BACKGROUND: Positive airway pressure (PAP) in subjects with both obstructive sleep apnea and COPD reduces the risk of pulmonary hypertension, death, and hospitalizations from COPD exacerbations, but adherence to the intervention is low, similar to the experience with noninvasive ventilation in stable COPD. We sought to assess whether hyperinflation on chest radiographs contributes to low adherence to PAP therapy in the overlap syndrome. METHODS: Records of patients with a listed diagnosis of COPD at the time of polysomnography were reviewed. Overlap syndrome was diagnosed when COPD was clinically confirmed with spirometry showing a fixed airway obstruction and when the apnea-hypopnea index was ≥ 5. Hyperinflation was evaluated by a review of the right diaphragm height on a lateral chest radiograph. Adherence was assessed clinically or through device download at a 3-month follow-up, and later adherence was assessed by telephone interviews. A receiver operating curve was used to determine whether diaphragm height was associated with adherence. RESULTS: Twenty-one of 41 subjects (51%) were considered adherent to PAP therapy at the 3-month visit. Adherent subjects were more overweight compared with non-adherent subjects (body mass index of 36.0 ± 5.7 vs 32.0 ± 5.7 kg/m², \( P = .03 \)), sleepier at the onset (Epworth sleepiness scale score of 13.0 ± 5.8 vs 9.4 ± 5.4, \( P < .05 \)), and less likely to have hyperinflation as defined by a right diaphragm height < 2.45 cm (33% vs 65%, \( P = .04 \)). The body mass index and initial sleepiness no longer predicted adherence beyond 3 months, but 35% of subjects with a right diaphragm height ≤ 2.45 cm were adherent beyond 3 months compared with 75% of those with a right diaphragm height > 2.45 cm (\( P = .04 \) by Fisher exact test). CONCLUSIONS: Hyperinflation is associated with decreased adherence to PAP therapy in the overlap syndrome. Key words: obstructive sleep apnea; chronic obstructive pulmonary disease; airway obstruction; continuous positive airway pressure; patient compliance; positive-pressure respiration. [Respir Care 2014;59(8):1267–1274. © 2014 Daedalus Enterprises]
in subjects with stable COPD. Therefore, the identification and remediation of factors that decrease adherence are necessary to extend the benefits of PAP therapy to patients with the overlap syndrome or with stable COPD.

One potential explanation for the decreased adherence to NIV in COPD with or without obstructive sleep apnea may be an increase in end-expiratory lung volume as a consequence of PAP. Although this effect may be beneficial in restrictive and neuromuscular disorders, it may contribute to intolerance in subjects with COPD, particularly those with hyperinflation at baseline. For instance, hyperinflation limits the ability of the diaphragm to increase lung volume and can further increase the oxygen cost of breathing during resistive breathing.

These considerations are of particular relevance in the overlap syndrome, in which PAP, as indicated for sleep apnea, may be met with the same adherence issues as with NIV in COPD. Accordingly, patients with the overlap syndrome provide a unique opportunity to assess determinants of adherence to PAP therapy in COPD. In this study, we specifically sought to determine whether hyperinflation, as measured by the position of the diaphragm on a lateral chest radiograph, is a marker of low adherence to PAP therapy in the overlap syndrome.

Methods

Subject Selection

This study was approved by the investigational review board of the Cleveland Clinic. We reviewed records of adults (≥ 18 y) referred for a full-night attended polysomnography from January 2005 to December 2009. Pregnant women were excluded. The polysomnographic records included a searchable database of patient-reported and technician-entered medical diagnoses with the search targeted at the terms chronic airway obstruction, chronic obstructive pulmonary disease, COPD, and emphysema. Demographics were collected, and subjects were considered to have the overlap syndrome when they had both COPD and obstructive sleep apnea. The diagnosis of COPD was confirmed by review of the medical records for a clinical diagnosis of COPD along with spirometric data meeting the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease with a post-bronchodilator FEV1/FVC of < 0.70. The obstructive sleep apnea-hypopnea syndrome was as defined by the American Academy of Sleep Medicine, with an apnea-hypopnea index of ≥ 5 along with signs or symptoms of disturbed sleep. A flow diagram of the final subject selection is shown in Figure 1.

QUICK LOOK

Current knowledge

Positive airway pressure (PAP) in patients with both obstructive sleep apnea and COPD reduces the risk of pulmonary hypertension, death, and hospitalizations from exacerbations. Adherence to PAP therapy is poor despite the known salutary effects.

What this paper contributes to our knowledge

A retrospective review of subjects with both sleep apnea and COPD suggests that hyperinflation, as assessed by the right diaphragm position on a lateral radiograph, adversely affects adherence to PAP therapy. In these subjects, increased hyperinflation may increase non-adherence.

Measures

Pulmonary function tests were performed with MasterScreen PFT systems (Erich Jaeger, Friedberg, Germany). The spirometric studies followed the specifications of the American Thoracic Society/European Respiratory Society. Predicted variables used the Third National Health and Nutrition Examination Survey reference. Diffusion capacity was also collected when available.

All sleep studies were full-night attended laboratory polysomnographies, manually scored by technicians and then reviewed by board-certified sleep medicine physicians using the 2007 scoring rules of the American Academy of Sleep Medicine.

Polysomnographic variables were collected, as well as the type of PAP (CPAP vs bi-level PAP [BPAP]) and the optimum pressure level achieved during the PAP titration. Optimum PAP was defined as the pressure value (CPAP or the inspiratory pressure for a BPAP device) that abolished all respiratory events, arousals, and desaturation episodes.

The chest roentgenograms were independently reviewed without information from the polysomnography or medical records. The electronic ruler in the viewers’ applications (Syngo and MagicWeb Image Viewer programs, Siemens, Berlin, Germany) was used to measure the right diaphragmatic arc on the lateral film. These systems conform to the quantitative criteria of the American Association of Physicists in Medicine with a spatial accuracy within 2%. Left lateral radiographs were obtained with the left chest against the film cassette and with a source-image distance of at least 180 cm to minimize beam divergence. The technique of Reich et al was used with measurement of a line normal to the right diaphragmatic...
A diagnosis of chronic airway obstruction, COPD, or emphysema was found in 153 subjects. Of those, 54 were confirmed as having COPD based on both a chart review and an existing spirometry showing a post-bronchodilator FEV₁/FVC of $\geq 0.70$. The overlap syndrome (ie, concur-

Fig. 1. Study flow chart. PSG = polysomnography; OSAHS = obstructive sleep apnea-hypopnea syndrome; PAP = positive airway pressure.

Fig. 2. The right diaphragmatic arc height was the measurement of a line normal to the right diaphragmatic curve at its apex and normal to a line drawn between the posterior and anterior costophrenic angles.

Statistical Analysis

All variables were assessed for normality using the Shapiro-Wilk test. Continuous variables were presented as mean $\pm$ SD. Comparison of variables between groups was performed by $t$ tests or the Mann-Whitney $U$ test depending on the data distribution. Two-by-two cross-tabulation analyses were performed using the Fisher exact test or chi-square test. Receiver operating characteristic (ROC) plots were obtained, and area under the ROC curve analysis was performed to assess the predictive value of diaphragm height for adherence to PAP therapy. The ROC table and curves were then reviewed to identify a cutoff with the best sensitivity and specificity. Significance was defined as $P < .05$. All analyses were done with SPSS 11.5 (SPSS, Chicago, Illinois).

Results

A diagnosis of chronic airway obstruction, COPD, or emphysema was found in 153 subjects. Of those, 54 were confirmed as having COPD based on both a chart review and an existing spirometry showing a post-bronchodilator FEV₁/FVC of $< 0.70$. The overlap syndrome (ie, concur-
RADIOMATIC HYPERINFLATION AND DECREASED PAP ADHERENCE IN THE OVERLAP SYNDROME

Table 1. Demographic, Polysomnographic, and Pulmonary Function Characteristics Separated by Positive Airway Pressure Adherence at 3 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Group (n = 41)</th>
<th>Non-adherent Group (n = 20)</th>
<th>Adherent Group (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.7 ± 8.8 (47–84)</td>
<td>69.0 ± 8.9</td>
<td>66.5 ± 8.7</td>
<td>.36</td>
</tr>
<tr>
<td>Proportion of females (males/females), %</td>
<td>41.4 (24/17)</td>
<td>45 (11/9)</td>
<td>38.1 (13/8)</td>
<td>.65*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>34.1 ± 6.0 (23.7–51.4)</td>
<td>32.0 ± 5.7</td>
<td>36.0 ± 5.7</td>
<td>.03</td>
</tr>
<tr>
<td>Epworth sleepiness scale</td>
<td>11.2 ± 5.9 (0–22)</td>
<td>9.4 ± 5.4</td>
<td>13.0 ± 5.8</td>
<td>.048</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>36.8 ± 26.1 (6.3–94.9)</td>
<td>37.9 ± 24.7</td>
<td>35.6 ± 28.1</td>
<td>.48†</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>14.2 ± 8.6 (0–47.5)</td>
<td>11.6 ± 6.7</td>
<td>16.9 ± 9.6</td>
<td>.09†</td>
</tr>
<tr>
<td>Non-REM sleep, %</td>
<td>84.0 ± 13.9 (16–100)</td>
<td>88.4 ± 6.7</td>
<td>79.9 ± 17.5</td>
<td>.06†</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>27.7 ± 24.3 (1–114)</td>
<td>32.1 ± 29.7</td>
<td>23.5 ± 17.4</td>
<td>.60†</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>68.6 ± 17.0 (28–98)</td>
<td>65.6 ± 18.3</td>
<td>71.4 ± 15.5</td>
<td>.28</td>
</tr>
<tr>
<td>Total sleep time &lt; 90%, %</td>
<td>36.1 ± 32.7 (0–95)</td>
<td>44.0 ± 32.7</td>
<td>27.9 ± 31.5</td>
<td>.06†</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>58.5 ± 17.4 (25–106)</td>
<td>61 ± 20</td>
<td>56 ± 15</td>
<td>.31</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.56 ± 0.11 (26–69)</td>
<td>0.54 ± 0.12</td>
<td>0.60 ± 0.10</td>
<td>.45</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>60 ± 19 (30–98)</td>
<td>59 ± 19 (n = 17)</td>
<td>62 ± 19 (n = 13)</td>
<td>.60</td>
</tr>
</tbody>
</table>

Values are means ± SD (range).
* Pearson chi-square test
† Mann-Whitney U test
BMI = body mass index
AHI = apnea-hypopnea index
REM = rapid eye movement
DLCO = diffusing capacity of the lung for carbon monoxide

rent obstructive sleep apnea-hypopnea syndrome) was found in 48 of those subjects. Positive airway therapy was prescribed for 46 of those subjects. Three subjects died before completing the compliance evaluation, and one subject declined to have a follow-up for a CPAP adherence evaluation. Another subject was excluded because his chest radiograph showed severe kyphoscoliosis (see Fig. 1).

The remaining 41 subjects were included in this cohort. Chest roentgenograms were available for all 24 male and 17 female subjects. This group tended to be older (mean age of 68 y) and overweight (mean body mass index of 34 kg/m²) and to have severe sleep apnea (mean apnea-hypopnea index of 37 events/h) and moderate COPD (mean FEV₁ 59%) (Table 1).

At the 3-month evaluation, adherence from a device download was available in 6 subjects, and the remaining adherence information was obtained from records. Twenty subjects were considered non-adherent to PAP therapy, and 21 were considered adherent (51% adherence). The baseline demographic, polysomnographic, and pulmonary function characteristics separated by adherence status at 3 months are shown in Table 1. Baseline characteristics associated with improved adherence included a higher weight and higher degree of sleepiness at the time of the initial polysomnography. There was no significant difference between the adherent and non-adherent groups in the apnea-hypopnea index or in COPD severity as assessed by the percent-of-predicted FEV₁ or FEV₁/FVC. Diffusion capacity was available for 30 subjects (17 non-adherent and 13 adherent) and was not significantly different between the 2 groups (non-adherent: 59 ± 19%, adherent: 62 ± 19%, P = .60). The modality of positive airway therapy and the pressure prescribed did not predict adherence. Specifically, 18 of 35 subjects on a CPAP mode (51.4%) were adherent compared with 3 of 6 subjects (50%) on a BPAP mode (P = .65 by Fisher exact test). BPAP was recommended in those 6 subjects because of intolerance of CPAP (4 subjects) or poor control of sleep apnea at CPAP ≥ 15 cm H₂O (2 subjects). The optimum pressure (CPAP or inspiratory PAP) was also similar between non-adherent and adherent groups (11.35 ± 3.0 vs 12.19 ± 3.0 cm H₂O, P = .44 by Mann-Whitney U test).

The right diaphragmatic arc was significantly higher with adherence such that the median (interquartile range) was 2.82 (2.02–3.71) cm for adherent subjects compared with 2.07 (1.69–3.08) cm for non-adherent subjects (P = .04 by Mann-Whitney U test). Similarly, an ROC curve indicated that diaphragm height on the lateral view was predictive of adherence at 3 months, with an area under the curve of 0.69 (P = .04) (Fig. 3). A review of the coordinates of this curve indicated the best sensitivity and specificity to predict adherence at a diaphragm height cutoff of 2.45 cm. The sensitivity and specificity of the right diaphragmatic arc at a cutoff of 2.45 cm for adherence were 65% and 67%, respectively. As a corollary, only 35% of subjects with a flatter diaphragm (right diaphragmatic arc ≤ 2.45 cm) were adherent to PAP at 3 months compared with 67% of those with a more curved diaphragm (right diaphragmatic arc > 2.45 cm) (P = .04 by chi-square test).

Compared with subjects with a flatter diaphragm, those with a more curved diaphragm were also more overweight...
(body mass index of 36.2 \pm 6.6 vs 31.8 \pm 4.3 \text{ kg/m}^2, P = .02), had more rapid eye movement sleep (18.3 \pm 9.1\% vs 10.2 \pm 5.8\%, P < .01 by Mann-Whitney U test) and a lower apnea-hypopnea index (31.3 \pm 28.0 \text{ events/h} vs 42.4 \pm 23.2 \text{ events/h}, P = .04 by Mann-Whitney U test), and trended toward a higher diffusion capacity (67.6 \pm 18.1\% vs 54.8 \pm 17.6\%, P = .06). Lung volumes were available in only 19 subjects (46\%), with a clear bias toward availability of lung volumes in subjects with a flatter diaphragm. For instance, lung volumes were available in 70\% of subjects (14/20) with a flatter diaphragm compared with only 23\% of subjects (5/21) with a more curved diaphragm (P < .01 by Fisher exact test).

Later adherence (beyond 3 months) was available for 33 subjects. The right diaphragmatic arc was associated with later adherence, with an ROC curve showing an area under the curve of 0.74 (P = .02). The same cutoff of 2.45 cm had the best sensitivity and specificity for predicting late adherence. Specifically, only 6 of 17 subjects (35\%) with a flatter diaphragm (right diaphragmatic arc \leq 2.45 cm) were adherent to PAP beyond 3 months compared with 12 of 16 subjects (75\%) with a more curved diaphragm (right diaphragmatic arc > 2.45 cm) (P = .04 by Fisher exact test). Heavier weight was no longer predictive of later tolerance, but later adherent subjects tended to have a higher diffusion capacity (Table 2). In general, adherence at 3 months predicted later adherence: 88\% of subjects (15/17) who were adherent at 3 months were also adherent at a later time point, and 81\% of subjects (13/16) who were non-adherent at 3 months were also non-adherent at a later time point. Of the 3 non-adherent subjects who became adherent, 2 had a flat diaphragm (\leq 2.45 cm), and both initially adherent subjects who became non-adherent also had a flat diaphragm.

**Discussion**

In this study of subjects with well-defined overlap syndrome, we found that hyperinflation, as assessed by the diaphragm position on a lateral view, is associated with reduced nocturnal adherence to PAP therapy. Specifically, the proportion of nocturnal adherence to PAP therapy in subjects with a more elevated (curved) diaphragm was twice that in subjects with a lower (flat) diaphragm (67\% vs 35\% for early adherence and 75\% vs 35\% for later adherence). We additionally confirmed results of other studies showing that increased body weight\(^{16-19}\) and more symptomatic severity of sleep apnea as assessed by sleepiness\(^{20,21}\) predict better early adherence. We did not find an association between the apnea-hypopnea index and adherence, consistent with studies showing a weak-to-absent association with the apnea-hypopnea index.\(^{22}\)

Increased severity of hyperinflation in COPD is associated with worse sleep efficiency, even after adjustment for confounders such as body mass index, apnea-hypopnea...
index, FEV\textsubscript{1}, or extent of nocturnal hypoxemia.\textsuperscript{23} The implications of our findings for positive airway therapy in COPD are significant since hyperinflation and consequent reduced adherence to PAP therapy may compound these issues. Some studies suggest that more judicious use of PAP therapy may be part of the solution. For instance, NIV reduces total lung capacity by 10% in stable hypercapnic COPD, possibly from increased cross-sectional areas of the airways, decreased airway resistance, and increased expiratory time, which may facilitate the emptying of diseased lung units.\textsuperscript{24,25} In contrast, other studies have shown that CPAP only temporarily decreases hyperinflation in COPD.\textsuperscript{26} Similarly, high-resolution computed tomographic studies show that although low CPAP (5 cm H\textsubscript{2}O) may cause regional deflation in some subjects, higher CPAP (10–15 cm H\textsubscript{2}O) may promote overinflation of already hyperinflated zones.\textsuperscript{25} One study showed that generally low CPAP (4–11 cm H\textsubscript{2}O) in COPD can be individualized to the level best associated with an improvement in inspiratory capacity particularly in subjects with an emphysema phenotype rather than a chronic bronchitis phenotype of COPD.\textsuperscript{27} Although we did not classify our subjects based on the COPD phenotype, our study does suggest that subjects with increased weight (more commonly associated with the chronic bronchitis phenotype) have better adherence (see Table 1), whereas those with lower diffusion capacity (more commonly associated with the emphysema phenotype) have a flatter diaphragm and reduced later adherence (see Table 2). Finally, in a landmark physiologic study performed in mechanically ventilated subjects, application of extrinsic PEEP in excess of intrinsic PEEP increased end-expiratory total gas volume.\textsuperscript{28} Therefore, a critical value for externally applied pressure may exist after which hyperinflation occurs, particularly in subjects with expiratory flow obstruction.

Taken together, these studies favor a strategy of a lower PAP in subjects with COPD, with the additional challenge that the selected pressure should also control the obstructive sleep apnea in the overlap syndrome. Although we were unable to show a difference in the optimum pressure delivered when comparing adherent and non-adherent subjects, our study suggests that such a lower PAP strategy may best be targeted to individuals with hyperinflation, thereby lowering the threshold for options such as positional therapy or auto-titrating PAP therapy, which can reduce overall pressure and promote adherence in the overlap syndrome, as has been shown in subjects with obstructive sleep apnea-hypopnea syndrome who require higher CPAP.\textsuperscript{29} The low adherence to PAP therapy in patients with the overlap syndrome is similar to the experience with NIV in subjects with stable COPD.\textsuperscript{2–6} This disappointing experience stands in sharp contrast to that with NIV in COPD exacerbations, where it is considered a standard of care.\textsuperscript{30} and that in subjects with more severe hypercapnic COPD, where NIV with higher airway pressures is generally better tolerated\textsuperscript{31} and can be associated with a survival advantage.\textsuperscript{9} The difference may be that in severe COPD, PAP can compensate for the threshold load imposed by intrinsic PEEP,\textsuperscript{32} decrease the intrinsic PEEP,\textsuperscript{7} and relieve the respiratory muscle fatigue and weakness imposed by the mechanically disadvantageous diaphragm configuration imposed by hyperinflation.\textsuperscript{8}

In contrast, intrinsic PEEP may or may not be significantly increased in stable COPD, with studies indicating a mean intrinsic PEEP of < 3 cm H\textsubscript{2}O in stable but severe COPD.\textsuperscript{7} Furthermore, any reduction of intrinsic PEEP with COPD results in a marginal deflating effect, and the reductions in effort of breathing may occur at the expense of increases in end-expiratory lung volume, which may aggravate the hyperinflation,\textsuperscript{7} which in turn limits the ability of the diaphragm to increase lung volume\textsuperscript{8} and increases oxygen cost of breathing during resistive breathing.\textsuperscript{9}

It is noteworthy that our best cutoff of 2.45 cm is close to the 2.6-cm cutoff of Reich et al.,\textsuperscript{13} who found that a right diaphragmatic arc height of ≤ 2.6 cm identified 68% of subjects with abnormal pulmonary function tests, suggesting COPD. Although other radiographic parameters such as lung length and retrosternal lucency are also correlated with a COPD diagnosis, we chose the height of the right diaphragmatic arc based on the results of Reich et al.,\textsuperscript{13} the greater dependence of other parameters (such as lung length) on the subject’s morphometry (such as height), and studies showing diaphragm flattening as having a better correlation with postmortem changes in emphysema.\textsuperscript{33} For instance, in our study, an ROC analysis showed that the lung length (distance from the tubercle of the first rib to the top of the dome of the right diaphragm on a posterior-to-anterior chest projection) did not predict adherence (area under the curve of 0.49, \( P = .91 \)) and that lung length significantly correlated with the subject’s height (\( r = 0.46, P < .01 \)).

Although the sample size was small, we were able to document the deleterious aspect of hyperinflation because of a large effect size with a doubling of adherence in subjects with a curved diaphragm compared with a flat diaphragm. Also, the small area under the ROC curve in our study fully answers our question of whether hyperinflation is associated with low adherence. A higher area under the curve would have been required for a diagnostic test in which accuracy is important but cannot be expected in this context, given the complexity of factors (interface, subjects’ characteristics, severity of sleep apnea, psychosocial, etc) associated with PAP adherence.\textsuperscript{34}

A limitation of our study is that fewer than half our subjects had lung volume studies, reducing our ability to compare adherence by physiologic rather than anatomic markers of hyperinflation or air trapping. This may reflect
the lesser importance of lung volumes in the assessment of obstructive relative to restrictive lung diseases. We were not able to show any significant difference in lung volumes between adherent and non-adherent groups or between subjects with flat or curved diaphragms. However, that comparison was limited by a clear bias toward obtaining lung volume studies in subjects with more anatomic hyperinflation such that only 5 subjects with a curved diaphragm had lung volume studies.

A more significant limitation of our study is that adherence was partially determined by subject interviews. This limitation would have the effect of overestimating the subjects considered to be adherent to therapy, as objective CPAP adherence is generally overestimated by $>60\text{ min}$.\(^{35}\) but cannot be expected to bias toward our findings of improved adherence in subjects who were overweight or severely sleepy or who had a more elevated diaphragm position.

Future studies could address this limitation given the more widespread use of adherence monitoring, assess the impact of physiologically as well as radiographically determined hyperinflation, and evaluate the effect of a lower PAP strategy on adherence in the overlap syndrome.

In conclusion, our findings indicate that hyperinflation, as assessed by the right diaphragm position on a lateral radiograph, may adversely affect adherence to PAP therapy in subjects with the overlap syndrome. Since hyperinflation in COPD is associated with worse sleep efficiency,\(^{23}\) increased non-adherence to treatment in the presence of hyperinflation may negatively impact the care of these particularly vulnerable subjects. This finding may have direct implications, such as possible selection of lower pressures in overlap syndrome subjects with hyperinflation.

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