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CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD

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ABSTRACT: Obstructive sleep apnoea syndrome (OSAS) often coexists in patients with chronic obstructive pulmonary disease (COPD). The present prospective cohort study tested the effect of OSAS treatment with continuous positive airway pressure (CPAP) on the survival of hypoxaemic COPD patients. It was hypothesised that CPAP treatment would be associated with higher survival in patients with moderate-to-severe OSAS and hypoxaemic COPD receiving long-term oxygen therapy (LTOT).

Prospective study participants attended two outpatient advanced lung disease LTOT clinics in São Paulo, Brazil, between January 1996 and July 2006. Of 603 hypoxaemic COPD patients receiving LTOT, 95 were diagnosed with moderate-to-severe OSAS. Of this OSAS group, 61 (64%) patients accepted and were adherent to CPAP treatment, and 34 did not accept or were not adherent and were considered not treated.

The 5-yr survival estimate was 71% (95% confidence interval 53–83%) and 26% (12–43%) in the CPAP-treated and nontreated groups, respectively ($p<0.01$). After adjusting for several confounders, patients treated with CPAP showed a significantly lower risk of death (hazard ratio of death *versus* nontreated 0.19 (0.08–0.48)).

The present study found that CPAP treatment was associated with higher survival in patients with moderate-to-severe OSAS and hypoxaemic COPD receiving LTOT.

KEYWORDS: Chronic obstructive pulmonary disease, continuous positive airway pressure, long-term oxygen therapy, obstructive sleep apnoea syndrome, survival

Chronic obstructive pulmonary disease (COPD) is a common condition that causes progressive loss of pulmonary function, and is expected to become the third leading cause of death worldwide by 2020 [1, 2]. Patients with COPD are more likely to present with systemic comorbid conditions, including diabetes and cardiovascular disease [3, 4]. Obstructive sleep apnoea syndrome (OSAS) is characterised by repetitive occlusions of the upper airway, resulting in sleep fragmentation, poor sleep quality, excessive daytime somnolence and cardiovascular dysfunction [5–7]. OSAS is common in the general population and often coexists in patients with COPD (overlap OSAS/COPD) [8]. Previous studies have demonstrated that the clinical profile of patients with overlap OSAS/COPD may be particularly severe, with such patients showing lower daytime arterial oxygen tensions (P_{a,O_2}), higher arterial carbon dioxide tensions (P_{a,CO_2}) and higher pulmonary arterial pressures than patients with OSAS or COPD alone [8–10]. Patients with overlap OSAS/COPD also exhibit increased mortality risk relative to patients with OSAS alone [11, 12].

Treatment with continuous positive airway pressure (CPAP) improves pulmonary function and gas exchange in patients with overlap OSAS/COPD [13, 14]. CPAP treatment may also reduce mortality in patients with OSAS who do not have clinically evident COPD [15–18]. Not all studies show a beneficial effect of CPAP on patients with OSAS [19], however, and the effects of CPAP on the treatment of central sleep apnoea are controversial [20]. The impact on survival of CPAP treatment in patients with concomitant hypoxaemic COPD is unknown.

Since CPAP is not universally covered by public health insurance programmes in Brazil and some covered patients decline its use, there was an opportunity to conduct a prospective cohort study comparing the impact on survival of CPAP use *versus* nonuse. The patients studied

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had overlap OSAS/COPD and were enrolled in a long-term oxygen therapy (LTOT) programme for hypoxaemic COPD. It was hypothesised that treatment with CPAP would be associated with improved survival in these patients.

MATERIALS AND METHODS

Setting and study subjects

A prospective cohort study was conducted on 95 outpatients with moderate-to-severe OSAS associated with hypoxaemic COPD. The patients attended two outpatient advanced lung diseases LTOT clinics, one at the State Public Hospital of São Paulo and one at São Paulo Hospital at the Federal University of São Paulo (both São Paulo, Brazil), between January 1996 and July 2006. COPD and hypoxaemia were diagnosed according to criteria published by the American Thoracic Society [21] (and subsequently adopted by the Global Initiative for Chronic Obstructive Lung Disease [22]). Moderate-to-severe OSAS was diagnosed by clinical symptoms plus a polysomnographically confirmed apnoea/hypopnoea index (AHI) of >15 events·h^{-1} [23].

All patients were managed according to the prevailing international recommendations for these diseases [22, 24], receiving education regarding COPD and OSAS care and pharmacological and nonpharmacological (*e.g.* supplemental oxygen) treatment of COPD. According to current guidelines, smokers are not eligible for LTOT and hence were excluded from the present analysis, as were patients with cancer diagnoses or with <6 months of LTOT use (see Statistical analysis section).

Baseline data were collected at the time of referral to the LTOT programme, and included demographics, lung function, arterial blood gas levels (in room air), body mass index (BMI), smoking information, hospitalisations due to respiratory causes in the previous 12 months and the Charlson Comorbidity Index [25]. In addition, all patients were classified as being of low or high socioeconomic risk according to the Paulista Index of Social Vulnerability, which is a measure of socioeconomic vulnerability based on the patient's home address in São Paulo. This socioeconomic vulnerability index is based on census data collected in 2000 [26]. All lung function measurements were assessed using post-bronchodilator spirometry according to standard guidelines [27]. Fisher's exact test was used to analyse differences between causes of death as a three-level categorical variable (respiratory, cardiovascular and other). The study was reviewed and approved by the local ethics committees of both hospitals.

Confirmation of OSAS and initial CPAP titration

All patients with hypoxaemic COPD and clinical symptoms and a history strongly suggestive of moderate-to-severe OSAS (loud snoring, frequent nocturnal arousals, fatigue or excessive daytime sleepiness, systemic arterial hypertension and obesity) were routinely referred for split-night polysomnography (Sonolab 620; Medtron, São Paulo, Brazil) [28, 29]. All sleep studies were performed at the Federal University of São Paulo sleep laboratory, and included continuous monitoring of electroencephalography, electro-oculography, electromyography, nasal canula, abdomen, respiratory effort, oxyhaemoglobin level measured by pulse oximetry (S_{p,O_2}), snoring and body position [28, 29].

The AHI was calculated as the total number of respiratory events (apnoeas plus hypopnoeas) per hour of sleep without CPAP [23]. Apnoea was defined as complete cessation of airflow for $\geqslant 10$ s, and hypopnoea as a significant reduction in respiratory symptoms for $\geqslant 10$ s associated with arousal or oxygen desaturation of $\geqslant 3\%$ [23]. Distinction was made between central hypoventilation related to rapid eye movement sleep and hypopnoea; central hypoventilation includes long periods of uniform flow reduction and sustained arterial oxygen desaturation lasting up to several minutes, whereas hypopnoea generally has a duration of 10–30 s. Moderate-to-severe OSAS was diagnosed as an AHI of >15 events·h^{-1}. Patients for whom OSAS was confirmed in the first half of the sleep study underwent CPAP titration during the second half of the night according to standard sleep laboratory protocols [24, 29]. Supplemental oxygen, provided by nasal canula or adapted nasal mask during the second half of the night [24], was titrated to achieve an S_{p,O_2} of $>90\%$.

Since all of the patients were already enrolled in an LTOT programme, the sleep study was used mainly to confirm OSAS and titrate CPAP. The levels of oxygen flow were kept constant in the second half of the study, and flow was increased only if hypoxaemia was persistent while CPAP was applied. Sleep stages were scored according to the criteria of RECHTSCHAFFEN and KALES [30], and arousals were scored according to American Sleep Disorders Association (now the American Academy of Sleep Medicine) guidelines [31].

CPAP treatment and follow-up

Although we routinely prescribe CPAP for all hypoxaemic COPD patients with polysomnographically confirmed moderate-to-severe OSAS, some patients decline its use due to cost (it is not a covered expense for patients attending the São Paulo Hospital) or other reasons. Others who accept CPAP treatment are found not to be adherent upon assessment after the first 3 months. Only those who report using CPAP for $\geqslant 5$ h·night^{-1} on $\geqslant 5$ nights·week^{-1} are deemed adherent and permitted to continue on treatment. For the purposes of the present analysis, CPAP adherents, as described above, constitute the CPAP-treated group, whereas all others constitute the nontreated group.

All patients were evaluated quarterly until July 2006 or death. Cause of death was determined from death certificate information, if available, or otherwise classified as unknown.

Statistical analysis

Differences between patients in the CPAP-treated and nontreated groups were compared by unpaired t-test, Wilcoxon rank-sum test or the Pearson Chi-squared statistic, as appropriate. Kaplan–Meier survival curves with log-rank test and Cox's proportional hazards model were used to compare differences in survival. Since determination of CPAP adherence (and hence treatment status) was performed 3 months after CPAP initiation, which was, on average, 6 months after initiation of LTOT, the analysis was conditioned on survival through the first 6 months of LTOT in order to avoid an immortal time bias [32]. Analyses were adjusted for baseline characteristics (age, sex, post-bronchodilator forced expiratory volume in 1 s (FEV1) as a percentage of the predicted value, P_{a,O_2}, P_{a,CO_2}, obesity (BMI of $\geqslant 30$ kg·m^{-2}) and smoking history

in pack-years), hospitalisations in the past 12 months (0, 1 or ⩾2), Charlson Comorbidity Index (1, 2 or ⩾3), AHI of >30 events·h^{-1}, S_{p,O_2} nadir and the percentage of sleep time with an S_{p,O_2} of <90%. Significance refers to a p-value of ⩽0.05.

RESULTS

Of 603 patients with hypoxaemic COPD who had received LTOT for ⩾6 months, 95 (15.7%) fulfilled criteria for moderate-to-severe OSAS and hence were candidates for CPAP. Of these 95 patients, 61 were treated with and adherent to CPAP after 3 months and make up the CPAP-treated group. The remaining 34 patients were not treated with CPAP (18 patients were offered but declined CPAP, nine patients were not eligible for CPAP due to lack of insurance coverage and seven patients had CPAP therapy withdrawn within 3 months of initiation due to nonadherence).

The study cohort was hypoxaemic and hypercapnic at rest, showed severe airflow obstruction and had moderate-to-severe OSAS (table 1). The sleep data presented in table 1 were acquired during the initial portion of the polysomnographic study, prior to the start of CPAP titration. CPAP (mean±SD) was titrated to 9.8±1.5 cmH_2O. Compared to the CPAP-treated group, patients not treated with CPAP were older, exhibited a lower percentage predicted post-bronchodilator FEV1 and were more likely to have been hospitalised for respiratory conditions during the previous 12 months. The proportion of patients classified as high risk based on the socioeconomic vulnerability index did not differ significantly between patients in the CPAP-treated and nontreated groups (13.1 *versus* 18.2%, respectively; p=0.55).

During the follow-up period of regular outpatient care, the majority of patients did not present with clinical symptoms of cor pulmonale except during severe COPD exacerbations. Both groups exhibited significant decreases in the mean±SD annual rate of hospitalisations following enrolment in the LTOT programme compared to the 12-month interval prior to enrolment (2.1±1.3 *versus* 0.3±0.5; p<0.001 in the CPAP-treated group; 1.3±1.0 *versus* 0.2±0.4; p<0.001 in the CPAP-nontreated group). These declines did not differ significantly between the two groups. Likewise, annual haematocrit levels in both groups exhibited similar declines toward normal values (55.1±5.2 *versus* 45.1±2.6%; p<0.001 in the CPAP-treated group; 54.6±4.9 *versus* 45.4±3.3%; p<0.001 in the CPAP-nontreated group).

During a median follow-up of 41 months (range 6–106 months), 39 deaths (41% mortality) were observed. This figure was significantly higher in the CPAP-nontreated group than in the CPAP-treated group (27 deaths (79.4% mortality) *versus* 12 deaths (19.7% mortality); p<0.001). Respiratory failure was the most common (46%) cause of death, followed by cardiovascular disease (31%) and other causes (10%); in five patients (13% of all deaths), death certificates were not available and the cause of death could not be determined. Causes of death for the CPAP-treated *versus* nontreated groups were respiratory failure (50 *versus* 48%), cardiovascular disease (40 *versus* 30%), other (10 *versus* 14%) and unknown (20 *versus* 14%), and did not differ significantly (p=0.36).

TABLE 1 Baseline characteristics of total population and according to obstructive sleep apnoea syndrome treatment group

	Total	CPAP-treated	CPAP-nontreated	p-value#
Subjects	95 (100)	61 (64)	34 (36)	
Age yrs	64±8	62±8	66±8	0.02
Females	54 (57)	32 (52)	19 (56)	0.75
BMI kg·m^{-2}	34.0±7.0	34.9±7.7	32.3±5.4	0.10
Smoking history pack-yrs	67.3±33.8	70.8±35.5	61.1±30.2	0.30
P_{a,O_2} mmHg	53.8±5.6	53.7±6.2	54.0±4.5	0.80
P_{a,CO_2} mmHg	45.9±6.2	45.3±6.4	47.0±5.7	0.20
FEV1 % pred	41.5±12.2	43.4±12.3	37.9±11.3	0.04
Charlson Comorbidity Index				
1	22 (23)	17 (28)	5 (15)	
2	39 (41)	23 (38)	16 (47)	0.34
⩾3	34 (36)	20 (34)	13 (38)	
Hospitalisations in past year				
0	16 (17)	14 (23)	2 (6)	
1	44 (46)	30 (49)	14 (41)	0.02
⩾2	35 (37)	17 (28)	18 (53)	
Total AHI events·h^{-1}	43.2±12.5	43.2±12.4	43.3±13.1	0.98
AHI of >30 events·h^{-1}	76 (80)	48 (79)	28 (82)	0.67
S_{p,O_2} nadir %	64.2±10.8	64.6±11.3	63.5±10.0	0.64
Sleep time¶ with S_{p,O_2} of <90%	87.0	85.5	89.6	0.15

Data are presented as n (%) or mean±SD unless otherwise indicated. CPAP: continuous positive airway pressure; BMI: body mass index; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; FEV1: forced expiratory volume in 1 s; % pred: % predicted; AHI: apnoea/hypopnoea index; S_{p,O_2}: oxyhaemoglobin level measured by pulse oximetry. #: two-sided value based on t-test, Pearson Chi-squared test or Wilcoxon rank-sum test as appropriate; ¶: percentage of total sleep time.

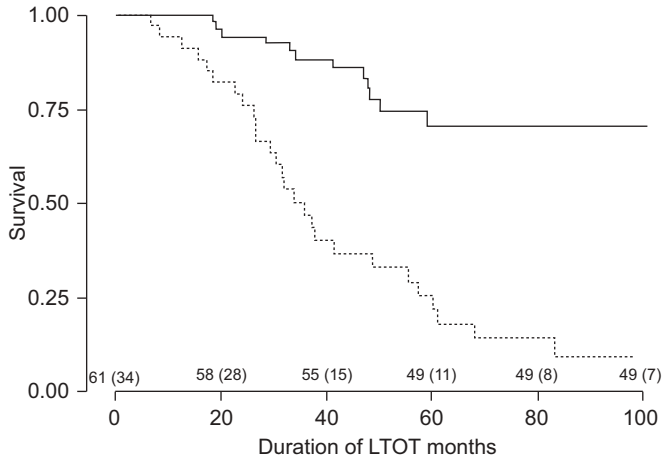

FIGURE 1. Kaplan–Meier survival curves comparing continuous positive airway pressure treated (——) *versus* nontreated patients (·····). The figures above the x-axis indicate the number of users (nonusers) at risk. The two curves differed significantly ($p<0.0001$) based on the log-rank test statistic. LTOT: long-term oxygen therapy.

Kaplan–Meier analysis indicated significantly higher survival in CPAP-treated patients compared to the nontreated group ($p<0.0001$) (fig. 1), with 5-yr survival estimates of 71% (95% confidence interval (CI) 53–83%) and 26% (12–43%), respectively. On multivariate analysis, higher percentage predicted post-bronchodilator FEV1, lower Charlson Comorbidity Index and treatment with CPAP were all significantly associated with an improved survival experience (table 2). In this analysis, the hazard ratio for death in CPAP-treated *versus* nontreated patients was 0.19 (95% CI 0.08–0.48).

TABLE 2 Multivariable Cox's proportional hazards regression model

	HR (95% CI)	p-value
CPAP use#	0.19 (0.08–0.48)	<0.001
Female sex#	2.24 (0.85–5.90)	0.10
Age yrs	1.04 (0.98–1.10)	0.17
Smoking history pack-yrs	1.00 (0.99–1.01)	0.61
P_{a,O_2} mmHg	0.96 (0.88–1.04)	0.30
P_{a,CO_2} mmHg	0.94 (0.88–1.01)	0.08
Post-BD FEV1 % pred	0.93 (0.89–0.98)	0.006
Obese#	1.31 (0.64–2.68)	0.45
Hospitalisations in past year n¶	0.84 (0.38–1.84)	0.66
Charlson Comorbidity Index+	1.85 (1.10–3.13)	0.02
AHI of >30 events·h^{-1}#	0.81 (0.28–2.33)	0.69
S_{p,O_2} nadir %	1.02 (0.98–1.05)	0.34
Sleep time§ with S_{p,O_2} of <90%	1.00 (0.96–1.03)	0.87

Hazard ratios (HRs) represent the hazard of death for a 1-unit increase in the predictor variable. CPAP: continuous positive airway pressure; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; BD: bronchodilator; FEV1: forced expiratory volume in 1 s; % pred: % predicted; AHI: apnoea/hypopnoea index; S_{p,O_2}: oxyhaemoglobin level measured by pulse oximetry. #: reference group was those without this factor/characteristic; ¶: possible values were 0 (reference), 1 or ⩾2; +: possible values were 1 (since all patients have chronic obstructive pulmonary disease; reference group), 2 or ⩾3; §: percentage of total sleep time.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the effects of CPAP treatment on survival among patients with moderate-to-severe OSAS and hypoxaemic COPD who are receiving LTOT. During a median follow-up of 41 months, CPAP treatment was associated with significantly higher survival, even after adjusting for possible confounders at baseline.

COPD is an increasing cause of death worldwide. The present study adds to current knowledge by suggesting that the treatment of moderate-to-severe OSAS in patients with concomitant hypoxaemic COPD requiring LTOT is associated with significantly higher survival. Although the present study was not designed to determine the prevalence of OSAS in this population, the identification of OSAS in 15.7% of patients with severe COPD who met criteria for LTOT suggest that this treatable comorbid condition is present in a significant proportion of hypoxaemic patients with COPD.

The mortality among severe COPD patients receiving LTOT was high in the present study, and similar to what has been previously published [33, 34]. We found no studies that compared the effects of OSAS treatment in this group of patients. However, the effects of CPAP on survival in the present study are comparable to the effects of LTOT in the two studies that established the importance of oxygen supplementation in patients with COPD and resting hypoxaemia (Nocturnal Oxygen Therapy Trial (NOTT) and UK Medical Research Council (MRC) studies) [33, 34]. In the present study, the 5-yr survival estimates in the CPAP-treated and nontreated groups were 71 and 26%, respectively, and, in the combined MRC and NOTT studies, the 5-yr survival estimates in the LTOT-treated and nontreated groups were 62 and 16%, respectively. The main causes of death in the present study (respiratory failure and cardiovascular disease) are consistent with those previously reported in patients with severe hypoxaemic COPD [35].

The benefits of CPAP may arise from improvement in respiratory mechanics, such as reducing the work of breathing by minimising hyperinflation. Previous studies have shown that the use of CPAP improves lung function, gas exchange and respiratory muscle function, and decreases the risk of hospitalisations in patients with COPD plus OSAS [13, 14]. It is also possible that CPAP protects against cardiovascular disease, particularly since it has been shown that CPAP reduced cardiovascular mortality in a population of OSAS patients referred for CPAP treatment [18]. Conversely, COPD patients were treated with LTOT, and it is possible patients not treated with CPAP were to some extent protected from the deleterious effects of the intermittent hypoxia–reoxygenation injury typical of OSAS.

The extrapolation of data from the general OSAS population to this particular population with overlap OSAS/hypoxaemic COPD must be made with caution, however. Intermittent hypoxia is thought to play a central role in the genesis of cardiovascular diseases by activating several pathways, such

as increased sympathetic activity, endothelial dysfunction, metabolic dysregulation and progression of atherosclerosis [36]. In the present study, all of the COPD patients were treated with LTOT and may have been, to some extent, protected from the deleterious effects of the intermittent hypoxia–reoxygenation injury typical of OSAS.

A strength of the present study is the inclusion of a cohort that was defined and treated according to well-established criteria for both COPD and OSAS [21–24]. Additionally, findings regarding the survival benefit of CPAP treatment persisted even after adjustment for multiple potential confounders. Indeed, there was little evidence of confounding; the adjusted hazard ratio of 0.19 in the present Cox's model was virtually identical to the unadjusted hazard ratio of 0.18 (data not shown). Care was taken to limit the analysis to individuals with $\geqslant$6 months of follow-up, since this is approximately how long it took to make a final determination of CPAP treatment status. This avoided the introduction of an immortal time bias into the results [32].

The present study has several limitations that may affect the generalisability of its findings. Most importantly, this is an observational study; patients were not randomised to receive or not receive CPAP. In addition, the CPAP-nontreated group included seven individuals who were withdrawn from CPAP after 3 months due to nonadherence. As a consequence of these factors, the CPAP-treated and nontreated groups could be expected to differ on the basis of a number of factors related to subsequent survival. Owing to the substantial clinical evidence that CPAP is an effective treatment of isolated moderate-to-severe OSAS [15–18], we felt that it would have been unethical to conduct a randomised trial. Further, the analysis was adjusted for a number of factors (including comorbidity, sex, age, smoking history in pack-years, P_{a,O_2}, P_{a,CO_2}, FEV1, obesity, severity of obstructive sleep apnoea, number of hospitalisations in the past year and hypoxaemia during sleep) that may be associated with survival. However, the possibility cannot be excluded that other unmeasurable differences between the CPAP-treated and nontreated patients (*e.g.* lifestyle factors) may have contributed to the observed survival advantage in the CPAP-treated group (healthy user effect) [37].

A second limitation is that, since only patients who required LTOT were studied, the findings may not be generalisable to patients with less-severe disease. Thirdly, we had to rely on self-reported adherence to the CPAP protocol, since most of the CPAP devices used do not record data on duration of use. If anything, this probably resulted in overestimation of CPAP adherence, which, in turn, would have produced a conservative bias (*i.e.* towards the null hypothesis). Fourthly, all patients referred for sleep evaluation underwent a split-night study rather than separate sleep studies for diagnosis and titration. To the extent that this practice, which was driven by cost considerations, resulted in suboptimal CPAP titration, however, it would also have produced a conservative bias. Finally, there were no data regarding adherence to LTOT. However, both groups exhibited clinical improvements in multiple surrogate end-points that would be expected with LTOT treatment (significant decrease in the number of hospitalisations, stabilisation of clinical cor pulmonale and haematocrit normalisation), suggesting that both groups benefited from LTOT during the follow-up period.

The present observational study indicates a positive effect of CPAP treatment on survival in moderate-to-severe OSAS patients with hypoxaemic COPD receiving LTOT. Given the survival benefit with CPAP therapy and the prevalence of moderate-to-severe OSAS (15.7%) found in patients with hypoxaemic COPD, our study suggests that an active search for OSAS in patients with hypoxaemic COPD using a screening questionnaire and/or nocturnal oximetry should be performed. In addition, from a public health perspective, our study suggests the need for policy makers to include coverage for CPAP treatment in patients with hypoxaemic COPD, similar to programmes in place for LTOT in patients with hypoxaemic COPD.

STATEMENT OF INTEREST

Statements of interest for W.M. Vollmer and G. Lorenzi-Filho can be found at www.erj.ersjournals.com/misc/statements.dtl

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