A New Method of Negative Expiratory Pressure Test Analysis Detecting Upper Airway Flow Limitation To Reveal Obstructive Sleep Apnea

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Background: Expiratory flow limitation (EFL) by negative expiratory pressure (NEP) testing, quantified as the expiratory flow-limited part of the flow-volume curve, may be influenced by airway obstruction of intrathoracic and extrathoracic origins. NEP application during tidal expiration immediately determines a rise in expiratory flow (V˙) followed by a short-lasting V˙ drop (ΔV), reflecting upper airway collapsibility.

Purpose: This study investigated if a new NEP test analysis on the transient expiratory V˙ after NEP application for detection of upper airway V˙ limitation is able to identify obstructive sleep apnea (OSA) subjects and its severity.

Methods: Thirty-seven male subjects (mean ± SD age, 46 ± 11 years; mean body mass index [BMI], 34 ± 7 kg/m²) with suspected OSA and with normal spirometric values underwent nocturnal polysomnography and diurnal NEP testing at −5 cm H2O and −10 cm H2O in sitting and supine positions.

Results: ΔV (percentage of the peak V˙ [%V˙peak]) was better correlated to apnea-hypopnea index (AHI) than the EFL measured as V˙ during NEP application, equal or inferior to the corresponding V˙ during control (EFL), and expressed as percentage of control tidal volume (%VT). AHI values were always high (> 44 events/h) in subjects with BMI > 35 kg/m², while they were very scattered (range, 0.5 to 103.5 events/h) in subjects with BMI < 35 kg/m². In these subjects, AHI still correlated to ΔV (%V˙peak) in both sitting and supine positions at both NEP pressures.

Conclusions: OSA severity is better related to ΔV (%V˙peak) than EFL (%VT) in subjects referred to sleep centers. ΔV (%V˙peak) can be a marker of OSA, and it is particularly useful in nonseverely obese subjects.

Key words: expiratory flow limitation; extrathoracic airway obstruction; negative expiratory pressure; obesity; obstructive sleep apnea; upper airway collapse

Abbreviations: AHI = apnea hypopnea index; BMI = body mass index; EFL = expiratory flow limitation; NEP = negative expiratory pressure; OSA = obstructive sleep apnea; V˙ = flow; ΔV = flow drop; %V˙peak = percentage of peak flow; %VT = percentage of control tidal volume

The obstructive sleep apnea (OSA) syndrome has important social implications related to accidents,1 cardiovascular risk,2,3 neuropsychological impairment,4 reduction in quality of life,5 and increased health-care utilization,6,7 so that its underrecognition may have important consequences. However, the diagnostic procedures are expensive, and predictive criteria are still unsatisfactory. Parameters of obesity are important predictors,8 but not all OSA patients are obese and not all obese subjects have OSA. Identification of new markers of OSA would be useful. As increased upper airway collapsibility is one of the main determinants of OSA,9,10 the response to negative expiratory pressure (NEP) application11 could be a predictor of this disorder.

The NEP test is performed by applying a negative pressure at the mouth during expiration.12 It is easy to perform and requires minimal subject cooperation. It is based on the principle that, in the absence of expiratory flow limitation (EFL), the increase in pressure gradient between the alveoli and the airway...
opening caused by NEP should result in increased expiratory flow. NEP was initially introduced as a test to evaluate intrathoracic EFL in patients with obstructive lung disease. These subjects are considered flow limited when NEP application does not elicit an increase in flow (V\dot) during the terminal portion of the tidal expiration compared to the previous flow-volume loop.20 More recently, NEP has also been applied to study upper airway properties in subjects with obesity and/or OSA.11,14–18 It has been suggested that in the absence of intrathoracic airway obstruction, the response to NEP application may reflect upper airway collapsibility.11,16–18

So far, EFL in obese and OSA subjects has been quantified by the percentage of tidal expiration over which NEP does not induce any appreciable increase in V\dot with respect to the control expired tidal volume.11,16,17 However, this method does not always discriminate if EFL is of extrathoracic or intrathoracic origins.11,16,17 Alternative assessments of the effects of NEP application to detect upper airway obstruction could be useful. NEP application elicits a V\dot spike due mainly to a dynamic airway compression downstream from the compliant oral and neck structures, and to a small extent to common mode rejection ratio of the differential pressure transducer used to measure V\dot,13,19 followed by a V\dot drop (\Delta V) of variable degree among subjects. The sudden \Delta V is caused by an increase in resistance of the oropharyngeal structures,18,19 reflecting upper airway collapsibility (extrathoracic EFL). The purpose of this study was to investigate if the transient expiratory \Delta V after NEP application is correlated with the presence and severity of OSA better than the EFL measurements previously used.

**Materials and Methods**

Thirty-seven male subjects referred to our sleep laboratory for suspected OSA syndrome after evaluation of spirometry to exclude subjects with bronchial obstruction were recruited for the study. Mean ± SD age was 46 ± 11 years, and mean body mass index (BMI) was 34 ± 7 kg/m². None of the subjects had acute or known chronic cardiopulmonary or neuromuscular diseases. Each patient gave informed consent, and the study protocol was approved by the local scientific committee. All subjects underwent spirometry, nocturnal monitoring by a portable cardiorespiratory system, and NEP testing during tidal expiration.

Pulmonary function tests were performed during the day with the patient in a sitting position with a pneumotachograph (Med Graphics Elite; Med Graphics Corporation; St. Paul, MN) according to the guidelines of the European Respiratory Society.20 Nocturnal monitoring was performed by a computerized system (Poly-MESAM; MAP; Martinsried, Germany). All recordings lasted > 6 h. V\dot was detected by nasal cannulas connected to a pressure transducer (Pneumoflow; MAP). Apneas and hypopneas were visually scored. Apneas were defined as lack of flow for at least 10 s. Hypopneas were defined as discernible reductions in V\dot or thoracoabdominal movements ≥ 10 s followed by an arterial oxygen saturation fall > 3%.21 Apnea-hypopnea index (AHI) was calculated as number of apneas plus hypopneas per hour of estimated total sleep time.

NEP was generated by a circular Venturi device (AeroMech Devices; Almonte, ON, Canada) attached to a tank of compressed air via an electrically operated solenoid valve. The solenoid valve had an opening time of 50 ms; it was automatically activated in early expiration and kept open for 2 s by software control (DirecWin version 2.18a; Raytech Instruments; Vancouver, BC, Canada). A pneumotachograph (model 3830; Hans Rudolph; Kansas City, MO) was connected to the mouthpiece. V\dot and mouth pressure were also measured (DirecNEP model 200A; Raytech Instruments). The changes in V\dot after application of NEP, inherent in our measuring set-up, were assessed by occluding the mouthpiece with a stopper and applying NEPs of –5 cm H₂O and –10 cm H₂O. As shown in Figure 1, after application of NEP, there was an initial spike in V\dot that lasted approximately 20 ms and was followed by progressively decreasing oscillations that became very small after another 80 ms when V\dot became constant. Similar results were obtained with NEP of –10 cm H₂O, except that the magnitude of the V\dot spike increased. With NEP of –5 cm H₂O, the initial spike in V\dot corresponded to approximately 0.3 L/s, while with NEP of –10 cm H₂O it amounted to approximately 0.4 L/s. In both instances, however, the initial V\dot spikes were much smaller that those observed in our experimental subjects.

In all subjects, NEP tests at –5 cm H₂O and –10 cm H₂O in sitting and supine positions were performed in a random order during quiet breathing with a nose clip. NEP was readministered after breathing pattern stabilization. For this purpose, at least four regular breaths were allowed between two consecutive NEP applications. During the test, care was taken to keep the neck in a neutral position and the subjects awake. The V\dot and mouth pressure signals were filtered through a low-pass filter and sampled at 200 Hz. Both digital signals were displayed in real-time on the computer screen and stored on computer for subsequent analysis. Data analysis was performed using software developed in our laboratory written in MATLAB 6.5 (The MathWorks; Natick, MA).

**Data Analysis**

A new method was assessed in this study to evaluate upper airway obstruction, ie, extrathoracic EFL, was measured as \Delta V expressed as percentage of the peak V\dot (%V\dot peak) immediately after NEP application (Fig 2). The minimum V\dot was identified in the first 200 ms of NEP application to avoid reflex and voluntary reactions to NEP stimulus.22 We also assessed EFL induced by NEP as V\dot in the flow-volume loop, during NEP application equal or inferior to the corresponding V\dot in any part of the control flow-volume loop (EFL), expressed as percentage of control tidal volume (%V\dot) [Fig 2] as previously performed.37 Values of EFL (%V\dot) and \Delta V (%V\dot peak) were the average of four measurements.

Data are reported as mean ± SD and range. The values of \Delta V (%V\dot peak) and EFL (%V\dot) were linearly correlated to AHI. Statistical analysis was performed by commercial software (StatView; Abacus Concepts; Berkeley, CA). A p < 0.05 was considered significant.

**Results**

All subjects had normal forced expiratory flow volume loops (FVC and FEV₁ of 101 ± 12%
predicted and 100 ± 12% of predicted, respectively). Nocturnal monitoring showed an AHI of 51 ± 32 events/h in the whole population studied. Most subjects were obese (BMI range, 27 to 59 kg/m²), and 10 of them had BMI > 35 kg/m². Table 1 shows anthropometric and respiratory characteristics of subjects with BMI < 35 kg/m² and with BMI > 35 kg/m².

NEP application during tidal expiration produced an immediate \( V_{\text{peak}} \) followed by a sudden drop of variable degrees in all subjects. Examples of different shapes of flow-volume loops during NEP application of –10 cm H₂O in the supine position are shown in Figure 3.

Figure 4 shows the scatter plots between AHI and EFL (%Vt) during NEP applications of –5 cm H₂O and –10 cm H₂O with subjects in the sitting and in the supine positions. Many subjects exhibited EFL.
Table 1—Anthropometric and Respiratory Data of Subjects According to BMI*  

<table>
<thead>
<tr>
<th>Variables</th>
<th>BMI &lt; 35 kg/m² (n = 27)</th>
<th>BMI &gt; 35 kg/m² (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>47 ± 11</td>
<td>44 ± 11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30 ± 2</td>
<td>44 ± 71</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>42 ± 2</td>
<td>49 ± 51</td>
</tr>
<tr>
<td>AHI, n/h</td>
<td>48 ± 33</td>
<td>76 ± 231</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>103 ± 11</td>
<td>98 ± 16</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>101 ± 11</td>
<td>95 ± 14</td>
</tr>
<tr>
<td>FEF₂₅–₇₅, % predicted</td>
<td>99 ± 5</td>
<td>98 ± 5</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>80 ± 20</td>
<td>84 ± 20</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>100 ± 9</td>
<td>99 ± 11</td>
</tr>
<tr>
<td>IC, % predicted</td>
<td>109 ± 15</td>
<td>110 ± 23</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± SD. FEF₂₅–₇₅ = forced expiratory flow, midexpiratory phase; FRC = functional residual capacity; TLC = total lung capacity; IC = inspiratory capacity.

†p < 0.0001, significant differences between the two groups.
†p < 0.02, significant differences between the two groups.

(%VT) equal to 0, particularly in the sitting position (23 subjects and 12 subjects in the sitting position at −5 cm H₂O and −10 cm H₂O; 9 subjects and 6 subjects in the supine position at −5 cm H₂O and −10 cm H₂O, respectively). In both positions, AHI was not correlated with EFL (%VT) obtained at a NEP of −5 cm H₂O, while they were correlated to values measured at NEP of −10 cm H₂O.

The same analysis performed with ΔV (%Vpeak) showed stronger correlations with AHI at both pressures and in both positions (Fig 5). The best relationship between ΔV (%Vpeak) and AHI was obtained in the sitting position at NEP of −10 cm H₂O.

In agreement with the well-known relationship between obesity and OSA, a significant correlation between AHI and BMI was found ($R^2 = 0.27$; $p < 0.001$); however, a lower degree of dispersion was found in subjects with BMI > 35 kg/m² (Fig 6). The patients with BMI < 35 kg/m² did not show a significant correlation between AHI and BMI, while the group with BMI > 35 kg/m² had a very close correlation ($R^2 = 0.77$; $p = 0.0008$). AHI values were always high (> 44 events/h) in the more obese subjects, while they were very scattered (range, 0.5 to 103.5 events/h) in the subjects with BMI < 35 kg/m².

In the subjects with BMI < 35 kg/m², the correlation between AHI and EFL (%VT) was present only at −10 cm H₂O in the sitting position ($R^2 = 0.16$; $p = 0.0396$). Conversely, the correlation between AHI and ΔV (%Vpeak) was significant in all

Figure 3. Examples of NEP tracing (−10 cm H₂O in the supine position). Observe how a 100% ΔV (%Vpeak) [top, left] is associated with a prolonged airway occlusion [top, right] and a low value of EFL expressed as %VT. Bottom, left, and bottom, right: a subject with OSA and a subject with a different ΔV, respectively.

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the tested conditions: at NEP of – 5 cm H₂O in the sitting ($R^2 = 0.19; p = 0.0249$) and supine ($R^2 = 0.17; p = 0.0315$) positions; at NEP of – 10 cm H₂O in the sitting ($R^2 = 0.22; p = 0.0136$) and supine ($R^2 = 0.32; p = 0.0022$) positions. Therefore, the supine position at NEP of – 10 cm H₂O showed the best relationship between $\Delta V (% V_{\text{peak}})$ and AHI also in the group with BMI < 35 kg/m² taken alone.

**Figure 4.** Relationship between AHI and EFL, expressed as EFL %Vₜ, with NEPs of – 5 cm H₂O and – 10 cm H₂O in the sitting and supine positions. Solid circles indicate subjects with BMI < 35 kg/m²; open circles indicate subjects with BMI > 35 kg/m². NS = not significant.

**Figure 5.** Relationship between AHI and $\Delta V$ expressed as %V_peak with NEPs of – 5 cm H₂O and – 10 cm H₂O in the sitting and supine positions. Solid circles indicate subjects with BMI < 35 kg/m²; open circles indicate subjects with BMI > 35 kg/m².
It has been suggested that the sharp transient decrease in V shortly after NEP application is not related to lower airway obstruction, and it may reflect a temporary increase in upper airway resistance, independent of any voluntary or reflex upper airway muscle activation. In fact, NEP is applied at the beginning of tidal expiration, and the ΔV is detected in the first 200 ms, before any voluntary or reflex muscular activation could actively influence upper airway patency: Tantucci et al have shown that during application of NEP, a reflex response of the genioglossus muscle, a major upper airway dilator muscle, is elicited much more commonly at the end rather than at the onset of expiration. Once the transient ΔV has been reversed, likely by the reflex activation of upper airway muscles, the subsequent behavior may be representative of lower airway properties.

Epidemiologic studies have shown that 40 to 98% of morbidly obese male subjects are affected by OSA. The data of this study, on a small sample of severely obese subjects referred to our sleep center, show that BMI alone is a good marker of OSA. By contrast, in moderately obese or normal-weight subjects, only ΔV (%Vpeak) measured after NEP application was always correlated to AHI. Therefore, the NEP test could prove particularly useful as a marker of OSA in nonseverely obese subjects.

In conclusion, the finding of a high ΔV (%Vpeak) value after NEP application during tidal expiration in patients with suspected OSA may reinforce the suspicion of OSA, while traditional analysis by EFL (%Vt) gives much more approximate indications. ΔV (%Vpeak) in the supine position at NEP of −10 cm H2O is the best indicator of OSA severity and may be of help particularly in nonseverely obese subjects. The NEP test is easy to apply and could be adopted as a screening test for the evaluation of suspected OSA patients if future analysis on larger samples of subjects shows high sensitivity and specificity of the ΔV (%Vpeak) for OSA.

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