even in the small subgroups of patients with initial pulmonary hypertension, no significant change in PAP from *t*0 to *t*2 could be observed. Thus, the present results still differ from those of FLETCHER *et al.* [16] when only patients with pulmonary hypertension are considered.

It must be emphasized that the favourable effects of oxygen therapy on pulmonary haemodynamics have only been observed, with the exception of the study of FLETCHER *et al.* [16] quoted above, in markedly hypoxaemic patients exhibiting some degree of pulmonary hypertension [3, 4, 23] and may not apply to patients with mild hypoxaemia and without significant pulmonary hypertension, such as the patients included in the present study. Moreover, since pulmonary haemodynamic evolution was similar in the two groups of the present study, this suggests that the isolated nocturnal hypoxaemia is not sufficient to induce with time sustained pulmonary hypertension. This is in agreement with previous results from the authors′ multicentric group [15], which showed that PAP was identical (~19 mmHg in each group) in nocturnal desaturators and nondesaturators who had comparable airway obstruction and a similar (modest) degree of daytime hypoxaemia. Furthermore, PAP was not correlated with the degree and duration of nocturnal hypoxaemia [15]. The present data confirm and extend the earlier ones by showing that sleep-related oxygen desaturation, in the absence of marked daytime hypoxaemia, does not induce, at least within 2 yrs, the development of permanent pulmonary hypertension.

In conclusion, this multicentric prospective controlled study has demonstrated that nocturnal oxygen therapy given for 2 yrs to chronic obstructive pulmonary disease patients with mild-to-moderate daytime hypoxaemia (arterial

oxygen tension in the range 7.4–9.2 kPa (56–69 mmHg)), thus not justifying conventional long-term oxygen therapy, but exhibiting sleep-related oxygen desaturation, did not modify the evolution of pulmonary haemodynamics, did not allow delay in the prescription of conventional long-term oxygen therapy, and did not improve survival (although the small numbers of deaths precluded any firm statistical conclusion). It ensues that the prescription of nocturnal oxygen therapy in isolation is probably not justified in chronic obstructive pulmonary disease patients.

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