Evidence for expiratory flow limitation of extrathoracic origin in patients with obstructive sleep apnoea

E Verin, C Tardif, F Portier, T Similowski, P Pasquis, J F Muir

Background: A study was undertaken to examine the expiratory flow response to a negative pressure (NEP) applied at the airway in patients with no abnormalities of the intrathoracic airway but suffering from the obstructive sleep apnoea syndrome (OSAS).

Methods: Nineteen patients with OSAS with normal spirometric values were studied. NEP of –5 cm H2O and –10 cm H2O was applied to the mouth when sitting and when supine.

Results: Thirteen patients exhibited expiratory flow limitation when supine (group 1). Of these, three also had flow limitation in the sitting position. The remaining six patients (group 2) had no flow limitation. Patients in groups 1 and 2 were similar with respect to age, sex, and body mass index, but the apnoea/hypopnoea index (AHI) was higher in group 1 than in group 2 (p<0.05). There was a significant correlation between the degree of flow limitation (expressed as a percentage of the expired tidal volume over which the NEP induced flow did not exceed spontaneous flow) and the AHI (p<0.05 for both pressure levels) as well as the desaturation index (DI, number of desaturations per hour of sleep; p<0.05 at –10 cm H2O).

Conclusion: This study confirms that the NEP technique can detect expiratory flow limitation of extrathoracic as well as of intrathoracic origin. This technique could be useful for studying the collapsibility of the passive upper airway in awake subjects and might help to predict the severity of OSAS.

The detection of expiratory flow limitation, defined as a lack of difference between tidal and forced expiratory flow, is relevant to the pathophysiological understanding of various clinical situations, including chronic obstructive pulmonary disease (COPD) and cardiac failure related airway obstruction. The advent of the negative expiratory pressure (NEP) technique has dramatically simplified the detection of expiratory flow limitation by obviating the need to resort to body plethysmography. The technique involves application of a negative pressure at the airway opening during tidal expiration. The ensuing flow-volume curve is then compared with that of the previous control expiration. Its non-volitional nature is a major advantage over methods based on forced expiratory manoeuvres. In addition, the technique detects flow limitation under the prevailing breathing conditions, thus providing clinically relevant information.

However, studying the expiratory flow in response to a negative pressure applied at the airway opening (as opposed to the expiratory flow in response to a positive alveolar pressure) has one major drawback—namely, except in tracheostomised or intubated patients, it can result in the collapse of the extrathoracic airway. In such a situation flow limitation will occur but will have a radically different meaning. Patients with the obstructive sleep apnoea syndrome (OSAS) are highly likely to exhibit such behaviour. Liistro et al. showed that expiratory flow limitation is common in a population of patients with OSAS with no airway obstruction. Once this problem is known and understood, advantage can be taken of it. In the absence of any underlying lung disease likely to promote intrathoracic flow limitation, the NEP technique could be used to study the flow dynamics of the passive upper airway during wakefulness and thus could possibly help to refine the diagnosis strategy of OSAS. It could be postulated that, in the absence of intrathoracic airway obstruction as detected by pulmonary function tests, the presence of flow limitation could indicate upper airway abnormalities and the degree of flow limitation could correlate with their severity. The data provided by Liistro et al., who found a statistically significant relationship between the degree of flow limitation and the number of desaturations per hour of sleep, indirectly support this hypothesis.

The present study was undertaken to assess the effects of NEP applied at the mouth in awake patients suffering from OSAS, and to relate the results to the apnoea/hypopnoea index (AHI).

METHODS

Patients

Nineteen patients with clinical features of OSAS were included in the study. The diagnosis had previously been confirmed by a polysomnographic sleep recording study. The anthropometric characteristics of the patients and the results of the sleep studies are reported in table 1. The study was approved by the appropriate regulatory authority and the patients gave informed consent to participate.

Measurements

All the measurements were obtained during the same visit to the laboratory in awake patients.

Sleep recording

The polysomnographic recordings (CJD102p Device, Cidelec, Saintes Gemmes-sur-Loire, France) consisted of in-laboratory continuous acquisition transcutaneous oxyhaemoglobin saturation (SpO2), chest wall and abdominal movements, and tracheal sounds. From these data, apnoeaic and hypopnoeic events and desaturation episodes were characterised according to standard criteria. In addition to the usual sleep parameters, the apnoea index (AI) and the apnoea/hypopnoea index (AHI) were calculated and the desaturation index (DI) was measured as the sleep time spent with a SpO2 below 90%.

Spirometric tests

Maximal flow-volume curves were obtained in the seated position. Vital capacity (VC) and forced expiratory volume in
of flow limitation (%VT) between the two levels of NEP study

analysis of variance (ANOVA). Differences between the degree
with those without flow limitation (group 2) using a one way

The patients with flow limitation (group 1) were compared

Statistical analysis

Data analysis

Flow limitation was deemed to be present when the NEP
induced expiratory flow did not exceed the corresponding
spontaneous expiratory flow, whatever the position and NEP
level. Figure 1 shows examples of the different patterns observed with an NEP of –5 cm H2O.

In the supine position 13 of the 19 patients exhibited
expiratory flow limitation with both levels of NEP (group 1; table 2). Only three of these patients also had flow limitation in the seated position, again with both levels of NEP. Flow limitation was absent in the remaining six patients (group 2), whatever the position and NEP level. Figure 1 shows examples of the different patterns observed with an NEP of –5 cm H2O. In the supine position the degree of flow limitation with NEP levels of –10 cm H2O and –5 cm H2O was not significantly dif-

correlation analysis. Statistics were calculated using Statview and SuperAnova software (Abacus Concept, Berkeley, CA, USA) on an Apple Macintosh computer. Results were consid-

RESULTS

All patients had normal forced expiratory flow/volume loops
except one (patient no 8) who had a moderate obstructive ventilatory defect (FEV1 = 79% predicted, FEV1/VC = 79% predicted). Four patients had a decreased FRC (<80% predicted) which was associated in two cases with a decreased TLC.

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expiratory flow limitation with both levels of NEP (group 1; table 2). Only three of these patients also had flow limitation in the seated position, again with both levels of NEP.

Table 1

Anthropometric characteristics, lung function, and polygraphic data

<table>
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<th>Age (years)</th>
<th>Sex</th>
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<th>FEV1 (% pred)</th>
<th>VC (% pred)</th>
<th>FEV1/VC (% pred)</th>
<th>FRC (% pred)</th>
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| Group 2  |             |     |             |               |             |                 |              |              |           |          |
| 10       | 55          | M   | 41          | 90            | 97          | 96              | 75           | 70           | 7         |          |
| Mean     | 57          | M   | 30          | 102           | 105         | 100             | 80           | 95           | 43        | 32       |
| SD       | 11          | M   | 5           | 17            | 17          | 7               | 18           | 16           | 21        | 26       |

BMI=body mass index; FEV1=forced expiratory volume in 1 second; VC=vital capacity; FRC=functional residual capacity; TLC=total lung capacity; AHI=apnea/hypopnea index (n per hour of sleep); DI=index of desaturation per hour of sleep (n/h).

1 second (FEV1) were measured using a Fleish no 2 pneumo-
tachograph (Spirometro Micro 5000; Medisoft, Dinan, Bel-
gium) and FEV1/VC was calculated. Maximal expiratory flow
and flow at 25%, 50%, and 75% of VC were also measured. In
12 patients the functional residual capacity (FRC) and total
lung capacity (TLC) were measured using a body plethysmo-
graph (Jaeger, Witzburg, Germany). Quality criteria and refer-
cence values were those of the European Community.7

Expiratory flow limitation

An NEP of –5 cm H2O and –10 cm H2O was applied at the
mouth during tidal breathing using a specially devised system
(Medisoft, Dinan, Belgium). The patients breathed through a
standard rubber mouthpiece connected to a low dead space
(45 ml) low resistance circuit while wearing a nose clip. Three
reproducible tracings were recorded for each patient, both in
the seated and the supine posture, and averaged to calculate
the degree of flow limitation (see below).

Data analysis

Flow limitation was deemed to be present when the NEP
induced expiratory flow did not exceed the corresponding spontaneous expiratory flow, whether present throughout expiration or during any part of it. The presence or absence of flow limitation was used as a dichotomous variable for the statistical analysis. When present, the degree of flow limitation was expressed as the percentage of tidal expiration over which NEP did not induce any appreciable change in flow with respect to the control expired tidal volume (%VT). The value of this index was, by definition, zero when flow limitation was absent.

Statistical analysis

The patients with flow limitation (group 1) were compared

with those without flow limitation (group 2) using a one way
analysis of variance (ANOVA). Differences between the degree
of flow limitation (%VT) between the two levels of NEP stud-
ied were assessed using the Wilcoxon non-parametric test.

The association between the degree of flow limitation and
variables derived from the sleep studies was studied using
but, as expected, a strong correlation existed between the AHI and DI (R = 0.79; p<0.001). Because visual inspection of the data suggested the existence of an apnoea/hypopnoea threshold beyond which the percentage flow limitation would be linked with the AHI, the correlation analysis was repeated after logarithmic transformation of the AHI data. This improved the strength of the above associations, again with NEP levels of both –5 cm H2O (R = 0.544, p = 0.0147, 95% CI 0.120 to 0.801) and –10 cm H2O (R = 0.531, p = 0.0179, 95% CI 0.010 to 0.794). This was also the case for the DI with an NEP of –10 cm H2O (R = 0.582, p = 0.0274, 95% CI 0.074 to 0.850).

No relationship was found between the degree of flow limitation and any of the anthropometric or spirometric variables.

In group 1 flow limitation of 20% or more of the tidal volume identified 100% of the patients with an AHI above 20. Flow limitation of 26% or more identified 77% of the patients with an AHI above 30.

**DISCUSSION**

This study confirms the work of Liistro et al. and shows that expiratory flow limitation in the supine position is common, although inconsistent, in patients with OSAS who are free of obstructive lung disease. It also shows a significant relationship between the extent of flow limitation over tidal expiration and the severity of OSAS. This would suggest that the greater the flow limitation over tidal volume, the more abnormal is the upper airway in the apnoeic population.

**Intrathoracic vs extrathoracic flow limitation**

It is not possible to discern the source of an expiratory limitation from NEP tracings, except when the NEP induced flow sharply and transiently becomes lower than the spontaneous expiratory flow. Such a pattern suggests acute airway closure and can be observed in normal subjects. It corresponds to the behaviour of the passive upper airway faced with a sudden negative pressure gradient (fig 4). The re-increase in the NEP induced flow that follows probably corresponds to a reflex activation of the airway dilator muscles, mainly the genioglossus. Apart from these accidents, a limited expiratory flow response to NEP is the same whatever the source of the limitation.

In patients with COPD, flow limitation at rest is closely linked to dynamic hyperinflation and tends to appear earlier in the supine position. All but one of our patients were free of any history of asthma or COPD. Their FEV1/VC ratios (table 1) and visual inspection of their expiratory flow/volume curves suggest that their limitation was not obstructive. In addition, none of them exhibited signs of hyperinflation on pulmonary function tests. We are therefore confident that the expiratory flow limitation that we observed could not be accounted for by COPD related abnormalities. Left heart failure can also induce expiratory flow limitation. To date this has been observed only in patients with severe cardiac disease and during episodes of acute left heart failure. Although we do not have precise cardiac evaluations in our patients and hence cannot rule out moderate cardiac dysfunction in some of them, there is no reason to think that any of them could have suffered cardiac failure to an extent sufficient to induce flow limitation. Finally, early small airway closure can be a feature of obesity in the absence of obstructive disease, and particularly so in the supine position where FRC tends to decrease independently of the absence of obstructive disease, and particularly so in the supine position where FRC tends to decrease independently of smoking habits. This could be another intrathoracic source of expiratory limitation. Only six patients in our study population had a BMI above 30 kg/m² and only one could be classified as severely obese (BMI 40.5 kg/m², table 1). We therefore consider it likely that the expiratory flow limitation patterns observed in our patients were extrathoracic rather than intrathoracic in origin.

**Expiratory flow limitation and upper airway collapsibility**

Augmented upper airway compliance typically occurs in patients with OSAS compared with normal subjects or non-apnoeic snorers and is a major determinant of the pathophysiology of OSAS. Indeed, the combination of increased airway compliance and abnormalities in the temporospatial repartition of the inspiratory command (that normally synchronises the activity of upper airway dilator muscle with that of inspiratory muscle) leads to an increased risk of airway collapse when the intrathoracic pressure becomes negative. In awake OSAS patients this can easily be shown using phrenic nerve stimulation to dissociate the activities of the upper airway dilators and the diaphragm.

The same phenomenon can occur when the direction of the pressure gradient across the upper airway is in the opposite direction: the application of subatmospheric pressure at the nose can collapse the airway. This gives access to measurements of the critical pressure (Pcrit), a widely used index

<table>
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<tr>
<th>Table 2</th>
<th>Degree of expiratory flow limitation (as % spontaneous tidal volume, %VT) when seated and supine at both pressure levels</th>
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for characterising upper airway collapsibility in patients with sleep disordered breathing. Expiratory flow limitation with the NEP technique is therefore to be expected in this clinical setting. Its predominant occurrence in the supine position is also expected. Indeed, shifting from the seating to the supine position decreases pharyngeal areas and increases upper airway collapsibility. Tantucci et al observed an NEP induced flow limitation in awake non-apnoeic snorers that was more pronounced in the supine position and associated with an increase in expiratory resistance.

Our study did not include a control group. This should not be an important limitation because we know from several studies that non-apnoeic and non-snoring patients of various ages do not exhibit NEP induced flow limitation. This has been shown by Tantucci et al and was also the case in the control group in the study by Duguet et al and in the series reported by Liistro et al in which 16 of the 22 patients with OSAS were flow limited with NEP whereas the six who were free of sleep related breathing disorders were not.

Liistro and coworkers’ found a statistically significant relationship between the degree of supine expiratory flow limitation (expressed as a percentage of tidal breathing, NEP of –5 cm H2O) and the frequency of desaturation episodes during sleep, but a possible relationship between flow limitation and the AHI was not tested. The frequency of desaturation episodes and the AHI do not provide exactly the same information. The latter is probably a more direct reflection of upper airway abnormalities than the former. In addition, the AHI is less sensitive to any prevailing gas exchange abnormality than the DI would be. This seems to be confirmed in our study by the slightly higher significance of the relationships between the degree of expiratory flow limitation and the AHI than with the DI (fig 3), particularly after logarithmic transformation of the AHI to account for the shape of the relationship. It is important to emphasise that a flow limitation of extrathoracic origin sustained during part or throughout expiration rather than being transient after the application of NEP might be taken as indicative of the incapacity of the airway dilator muscle to re-open the airway. Indeed, the genioglossus muscle is normally reflexively activated by a negative pressure at the airway opening which accounts for the restoration of flow that, in some cases, follows a transient limitation (fig 4). The absence of this restoration could be due either to a defect in the activation of the

Figure 1  Examples of negative expiratory pressure (NEP) tracings (NEP –5 cm H2O; left tracings in sitting position, right tracings in supine position) illustrating the absence of flow limitation in both positions (top), the occurrence of flow limitation when shifting from the sitting to the supine position (middle), and flow limitation in both positions (bottom).
Expiratory flow limitation and the obstructive sleep apnoea syndrome

Figure 2 Comparison of (A) the apnoea/hypopnoea index (AHI) and (B) body mass index (BMI) in groups 1 (flow limitation) and 2 (no flow limitation). Each point represents one patient, the horizontal bar marks the median of the distribution.

Figure 3 Relationship between flow limitation (fL), expressed as the percentage of tidal volume over which the NEP induced flow does not exceed the spontaneous expiratory flow, and the apnoea/hypopnoea index (AHI) with a negative expiratory pressure (NEP) of (A) –5 cm H2O and (B) –10 cm H2O in the supine position. Closed symbols correspond to patients from group 1 (flow limited) and open symbols represent patients from group 2 (no flow limited).

Figure 4 Example of a negative expiratory pressure (NEP) tracing (–5 cm H2O) highly suggestive of extrathoracic expiratory flow limitation. At the beginning of the NEP induced expiration the flow in response to NEP falls below the spontaneous expiratory flow; both traces are then briefly matched and finally flow limitation disappears. This dynamic probably illustrates the effects of the activation of the genioglossus muscle in response to NEP (see text for details).
the collapsibility of the upper airway in patients with OSAS. Larger studies will be needed to determine the operating characteristics of the technique for OSAS screening in awake patients in routine clinical applications.

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