SLEEP DISORDERED BREATHING

A simple procedure for measuring pharyngeal sensitivity: a contribution to the diagnosis of sleep apnoea

M Dematteis, P Lévy, J-L Pépin

Background: Patients with severe apnoea may have an impaired pharyngeal dilating reflex related to decreased pharyngeal sensitivity. The accuracy of a simple new procedure to measure pharyngeal sensitivity and to diagnose sleep disordered breathing (SDB) was investigated.

Methods: Pharyngeal disappearance and appearance sensory perception thresholds were measured by delivering different airflow rates on the soft palate using an intraoral device in 17 controls and 50 patients suffering from SDB evaluated by overnight polygraphy. The procedure was performed before (baseline) and after three successive administrations of a topical anaesthetic to sensitise the pharyngeal sensory impairment. Pharyngeal sensitivity was then evaluated according to SDB severity. SDB was classified as mild, moderate or severe according to the relative proportion of obstructive apnoeas-hypopnoeas and the amount of desaturation.

Results: Patients had higher baseline disappearance and appearance sensory thresholds than controls (mean (SD) 0.62 (0.44) l/min and 0.85 (0.40) l/min, p<0.001, respectively). Such differences were enhanced by topical anaesthesia. Impairment of pharyngeal sensitivity and the number of patients with impaired sensitivity increased from the least to the most severe SDB group as indicated by the test sensitivity for a respiratory disturbance index of >20/hour (50%, 73.7% and 88.5% in the mild, moderate, and severely affected groups, respectively).

Conclusions: This simple and safe procedure showed that impairment of pharyngeal sensitivity is correlated with severity of SDB. Using this test in routine clinical practice may simplify the diagnosis of sleep apnoea, particularly for the most severe patients.

Sleep disordered breathing (SDB) corresponds to a continuous clinical spectrum from snoring, upper airway resistance episodes, to obstructive apnoeas and apnoeas according to the severity of upper airway collapsibility. The common characteristic is a repetitive partial or complete collapse occurring during sleep at the pharyngeal level, a region lacking rigid support. Thus, pharyngeal patency is dependent on both its anatomy (calibre) and on the activity of pharyngeal dilator muscles (PDM) such as the genioglossus muscle. PDM have inspiratory phasic activity preceding diaphragmatic contraction, thus anticipating the development of intrapharyngeal negative pressure related to inspiration. This muscle activity is reduced during sleep leading to pharyngeal obstruction in patients with high pharyngeal collapsibility. There is increased evidence that upper airway mucosal sensory receptors may play a role in the patency of the upper airway through a reflex PDM activation. During wakefulness a negative pressure applied to the upper airway increases genioglossus muscle activity. This response is reduced by topical anaesthesia, suggesting that upper airway receptors may be involved in the afferent limb of this reflex. Anaesthesia of the upper airway increases pharyngeal airflow resistance, induces apnoeas/hypopnoeas in healthy subjects, and increases the frequency of obstrusive events in snorers and the duration of apnoeas in apnoeic subjects. Thus, impairment of pharyngeal sensitivity may play a role in the pathophysiology of SDB through impairment of the pharyngeal dilator reflex.

Sleep apnoea syndrome is highly prevalent and represents a major public health problem. Diagnosis is by polysomnography which is expensive, labour intensive and time consuming. Simpler alternative diagnostic procedures are therefore strongly welcomed. Assessment of pharyngeal sensitivity could facilitate the diagnosis of SDB in some groups of patients with high clinical probability. While the anatomy of the upper airway can only predict the severity of SDB in young lean subjects who represent only a small proportion of SDB patients, evaluation of functional pharyngeal impairment may allow the presence and severity of SDB to be predicted.

We therefore investigated, in a prospective study, the accuracy of a new simple technique to evaluate whether impairment of pharyngeal sensitivity correlates with SDB severity and assessed the clinical usefulness of this procedure in the diagnosis of SDB.

METHODS

Study design

Seventeen controls and 50 patients with SDB (all men aged over 20 years who were not receiving any medication that may produce drowsiness and had no recognised cause of polyneuropathy, recent upper airway infection, or history of surgery of the upper airway except past tonsillectomy) were included in the study. Patients had SDB symptoms and a respiratory disturbance index (RDI) of >20 events/hour. Control subjects did not report any symptoms compatible with SDB such as habitual snoring, daytime fatigue or sleepiness, morning headache, and had normal nocturnal oximetry. In accordance with the ethical standards of the Grenoble University Hospital, all subjects gave informed consent to participate in the study.

Abbreviations: AHI, apnoea/hypopnoea index; BMI, body mass index; PDM, pharyngeal dilator muscles; RDI, respiratory disturbance index; SDB, sleep disordered breathing.
The catheter was introduced in the guide and gently pushed until adjusted to aim at the central part of the soft palate. The distal part of the guide was inserted into the subject’s mouth and firmly maintained by the teeth and lips. The distal part of the guide was therefore reassessed after graded mucosal anaesthesia. Application of an anaesthetic on diseased nerves should induce a greater anaesthesia (that is, higher sensation thresholds in patients with pharyngeal neuropathy) and allow better discrimination between patients and controls and between different subgroups of patients. One spray was applied to the test site and the procedure was repeated 5 minutes later, followed by measurements after two further applications of anaesthetic. Hence, for each subject, measurement of the appearance and disappearance of sensory detection thresholds at baseline and after successive administrations of topical anaesthetic enabled us to determine a slope between sensory thresholds obtained at baseline and after anaesthesia (appearance threshold slope and disappearance threshold slope, respectively), reflecting their response to anaesthesia. The slope was calculated using Excel software and corresponded to the slope of a linear regression for the measurements obtained at baseline and after anaesthesia.

Quality control and repeatability of the procedure
To improve the sensitivity of the procedure, the test was repeated after successive administrations of a topical anaesthetic (Xylocaine 5%, AstraZeneca Laboratory, France). We hypothesised that measuring pharyngeal sensitivity as previously described may not be sufficient to detect changes in sensitivity in patients suffering from mild neuropathy—that is, not severe enough to increase the baseline threshold perception. To avoid such limitation, pharyngeal sensitivity was therefore reassessed after graded mucosal anaesthesia. Quality control and repeatability of the procedure
To test the procedure, the subject was instructed to give his best response—that is, the smallest pharyngeal sensation that could be felt.

Description of test session
After description of the device and the procedure, the subject signed a consent form and characteristics were collected throughout the session test by regularly asking the subject to give his best response—that is, the smallest pharyngeal sensation that could be felt.

Figure 1 Device for the determination of pharyngeal sensory perception thresholds. Schematic representation of the device superimposed on a teleradiography. The device consists of an intraoral apparatus through which airflow is administered 1 cm in front of the central part of the soft palate mucosa using a graduated and adjustable catheter (white arrows).
>10 seconds. Inspiratory flow limitation episodes had a "plateau" aspect of the inspiratory flow curve of 10 seconds ending by a microarousal or returning to a rounded aspect of the flow curve. Apnoea and hypopnoea events were classified as obstructive based on the presence or the increase in respiratory effort, respectively. The RDI (number of apnoeas + hypopnoeas + flow limitation episodes) was considered abnormal above 20/hour of sleep.

### Statistical analysis

For the 10 control subjects assessed twice, a two way analysis of variance (ANOVA) for repeated measurements was used to assess the effect of measurement conditions (baseline and successive anaesthesias) for each session, as well as the effect of session and the interaction between condition measurements and sessions. The repeatability of the procedure performed in these 10 control subjects was analysed in two different ways:

1. **Repeatability** was further assessed using the Bland-Altman procedure, plotting the differences between the repeated measurements (y axis) against their average (mean of the differences, x axis). Since the Bland-Altman procedure assumes independent subjects, the calculations were done separately for measurements obtained at baseline and after each administration of anaesthetic for both the disappearance and appearance sensory thresholds. Using this method, 95% limits of agreement were calculated (mean ± 1.96 SD—that is, the range in which the difference may be expected to lie in 95% of the measurements—where SD is the standard deviation of the differences between paired measurements); 95% confidence intervals (95% CI) were calculated to indicate the precision of the limits of agreement. As a measure of repeatability, the British Standards Institution repeatability coefficient was calculated as 1.96 times the standard deviation of the differences. This coefficient indicates the maximum difference likely to occur between the measurements of the two sessions.

2. For the rest of the analyses, heterogeneity of variances (Levene’s test) required the use of non-parametric tests to analyse the results, expressed as mean (SD) values. Intergroup comparisons were done with the Kruskall-Wallis test followed, if necessary, by a post hoc pairwise Mann-Whitney U test between controls and patients. The Spearman rank correlation test was used for correlation analysis between sensory values and anthropometric data and polysomnographic measurements, and was performed for the whole patient cohort. Pharyngeal sensitivity was then analysed according to SDB severity using classical indices such as apnoea/hypopnoea index (AHI) and RDI. However, since AHI and RDI only referred to the frequency of the

### Table 1: Characteristics of controls and patients with sleep disordered breathing (SDB)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n = 17)</th>
<th>All patients (n = 50)</th>
<th>p value†</th>
<th>Mild group (n = 5)</th>
<th>Moderate group (n = 19)</th>
<th>Severe group (n = 26)</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.1 (7.82)</td>
<td>48.5 (12.77)</td>
<td>0.0378</td>
<td>31.4 (8.82) *</td>
<td>50.1 (8.27) *</td>
<td>50.6 (13.8) *</td>
<td>0.0020</td>
</tr>
<tr>
<td>SWS (min)</td>
<td>6.9 (2.96)</td>
<td>8.0 (2.87)</td>
<td>0.2176</td>
<td>6.6 (2.87) *</td>
<td>7.1 (3.11) *</td>
<td>7.5 (2.63) *</td>
<td>0.0010</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 (2.57)</td>
<td>28.5 (4.54)</td>
<td>0.0004</td>
<td>25.6 (3.29) *</td>
<td>27.4 (3.39) **</td>
<td>29.7 (5.08) **</td>
<td>0.0003</td>
</tr>
<tr>
<td>Sleepiness Epworth score (0–24)</td>
<td>4.76 (3.29)</td>
<td>11.0 (4.37)</td>
<td>0.0001</td>
<td>13.6 (4.34) **</td>
<td>10.9 (3.45) ***</td>
<td>10.5 (4.89) ***</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gog reflex intensity (0–3)</td>
<td>1.42 (0.52)</td>
<td>1.54 (0.82)</td>
<td>0.6809</td>
<td>2.10 (0.89)</td>
<td>1.50 (0.81)</td>
<td>1.48 (0.80)</td>
<td>0.4917</td>
</tr>
<tr>
<td>Tobacco consumption (packs/year)</td>
<td>13.1 (4.7)</td>
<td>13.5 (7.07)</td>
<td>0.1993</td>
<td>6.15 (7.94)</td>
<td>11.1 (11.8)</td>
<td>16.4 (20.4)</td>
<td>0.8327</td>
</tr>
<tr>
<td>Alcohol consumption (drinks/day)</td>
<td>0.70 (0.74)</td>
<td>1.88 (2.04)</td>
<td>0.0377</td>
<td>0.51 (0.47)</td>
<td>1.12 (1.22)</td>
<td>2.70 (2.36) **</td>
<td>0.0079</td>
</tr>
<tr>
<td>Spicy food consumption (0–3)</td>
<td>0.79 (0.93)</td>
<td>0.17 (0.69)</td>
<td>0.2146</td>
<td>0.28 (0.15)</td>
<td>0.46 (0.55)</td>
<td>0.66 (0.64)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean nocturnal SaO2 (%)</td>
<td>95.3 (1.16)</td>
<td>92.7 (2.55)</td>
<td>0.0001</td>
<td>95.5 (1.95)</td>
<td>93.8 (2.27)</td>
<td>95.4 (2.02)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Minimal nocturnal SaO2 (%)</td>
<td>91.8 (1.89)</td>
<td>79.5 (11.2)</td>
<td>0.0001</td>
<td>91.6 (1.82)</td>
<td>83.6 (9.07) **</td>
<td>74.4 (10.8) **</td>
<td>0.0001</td>
</tr>
<tr>
<td>Percentage of time spent below 90% of SaO2 (%)</td>
<td>0.05 (0.19)</td>
<td>15.1 (20.4)</td>
<td>0.0001</td>
<td>0.00 (0.00)</td>
<td>7.81 (16.6)</td>
<td>23.4 (21.4) **</td>
<td>0.0001</td>
</tr>
<tr>
<td>RDI (events/h of sleep)</td>
<td>NA</td>
<td>47.0 (20.5)</td>
<td>0.0001</td>
<td>28.7 (10.77)</td>
<td>41.4 (16.2)</td>
<td>54.6 (21.5)</td>
<td>0.0172</td>
</tr>
<tr>
<td>Apnoea index (events/h of sleep)</td>
<td>NA</td>
<td>41.7 (21.3)</td>
<td>0.0001</td>
<td>15.6 (5.74)</td>
<td>32.5 (11.9)</td>
<td>53.4 (21.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypopnoea index (events/h of sleep)</td>
<td>NA</td>
<td>9.54 (13.1)</td>
<td>0.0001</td>
<td>0.25 (0.22)</td>
<td>6.54 (9.05)</td>
<td>13.5 (15.3)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Flow limitation index (events/h of sleep)</td>
<td>NA</td>
<td>32.2 (16.7)</td>
<td>0.0001</td>
<td>15.3 (5.59)</td>
<td>26.0 (9.37)</td>
<td>39.9 (18.2)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Obstructive index (events/h of sleep)</td>
<td>NA</td>
<td>5.31 (6.48)</td>
<td>0.0001</td>
<td>13.2 (5.18)</td>
<td>8.90 (6.89)</td>
<td>11.8 (1.97)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Central index (events/h of sleep)</td>
<td>NA</td>
<td>45.3 (19.8)</td>
<td>0.0001</td>
<td>26.7 (10.4)</td>
<td>40.1 (15.9)</td>
<td>52.6 (20.4)</td>
<td>0.0128</td>
</tr>
<tr>
<td>Central index (events/h of sleep)</td>
<td>NA</td>
<td>1.75 (2.51)</td>
<td>0.0001</td>
<td>2.07 (1.36)</td>
<td>1.37 (2.19)</td>
<td>1.96 (2.90)</td>
<td>0.5527</td>
</tr>
</tbody>
</table>

BMI, body mass index; SaO2, oxygen saturation; RDI, respiratory disturbance index; AHI, apnoea-hypopnoea index.

*Patients were classified into three groups according to the proportion of the different respiratory events constituting the sleep disordered breathing: *‘mild’* patients had apnoea-hypopnoea events <60%; *‘moderate’* patients had apnoea-hypopnoea events 60–90%; *‘severe’* patients had apnoea-hypopnoea events >90%.

†Comparison between controls and all patients using Mann-Whitney U test.

‡Analysis of variance (Kruskal-Wallis test) between controls and the three groups of patients, or only between the three groups of patients when data in controls were not available.

Each group was compared with controls using the Mann-Whitney U test: *p* < 0.05, **p** < 0.01, ***p*** < 0.001.

Gog reflex was scored 0 (absent), 1 (decreased), 2 (normal) and 3 (exaggerated). Spicy food consumption was scored 0 (no consumption), 1 (little), 2 (moderate) and 3 (high consumption). Obstructive index includes plus obstructive apnoea and hypopnoeas and flow limitation episodes. Central index includes central apnoeas and hypopnoeas.
respiratory events without prejudging their respective proportion, we also defined SDB severity according to the proportion of the different respiratory events constituting the SDB. Indeed, as SDB pathophysiologically corresponds to a continuous spectrum of overlapping entities with increasing severity related to collapsibility of the upper airway (from flow limitation events to obstructive hypopnoeas and apnoeas), patients were classified into three groups according to the proportion of the different respiratory events. The cut-off values were arbitrarily chosen and allowed us to distinguish between patients with a high proportion of inspiratory flow limitations, patients with a high proportion of apnoea-hypopnoea, and patients in an intermediate situation. The less severely affected group (“mild”) included patients with apnoea-hypopnoea events <60% and flow limitation episodes >40% of events; the moderately affected group (“moderate”) included patients with apnoea-hypopnoea events of 60–90% and flow limitation episodes of 10–40% of events; and the most severely affected group (“severe”) included patients with apnoea-hypopnoea events >90% and flow limitation episodes <10% of events. The differences between these three subgroups of patients also referred to the severity of the AHI, RDI, and oxygen desaturation as reflected by mean and minimum nocturnal SaO₂ (table 1). The significance was set at p = 0.05.

Finally we assessed the sensitivity of the test (that is, how effective it is at identifying patients with SDB) in the same set of patients. For these calculations the pharyngeal sensitivity of the patients was considered abnormal when at least one parameter of the test (appearance or disappearance thresholds or slopes) was higher than the 97.5th percentile of values obtained in the 17 control subjects. The accuracy of the test (percentage of SDB correctly diagnosed (RDI >20/hour) for all patients and for each subgroup of patients) was determined by comparison with the gold standard polygraphy.

RESULTS

Pharyngeal sensitivity was easily measured in all subjects, regardless of gag reflex intensity or mouth opening. The characteristics of the patients are summarised in table 1. Patients were older and had a higher BMI, sleepiness, and alcohol consumption than controls.

Differences between the three subgroups of patients and controls were then assessed. The “mild” group was younger while the two other groups were older with a higher BMI. All three groups had more sleepiness than controls. Nocturnal desaturation was greater in the “moderate” and “severe” groups, while controls and the “mild” group were not different. Alcohol and spicy food consumption was higher in the “severe” group while gag reflex intensity did not differ between the three groups. Gag reflex was re-assessed in some patients at the end of the procedure and no change in intensity was found despite the anaesthesia.

Pharyngeal sensitivity in controls and patients

Patients had a higher baseline pharyngeal sensory detection threshold. Differences between controls and patients were enhanced by anaesthesia, as reflected by the slopes (table 1 and fig 3).

Sensory thresholds were significantly correlated with age (appearance threshold at baseline (r = 0.33, p = 0.024) and after anaesthesia (first anaesthesia: r = 0.48, p = 0.001; second anaesthesia: r = 0.37, p = 0.010; third anaesthesia: r = 0.35, p = 0.017). They were positively correlated with BMI (appearing threshold at baseline (r = 0.33, p = 0.027; first anaesthesia: r = 0.38, p = 0.010) and the appearance threshold (first anaesthesia: r = 0.29, p = 0.049).

For the other sensory thresholds a trend emerged that did not reach statistical significance.

Pharyngeal sensitivity and severity of SDB

Individual values for baseline sensory thresholds and slopes in controls and the three groups of patients are shown in fig 4. At baseline, control values were grouped in a narrow range, particularly for the appearance sensory threshold, while values in “moderate” and “severe” patients were widely dispersed with a mean value significantly higher than that of controls. In contrast, pharyngeal sensory perception of the “mild” group was close to that of controls (see also table 1 and fig 3). However, some patients in the two most severe groups had sensory thresholds similar to controls. Patients with normal sensitivity were compared with patients exhibiting an impaired sensitivity in the same groups. Patients with normal sensitivity had a higher proportion of flow limitation episodes (15.0 (9.32) v 9.07 (11.4%), p = 0.049) reflecting less severe SDB, and a lower BMI (25.4 (4.24) v 29.6 (4.34), p = 0.014) than patients with impaired pharyngeal sensitivity.

Significant differences in response to topical anaesthesia were identified in the different groups (fig 4, lower panel).
While controls and “mild” patients behaved similarly, some patients in the “moderate” and “severe” groups clearly had an increased response to anaesthesia. This allowed us to discriminate some patients with normal baseline values from controls, and moderate from severely affected groups, while their baseline values were close (fig 3).

Sensory detection thresholds were negatively correlated with the flow limitation index (disappearance threshold at baseline and after anaesthesia: $r = -0.32$, $p = 0.030$; $r = -0.30$, $p = 0.050$ respectively). In contrast, detection thresholds were positively correlated with the obstructive hypopnoea index (appearance threshold at baseline ($r = 0.28$, $p = 0.058$) and after anaesthesia (first anaesthesia: $r = 0.33$, $p = 0.026$; second anaesthesia: $r = 0.32$, $p = 0.029$; third anaesthesia: $r = 0.29$, $p = 0.044$); disappearance threshold after one anaesthesia: $r = 0.30$, $p = 0.038$). While a trend was apparent, no significance was reached for the other disappearance sensory thresholds.

The higher the percentage of hypopnoeas constituting SDB, the higher the sensory threshold (disappearance sensory threshold after anaesthesia (first anaesthesia: $r = 0.29$, $p = 0.049$; second anaesthesia: $r = 0.33$, $p = 0.030$); appearance sensory threshold at baseline ($r = 0.25$, $p = 0.085$) and after anaesthesia (first anaesthesia: $r = 0.28$, $p = 0.055$; second anaesthesia: $r = 0.32$, $p = 0.028$; third anaesthesia: $r = 0.37$, $p = 0.011$)). Similarly, the percentage of apnoeas + hypopnoeas constituting SDB was positively correlated with the sensory thresholds (disappearance sensory detection thresholds at baseline ($r = 0.32$, $p = 0.032$) and after anaesthesia ($r = 0.30$, $p = 0.053$)). In contrast, there was no significant correlation or any trend between sensory detection thresholds and the classical AHI and RDI and nocturnal oxygen saturation.

**Pharyngeal sensitivity and diagnosis of SDB**

Overall, the sensitivity of the test for SDB diagnosis (RDI $>20$/hour) was 79.6% and decreased from the most severe (88.5%) to the least severe (50%) group, with an intermediate sensitivity (73.7%) for the “moderate” group.

**DISCUSSION**

The simple new approach described in this study enabled us to measure pharyngeal sensory perception easily and reliably without any side effects. Using this system, we have confirmed that impairment of pharyngeal sensory perception is correlated with the severity of SDB. When evaluated as a diagnostic tool, the test showed a high repeatability and sensitivity for SDB diagnosis in our sleep clinic population.

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**Figure 2** Repeatability of the procedure. Ten control subjects were re-evaluated after a mean (SD) interval of 31.9 (3) weeks before and after three successive administrations of topical anaesthetic. Upper panel: Individual circles correspond to the measurement of one subject. Numbered circles indicate the number of subjects with a similar value. Mean values are indicated by the horizontal bars. Lower panel: Bland-Altman plot where the differences between the repeated measurements are plotted against their average, with 95% limits of agreement (mean ± 1.96SD). SD is the standard deviation of the differences. CR is the British Standards Institution repeatability coefficient calculated as 1.96 times the standard deviation of the differences.
Table 2  
Repeatability of the procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>One way ANOVA</th>
<th>Bland-Altman procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Anaesthesia 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of differences</td>
<td>0.051</td>
<td>0.30</td>
</tr>
<tr>
<td>SD of differences</td>
<td>0.169</td>
<td>0.377</td>
</tr>
<tr>
<td>Repeatability coefficient (1)</td>
<td>0.332</td>
<td>0.777</td>
</tr>
<tr>
<td>95% CI of lower LA</td>
<td>-0.071 to 0.007</td>
<td>0.049 to 0.076</td>
</tr>
<tr>
<td>95% CI of upper LA</td>
<td>0.179 to 0.382</td>
<td>0.197 to 0.416</td>
</tr>
<tr>
<td>Baseline Anaesthesia 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of differences</td>
<td>0.049</td>
<td>0.312</td>
</tr>
<tr>
<td>SD of differences</td>
<td>0.176</td>
<td>0.431</td>
</tr>
<tr>
<td>Repeatability coefficient (1)</td>
<td>0.435</td>
<td>0.538</td>
</tr>
<tr>
<td>95% CI of lower LA</td>
<td>-0.032 to 0.043</td>
<td>0.107 to 0.219</td>
</tr>
<tr>
<td>95% CI of upper LA</td>
<td>0.288 to 0.572</td>
<td>0.436 to 0.572</td>
</tr>
<tr>
<td>Baseline Anaesthesia 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of differences</td>
<td>0.044</td>
<td>0.338</td>
</tr>
<tr>
<td>SD of differences</td>
<td>0.107</td>
<td>0.399</td>
</tr>
<tr>
<td>Repeatability coefficient (1)</td>
<td>0.460</td>
<td>0.572</td>
</tr>
<tr>
<td>95% CI of lower LA</td>
<td>-0.059 to 0.086</td>
<td>0.107 to 0.219</td>
</tr>
<tr>
<td>95% CI of upper LA</td>
<td>0.312 to 0.535</td>
<td>0.436 to 0.572</td>
</tr>
</tbody>
</table>

The mechanisms underlying the impairment of pharyngeal sensitivity may include chronic upper airway inflammation with mucosal oedema, fat deposition, and pharyngeal neuropathy. The presence of oedema has been histologically demonstrated. Oedema may be related, at least in part, to repeated mechanical trauma in the upper airway from snoring-related vibration and apnoea-related suction and stretching. Such oedema is indeed reduced during chronic treatment with continuous positive airway pressure. Infectious disease, allergy, tobacco, alcohol, gastro-oesophageal reflux, oral hygiene, and hot spicy foods may also contribute to upper airway inflammation as suggested by the higher intake of alcohol and spicy food in our apnoeic group. However, the higher rate of spicy food consumption observed may have been a consequence rather than a cause of decreased pharyngeal sensitivity.

The existence of pharyngeal neuropathy in patients with SDB is supported by the increased density in sensory nerve endings in biopsy specimens from the soft palate mucosa of snorers and apnoeic subjects, and by focal degeneration of the myelin sheaths and axons in uvulopalatopharyngoplasty specimens from subjects with apnoea. These observations suggest that progression from mild occasional snoring to heavy habitual snoring and then to sleep apnoea may represent a progressive local neuropathy. Mechanisms that could lead to sensory receptor or nerve damage in the upper airway may include mucosal oedema resulting from mechanical stress, vascular changes and inflammation that could interfere with the function of nerve endings, and direct vibration-related injury analogous to nerve lesions in the upper extremities of hand held vibrating tool users. In addition, the course of this vibration syndrome may be affected by associated diseases, smoking, neurotoxic drugs, and alcohol intake. As we have previously shown for peripheral nerves, hypoxia related to apnoea may also contribute to the neuropathy. All these mechanisms may explain the difference in sensitivity impairment observed between the three groups of patients. The “severe” group was overweight and had the most severe respiratory events which are stressful for the upper airway and lead to significant oxygen desaturation. In addition, this group was older, suggesting a longer disease duration and possibly a physiological age-related decreased sensitivity.
peripheral nerves. Such difference in sensitivity impairment between the three groups may in turn contribute to the difference in SDB severity.

**Advantages and limitations of the procedure for measuring pharyngeal sensitivity**

Our device allowed easy and non-invasive assessment of pharyngeal sensitivity in terms of tactile perception without requiring specialised materials or professional skills. The device is simple and the procedure can be performed with standard equipment readily available in any sleep laboratory.

Compared with previously described procedures, we were able to assess pharyngeal sensitivity in subjects with an intense gag reflex and small oropharyngeal cavity, thus excluding possible bias selection. Using devices of different calibre, our system could be adapted to various degrees of mouth opening. As previously described, unlike measurement of pharyngeal sensation, gag reflex was not informative since we found no difference between groups.

Measurements were obtained rapidly (around 30 minutes) and were repeatable, thus making the test reliable and unconstrained for both the patient and the investigator. One limitation of psychophysical evaluations is the subjective character of the answers which rely on the subject’s cooperation. However, although our results require further validation in a larger population, the repeatability of the measurements (fig 2, table 2) shows that the subjectivity of the answers was reduced by repeating the measurements during each test session and by using random null stimuli.

The anatomical region tested was the soft palate because of its critical involvement in the pathophysiology of SDB (see above). Experiments are currently in progress in our laboratory to test additional areas. Indeed, the adjustability of the guide allows testing of other oropharyngeal areas such as the tonsil pillar, hard palate and uvula (data not shown) which are either differently innervated and/or differently exposed to mechanical stress during sleep.

We have shown that pharyngeal sensitivity is differentially impaired according to the severity of SDB in terms of the type of respiratory events while no significant correlation was found with the classical AHI and RDI or with nocturnal desaturation. This argues for the pathophysiological involvement of pharyngeal sensitivity in collapsibility of the upper airway. Compared with patients in the two most severely affected groups, patients in the “mild” group were younger and suffer from SDB with a high proportion of flow limitation episodes and no nocturnal desaturation. The “mild” group therefore represented patients suffering from upper airway resistance syndrome or mild obstructive sleep apnoea, while the “moderate” and “severe” groups represented hypopnoeic and apnoeic patients respectively. Patients in the “mild” group had pharyngeal sensitivity which was close to controls or intermediate between controls and “moderate/severe” patients. These results are in agreement with a previous study showing that collapsibility of the upper airway during sleep in upper airway resistance syndrome is intermediate between that of normal subjects and patients with mild to moderate obstructive sleep apnoea.

Our ability to demonstrate a difference in impairment of pharyngeal sensitivity testifies to the higher capacity of discrimination of our procedure. Indeed, our stimulus consisted of an air pulse administered at a constant distance from the mucosa. Unlike previous studies, we did not use any device that may induce gag reflex or interfere with the sensory perception because of the difficulty in maintaining a constant contact pressure with the mucosa, particularly on the soft palate. Another explanation for the capacity to discriminate between SDB severity levels was the use of topical anaesthesia. As we suspected, it clearly enabled us to separate some patients with normal baseline values from controls, and medium from severely affected groups while values were close at baseline. However, despite a dose-effect response, differences between subgroups were not statistically significant due to overlapping values. Indeed, even patients with severe SDB could have normal pharyngeal sensitivity at baseline and under anaesthesia (see below). Compared with previous studies, the anaesthesia was light and localised since the gag reflex was unchanged by the procedure. Such anaesthesia was, however, sufficient to sensitise the test from the first spray and may be useful to simplify the procedure by decreasing the number of measurements and the duration of the examination.

**Pharyngeal sensitivity: a tool to predict the severity of SDB?**

Overall, this test (appearance and disappearance thresholds, slopes) revealed a high sensitivity for identifying patients suffering from sleep apnoea syndrome in our sleep clinic.
population. With the chosen cut-off value, pharyngeal sensitivity considered abnormal was systematically associated with SDB. In contrast, the existence of SDB was not systematically associated with an impairment of pharyngeal sensitivity, as shown by the sensitivity of the test in the "mild" (50%), "moderate" (73.7%), and "severe" (88.5%) groups. These findings confirm that pharyngeal sensitivity is only one determinant—together with airway anatomy—among the predisposing factors of collapse of the upper airway. In subjects with an anatomical predisposition to upper airway obstruction, partial impairment of the upper airway dilating muscle function may be sufficient to cause collapse of the airway. On the other hand, patients with a normal upper airway anatomy may be less vulnerable to impairment of the reflex dilatation of the airway. Both the existence and severity of SDB are not dependent only on anatomical and functional factors that are likely to worsen SDB. In the multifactorial equation resulting in SDB, pharyngeal sensitivity is probably one of the key factors in our study, predictive not only of the existence but also of the severity of SDB.

Taken together, our results suggest a flow diagram for the diagnosis of sleep apnoea: on the one hand, lean and young patients preferentially suffer from upper airway resistance events and/or mild hypopnoeas. The pharyngeal sensitivity is then normal or subnormal. In this context, full polysomnography including respiratory effort assessment is required for diagnosis. On the other hand, more obese or older patients preferentially suffer from hypopnoea and/or apnoea. Impairment of pharyngeal sensitivity in such patients could provide a simplified diagnostic procedure. This proposed diagnostic flowchart should be prospectively validated in a larger sleep clinic population as well as in the general population.

In conclusion, we have developed a simple, repeatable, and safe procedure which confirms the presence of impaired pharyngeal sensitivity in patients with SDB and have shown

In conclusion, we have developed a simple, repeatable, and safe procedure which confirms the presence of impaired pharyngeal sensitivity in patients with SDB and have shown...
that such impairment is correlated with the severity of SDB. Although this new procedure needs to be fully validated in a larger population, its simplicity suggests that it may be of use in routine clinical practice to evaluate the role of pharyngeal sensitivity in the pathophysiology of SDB and its value for simplification of the SDB diagnosis procedure.

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