Orthopnea and Tidal Expiratory Flow Limitation in Patients With Stable COPD*

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**Background:** Orthopnea is a common feature in COPD patients, although its nature is poorly understood.

**Objective:** To study the role of tidal expiratory flow limitation (FL) in the genesis of orthopnea in patients with stable COPD.

**Measurements:** Tidal FL was assessed in 117 ambulatory COPD patients in sitting and supine positions using the negative expiratory pressure method. The presence or absence of orthopnea was also noted.

**Results and conclusions:** In patients with stable COPD with tidal expiratory FL in seated and/or supine position, there is a high prevalence of orthopnea, which probably results in part from increased inspiratory efforts due to dynamic pulmonary hyperinflation and the concomitant increase in inspiratory threshold load due to intrinsic positive end-expiratory pressure. Increased airway resistance in supine position due to lower end-expiratory lung volume probably also plays a role in the genesis of orthopnea.

Key words: inspiratory work; intrinsic positive end-expiratory pressure; negative expiratory pressure method to detect flow limitation; posture; routine lung function

Abbreviations: ATS = American Thoracic Society; BMI = body mass index; EELV = end-expiratory lung volume; FL = flow limitation; FRC = functional residual capacity; HD = heart disease; LHF = left heart failure; NEP = negative expiratory pressure; NFL = not flow limited; PEEPi = intrinsic positive end-expiratory pressure; RHD = right heart disease; RV = residual volume; TLC = total lung capacity; Vr = relaxation volume; WPEEPi = inspiratory work due to PEEPi

Patients with severe COPD often exhibit expiratory flow limitation (FL) during resting breathing, ie, their tidal expiratory flows are maximal under the prevailing conditions.1–3 While the maximal expiratory flow volume curve is essentially independent of body position,4 the functional residual capacity (FRC) in patients with mild-to-moderate COPD is smaller when in the supine position than when sitting.5 As a result, tidal expiratory FL is an earlier manifestation of COPD in the supine than in the sitting position.2,3 At a later stage, however, COPD patients eventually exhibit tidal expiratory FL both seated and supine.2,3 The presence of expiratory FL promotes dynamic pulmonary hyperinflation, a condition in which the FRC is higher than the elastic equilibrium volume (the relaxation volume [Vr]) of the respiratory system, the difference between the FRC and Vr being termed ΔFRC.6,7 As a result of dynamic hyperinflation, there is a positive end-expiratory elastic recoil pressure, which has been labeled intrinsic positive end-expiratory pressure (PEEPi), which acts as an inspiratory threshold load.6,7 Dynamic hyperinflation is associated with increased inspiratory work due to PEEPi6,7 and impaired inspiratory muscle function.8 These are probably the main causes of chronic dyspnea in COPD patients.2

Patients with COPD often experience more severe dyspnea in supine than in sitting positions, ie, orthopnea.9,10 The nature of this phenomenon is not clear. Since in COPD patients diaphragmatic function is probably not impaired in supine position compared to sitting position, this cannot explain orthopnea.11,12 In contrast, increased inspiratory work due to PEEPi (WPEEPi) and airway resistance in supine position is a more likely explanation. Since airway resistance increases with decreasing lung...
volume, the lower FRC in supine position should be associated with an augmented inspiratory resistive work. Furthermore, in patients with mild-to-moderate COPD, who during resting breathing exhibit expiratory FL only in the supine position, the presence of WPEEPi in the supine position should promote orthopnea. The same should also occur in patients with severe COPD who exhibit tidal expiratory FL both seated and supine. Indeed, while in such patients the end-expiratory lung volume (EELV) during resting breathing is essentially the same in seated and supine position, as a result of gravitational factors the VR is lower supine than sitting. As a result, in COPD patients who are flow limited both seated and supine, the ΔFRC and the WPEEPi should also be greater in supine position, promoting orthopnea.

The present study was undertaken on 117 COPD patients to (1) assess if the prevalence of orthopnea is related to the presence of tidal expiratory FL in sitting and supine positions, and (2) to further characterize the relationship of orthopnea with other physiologic and clinical findings, in particular routine spirometric variables and heart disease (HD).

Materials and Methods

Subjects

A cross-sectional study was carried out on 117 consecutive ambulatory COPD patients (75 men and 42 women). All patients were suffering from COPD according to the American Thoracic Society (ATS) guidelines, and were studied in a stable clinical state. Subjects in whom heart disease (HD) was considered also available. The predicted values for routine spirometry and physiologic and clinical findings, in particular routine spirometric variables and heart disease (HD).

Pulmonary Function Tests

The FVC and FEV₁ were measured with the patient in sitting position using a spirometer (Spiro Analyzer ST-250R; Fukuda Sangyo, Tokyo, Japan). This system, which meets the ATS standards, was calibrated every day with standardized techniques according to the guidelines of the ATS. In 83 patients, thoracic gas volumes obtained with a pressure/flow whole body plethysmograph (Autobox 2800; SensorMedics; Yorba Linda, CA) were also available. The predicted values for routine spirometry and thoracic gas volumes were those of Morris and coworkers. In 27 patients, PaO₂ and PACO₂ measured with a blood gas analyzer (ABL 330; Radiometer; Copenhagen, Denmark) were also available.

Expiratory FL

The experimental set-up used to assess tidal FL by negative expiratory pressure (NEP) was similar to that described in detail previously. All patients were studied both seated upright in a comfortable chair and lying supine on a comfortable couch, in random order. The pattern of breathing was continuously monitored on a computer screen. After reaching steady-state breathing, we performed a series of three to five test breaths in which NEP of −5 cmH₂O was applied at the beginning of expiration and maintained throughout expiration. These expiratory flow-volume loops were compared by superimposition with those obtained during the immediately preceding breaths. The volume signal was corrected for any offset based on the assumption that inspired and expired volumes of the preceding breath were identical. In the absence of preexisting FL, the increase in pressure gradient between the alveoli and the airway opening caused by NEP should result in increased expiratory flow, whereas in flow-limited subjects, NEP should enhance dynamic airway compression downstream from the flow-limiting segments, without substantial effect on pressure or flow upstream. Accordingly, in flow-limited subjects, expiratory flow does not change with NEP, except for a brief flow transient (spike), which is thought to mainly reflect sudden reduction in volume of the compliant oral and neck structures. To a lesser extent, however, enhanced dynamic airway compression and a small artifact caused by the common-mode rejection ratio of the system for measuring flow also contributed to such flow transients. In line with previous studies, after the application of NEP, the expiratory flow either increased (reflecting absence of FL) or did not change (reflecting presence of FL). There was no instance in which application of NEP resulted in a sustained decrease of expiratory flow below the corresponding control values as a consequence of upper-airway collapse.

Subjects in whom the application of NEP did not elicit an increase of flow over all or part of the control tidal expiration were considered flow limited. By contrast, subjects in whom flow increased with NEP over the entire range of the control tidal expiration were considered not flow limited (NFL). The degree of expiratory FL was assessed in terms of a 3-point FL score: score 0 = NFL both supine and seated; score 1 = FL when supine but not seated; and score 2 = FL both supine and seated. As previously described, we found that all COPD patients in whom the application of NEP did not elicit an increase of flow over all or part of the control tidal expiration were considered flow limited.

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Orthopnea</th>
<th>Orthopnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td>24</td>
<td>93</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>9/15</td>
<td>33/60</td>
</tr>
<tr>
<td>Age, yr</td>
<td>71 ± 6</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164 ± 10</td>
<td>163 ± 8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63 ± 11</td>
<td>70 ± 17</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 6</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>43 ± 18</td>
<td>34 ± 13†</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>66 ± 18</td>
<td>61 ± 17</td>
</tr>
<tr>
<td>FEV₁/FVC, % predicted</td>
<td>63 ± 18</td>
<td>55 ± 17</td>
</tr>
<tr>
<td>3-point FL score (0, 1, and 2)</td>
<td>0.4 ± 0.7</td>
<td>1.6 ± 0.7†</td>
</tr>
<tr>
<td>Subjects, No.</td>
<td>17</td>
<td>66</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>122 ± 19</td>
<td>131 ± 20</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>138 ± 24</td>
<td>158 ± 38†</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>157 ± 32</td>
<td>189 ± 45†</td>
</tr>
<tr>
<td>RV/TLC, % predicted</td>
<td>130 ± 20</td>
<td>150 ± 20†</td>
</tr>
<tr>
<td>Subjects, No.</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>85 ± 5</td>
<td>66 ± 9†</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>41 ± 1</td>
<td>47 ± 4</td>
</tr>
</tbody>
</table>

*Values are presented as means ± SD unless otherwise indicated. †p < 0.05 between the two groups (unpaired t test).
patients who had FL when seated also had FL when supine, while many COPD patients who had FL when supine were NFL when seated. With patients both seated and supine, the NEP tests were reproducible in the sense that each patient was classified as either FL or NFL on all three to five NEP tests performed in any given position.

During the application of NEP, air may leak around the lips into the expired line and contribute to the expiratory flow. Such leaks, however, are easily detected because they result in a sustained decrease of the EELV during the tidal breaths following NEP application. Accordingly, great care was taken to avoid such leaks by proper positioning of the mouthpiece and by asking the subjects to hold their lips tight.

Orthopnea

During the above session, the occurrence and the severity of orthopnea were assessed by the following two questions: (1) “Do you feel more breathless when you are lying on your back than when you are seated?” Based on this question, the patients were classified into two groups: group 0, patients who did not report orthopnea (by answering No to the question); and group 1, patients who reported orthopnea (by answering Yes to the question), (2) “How many pillows do you use when sleeping?”

The reproducibility of the above two questions was assessed on a pilot study on 10 subjects. These subjects were chosen from the outpatient clinics of the Saint-Luc Hospital, Montreal, Canada. Five of them were selected based on a physician’s diagnosis of stable COPD. The five other subjects chosen from the list of nonrespiratory outpatient clinics did not have any respiratory disease and did not complain of dyspnea. They were scheduled for two visits, 2 weeks apart.

They completed the FL measurements in seated and supine position and answered the above orthopnea questions. The reproducibility in this sample was 95%. The reproducibility of assessment of FL was also high, as previously reported.

Statistical Analysis

Values reported in the text are means ± SD. Statistical analysis was made using the unpaired t test, with the level of significance set at p < 0.05. In addition, multiple logistic regression analysis was used, as explained below.

Results

There were 24 patients (20.5%) who did not report orthopnea and 93 patients (79.5%) who did. None of the 24 patients who did not report orthopnea used two or more pillows. Among the 93 patients who reported orthopnea, 40 patients (43%) used two pillows, 35 patients (38%) used three pillows, and 18 patients (19%) used four or more pillows.

The anthropometric and lung function data of the 117 COPD patients stratified according to presence or absence of orthopnea are shown in Table 1. While age, height, and weight did not differ significantly between the two groups, the average BMI of the group without orthopnea was slightly though significantly different from that with orthopnea. The FEV1 percent of predicted was significantly lower in the patients with orthopnea, while no significant differences were found in either FVC or FEV1/FVC (percent predicted). The 3-point FL score was significantly higher in the orthopnea group.

Figure 1A depicts the individual values of the 3-point FL score stratified according to the two orthopnea groups. Although most of the patients who reported orthopnea had FL when seated and/or

\[
\begin{align*}
\text{Flow limited supine and seated} & \quad p < 0.0001 \\
\text{Flow limited supine} & \\
\text{Not flow limited} & \\
\text{No reported orthopnea} & n = 24 \\
\text{Reported orthopnea} & n = 93
\end{align*}
\]

\[
\begin{align*}
\text{Flow limited supine} & \\
\text{No reported orthopnea} & n = 18 \\
\text{Reported orthopnea} & n = 63
\end{align*}
\]

\[p < 0.0001\]

\[p < 0.0001\]

**Figure 1.** Left, A: Individual values of 3-point FL score of all 117 COPD patients studied stratified according to the two orthopnea groups. Right, B: Same as left, A, but without the 36 patients with RHD. All p values (unpaired t test) refer to significant differences between the two groups.
supine (scores 1 or 2), there were nine patients who reported orthopnea in spite of the fact that they were NFL both seated and supine. Figure 1, right, B depicts the individual values of the 3-point FL score after exclusion of the patients who had RHD. In this case, there were only four NFL patients left in the orthopnea group.

As shown in Table 1, in the subset of COPD patients in whom thoracic gas volume was measured (n = 83), those who reported orthopnea exhibited a significantly higher residual volume (RV), FRC, and RV/total lung capacity (TLC) (percent predicted) than those who did not. In the subset of COPD patients in whom arterial blood gases were analyzed (n = 27), those with orthopnea had a significantly lower PaO2 and higher PaCO2.

According to the multiple logistic regression analysis in Table 2, the only variables significantly related to orthopnea were the 3-point FL score and HD, while FEV1 (percent predicted), age, gender, and BMI were found to carry no significant risk. However, when the logistic regression analysis was carried out by omitting the 3-point FL score, the FEV1 (percent predicted) was found to be significantly related to orthopnea, though the significance level was lower than that for the 3-point FL score (p < 0.05 vs 0.01). To the extent that FEV1 (percent predicted) is an indirect index of FL, after omission of the 3-point FL score a significant correlation was necessarily found between orthopnea and FEV1 (percent predicted).

**DISCUSSION**

In this study, we have examined the association of orthopnea with the 3-point FL score and routine lung function data in 117 patients with stable COPD. The main finding is that FL is the strongest risk factor for reported orthopnea.

The fact that patients with severe COPD may be FL during resting breathing is well recognized, and the consequences in terms of dynamic pulmonary hyperinflation, increased work of breathing, and impaired inspiratory muscle function and hemodynamics have been well documented. In a previous study, we have shown that chronic dyspnea, as assessed with the modified Medical Research Council scale, is more closely correlated with the degree of FL than with routine lung function data. In the present study, we found that orthopnea is more prevalent in patients with tidal FL (Fig 1). In COPD patients who are FL only in the supine position, the inspiratory work of breathing would be expected to be higher when supine than seated because of the additional WPEEPi and increased airway resistance in the supine position. Accordingly, the degree of dyspnea should be greater in the supine position. In this connection, it should be noted that in some COPD patients receiving mechanical ventilation, the degree of expiratory FL is reduced or abolished by shifting from the supine to the semirecumbent position, presumably because of increased EELV. In patients who are FL in the sitting position, WPEEPi should also be greater in supine than in the sitting position because of greater WPEEPi. In fact, in patients with severe COPD who presumably were FL both seated and supine, the changes in FRC when shifting from seated to supine position have been found to be either very small or absent. Since, as a result of gravitational factors, Vr is expected to be higher seated than supine, it follows that the degree of dynamic pulmonary hyperinflation (ΔFRC) and, hence, WPEEPi should be greater in the supine position. The possible role of tidal FL in the genesis of orthopnea is supported by two recent studies. Duguet and coworkers studied patients with acute left heart failure (LHF), in whom orthopnea is a clinical hallmark. As airway obstruction is common in LHF, they hypothesized that postural aggravation of tidal FL could contribute to LHF-related orthopnea. In 9 of 12 of their patients with LHF, they observed that tidal FL was induced or aggravated by the supine position and that this coincided with orthopnea. They concluded that, in acute LHF, tidal FL is more frequent or prominent in the supine position with a concomitant increase in PEEPi and hence in load on the inspiratory muscles, contributing to orthopnea. Pankow and coworkers assessed tidal FL and PEEPi in eight healthy obese subjects in both sitting and supine position. In seven of these subjects, they found that tidal FL and PEEPi were either induced or aggravated by the

### Table 2—Multiple Logistic Regression Equations of Reported Orthopnea With Various Covariables

<table>
<thead>
<tr>
<th>Covariables/Categories</th>
<th>Odds Ratio</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point FL score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NFL</td>
<td>Reference category</td>
<td></td>
</tr>
<tr>
<td>FL when supine</td>
<td>6.55*</td>
<td>0.70</td>
</tr>
<tr>
<td>FL when seated and supine</td>
<td>32.41*</td>
<td>0.77</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Reference category</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.52</td>
<td>0.67</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.03</td>
<td>0.03</td>
</tr>
<tr>
<td>HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference category</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.50†</td>
<td>0.35</td>
</tr>
<tr>
<td>Constant</td>
<td>1.15</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.01.
† p < 0.05.
supine position, with a concomitant increased load on the diaphragm. Unfortunately, they did not assess orthopnea. Similar to patients with acute LHF and obese subjects, in many COPD patients tidal FL is either induced or aggravated by the supine position and may contribute to orthopnea. However, other factors could contribute to orthopnea. O’Donnell and coworkers suggested that flow-limiting dynamic airway compression may per se elicit dyspnea. However, a recent study on normal subjects with methacholine-induced tidal expiratory FL does not support this hypothesis. On the other hand, there is evidence that expiratory FL just precedes dependent airway closure (closing volume) at low flow rates. This should lead to abnormal distribution of ventilation within the lung with concomitant hypoxemia. While hypoxia per se may not cause dyspnea, it does increase ventilation. This would increase the degree of expiratory FL, with a concomitant increase in dynamic hyperinflation and PEEPi, enhancing dyspnea in the supine position.

Although the 3-point FL score was significantly higher in the orthopnea group (Table 1), 8% of the patients reported orthopnea in absence of FL (Fig 1, left, A). This was due in part to the fact that our COPD population included patients with concurrent RHD. After exclusion of the HD patients (30%), only four of the COPD patients who were NFL did report orthopnea (Fig 1, right, B). An association of orthopnea and tidal expiratory FL has been recently demonstrated in patients with acute LHF. None of our COPD patients, however, exhibited left ventricular dysfunction, which is a rare occurrence even in patients with severe airway obstruction.

There was a significant difference in PaO2 and PaCO2 between the two orthopnea groups, which could be attributed in part to the fact that the patients with orthopnea had more severe COPD than the patients without orthopnea (Table 1). The decreased PaO2 in the orthopnea group is predictable in view of the fact that these patients exhibited a more severe degree of FL than the nonorthopnea groups (Fig 1, Table 1). Indeed, the onset of expiratory FL heralds peripheral airway closure in dependent lung zones with concomitant abnormality in ventilation distribution and gas exchange. An increased PaCO2 has been previously found in COPD patients with tidal FL both seated and supine. We also found a significant difference in BMI and FEV1 (percent predicted) between the two orthopnea groups (Table 1). However, neither represented a significant risk for orthopnea according to the multiple logistic regression analysis in Table 2. According to Table 2, the 3-point FL score and HD were the only significant risk factors for orthopnea, with the former playing the main role. Indeed, the COPD patients who were FL both sitting and supine had a 32-fold greater risk of reporting orthopnea than the patients who were NFL. Though the HD covariable was not as strong and significant as the 3-point FL score, the COPD patients with right heart dysfunction had an almost threefold higher risk of reporting orthopnea than those without RHD.

When the 3-point FL score was omitted from the multiple logistic regression analysis, FEV1 (percent predicted) became a statistically significant risk factor for orthopnea, although at a lower level of significance than the 3-point FL score. This probably merely reflects the fact that FEV1 (percent predicted) is a poor, though significant, indirect index of FL.

In conclusion, in patients with stable COPD with tidal expiratory FL in seated and/or supine position, there is a high prevalence of orthopnea, which may be due to increased inspiratory effort due to PEEPi and increased airway resistance in supine position. Further studies, including measurements of inspiratory work and its components, are required to explain orthopnea.

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REFERENCES


12. Heijdra YF, Dekhuisen PN, van Herwaarden CLA, et al. Effects of body position, hyperinflation, and blood gas tensions on maximal respiratory pressures in patients with chronic ob-
18 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225–244