Characterization of pharyngeal resistance during sleep in a spectrum of sleep-disordered breathing

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The relationship between airflow and pressure in the upper airway has been well characterized during wakefulness and can be adequately predicted by the Rohrer polynomial equation (20), which assumes that the caliber of the conduit through which airflow is passing is constant. However, during sleep, loss of muscle tone results in variable narrowing of the upper airway during inspiration, with consequent flow limitation. As the negative inspiratory pressure increases in magnitude, so too does the degree of airway narrowing, and hence the pressure-flow relationship becomes curvilinear. For normal subjects during sleep, Hudgel et al. (9) have proposed a mathematical model incorporating a hyperbolic equation, which better describes this pressure-flow relationship. This model worked well in a study on normal, nonobese, nonsnoring subjects. However, the airflow limitation during sleep in these subjects was relatively small, and the intrathoracic pressure generated to overcome this was also small (in the range 0 to −5 cmH2O). The degree of flow limitation does not allow anticipation of the absolute level of inspiratory efforts found in different subgroups of subjects (i.e., normal and apneic). Moreover, for a given flow, upper airway narrowing has to intensify as the downstream pressure increases. The upper airway shape and cross-sectional area are modified in apneic subjects. It is well known that upper airway collapsibility is much higher in apneic subjects than in normal subjects. These anatomic and functional differences may result in different pressure-to-flow ratios (ΔP/ΔV) both before, e.g., the variable part of the linear relationship between flow and pressure, and after the inspiratory flow limitation has been established because downstream pressure is much greater during sleep in OSAS than in normal subjects. Accordingly, it has been clearly demonstrated that a visual aspect of flow-limited breath may correspond to various ΔP/ΔV relationships (3). Thus these specific conditions in apneic subjects could have modified ΔP/ΔV compared with that of normal subjects. It is not known whether Hudgel’s model also applies to episodes of more severe upper airflow flow limitation that occur in patients with obstructive sleep apnea or with the upper airway resistance syndrome (UARS), in which the intrathoracic pressure swings may be as large as −60 cmH2O (5). Nor is it known whether this model is flexible enough to predict the pressure-flow relationship in these patients, because the upper airway resistance changes with different sleep stages.

In contrast to the situation for normal subjects (9, 28), there are currently few data in the published literature that describe changes in upper airway resistance during sleep in individuals with different sleep-related respiratory disorders. The aims of this study were, therefore, 1) to compare Hudgel’s hyperbolic model with Rohrer’s polynomial model in describing
the pressure-flow relationship in patients with abnormal sleep-related upper airway resistance; 2) to use this pressure-flow relationship to describe upper airway resistance in a spectrum of patients with sleep-disordered breathing; 3) to confirm that the measurements of resistance derived from the hyperbolic model and from the $\Delta P/\dot{V}$ provided a comparable value; and 4) to evaluate the effects of different sleep stages on upper airway resistance.

In this study, obstructive apnea is disordered breathing characterized by a complete cessation of breathing during 10 s or longer, and obstructive hypopnea is characterized by a clear decrease from baseline in the amplitude of breathing, as measured with a pneumotachometer, $\geq 50\%$ with a duration of $\geq 10$ s. High resistance (HR) is an event in which effort progressively increases (pharyngeal pressure becomes more negative), terminated by a sudden change in pressure to a less negative level, during 10 s or longer. Patients with obstructive sleep apnea syndrome (OSAS) exhibit an apnea-hypopnea index (AHI) $>10$/h with predominantly apneas, those with obstructive sleep hypopnea syndrome (OShS) have an AHI $>10$/hr with predominantly hypopneas, and those with UARS have a high resistance index (HRI) $>10$/h and AHI $<10$. Individuals classified as exhibiting simple snoring (SS) have combined AHI and HRI $<10$/h.

**METHODS**

Twelve patients (9 men) with suspected sleep-disordered breathing attending the sleep laboratory for investigation were studied. Their age was $51.3 \pm 11.0$ yr, and their body mass index was $25 \pm 2.3$ kg/m$^2$ (means $\pm$ SD).

**Protocol**

*Polysonography.* All patients had full nocturnal polysomnography (Respisomnograph system, Nellcor Puritan Bennett, Minneapolis, MN) analyzed manually with the Knight-Scan software package (Nellcor Puritan Bennett). The physiological signals, recorded at 128 Hz, included two electroencephalogram channels (CZ-O1 and C3-A2), submental electromyogram, and electrooculogram. Sleep stages were analyzed by use of the standard criteria of Rechtschaffen and Kales (19). Microarousals were scored by using ASDA criteria (1). Chest wall and abdominal movements were assessed by noncalibrated inductive plethysmography and oxygen saturation by pulse oximetry (Bioc 3740 Ohmeda, Louisville, CO). The pressure and flow measurements are detailed in the following paragraph. Respiratory events were scored according to usual criteria, enabling stratification of patients into different types of sleep-disordered breathing. Body position was monitored continuously.

*Upper airway pressure and flow measurements.* Airflow was measured via a pneumotachometer (Kontron Instruments, Quentin, France) installed on a full-face mask. This system had a dead space of $<100$ ml and produced a linear reading of airflow within the range 0–1.5 l/s, with an estimated error of $\pm 0.01$ l/s. Before each study, the pneumotachometer was reset to zero and calibrated with a fixed-flow generator. Leaks were detected when a drift in the baseline of the signal occurred. A pressure transducer was connected to the mask by a noncollapsible tube to measure the mask pressure. A solid-state multitransducer catheter was used to measure pressures at three different levels in the pharynx simultaneously (Gaeltec, Isle of Skye, Scotland, UK). The frequency response for each microtransducer was 10 Hz at 10°. For a pressure that cycled between $+4$ and $-4$ cmH$_2$O, the latency of response was 2.5 ms. Three pressure transducers were integrated in the Gaeltec. They were positioned 80, 120, and 180 mm from the nostril, in the nasopharynx, velopharynx, and oropharynx, respectively (Fig. 1). Care was taken to ensure that the membrane of each transducer was positioned parallel to the direction of airflow. Direct inspection of the pharynx and prerecording visualization of the pressure curves permitted control of the Gaeltec position. Correct positioning of each transducer was subsequently confirmed with cephalometry at the end of the night. The neck position was standardized at the start of the night, all patients being in a comparable supine position. In 10 of the 12 patients, a cephalometric X-ray was done to evaluate the upper airway morphology and allowed assessment of the pharyngeal catheter's positioning. These X-rays were made on the morning after the polysomnography, with the Gaeltec still in place. This allowed us to control for the position of each transducer, although this was less critical regarding the naso- and hypopharyngeal sensors. In four patients, all the transducers were in an adequate position, including those at the tip of the soft palate. In six patients, the naso- and hypopharyngeal transducers were correctly positioned, but, in five of these six patients, the velopharyngeal transducer was 10, 12, 19, 21, and 27 mm above the uvula, and one patient had the transducer close to the uvula. However, this limitation affects any study addressing this issue in sleep breathing disorders. In this condition, there are marked changes in upper airway anatomy (i.e., soft palate length) that are much more pronounced than in normal subjects. Thus, when the sensor was adjusted above the hard palate and at the basis of the tongue level, because of the variable length of the soft palate and the uvula, an adequate location of the velopharyngeal sensor was not systematically obtained. This explains why, although we ensured the positioning of the two sensors that provided our transpharyngeal measurements very cautiously, we were unable to provide a velopharyngeal resistance measurement.

![Fig. 1. Catheter with pressure sensors at different levels of the pharynx.](http://jap.physiology.org/ Downloaded from)
Calibration of the Gaeltec catheter was performed before each study using a humidified pressure chamber heated to 37°C. The signal was recorded at 16 Hz, and the maximum error of the system was estimated to be 0.6 cmH₂O. The pressure detected with this type of catheter is restricted to static pressure because the membrane of the sensor was parallel to the flow. In the present study, the dynamic pressures were considered to be negligible (see Appendix). Data were stored and analyzed on Excel software (Microsoft, Redmond, WA), and calculation of regression curves and correlation coefficients was performed by Kaleidagraph software (Synergy Software, Reading, PA).

Analysis

Comparison between the two mathematical models of pressure-flow relationship. Two different equations that have been used to describe the pressure-flow relationship in the upper airway were compared (Fig. 2).

First is the Rohrer equation (20)

$$P = K_1 \cdot V + K_2 \cdot V^2$$

where $P$ is the pressure (cmH₂O), $V$ is flow (l/s), and the constants $K_1$ and $K_2$ represent the y-intercept and slope, respectively, of the linear form of the Rohrer equation. The second is Hudgel's hyperbolic equation (9)

$$V = \frac{\alpha P}{\beta + P}$$

where $\alpha$ is the asymptote for peak flow (i.e., the flow at which pressure reaches infinity), and $\beta$ is the pressure at 50% of this flow.

Two hundred fifteen respiratory cycles were randomly selected. They were observed in different sleep stages [stage 1, stage 2, stage 3/4, and rapid eye movement (REM) sleep] and during wakefulness. One non-flow-limited cycle was chosen during stable respiration and two flow-limited cycles at the beginning and the end of an episode of increased upper airway resistance (i.e., HR). Flow-limited cycles were selected on the visual aspect of flow. Approximately the same number of respiratory cycles was chosen for each patient in each sleep stage. Each respiratory cycle was fitted by the polynomial and hyperbolic equations. Nonlinear regression by the Marquardt method, which combines the method of steepest descent and the Gauss-Newton method (17), was used to correlate the data with each equation and thus to determine which model best describes the pressure-flow relationship in this group of patients. Pearson's correlation test ($r^2$) was used to compare the polynomial and hyperbolic regression curves for each sleep stage. This test was valid because the two equations had the same number of parameters.

Upper airway resistance measurements in a spectrum of sleep-disordered breathing. Recordings of 5 to 10 stable (in terms of pressure and flow aspects) consecutive respiratory cycles were made during each sleep stage and during wakefulness for each subject, representing 600 respiratory cycles. The breaths were selected during stable respiration in undisturbed sleep periods. In the 20 s preceding the period of analysis, no respiratory events should be present and no microarousal should be detectable. This prevented analysis of periods including either respiratory events or hyperventilation breaths just after apneas or hypopneas. The only exclusion criterion applied for selecting the period of analysis in OSAS, OSHS, UARS, and SS was the occurrence of an event (e.g., apnea, hypopnea, HR episode). In HR episodes, there is a progressive increase in inspiratory flow limitation that accompanies the increase in respiratory effort. However, stable inspiratory flow limitation could be included in the analysis.

For each respiratory cycle, the resistance was estimated from the values of peak flow ($V$) and pressure ($P$). There were actually three different situations: 1) If there was no flow limitation, the flow used to calculate resistance was clearly the peak of flow, which coincided with the peak of pressure. 2) The cycle was flow limited, but there was a plateau without further decrease in flow. The plateau value of flow was taken together with the value of peak pressure, which again coincided. 3) The cycle was flow limited, but there was a decrease in flow after the plateau. The reduction in flow preceded the occurrence of the peak pressure. The last part of the breath was not taken in account; the last value of the flow plateau and the corresponding pressure value were used to calculate resistance. Regarding the third situation, we chose the last flow value of the plateau so as not to include periods of rapid reduction in sections of the pharynx, as suggested by a reduction in flow concomitant with a further increase in pressure. Resistance (R) was calculated by using the equation

$$R_{\text{hyperbolic}} = \frac{\beta + \Delta P}{\alpha}$$

derived from the hyperbolic Hudgel equation

$$R_{\text{hyperbolic}} = \frac{\Delta P}{V} = \frac{\beta}{\alpha} + \frac{\Delta P}{\alpha}$$

and also directly from the pressure-flow relationship $R_{\text{MPV}} = \Delta P/V$. Mean values and SD of resistance for each period were calculated from the two methods and subsequently compared. All interpretation of resistance variation in different sleep-disordered breathing, during wake and sleep stages, was done with resistance calculated by the equation derived from the hyperbolic model.

RESULTS

The demographic data and polysomnographic characteristics of the patients are presented in Tables 1 and 2 and Fig. 3. The patients demonstrated a spectrum of respiratory sleep disorders. Two individuals were considered as exhibiting SS, three as having UARS, four as having OSHS, and three as having OSAS.
Comparison Between the Two Mathematical Models of the Pressure-Flow Relationship

The two equations (hyperbolic and polynomial) were applied to 215 respiratory cycles, both flow limited and non-flow limited (~18 cycles studied in each of the 12 patients). A Pearson’s square correlation was done for each respiratory cycle to assess the validity of the two models. Median (range) $r^2$ values were 0.88 (0.31–0.99) and 0.92 (0.53–0.99) in the polynomial and hyperbolic models, respectively. In 78% of the cases, the value of Pearson’s square was greater when the hyperbolic model was used. The difference in correlation for the flow-limited respiratory cycles was even more pronounced, the hyperbolic model being better in 86% of the cases. In this condition, the median (range) $r^2$ was 0.83 (0.31–0.99) in the polynomial vs. 0.91 (0.65–0.99) in the hyperbolic model. Using the hyperbolic model, we calculated resistance at the peak of pressure, aiming to demonstrate that cycle-by-cycle measurement of resistance perfectly reflected the progressive occurrence of a HR episode (Fig. 4).

Comparison of $R_{\text{hyperbolic}}$ and $\Delta P/V$

Resistances were calculated by using $\Delta P/V$ at the peak pressure in 600 respiratory cycles during stable breathing at different sleep stages. The obtained values correlated very closely with those derived directly from the calculation using the hyperbolic model. This was demonstrated both by the linear correlation test ($r^2 = 0.98$, $P < 0.0001$) and the Bland and Altman plot (Fig. 5). Thus $R_{\text{hyperbolic}}$ gives no additional information than $\Delta P/V$ when upper airway resistance is measured during different sleep stages. Furthermore, Fig. 4 demonstrates that cycle-by-cycle measurement of resistance at the peak pressure perfectly reflected the progressive occurrence of a HR episode.

Nasal Resistance Changes from Wakefulness to Sleep

In all subjects, awake nasal resistance was higher than in the “normal” range. There was no clear trend to increase from wakefulness to deep sleep (stage 3/4), except in the UARS group. See Fig. 6 and Table 3.

Pharyngeal Resistance Changes from Wakefulness to Sleep

Awake upper airway resistance in OSAS, OSHS, and SS were in the “normal” range. Conversely, UARS demonstrated a threefold increase in upper airway resistance compared with normal subjects (11.9 ± 6.3 vs. 4.6 ± 0.8 cmH$_2$O · s · 1$^{-1}$). There was a general trend toward an increase in pharyngeal resistance from wakefulness to deep sleep (stages 3 and 4). The magnitude of this increase varied considerably depending on the subgroup of patients. The progression of increase in mean resistance ($R_{\text{max}}$) during stable respiration between wakefulness and stage 3/4 was frank in UARS but lesser in SS, OSHS, and OSAS. See Fig. 7 and Table 4.

UARS thus exhibited a high awake upper airway resistance and demonstrated a further increase in deep sleep, with a mean value of 161.53 ± 75.24 cmH$_2$O · s · 1$^{-1}$. Huge variations in respiratory drive, leading to pressure and flow irregularities, were observed during phasic episodes in REM sleep. Accordingly, it was difficult to identify periods of stable respiration (consecutive respiratory cycles) suitable to calculate upper airway $R_{\text{max}}$ (see below) during REM sleep in all patients. As a consequence, during REM sleep, upper airway resistances exhibited considerable cycle-to-cy-

Table 1. Anthropometric and nocturnal breathing characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>OSAS ($n = 3$)</th>
<th>OSHS ($n = 4$)</th>
<th>UARS ($n = 3$)</th>
<th>SS ($n = 2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI/h of sleep</td>
<td>48.9 ± 11.8</td>
<td>23.9 ± 13.5</td>
<td>7.8 ± 1.3</td>
<td>4.3 ± 2.1</td>
</tr>
<tr>
<td>Al/h of sleep</td>
<td>21 ± 10</td>
<td>3.1 ± 3.1</td>
<td>0.6 ± 0.3</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>HH/h of sleep</td>
<td>26.6 ± 4.7</td>
<td>19.2 ± 13.2</td>
<td>6.5 ± 1.7</td>
<td>3.8 ± 1.3</td>
</tr>
<tr>
<td>HRI/h of sleep</td>
<td>2.8 ± 3.8</td>
<td>12.7 ± 10.9</td>
<td>18.2 ± 9.2</td>
<td>3.5 ± 0.2</td>
</tr>
<tr>
<td>Age, yr</td>
<td>59.3 ± 4.2</td>
<td>49.3 ± 13.2</td>
<td>53 ± 10.4</td>
<td>40.5 ± 10.6</td>
</tr>
<tr>
<td>BMI kg/m$^2$</td>
<td>25 ± 3.5</td>
<td>26.4 ± 1.1</td>
<td>24.6 ± 1.8</td>
<td>22.6 ± 1.2</td>
</tr>
<tr>
<td>Mean oxygen saturation, %</td>
<td>93 ± 3.2</td>
<td>94.7 ± 1.1</td>
<td>94.3 ± 0.5</td>
<td>94.7 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n =$ no. of subjects. OSAS, obstructive sleep apnea syndrome; OSHS, obstructive sleep hypopnea syndrome; UARS, upper airway resistance syndrome; SS, simple snoring; AHI, apnea hypopnea index; AI, apnea index; HI, hypopnea index; HRI, high resistance index.

Table 2. Sleep structure

<table>
<thead>
<tr>
<th></th>
<th>OSAS ($n = 3$)</th>
<th>OSHS ($n = 4$)</th>
<th>UARS ($n = 3$)</th>
<th>SS ($n = 2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, min</td>
<td>387 ± 26.2</td>
<td>363.8 ± 26.2</td>
<td>325.7 ± 62.8</td>
<td>343 ± 87.7</td>
</tr>
<tr>
<td>Microarousal index of sleep</td>
<td>32.6 ± 11.4</td>
<td>12 ± 3.2</td>
<td>9.6 ± 5.9</td>
<td>7.3 ± 1.5</td>
</tr>
<tr>
<td>Total number of sleep stage changes</td>
<td>201 ± 39.3</td>
<td>200.3 ± 67.3</td>
<td>177.7 ± 66.1</td>
<td>111.5 ± 17.7</td>
</tr>
<tr>
<td>Time spent in stage 1, min</td>
<td>98.3 ± 31.4</td>
<td>82.3 ± 50.7</td>
<td>69.8 ± 51.7</td>
<td>42.5 ± 1.8</td>
</tr>
<tr>
<td>Time spent in stage 2, min</td>
<td>188.7 ± 28</td>
<td>203.8 ± 42.3</td>
<td>142.3 ± 34.4</td>
<td>176.8 ± 89.5</td>
</tr>
<tr>
<td>Time spent in deep sleep, min</td>
<td>3.5 ± 2.3</td>
<td>27.1 ± 28.6</td>
<td>32.7 ± 22.7</td>
<td>35.8 ± 37.1</td>
</tr>
<tr>
<td>Time spent in REM sleep, min</td>
<td>66.7 ± 29.9</td>
<td>45.7 ± 94.7</td>
<td>78.8 ± 33.9</td>
<td>87.8 ± 36.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. REM, rapid eye movement.
cle variation (see Fig. 8 and large SD in Table 4), and mean values during this period tended to be quite different from those obtained during other sleep stages.

**DISCUSSION**

Our study provides the first evaluation of upper airway resistance in different types of sleep-disordered breathing, ranging from SS to OSAS. In the present study, OSAS, OSHS, and SS subjects had normal awake resistance, whereas UARS patients exhibited awake resistance threefold higher than normal subjects (28). Moreover, upper airway resistance was further greatly increased (fourfold) during slow-wave sleep in UARS. In all subjects, the hyperbolic Hudgel equation was a better mathematical model to describe the pressure-flow relationship during sleep. This was particularly true for flow-limited cycles. This model was robust enough to accurately quantify the changes in upper airway resistance encountered during the different sleep stages. Finally, the resistance derived from the hyperbolic model at the peak of pressure and flow was comparable to the value provided by the $\Delta P/V$ equation.

**Limitations in Pharyngeal Pressure Measurements**

The presence of a pharyngeal catheter could potentially alter the dynamics of the upper airway. It could also disturb the structure and quality of sleep (2). Acceptance by the patient is also an issue (we experi-
enced at least 10% refusal; see Ref. 12). Finally, positioning is critical because the sensor may be in contact with pharyngeal structures, making the measurement highly sensitive to any movement of the catheter, particularly during increased respiratory efforts.

The second transducer was theoretically at the tip of the soft palate and thus could have been used to estimate the velopharyngeal resistance. However, this was not possible in the present study because this transducer was not always at the tip of the soft palate on account of the variability of the length and shape of the uvula in sleep-disordered-breathing patients. Taking in account these limitations, we determined that estimation of the velopharyngeal resistance was not possible. Apart from these general limitations, the type of catheter used to detect pharyngeal pressures may be of importance, depending on its ability to detect dynamic pressure. These physical characteristics are detailed in the Appendix. Because our sensor was poorly sensitive to dynamic pressure, this component should be negligible in our experiment; thus this supports the validity of our pressure measurements.

**Flow Measurements**

The use of a facial mask had the advantage of adequately measuring airflow but excluded the possibility of separately quantifying nasal and oral breathing. The equipment probably favored nasal respiration because mouth opening is more difficult in that condition. Different routes of breathing have been shown to be associated with different levels of collapsibility (14). However, during our measurements, we never detected any abrupt change in transpharyngeal resistance that could have resulted from a shift from nasal to oral breathing or the converse.

**Impact of Body Position**

We carefully looked to the position in which the measurements were performed. For 7 of the 12 patients, body position was identical for all measurements (3 supine, 1 in left lateral, and 3 in right lateral position). There was no clear difference in resistance values according to body position. Four patients were in lateral position when awake and supine when asleep. Although this might have led to slight underestimation of the awake resistance value, there was no systematic trend to support that hypothesis. In the last patient, the awake and stage 1 measurements were obtained when the patient was supine, whereas the other measurements were performed in right lateral position. In that case, the increase in resistance in
stage 2, stage 3/4, and REM sleep is so high that, again, no effect of body position was detectable.

Regarding neck position, this was standardized in all the patients at the start of the night, but patients were not maintained in a fixed position throughout the night. A fixed position would have been difficult to tolerate in addition to the catheter and the facial mask and probably would have strongly interfered with sleep quality.

Validation of Pressure-Flow Relationship

Hudgel et al. (9) demonstrated in 1988 that the hyperbolic model was the best fit of pressure-flow curves in normal men. We have also demonstrated that, in a spectrum of patients with sleep-disordered breathing, the hyperbolic model was the more accurate fit of pressure-flow relationship, whatever the sleep stage and whether or not inspiratory flow limitation occurred. Flow limitation represents a stagnation of flow despite an increase in driving pressure, and, in this condition, the pressure-flow curve must be asymptotic. The polynomial equation does not lead to any asymptote. Thus, as expected, particularly for flow-limited cycles, the hyperbolic model was better.

Validation of the Methods Used to Estimate Pharyngeal Resistance

We compared the values of resistance, determined at peak pressure in 600 inspiratory cycles, derived by either the hyperbolic model or a pressure-to-flow ratio. At high resistance values (>80 cmH2O · s · L−1), any method is questionable because the flow is very low. Although we did not find any statistical difference between \( R_{\text{hyperbolic}} \) and \( R_{\text{P/V}} \), this is also evidenced by the dispersion of the Bland-Altman plot above 80 cmH2O · s · L−1 (see Fig. 5). However, these differences may not be clinically relevant. This finding was actually not expected because the only situation in which the resistance should be fully described by \( \Delta P/V \) is when each point corresponds to a constant section and a laminar flow of the fluid. None of these conditions is met when resistance is measured at the pharyngeal level. First, cross-sectional area is highly variable throughout the different levels of upper airway. Moreover, variations of cross-sectional area occur within breaths. These conditions determine the regime of the flow, which is likely to be highly turbulent. Second, the pharyngeal walls are mobilized by a suction effect related to the velocity of the fluid. These two factors result in a loss of energy by friction and pharyngeal wall displacement. Thus the concordance between these two values actually reflects the adequacy of the model to fit with the experimental values, which indicates the strength of the correlation. However, this is no longer true when flow decreases with increasing inspiratory efforts, as mentioned under METHODS. In this case, the resistance determined by the hyperbolic fit underestimates the true resistance, which is better estimated by \( \Delta P/V \). We thus did not include the last part of the breaths exhibiting a diminished flow after the plateau of inspiratory flow limitation. In this case, the resistance value is affected by several uncontrolled factors, such as reduction in cross-sectional area and increase in the dynamic pressure value.

Upper Airway Resistance in Different Sleep Stages in a Spectrum of Sleep-Disordered Breathing

We chose to calculate resistance during stable respiration periods to compare the different subgroups of patients. The comparison was valid because the same criteria were used for the breath selection. Stable inspiratory flow limitation could be included in the analysis. In that case, flow limitation occurred when the

### Table 3. Nasal resistance in stable respiration

<table>
<thead>
<tr>
<th></th>
<th>OSAS (n = 3)</th>
<th>OSHS (n = 4)</th>
<th>UARS (n = 3)</th>
<th>SS (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>10.4 ± 6.1</td>
<td>5.6 ± 3.8</td>
<td>10.0 ± 3</td>
<td>8.7 ± 1.3</td>
</tr>
<tr>
<td>Stage 1</td>
<td>15.2 ± 11.7</td>
<td>6.4 ± 13.6</td>
<td>13.4 ± 8.4</td>
<td>8.7 ± 2.1</td>
</tr>
<tr>
<td>Stage 2</td>
<td>11.1 ± 9.4</td>
<td>9.4 ± 8.8</td>
<td>21.2 ± 12.8</td>
<td>15.6 ± 9.7</td>
</tr>
<tr>
<td>Deep sleep</td>
<td>NA</td>
<td>10.2 ± 11</td>
<td>33.2 ± 28.8</td>
<td>NA</td>
</tr>
<tr>
<td>REM sleep</td>
<td>26.6 ± 2.6</td>
<td>9.6 ± 8.8</td>
<td>17.6</td>
<td>9.3 ± 3.8</td>
</tr>
</tbody>
</table>

Values are means ± SD (in cmH2O · s · L−1). Deep sleep measure for UARS concerns just one patient. No measure of flow during deep sleep in SS for technical reasons. NA, not applicable.

### Table 4. Pharyngeal resistance in stable respiration

<table>
<thead>
<tr>
<th></th>
<th>OSAS (n = 3)</th>
<th>OSHS (n = 4)</th>
<th>UARS (n = 3)</th>
<th>SS (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>4.6 ± 2.1</td>
<td>1.5 ± 1</td>
<td>11.9 ± 6.3</td>
<td>3 ± 0.5</td>
</tr>
<tr>
<td>Stage 1</td>
<td>10.2 ± 4.7</td>
<td>3.6 ± 1.4</td>
<td>15 ± 7.7</td>
<td>16 ± 1.2</td>
</tr>
<tr>
<td>Stage 2</td>
<td>53.6 ± 60.8</td>
<td>26.3 ± 34.3</td>
<td>75.7 ± 31.5</td>
<td>31 ± 23.7</td>
</tr>
<tr>
<td>Deep sleep</td>
<td>NA</td>
<td>63.8 ± 52</td>
<td>161.5 ± 75.2</td>
<td>NA</td>
</tr>
<tr>
<td>REM sleep</td>
<td>21.3 ± 3.3</td>
<td>17.8 ± 22.3</td>
<td>57.9</td>
<td>20.1 ± 8.2</td>
</tr>
</tbody>
</table>

Values are means ± SD (in cmH2O · s · L−1). REM sleep measure for UARS concerns just one patient. No measure of flow during deep sleep in SS for technical reasons.
resistance was high but stable, as it frequently occurred in stage 3/4 or in deep stage 2. We observed this phenomenon in all the UARS patients but also in some of the OSAS and OSHS patients. However, this inspiratory flow limitation was clearly distinct from a HR episode. In HR, resistance increased progressively breath by breath (see Fig. 4). Moreover, the estimation of the resistance was made in 5 to 10 consecutive breaths, and the small standard deviation for each resistance measurement supports the fact that the upper airway was actually stable. Thus we believe that the selection criteria that we used made the resistance values obtained in the different groups of patients comparable. Sleep stages are known to influence resistance of the upper airway in normal individuals (28). With the onset of sleep, muscle activity is progressively reduced in both tonic and phasic components of upper airway dilating muscle activity (26, 30). Upper airway narrowing occurs during sleep and varies significantly, depending on a number of factors such as pharyngeal anatomy, posture, sleep stage, and level of muscle tone (16, 21). The reduction in pharyngeal size associated with the loss of muscle tone modifies the properties of the pharyngeal wall and diminishes the upper airway’s ability to resist the negative intraluminal pressures generated during inspiration (7). Thus, even in normal individuals, marked changes in upper airway resistance have been described during sleep (28) and tend to become more pronounced during slow-wave sleep (stage 3/4), especially in men (27). This increase in resistance has been described as being at least partly responsible for the fall in minute ventilation at the onset of sleep (10, 30). Our study is the first to describe the effects of sleep stage on pharyngeal resistance in a group of individuals representing a spectrum of sleep-disordered breathing. As in normal subjects, there was a general trend for patients to progressively increase their pharyngeal resistance as they entered deeper sleep stages. However, the magnitude of increase from light to deep slow-wave sleep was higher than in normal subjects (25).

**Upper Airway Resistance and Pathophysiology of Upper Airway Collapse**

Although the subgroups of patients were small, there were differences in the progressive increase of upper airway resistance from wakefulness to sleep according to the predominant type of sleep breathing disorders (Fig. 6). This suggests different underlying mecha-
nisms in upper airway control (7). Pharyngeal patency is dependent on both the size of the upper airway and the stiffness of the pharyngeal walls. A substantial reduction in upper airway size while awake has been demonstrated in OSAS patients compared with snorers (6, 18). To counteract small upper airway size, the level of neural activation of upper airway dilator muscles is abnormally elevated in patients with obstructive apneas or hypopneas (15). Schwab et al. (22), using ultrafast CT scan, have studied upper airway cross-sectional area during awake tidal breathing. They found larger variations in OSAS patients, suggesting increased airway compliance. This was particularly true during expiration, i.e., when the dilator muscles become less active. In patients with simple snoring, and probably in UARS, upper airway size is less reduced than in apneic subjects (13), and wall stiffness is generally considered to be higher compared with OSAS patients. As expected, pharyngeal collapsibility, as assessed by the measurement of critical pressure (4), is progressively increased from snorers to hypopneic and, finally, apneic patients. When collapsibility is high and the lumen is already narrowed, as in OSAS, a small increase in resistance and negative inspiratory pressure is able to produce complete airway collapse. Thus apneic subjects can demonstrate normal upper airway resistance during awake periods as a result of pharyngeal dilator compensatory hyperactivity. They can also demonstrate infinite upper airway resistances during apneas, but their upper airway are not stable enough to sustain intermediate levels of upper airway resistance. On the contrary, UARS patients who exhibit more stiffening of pharyngeal walls may generate very high levels of upper airway resistance and marked negative inspiratory pressure during sleep without apnea or frank hypopnea. Our data support this view, because awake upper airway resistance in UARS patients was threefold higher than in normal subjects and was further augmented during sleep (being fourfold higher in slow-wave sleep compared with wakefulness). As expected, the patients with predominant hypopnea (i.e., with an intermediate collapsibility between SS and OSAS) exhibited levels of resistance in stage 3/4 comparable to those of the apneic subjects in stage 2. The mechanism underlying obstructive hypopneas is less clear. It is likely that many hypopneas are incomplete obstructive apneas, i.e., there is partial collapse of a highly compliant airway wall in response to a relatively smaller increase in resistance and negative intrathoracic pressure than during an apnea. Alternatively, an obstructive hypopnea may be a variant of a HR episode during which high inspiratory resistance is applied to an upper airway that is not stiff enough to maintain normal airflow. These two mechanisms are distinct but are not necessarily distinguishable. We looked at the difference between hypopnea and HR episodes in another experiment with OSHS patients (IHA = 30 ± 25/h with IA = 3 ± 5/h), using a facial mask, a pneumotachometer, and esophageal pressure measured by a balloon catheter (data still unpublished). There was no significant difference in maximal esophageal pressure between hypopnea and HR episode (22 ± 6 vs. 19 ± 6 cmH₂O), whereas the difference in flow reduction was, by definition, very significant (58 ± 11 vs. 21 ± 5%, P < 0.001). This supports the fact that collapsibility is increased during hypopneas compared with HR episodes. The data of the present study, however, apply to resistance during stable respiration. In the OSHS group, the resistance values seem to be lower than in OSAS. Conversely, in the UARS group, in which both hypopneas and HR episodes coexist, the resistance observed during stable respiration is much higher than in patients exhibiting mainly hypopneas. The length of events is different, with the HR episodes being longer than hypopneas. We can then hypothesize that 1) HR during stable respiration is probably not possible for hypopneic patients because of their pharyngeal collapsibility, 2) the resistance obtained during hypopneas is higher (this is supported by the results of esophageal pressure provided above, because the “transpharyngeal” resistance is actually higher during hypopneas), and 3) the slope of increase in resistance in HR episodes is lower compared with hypopnea but is not contradictory with a higher resistance during stable respiration. Both are in favor of a more stable pharynx. Whether the difference in resistance between apneic and UARS in REM and stage 3/4 is actually related to different levels of collapsibility, however, remains to be further established by critical pressure measurements during sleep in these different subgroups of patients.

The physiology of the upper airway during REM sleep is still unclear. Some authors have found that upper airway collapsibility or compliance is increased (24). This seems logical given that the reduction in muscle tone is at a maximum during this state of vigilance (29). This is supported by the fact that apneic events are more frequent and longer during REM sleep (23). Conversely, cross-sectional area during both tonic and phasic REM, although reduced, seems to be stable within the breath (16), suggesting a limited collapsibility. In our study, in REM sleep, the cycle-by-cycle fluctuation in resistance was important. This was at least partly due to the large cycle-by-cycle variability in driving pressure explained by the changes in respiratory drive during phasic REM (11). During REM sleep (Fig. 8), resistance at peak pressure is highly variable compared with that in non-REM sleep, in which upper airway resistance showed very little variation, as attested by the limited standard deviation of the mean value of upper airway resistance (see Table 4).

The nonlinearity in the pressure-flow relationship during inspiration is commonly caused by narrowing of an hypotonic upper airway in response to the negative intrathoracic pressure developed during inspiration (3, 8). It is generally accepted that the recognition of inspiratory flow limitation is an adequate tool to identify elevated upper airway resistance both in normal subjects and in patients with sleep-disordered breathing (3, 8). Hosselet et al. (8) found that, in each sleep stage, including REM sleep, the resistance of an abnor-
mal-contour breath (i.e., flow limited) was higher than the resistance of a breath with normal contour. Clark et al. (3) were less categorical and found that, during non-REM sleep, flow-rate shape was effective in differentiating severe types of inspiratory flow limitation but was not able to consistently detect low levels of increased resistance. We have shown that, during HR episodes in non-REM sleep (Fig. 4), an increase in resistance progressively occurs in accordance with an aggravation of inspiratory flow limitation. During REM sleep, effort-related pressure swings are often low and erratic. In these conditions, flattened flow contour or esophageal pressure, if considered alone, are probably unable to describe the fluctuation in upper airway resistance accurately.

In conclusion, upper airway resistance measurements were performed in a spectrum of patients with sleep-disordered breathing. The more accurate fit of the pressure-flow relationship was the hyperbolic model. ΔP/ΔV at peak pressure is a reliable method to estimate upper airway resistance. We found, as in normal subjects, a general trend for patients to progressively increase their pharyngeal resistance as they entered deeper sleep stages. The slope of increase in upper airway resistance from wakefulness to sleep was substantially different in UARS patients compared with snorers or apneic subjects. This suggests different underlying mechanisms in upper airway control in these different subgroups of patients.

APPENDIX

There are three physical components for the pressure in a tube: viscoelastic pressure, which depends on flow and viscosity of the fluid; dynamic pressure, which depends on flow and the section of the tube; and static pressure, which depends on the volume of the tube and the quantity of fluid. The measurement of pharyngeal pressure performed via balloon catheter [such as that used by White et al. (28)] includes static pressure and a variable proportion of dynamic pressure. When this type of catheter is used in a narrowed upper airway, a further reduction of upper airway size is induced by the inflated balloon, and thus the relative proportion of dynamic pressure is likely to increase. By contrast, we used a catheter that mainly detected static pressure. The dynamic component, which could be present, was undetected by this type of catheter, and, therefore, the inspiratory change in pressure could potentially be overestimated. In the present study, the pressure sensors were at the two pharyngeal levels (nasopharynx and hypopharynx), at which the changes in cross-sectional area are rather limited through the respiratory cycle. In this context, a theoretical calculation of dynamic pressure suggested that the dynamic component was negligible at both the nasopharyngeal and hypopharyngeal levels. Static and dynamic pressures are the two principal components of the driving pressure.

Driving pressure = static pressure + dynamic pressure

Dynamic pressure is correlated with the square of fluid velocity. The speed of the fluid is determined by the section of the tube where the measure is made and by the flow crossing the tube. With increase of flow, the more dynamic pressure increases, the more the static pressure is underestimated. In sleep-disordered breathing, the respective sections of nasopharynx and hypopharynx are ~100 and 200 mm^2 (7). During sleep, flow is in a range of 0–0.5 l/s. In this condition, the dynamic pressure calculated at 0.5 l/s was 0.14 cmH2O in the nasopharynx and 0.025 in the hypopharynx.

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