The influence of episodic hypoxia on upper airway collapsibility in subjects with obstructive sleep apnea


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Rowley JA, Deebajah I, Parikh S, Najar A, Saha R, Badr MS. The influence of episodic hypoxia on upper airway collapsibility in subjects with obstructive sleep apnea. J Appl Physiol 103: 911–916, 2007. First published June 14, 2007; doi:10.1152/japplphysiol.01117.2006.—We have previously shown that in subjects with obstructive sleep apnea, repetitive hypoxia is associated with long-term facilitation as manifested by decreased upper airway resistance (Rua). Our objective was to study the influence of long-term facilitation on upper airway collapsibility as measured by the critical closing pressure (Pcrit) model and to determine whether changes in Rua correlated with changes in collapsibility. We studied 13 subjects (10 men, 3 women) with a mean apnea-hypopnea index of 43.9 ± 24.0 events/h. In the first protocol with 11 subjects, we measured collapsibility using a Pcrit protocol before and after episodic hypoxia. Brief (3 min) isocapnic hypoxia (inspired O2 fraction = 8%) followed by 5 min of room air was induced 10 times. A sham study without hypoxia was performed on eight subjects. Ventilatory parameters, Rua, and Pcrit before and after episodic hypoxia were measured. At 20 min of recovery, there was no change in minute ventilation but there was a significant decrease in Rua compared with the control period (control, 8.6 ± 4.8 cmH2O·1−1·s vs. recovery, 5.9 ± 3.8 cmH2O·1−1·s; P < 0.05). However, there was no change in Pcrit between the control (2.3 ± 1.9 cmH2O) and recovery (2.7 ± 3.2 cmH2O) periods. No changes in Rua or Pcrit were observed in the sham protocol. We conclude that long-term facilitation of upper airway dilators is not associated with changes in upper airway collapsibility in subjects with obstructive sleep apnea. These results corroborate previous evidence that changes in upper airway resistance and caliber can be dissociated from changes in upper airway collapsibility.

long-term facilitation; upper airway resistance; control of breathing; critical closing pressure

VENTILATORY MOTOR OUTPUT IS an important determinant of upper airway patency during sleep. Induction of periodic breathing results in oscillation of ventilatory drive and ventilation with reciprocal changes in upper airway resistance (Rua) (12, 15, 29). Chemoreceptor stimulation with hypoxia or hypercapnia decreases Rua during wakefulness and sleep (5, 6). Thus increased ventilatory drive exerts salutary effects on upper airway patency.

Although the measurement of Rua is primarily used as a measure of upper airway patency, it has also been used as a measure of upper airway collapsibility (19, 30). However, although there is evidence that a smaller upper airway is associated with increased collapsibility (10), there is evidence from an animal model that suggest that a smaller airway could be associated with decreased collapsibility (21). Therefore, it is unclear whether changes in Rua truly reflect changes in the collapsibility of the upper airway.

A case in point is the effect of long-term facilitation (LTF) on upper airway mechanics. Our group has shown that repetitive hypoxia is followed by LTF of ventilation and decreased Rua (1, 28). Decreased Rua in the aftermath of episodic hypoxia has been demonstrated in snorers and in patients with sleep apnea. However, inspiratory flow limitation persisted, and maximal flow (Vmax) was unchanged.

According to the principles of flow in collapsible tubes, Vmax is a function of upstream pressure, upstream resistance, and the critical closing/opening pressure of the upper airway (Perit of the collapsible segment). Although Perit is not the sole determinant of Vmax, there is an inverse correlation between Vmax and Pcrit (higher Vmax = lower Pcrit = less collapsible upper airway) under most conditions. The advantage of Pcrit as a measure of collapsibility is that it gives a composite measure of upper airway collapsibility that includes both the structural and neuromuscular factors that determine upper airway collapsibility (9, 21, 23).

The goal of the present study was to study the influence of LTF on upper airway collapsibility as measured by the Pcrit model and to determine whether changes in Rua correlated with changes in collapsibility. We hypothesized that upper airway collapsibility would decrease after LTF associated with decreased Rua. Preliminary data from this investigation have been previously presented as an abstract (7).

METHODS

The experimental protocols described below were approved by the Human Investigation Committee of the Wayne State University School of Medicine and the John D. Dingell Veterans Affairs Medical Center. Informed written consent was obtained from all subjects.

Measurements

The following parameters were measured in all subjects. Standard sleep parameters were recorded using the international 10–20 system of electrode placement. Airflow (V̇) was measured by a pneumotachometer (model 3700A, Hans Rudolph) attached to a nasal mask. Tidal volume (Vt) was obtained from the integrated V̇ signal. Supraglottic airway pressures were measured using a pressure-tipped catheter (model TC-500XG, Millar) threaded through the mask and positioned in the oropharynx just below the base of the tongue. Correct placement was verified by visually inspecting the catheter’s position in the oropharynx. Mask pressure was measured in all subjects and used as the surrogate of nasal pressure (Pn). End-tidal PCO2 (PETCO2) level in the oropharynx was measured by ETCO2 (EtCO2) probe attached to a nasal mask.

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was measured using air sampled continuously from the nasal mask by an infrared analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Arterial oxygen saturation (\(\text{SaO}_2\)) was measured by a pulse oximeter (Biox 3700, Ohmeda). All signals were displayed on a polygraph recorder (Grass/Telefactor, West Warwick, RI) and recorded using data acquisition software (PowerLab, Colorado Springs, CO) for further analysis (see below).

**Experimental Setup**

The subject was connected to the circuit with an airtight silicone rubber mask strapped and glued to the face to prevent leaks (see Fig. 1 in Ref. 1). The mask was connected to a Plateau Exhalation Valve (Respironics, Pittsburgh, PA) via a heated pneumotachometer. The valve, which provides a continuous leak path in the breathing circuit and serves as an exhaust vent, was connected on the inspiratory line. The pneumotachometer was attached to a Y-shaped circuit with two balloon valves. The first balloon valve, when open, allowed the subject to breathe a gas mixture from three cylinders containing the following gases: 100% \(\text{N}_2\), 8% \(\text{O}_2\), or 100% \(\text{O}_2\). To maintain isocapnia, supplemental \(\text{CO}_2\) was added to the inspiratory line from an external source, and \(\text{PETCO}_2\) was maintained at control levels.

The other half of the Y-shaped circuit was connected to a continuous positive pressure generator; the valve for this part of the circuit was open throughout the study protocol. A negative pressure generator (modified REM-Star, Respironics, Murrysville, PA) was also available to put in series with the Y-shaped circuit if it was determined that the subject had a negative \(\text{Pcrit}\). If needed, the negative pressure generator could generate a subatmospheric pressure in the upper airway as indicated by a decrease in \(\text{Pn}\). The level of subatmospheric pressure generated could be preset on the modified REM-Star unit.

**Protocol**

All patients were monitored in the supine position and used a U-shaped pillow to maintain head and neck position. Patients were allowed to fall asleep breathing at a continuous positive airway pressure (CPAP) level that eliminated apneas and hypopneas but at which flow limitation was present for \(>50\%\) of the breaths (\(\text{Pn-FL}\)). A \(\text{Pcrit}\) protocol as previously described was performed after the onset of stage 2 sleep (25, 26). During periods of stable stage 2 sleep, \(\text{Pn}\) was abruptly reduced by decreasing \(\text{Pn}\) by 1 cmH\(_2\)O at the end of expiration; the decreased \(\text{Pn}\) was maintained for two breaths and then raised back to the holding pressure. \(\text{Pn}\) was subsequently reduced in 1.0-cmH\(_2\)O decrements at 1- to 2-min intervals (with return to atmospheric after 2 breaths) until airflow ceased. The \(\text{Pn}\) drop associated with zero flow was repeated to ensure that zero flow was achieved at this pressure. If there was not complete airway closure, at a \(\text{Pn} = 0\) cmH\(_2\)O, the negative pressure generator was attached to the circuit and negative pressure was generated in 1.0-cmH\(_2\)O decrements. Complete airway collapse was achieved in all subjects.

After the \(\text{Pcrit}\) was obtained, the LTF protocol was performed with the patient breathing at the \(\text{Pn-FL}\). The subjects breathed room air for 5 min (control period), followed by 3 min of hypoxic gas (8% \(\text{O}_2\)); this sequence was repeated 10 times. Hypoxia was rapidly induced by having the subject breathe one or two breaths of 100% \(\text{N}_2\) followed by continuous 8% \(\text{O}_2\) for 3 min to maintain hypoxia (\(\text{O}_2\) saturation <88%). Care was taken to ensure that isocapnia was maintained throughout the hypoxia period by measuring \(\text{PETCO}_2\), and 5% \(\text{CO}_2\) was supplemented as needed. Hypoxia was abruptly terminated with one breath of 100% \(\text{O}_2\). Twenty minutes after the last hypoxic exposure, a repeat \(\text{Pcrit}\) determination was performed. Note that hypoxia was always initiated when the patient was in stage 2 sleep but was continued for 3 min even if there was a change in sleep stage or return to wakefulness.

Subjects were invited to return for a sham study. During the sham study, a \(\text{Pcrit}\) determination was performed after the onset of stable non-rapid eye movement (NREM) sleep. The patient was then allowed to sleep for 80 min with no hypoxia interventions with a repeat \(\text{Pcrit}\) determination at the end of the 80 min.

**Data Analysis**

**Sleep state.** Wakefulness/sleep stage was scored according to standard criteria (20). The subjects were in stable stage 2 or stage 3 sleep during the hypoxic exposures, \(\text{Pcrit}\) protocols, and data collection.

**Selection of breaths.** The control period consisted of 3 min immediately preceding the first hypoxic exposure. The last 20 breaths were used for measurement of resistance and ventilation. For each hypoxia period, the last 10 breaths were chosen for analysis. Starting at 20 min after the last hypoxia period, 20 breaths were chosen for analysis to represent recovery. For the sham studies, 20 breaths immediately following the \(\text{Pcrit}\) protocol were chosen for control; 20 breaths were chosen for the recovery period starting at 80 min after the control breaths. All breaths were chosen during periods of stable stage 2 sleep; breaths associated with arousals were not analyzed. The criteria for selecting the recovery segment included a similar sleep state to the control period and similar distribution of various sleep waveforms. An independent observer matched the sleep state between the control and the recovery period without knowledge of the breathing in either segment.

**Ventilation and timing.** Inspired tidal volume (\(\text{Vt}\)), breathing frequency (\(\text{fb}\)), minute ventilation (\(\text{V˙I}\)), inspiration time (\(\text{TI}\)), total time of a breath (\(\text{TT}\)), \(\text{PETCO}_2\), and \(\text{SaO}_2\) were calculated for each breath chosen for the control, hypoxia, and recovery periods. \(\text{R}_{\text{ua}}\) was measured for the same breaths. \(\text{R}_{\text{ua}}\) was measured on the linear portion of the inspiratory portion of the pressure-flow curve, independent of flow rate, using a polynomial equation-based method that allows for precise, automated measurements (13).

**Determination of \(\text{Pcrit}\).** For each reduction in \(\text{Pn}\), the second breath was analyzed. \(\text{Pcrit}\) was defined as the first measured \(\text{Pn}\) at which flow was zero. If there was more than one \(\text{Pn}\) at which flow was zero, the largest (most positive) \(\text{Pn}\) was used as the \(\text{Pcrit}\) value for the subject. Upstream resistance or \(\text{Rn}\) was calculated as previously described (Fig. 1) (26). For each trial, \(\text{Vmax}\) and \(\text{Pn}\) were plotted and a regression line drawn. \(\text{Rn}\) was calculated as the inverse of the slope of the regression line.

**Statistical Analysis**

Repeated-measures one-way ANOVA was performed to compare respiratory parameters and \(\text{PETCO}_2\) between control, hypoxia and recovery. Paired \(t\)-test was used to compare \(\text{R}_{\text{ua}}, \text{Pcrit}\), and \(\text{Rn}\) before and after episodic hypoxia in the experimental protocols and to compare all parameters for the sham studies.

**RESULTS**

We studied 13 subjects; subject demographics are provided in Table 1. Eleven subjects completed the episodic hypoxia study; six of these subjects also completed a sham study. Two additional subjects were unable to sleep during the episodic hypoxia study but completed a sham study, for a total of eight sham studies.

For the episodic hypoxia trials, the mean \(\text{SaO}_2\) associated with the breaths chosen for analysis was 85.3 ± 3.3%. Mean \(\text{PETCO}_2\) was 40.8 ± 6.5 Torr during the control period, 38.4 ± 4.1 Torr during the hypoxia periods and 40.7 ± 4.8 Torr during the recovery period (\(P = \) not significant). Results of the analysis for the respiratory parameters are shown in Table 2. There was an increase in \(\text{Vt}/\text{Ti}\) during hypoxia but not during the recovery period. There was an increase in \(\text{Vt}\) and \(\text{V˙I}\) during hypoxia with no difference between control and recovery. There was no difference between control, hypoxia, and recov-
The aim of this study was to determine whether LTF secondary to episodic hypoxia is associated with changes in the collapsibility of the upper airway as measured by the Pcrit. In

DISCUSSION

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Table 1. Subject demographics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Studies</th>
<th>Sex</th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>NC, cm</th>
<th>AHI, events/h</th>
<th>CPAP, cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LTF/sham</td>
<td>F</td>
<td>46</td>
<td>25.8</td>
<td>34.5</td>
<td>12.5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>LTF/sham</td>
<td>M</td>
<td>28</td>
<td>25.8</td>
<td>40.5</td>
<td>57.9</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>LTF/sham</td>
<td>F</td>
<td>47</td>
<td>32.9</td>
<td>43.0</td>
<td>41.7</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>LTF/sham</td>
<td>M</td>
<td>48</td>
<td>42.8</td>
<td>48</td>
<td>38.8</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>LTF/sham</td>
<td>M</td>
<td>44</td>
<td>30.7</td>
<td>44</td>
<td>54.8</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>LTF/sham</td>
<td>M</td>
<td>45</td>
<td>31.0</td>
<td>42.5</td>
<td>47.6</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>LTF</td>
<td>M</td>
<td>49</td>
<td>29.3</td>
<td>44.5</td>
<td>78.9</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>LTF</td>
<td>F</td>
<td>48</td>
<td>27.7</td>
<td>36</td>
<td>95.1</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>LTF</td>
<td>M</td>
<td>51</td>
<td>29.8</td>
<td>40</td>
<td>44.2</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>LTF</td>
<td>M</td>
<td>48</td>
<td>35.0</td>
<td>49</td>
<td>32.5</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>LTF</td>
<td>M</td>
<td>44</td>
<td>35.5</td>
<td>42</td>
<td>32.5</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>Sham</td>
<td>M</td>
<td>43</td>
<td>22.5</td>
<td>38</td>
<td>16.9</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>Sham</td>
<td>M</td>
<td>38</td>
<td>29.3</td>
<td>44.5</td>
<td>16.6</td>
<td>9</td>
</tr>
</tbody>
</table>

Mean±SE 44.5±6.0 30.6±5.2 42.1±2.3 43.9±24.0 10.5±2.9

BMI, body mass index; NC, neck circumference; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; LTF, long-term facilitation; F, female; M, male.

Values are means ± SD. Ti, inspiration time; Tr, total time for each breath; Vl, tidal volume; fSp, breathing frequency. *Hypoxia vs. control, recovery, P < 0.05; control vs. recovery, not significant. †Recovery vs. hypoxia, P < 0.05; control vs. hypoxia, recovery, not significant.

P = 0.571). Rn was also not significant different before (25.5 ± 17.2 cmH₂O·l⁻¹·s⁻¹) and after (23.7 ± 13.6 cmH₂O·l⁻¹·s⁻¹; P = 0.734) repetitive hypoxia.

For the sham studies, mean PETCO₂ was 40.6 ± 8.1 Torr during the control period and 39.3 ± 8.4 Torr during the sham recovery period (P = not significant). Ventilatory parameters are presented in Table 3; there were no differences between the control and recovery periods for any parameter, including Vl. Rua did not change over the course of the sham study (control, 6.9 ± 3.3 cmH₂O·l⁻¹·s⁻¹ vs. 80 min, 7.1 ± 3.2 cmH₂O·l⁻¹·s⁻¹; P = 0.85; Fig. 3). The results of the Pcrit protocol are presented in Fig. 3. Pcrit at baseline (2.1 ± 1.9 cmH₂O) was not different from the Pcrit after 80 min of stable NREM sleep (2.5 ± 2.7 cmH₂O; P = 0.279). There was no change in Rn during the course of the study (baseline, 18.2 ± 6.8 cmH₂O·l⁻¹·s⁻¹ vs. 80 min, 21.3 ± 12.8 cmH₂O·l⁻¹·s⁻¹; P = 0.413).

We performed a repeated-measures two-factor ANOVA of the six subjects who had both episodic hypoxia and sham studies. The factors were night (episodic hypoxia vs. sham) and group (control vs. recovery). There were no differences in Pcrit or Rn between the two nights of study or between control and recovery.

Table 2. Respiratory parameters: episodic hypoxia study

<table>
<thead>
<tr>
<th>Value</th>
<th>Control</th>
<th>Hypoxia</th>
<th>Recovery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti, s</td>
<td>1.94±0.36</td>
<td>1.75±0.37</td>
<td>2.14±0.44</td>
<td>0.344</td>
</tr>
<tr>
<td>Tr, s</td>
<td>4.02±0.77</td>
<td>3.51±0.73</td>
<td>4.11±0.94</td>
<td>0.772</td>
</tr>
<tr>
<td>Vl/liter</td>
<td>0.49±0.08</td>
<td>0.46±0.06</td>
<td>0.53±0.08</td>
<td>0.458</td>
</tr>
<tr>
<td>Vl/Ti</td>
<td>0.576±0.125</td>
<td>0.627±0.130</td>
<td>0.566±0.129</td>
<td>0.03*</td>
</tr>
<tr>
<td>fSp, breaths/min</td>
<td>15.7±3.1</td>
<td>15.6±3.7</td>
<td>15.4±3.6</td>
<td>0.776</td>
</tr>
<tr>
<td>Vl/I, l/min</td>
<td>9.0±2.8</td>
<td>10.9±3.2</td>
<td>9.6±3.4</td>
<td>0.013*</td>
</tr>
<tr>
<td>Vl/Ti, l/s</td>
<td>0.31±0.09</td>
<td>0.35±0.10</td>
<td>0.28±0.08</td>
<td>0.041†</td>
</tr>
</tbody>
</table>

Values are means ± SD. Ti, inspiration time; Tr, total time for each breath; Vl, tidal volume; fSp, breathing frequency. *Hypoxia vs. control, recovery, P < 0.05; control vs. recovery, not significant. †Recovery vs. hypoxia, P < 0.05; control vs. hypoxia, recovery, not significant.
In this study, we demonstrated that episodic hypoxia in patients with sleep apnea evokes LTF, manifesting as decreased Rua. However, decreased Rua was not associated with a change in Pcrit, suggesting that upper airway collapsibility was not altered. In addition, there was no change in collapsibility after 80 min of sleep without hypoxia intervention in eight subjects who underwent sham studies.

We showed that repetitive hypoxia results in decreased Rua indicative of upper airway dilatation. Decreased Rua without increased Vt or Vt/Ti suggests LTF of the ventilatory motor output to upper airway dilators but not to thoracic pump muscles. These findings confirm our previous work demonstrating reduced Rua, without change in inspiratory thoracic EMG, after episodic hypoxia (1). In addition, we have preliminary data that indicates the genioglossus muscle activity is increased in normal subjects after episodic hypoxia (S. Chowdhuri, personal communication). Our findings corroborate animal studies demonstrating that repetitive hypoxia elicits LTF of ventilatory motor output to upper airway dilators. Mateika and Fregosi (14) showed that repetitive hypoxia in vagotomized cats is followed by increased activity of the genioglossus and the alae nasae but not the diaphragm (14).

Upper airway mechanics during sleep have been studied and measured by a variety of measures, including Rua (19, 30) and collapsibility (8, 25, 26). Rua, when measured on the linear portion of the pressure-flow loop, is commonly used as a surrogate of upper airway caliber (2, 4, 27) during sleep. However, the computation of Rua is predicated on a constant relationship between driving pressure and inspiratory flow, which is true only on the linear portion of the pressure-flow loop; in fact, flow limitation develops after 10–15% of Ti (5, 11). Thus Rua as measured in our study likely reflects the behavior of the upper airway only at the beginning of inspiration. In other words, the Rua provides only a partial picture of the dynamic behavior of the pharyngeal airway during sleep. The dynamic behavior of the airway, including its propensity to collapse, can be better characterized by measuring collapsibility using the critical closing pressure methodology as in this study. An advantage of the Pcrit methodology is that closely approximates the inspiratory flow limitation condition; thus Pcrit likely reflects the behavior and properties of the upper airway as inspiratory flow limitation develops later in the inspiratory cycle.

The dissociation between Rua and Pcrit observed in this study could be occurring because these parameters are measuring properties of the upper airway properties at different points of the inspiratory cycle with the Rua measuring the behavior at the beginning of inspiration and Pcrit at the peak of inspiration. Alternatively, the dissociation could be secondary to the two parameters measuring the behavior of the airway at different locations of the upper airway. Pcrit most likely reflects collapsible segments at either the naso- or oropharynx. However, Rua may reflect the cross-sectional area of the airway at multiple different locations, although not likely the nasal cavity given the lack of change in Rn.

Another advantage of the Pcrit technique is the ability to partition the upper airway into several segments, which allows measurement of the upstream resistance or Rn. In this study, we have found no change in Rn after episodic hypoxia. The lack of change is likely due to the fact that the Rn is primarily determined by the bony and cartilaginous structures of the nasal cavity. However, the lack of change in Rn also indicates that episodic hypoxia is not altering the vascular and properties of the nasal mucosa.

The results of our study indicate that the various measures of upper airway mechanics cannot be used interchangeably. For

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Table 3. Respiratory parameters: sham studies

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Recovery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI, s</td>
<td>2.04±0.44</td>
<td>2.14±0.47</td>
<td>0.191</td>
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<tr>
<td>TV, s</td>
<td>3.81±0.71</td>
<td>3.89±0.79</td>
<td>0.310</td>
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<td>TV/TI</td>
<td>0.54±0.12</td>
<td>0.56±0.12</td>
<td>0.351</td>
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<td>VT, liter</td>
<td>0.554±0.782</td>
<td>0.586±0.107</td>
<td>0.267</td>
</tr>
<tr>
<td>I/E, breaths/min</td>
<td>15.1±1.9</td>
<td>14.9±2.9</td>
<td>0.514</td>
</tr>
<tr>
<td>VI, l/min</td>
<td>8.3±1.5</td>
<td>8.2±2.4</td>
<td>0.912</td>
</tr>
<tr>
<td>VT/TI, l/s</td>
<td>0.28±0.07</td>
<td>0.28±0.07</td>
<td>0.976</td>
</tr>
</tbody>
</table>

Fig. 2. Group mean upper airway resistance (Rua), Pcrit, and Rn values before and after episodic hypoxia. Values are means ± SD. *There was a significant decrease in the Rua after episodic hypoxia (P = 0.012). There was no difference in the group mean Pcrit or Rn values after episodic hypoxia.
instance, Rua has frequently been measured as an index of upper airway collapsibility with an increase in resistance between two conditions believed to be indicative of increased upper airway collapsibility (19, 30). However, we found that decreased Rua was not associated with a change in Pcrit, suggesting that upper airway collapsibility was not altered. This finding corroborates our laboratory’s previous studies in sleep apnea patients and in normal snoring subjects demonstrating no change in V\textsubscript{max} despite decreased Rua and increased V\textsubscript{T} (1, 28).

**Methodological Considerations**

Several limitations have to be considered for proper interpretation of our findings. First, changes in sleep state might have caused a misinterpretation of the data. However, we performed the Pcrit protocol only during periods of stage 2 sleep and analyzed the breath by breath data only when sleep was in stable stage 2 or greater, with no evidence of arousal. Thus the data reported here were from periods where there was no change in sleep state. Second, we were unable to maintain precise isocapnia during hypoxia. However, the reduction in Pt\textsubscript{CO2} was minimal and not significant. Third, the study was conducted while the patients were receiving nasal CPAP therapy. Subjects were studied on CPAP because we have previously shown that manifestations of LTF are most likely observed under conditions of inspiratory flow limitation (3). Fourth, we did not change the CPAP setting during the recovery period. In theory, the decreased Rua during recovery would indicate a larger upper airway caliber; therefore, upper airway collapsibility measurements starting at different airway calibers may not be comparable. To our knowledge, this hypothesis has not been specifically tested. Fifth, we chose to use Rua as an indicator of upper airway caliber. However, there is evidence that changes in upper airway cross-sectional area during sleep does not necessarily correlate with changes in Rua (22, 24).

Our protocol differed from previous Pcrit protocols. First, we did not intend to partition the Pcrit into its active and passive components as previously described (18). However, we likely studied a neurally intact upper airway because passive Pcrit pressure is measured when the upper airway is studied under hypotonic conditions, generally achieved when CPAP is set at a level sufficient to eliminate inspiratory flow limitation. We studied our patients at a CPAP level at which inspiratory flow limitation and inhibition on total pulmonary resistance in humans during NREM sleep. J Appl Physiol 91: 33–45, 1997.


