Impact of CPAP Use and Age on Mortality in Patients with Combined COPD and Obstructive Sleep Apnea: The Overlap Syndrome

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Background: The overlap syndrome, defined by concurrent existence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), is associated with poor outcomes. From a large outpatient cohort we aimed to define better the risk factors for increased mortality in the overlap syndrome and hypothesized that CPAP adherence would be associated with improved survival in patients with overlap syndrome.

Methods: A post hoc analysis from an outpatient database of 10,272 patients from 2007-2010, identified 3,396 patients which were classified in 6 groups; patients both alive or deceased, with the known diagnosis of COPD, OSA, and the overlap of COPD plus OSA. Information regarding their gender, age, pulmonary function, obstructive sleep apnea parameters, and CPAP compliance was collected. A multivariate Cox proportional hazards model was generated for the determinants of mortality.

Results: 1,112 COPD patients and 2,284 OSA patients were identified by diagnostic coding and then comprehensive chart

review. Of these, 227 patients were identified with the overlap syndrome. From this group, 17 patients (7.4%) died. Multivariate analysis revealed hours of CPAP use and age as independent predictors of mortality (HR 0.71 and 1.14, $p < 0.001$, 0.002). Greater time on CPAP was associated with reduced mortality; although age did not correlate with CPAP use ($p = 0.2$), mean age of those with CPAP use < 2 hours per night was significantly higher than those using CPAP > 2 hours per night.

Conclusions: From this observational cohort, mortality in the overlap syndrome is impacted by CPAP use. Age is also an independent factor which has a negative association with survival and CPAP usage.

Keywords: Mortality, OSA, COPD

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Obstructive sleep apnea (OSA) is a common disorder characterized by repeated collapse of the airway during sleep and is associated with considerable functional impairment, as well as end-organ damage and mortality.^{1,2} Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow obstruction, chronic bronchitis, and emphysema, and is associated with major morbidity.³ In addition, COPD accounts for approximately 4% of all American deaths, making it now the third most common cause of death in the US.⁴ The concurrent diagnosis of COPD and obstructive sleep apnea (*the overlap syndrome*) is associated with excess mortality typically from cardiovascular causes, and is above and beyond that attributable to the individual entities. Treatment with continuous positive airway pressure (CPAP) has been shown to reduce fatal and non-fatal cardiovascular events.⁵ In addition, without treatment of OSA with CPAP, poor COPD outcomes have been reported.⁶ CPAP may both improve cardiovascular outcomes and reduce exacerbations in patients with the overlap syndrome, but the mechanisms leading to these improvements remain unclear, as do the CPAP requirements. In patients with OSA alone (no COPD), the optimal level of CPAP adherence remains unclear.⁷⁻¹¹

However, two recent studies assessing long term CPAP use in overlap patients have suggested benefits in mortality. Machado

BRIEF SUMMARY

Current Knowledge/Study Rationale: The overlap syndrome (combination of obstructive sleep apnea and chronic obstructive pulmonary disease) is associated with excess mortality. This study aimed to better define the applicable risk factors of mortality and the mitigating effect of CPAP adherence on outcomes.

Study Impact: More time on CPAP in patients with the overlap syndrome was associated with a reduced risk of death, after controlling for common risk factors. Age is also an important contributor to mortality although the mechanism of the aging effect is unclear, emphasizing the need for further research in this area.

and colleagues added the use of CPAP to long-term oxygen therapy and observed differences in long term survival of 71% versus 26%.¹² Recently, Marin et al. have shown that hospitalization rates and mortality from COPD can be mitigated if CPAP is prescribed, compared to those with COPD alone,⁶ but the amount of use of CPAP required to achieve optimal outcomes remains unknown.

In the present study we reviewed records from a large community-based sample of patients with OSA, COPD, and overlap syndrome to assess the impact of CPAP use and other risk factors on mortality. We hypothesized greater CPAP adherence would reduce mortality in the overlap syndrome.

METHODS

Study Population

A post hoc analysis on 10,272 outpatients was performed by first searching the database for diagnosis codes related to OSA/COPD (CPT 496.0; 491.21; 492, 327.23; 327.20; 780.51; 780.53), followed by a full chart review for appropriate clinical diagnosis and categorization of all potential patients from the cohort. From this sample 3,396 patients from 2007-2010 were identified and characterized into 6 groups; patients alive or deceased, with the known diagnosis of COPD,³ OSA, and the overlap of COPD plus OSA. All patients did respond to pre-visit questionnaires containing standardized clinical risk assessments for both OSA and COPD during their initial and routine clinical follow-up.^{3,13,14}

Data Series/Collection

Information regarding their gender, age, BMI, pulmonary function (FEV1 in Liters [L], FEV1% predicted, FEV1/FVC ratio), current smoking status, number of comorbid conditions (Charlson index) and baseline OSA severity/sleepiness (apnea-hypopnea index [AHI], Nadir SaO₂ (%), Epworth sleepiness score) was recorded.

Sleep Studies and Pulmonary Function

All patients identified with OSA had full in-lab polysomnograms (PSG) and CPAP titrations or split-night polysomnograms through a single American Academy of Sleep Medicine (AASM) accredited Center with 3 locations in Rhode Island. All patients with COPD had pulmonary function testing based on American Thoracic Society standards^{3,15} and were characterized using the GOLD guidelines.

CPAP Therapy/Compliance Data

All patients with the diagnosis of OSA were offered CPAP therapy; PAP settings prescribed were based on AASM standards after in-lab manual titration.¹⁶ No patients in the overlap cohort were on bilevel or auto-titrating PAP modes during the study period. All patients were treated with expiratory pressure relief (EPR or C-Flex).⁹ CPAP levels (cm H₂O) and compliance data (% nights used > 4 h and median daily usage) from a 1-3 month period were recorded from the individual patient CPAP units via the hard drive of the device or a removable monitor (e.g., Smart Card) downloaded into a central databases by the patients' respective durable medical equipment (DME) providers. All patients within the overlap cohort agreed to try CPAP, and no patients refused from the start of diagnosis. Patient data were recorded for a 1- to 3-month period after initiation of therapy. Patients were not included in the sample if reliable compliance data were not available. If patients were using supplemental oxygen (O₂) prior to titration, this liter flow was continued and bled into the CPAP circuit. Supplemental O₂ was recommended for patients with the overlap syndrome found to have residual hypoxemia on CPAP despite elimination of all sleep disordered breathing, based on standard AASM protocol.¹⁶

Statistical Analysis

A Cox proportional hazards model was developed for the overlap patients to determine univariate and multivariate pre-

dictors of survival. The predictors of survival in this model were then analyzed controlling for the other predictors. The patient's initial visit/treatment dates were recorded, and time-to-event data were noted. Patients remaining alive were censored at the time at which no further follow-up could be proven or at study end. Patients who died were recorded as failure at the date of their death. Continuous covariates included hours on CPAP per night, FEV1, AHI, age, BMI, and number of comorbid conditions (including concurrent CHF, atrial fibrillation, coronary artery disease, stroke, hypertension, diabetes, cancer, and pulmonary hypertension), with the comorbid conditions presented as a Charlson index.¹⁷ Dichotomous covariates included gender and current active smoking.¹⁸ Kaplan-Meier survival plots were generated for the group and were compared using a log-rank test, with Holm-Sidak test used for multiple comparisons. An additional analysis of variance was used to compare patient age across differing levels of CPAP use. Alpha was set at 0.05. The study was approved by the Rhode Island Hospital Institutional Review Board.

RESULTS

Between January 2007 and October 2010, from a cohort of 10,721 outpatients, a sample of 3,760 patients with the diagnosis of either OSA or COPD (or both diagnoses) were identified using evaluation and management CPT codes (496.0, 491.21, 327.23, 327.20, 780.51, 780.53). From this group, 227 patients were identified with the overlap syndrome. Every patient in the overlap group was offered CPAP and was initiated on PAP therapy. Data from 8 patients in this group were lost to follow-up and were "censored" at the time of last clinical visit in the survival analysis. Seventeen patients (7.4%) in the overlap group died (**Figure 1**). From **Table 1** the FEV1 and FEV1 percent predicted (FEV1%) vs. the COPD only group were similar, as were the AHI, BMI, Epworth, and Nadir SaO₂ compared to the other groups (**Table 1**). The percent of patients who were current active tobacco users was more prevalent in the overlap group than the COPD group ($p = 0.02$). Supplemental oxygen use was relatively low in all groups (with CPAP in the overlap group in 3.2% of patients and in 3.7% of the COPD only group; $p = 0.47$). CPAP levels for the OSA and overlap groups were not substantially different (**Table 1**). The overlap alive patients ($n = 210$) had mean compliance with CPAP of $65.9\% \pm 1.8\%$ nights used > 4 h and 5.4 ± 0.1 h/night, versus the overlap dead patients with a mean compliance of $21.2\% \pm 8.1\%$ nights used > 4 h and 1.7 ± 0.2 h/night ($p < 0.001$ and $p = 0.001$; **Figures 2, 3**). Compliance data were not available in 10% of the cohort and were not included in the analysis.

Cox Proportional Hazards Model

The results for the univariate Cox proportional hazards model for predictors of mortality in the overlap group are presented in **Table 2**. Hazard ratios (HR) were 1.10 (1.05-1.17, $p < 0.001$) for age, 1.75 (1.32-2.32, $p = 0.01$) for the Carlson index (comorbid conditions), and 0.59 (0.48-0.73, $p < 0.001$) for CPAP. Gender, AHI, FEV1 percent predicted, BMI, and current smoking status did not have an impact on mortality in this analysis. In the multivariate Cox proportional hazards analysis (**Table 3**), only CPAP use ([h/night],

HR 0.71 [0.55-0.90], $p = 0.004$) and age (HR 1.14 [1.04-1.23], $p = 0.003$) significantly contributed to the model. **Figure 4** reveals the Kaplan-Meier analysis comparing survival of patients with the overlap syndrome stratified by h/night CPAP usage. When the group was stratified by CPAP use (0-2 h; 2-4 h; 4-6 h, and 6-8 h/night, as determined from the first 1-3 months of use), there was increased mortality in the 0-2 h group compared to the others (log rank statistic, 0-2 h/night vs. 2-4 h/night $p = 0.04$; 0-2 h/night vs. 4-6 h/night $p < 0.001$; 0-2 h/night vs. 6-8 h/night $p < 0.001$; **Figure 4**.)

Patients in the overlap group with CPAP use 0-2 h/night group had a mean age of 68.2 years; 2-4 h/night 63.7 years; 4-6 h/night 59.4/h; 6-8 h/night 62.9 years (ANOVA: $p = 0.02$ for

0-2 h vs. 4-6 h). Age did not correlate with CPAP use (h/night) ($r^2 = 0.006$, $p = 0.20$). In addition, BMI, AHI, and FEV1% predicted did not correlate with CPAP use/adherence. The Charlson index did reveal a small but statistically significant correlation with CPAP use ($r^2 = 0.07$, $p = 0.004$).

DISCUSSION

The major finding of this observational study was the identification of age and any CPAP use at night, as determined by

Figure 1—Flow chart of the inclusion/exclusion of patients from the outpatient cohort

Figure 2—Box plots of mean hours per night use of CPAP in overlap group deceased and alive

Figure 3—Box plots of % nights with > 4 hours use of CPAP in the overlap group deceased and alive

Table 1—Baseline characteristics for the OSA, COPD and overlap patients

	Age years	BMI kg/m ²	Charlson index	FEV1 %predicted	AHI events/h	SaO ₂ nadir %	Epworth score	Tobacco Use Active %	CPAP cm H ₂ O
OSA	61.6	33.1	1.5		28.2	80.8	10.2	0.9	10.1
COPD	69.0	28.0	1.7	59.2				3.9	
Overlap	61.4	37.0	2.0	56.7	33.2	78.3	9.9	14.6*	11.2

* $p = 0.02$ active tobacco use (overlap group vs. COPD and OSA group).

Table 2—Univariate Cox proportional hazards model for factors associated with mortality

	Hazard Ratio	95% Lower Confidence Interval	95% Upper Confidence Interval	p
CPAP (h/night)	0.59	0.48	0.73	< 0.001
Gender (m, f)	0.37	0.11	1.32	0.125
FEV1 (% predicted)	0.98	0.95	1.01	0.229
AHI (events/h)	0.98	0.96	1.02	0.396
BMI (kg/m ²)	0.95	0.90	1.09	0.432
Age (years)	1.10	1.05	1.17	< 0.001
Tobacco active use (y, n)	0.99	0.09	10.6	0.996
Charlson index	1.75	1.32	2.32	0.010

Figure 4—Kaplan-Meier curves for survival over the three year study period stratified by average CPAP use per night for the overlap patients

Mortality was reduced with more time on CPAP. 0-2 h/night vs. 2-4 h/night $p = 0.04$; 0-2 h/night vs. 4-6 h/night $p < 0.001$; 0-2 h/night vs. 6-8 h/night $p < 0.001$.

objective monitoring, were associated with mortality in patients with the combination of OSA and COPD (the overlap syndrome). Through objective monitoring from patient CPAP devices during the first 1-3 months of use, we determined that this association persisted after adjustment for known confounders, suggesting that overlap patients who use CPAP have a higher

Table 3—Multivariate Cox proportional hazards model for factors associated with mortality

	Hazard Ratio	95% Lower Confidence Interval	95% Upper Confidence Interval	p
CPAP (h/night)	0.71	0.55	0.90	0.004
Age (years)	1.14	1.04	1.23	0.003
Charlson index	1.31	0.86	1.93	0.179

survival than those who do not. Any level of CPAP used was associated with some mortality benefit over no use of CPAP. Age was also a predictor of survival; although there was no correlation between hours of CPAP use and age, the mean age was greater in the patients using CPAP the least compared to those who were more adherent. Lastly, although the number of comorbid conditions seen (Charlson index) was not associated with mortality in this analysis (multivariate model), there was reduced CPAP use in those with the greatest number of comorbid conditions.

Recent studies by Marin et al. have shown that the combination of OSA and COPD leads to increased mortality and that use of CPAP reduces exacerbation rates for concurrent COPD.⁶ However, the optimal prescription for CPAP was unclear. Their patients were included in the group if they used CPAP ≥ 4 h/night and, if not, the device was withdrawn. Similar to the Spanish study, our analysis shows an association with high mortality when CPAP use is < 4 h/night. We have further demonstrated that any CPAP use may actually be good (i.e., better than nothing), but more use is likely better. The Cox analysis did suggest trends to further reductions in mortality with increasing time on the device; however, the changes were small. This part of the analysis was limited by low power due to low numbers of patients who died while using CPAP. However, this study adds to our growing knowledge, suggesting that longer times on CPAP are associated with better outcomes.

The issue of whether there is a true threshold for optimal CPAP use remains unanswered by this study, as some patients had significant mortality reductions with CPAP use < 4 h/night, which has previously been suggested as a minimal level needed for reductions in OSA morbidity. However, studies by Weaver et al. have suggested near linear improvements in sleepiness and cognitive function with increasing time on CPAP at night (2 versus 4 versus 6 hours).¹⁰ This linear improvement on CPAP has been confirmed even more recently by Antic et al.¹¹ However, limited data exist for the impact of increasing CPAP usage (hours on device) on other outcomes such as cardiovascular disease morbidity or overall mortality. Interestingly, the blood pressure improvement dose response curve (recently shown by Haentjens et al.) with CPAP looks similar to the mortality curve in our analyses, with no threshold effect appreciable in either analysis.¹⁹

The compliance rates of 65% vs. 21% nights used with CPAP in the overlap alive vs. deceased patients deserve mention. The long-term rates of CPAP use in patients with OSA vary between studies; but despite the mortality advantage seen here, our rates are still low. Nonetheless these levels are similar in magnitude to those in prior reports by Kribbs et al.¹⁸ of 63% regular use. McArdle reported rates of 75% long-term use²⁰ and slightly bet-

ter use (46%) than our prior reports in Providence, RI.⁸ Thus we think this sample is further representative of a typical community of OSA/COPD patients.

Our finding of age as an independent predictor of survival in the overlap group is interesting given the relatively low mean age of this population. Although age did not correlate with CPAP use, the oldest quartile was the group that used CPAP 0-2 h/night (compared to those who use CPAP 4-6 h/night). These data support the notion that older patients with overlap syndrome may have an amplification of their mortality risk due to both aging itself (which is a risk factor for worsening OSA prevalence and cardiovascular complications) and to limited use of PAP therapy.²¹ In addition, despite therapy, age may impact overall improvements with PAP therapy as reported by Ayalon and colleagues,²² who have noted that older patients with comorbid depression tend to have less long-term cognitive improvement than younger counterparts.

Although the Cox hazards model did not find that the Charlson index was independently associated with mortality, there was an association between numbers of comorbid conditions and CPAP use. There was a small but statistically significant correlation between the Charlson index and PAP use, suggesting that for some patients increasing numbers of comorbid conditions may negatively impact PAP use.

The lack of association between mortality and the presence of active smoking, the FEV1% predicted or the use of supplemental oxygen deserves comment. We found no difference in the number of patients using supplemental oxygen in the overlap group who died versus still living. This finding is important because in addition to the landmark studies showing reduced mortality in patients with severe COPD using supplemental oxygen, prior reports have also suggested improved sleep quality and improvements in the apnea hypopnea index in patients with OSA using supplemental oxygen at night.²³⁻²⁵ In addition, current smoking rates were not different between groups but were higher in those with the overlap syndrome. There was no difference in the current smoking rates of overlap patients who died versus remaining alive, but there were more active smokers in the overlap group than the COPD or OSA group alone. This observation may explain some of the amplification of symptoms noted when moderate COPD and moderate OSA are seen together in the overlap syndrome. The FEV1% predicted was not found associated with mortality in this cohort. However, the mean FEV1% predicted was lower in those who died in the overlap group than those in the COPD only group, similar to the findings of the Spanish study and that of Chaouat et al.²⁶

Despite our study's strengths, we acknowledge a number of weaknesses. First, is the study's post hoc, non-randomized design with CPAP use. However, the single-center large cohort without participation bias and low loss of follow-up strengthen this report. Based on the healthy user effect, some but not all data suggest that CPAP use may track with other health care outcomes. Thus, in theory, patients who were motivated and educated may use CPAP faithfully but also may use medications that reduce cardiovascular morbidity (inhalers, β -blockers, statins) and closely follow diet and exercise recommendations.^{27,6} Age certainly did contribute to mortality in this study, but we did not have a complete enough data set recorded from this cohort on medication or dosage changes to be able to

determine clearly if patients who did not use CPAP also did not use their medications for COPD. Although increasing numbers of comorbid conditions (Charlson index) were not clearly associated with increased mortality in this cohort, the index was associated with CPAP use. Further randomized trials will be required to determine whether CPAP per se improves mortality in overlap syndrome. Second, we had only roughly three years of follow-up in our cohort. Given the poor prognosis of these patients, it is true that many more deaths would have been observed had we had longer duration of follow-up. Thus, we cannot determine whether CPAP is actually preventing death or simply delaying death somewhat. Nonetheless, we view any prolongation of life as important in these conditions where outcome is generally poor. Third, we had no patients within the overlap cohort on other PAP delivery modes and thus could not compare outcomes with CPAP and other modes such as bilevel PAP. Some would argue that patients with COPD may experience hypoventilation during sleep, particularly REM sleep, such that bilevel PAP may be required to alleviate gas exchange disturbances. For example, transient elevations in PaCO₂ may promote pulmonary vasoconstriction, which could represent a burden on the right ventricle. Thus, further data will be required to determine whether bilevel PAP is superior to CPAP in terms of outcome in overlap patients. Fourth, because of the post hoc design of the study, some patients from the larger cohort may have had the overlap syndrome and may have been inadvertently left out of the analysis, which may introduce bias. We made efforts to apply clinical criteria for COPD and OSA to the available charted information to reduce risk of missing potential study patients or misclassifying them. A future randomized trial with systematic inclusion/exclusion criteria would eliminate this type of bias. Despite these limitations, we believe that our data are robust and represent an important addition to the literature. However, we clearly support further efforts in this area given that OSA has been excluded from essentially all randomized trials to date of PAP therapy in COPD.^{28,29}

In summary this study adds to a growing body of literature regarding the combined impact of OSA in patients with COPD. We have shown that more time on CPAP in patients with the overlap syndrome was associated with a reduced risk of death, after controlling for common risk factors. Age is also an important contributor to mortality although the mechanism of the aging effect is unclear, emphasizing the need for further research in this area.

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