Effect of episodic hypoxia on upper airway mechanics in humans during NREM sleep

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Shkoukani, Mahdi, Mark A. Babcock, and M. Safwan Badr. Effect of episodic hypoxia on upper airway mechanics in humans during NREM sleep. J Appl Physiol 92: 2565–2570, 2002.—We hypothesized that long-term facilitation (LTF) is due to decreased upper airway resistance (Rua). We studied 11 normal subjects during stable non-rapid eye movement sleep. We induced brief isocapnic hypoxia (inspired \( \text{O}_2 \) fraction = 8%) (3 min) followed by 5 min of room air. This sequence was repeated 10 times. Measurements were obtained during control, hypoxia, and at 20 min of recovery (R20) for ventilation, timing, and Rua. In addition, nine subjects were studied in a sham study with no hypoxic exposure. During the episodic hypoxia study, inspiratory minute ventilation (Vi) increased from 7.1 ± 1.8 l/min during the control period to 8.3 ± 1.8 l/min at R20 (117% of control; \( P < 0.05 \)). Conversely, there was no change in diaphragmatic electromyogram (EMGdia) between control (16.1 ± 6.9 arbitrary units) and R20 (15.3 ± 4.9 arbitrary units) (95% of control; \( P > 0.05 \)). In contrast, increased Vi was associated with decreased Rua from 10.7 ± 7.5 \( \text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1} \) during control to 8.2 ± 4.4 \( \text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1} \) at R20 (77% of control; \( P < 0.05 \)). No change was noted in Vi, Rua, or EMGdia during the recovery period relative to control during the sham study. We conclude the following: 1) increased Vi in the recovery period is indicative of LTF, 2) the lack of increased EMGdia suggests lack of LTF to the diaphragm, 3) reduced Rua suggests LTF of upper airway dilators, and 4) increased Vi in the recovery period is due to “unloading” of the upper airway by LTF of upper airway dilators.

Peripheral chemoreceptors; unloading; upper airway; non-rapid eye movement sleep.

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) (15, 22, 33). Conversely, chemoreceptor stimulation with hypoxia or hypercapnia decreases Rua during wakefulness and sleep (7–9). Thus increased ventilatory drive exerts salutary effects on upper airway patency.

Increased ventilatory motor output may persist after removal of a ventilatory stimulus. For example, brief peripheral chemoreceptor stimulation is followed by a transient elevated ventilatory motor output, referred to as short-term potentiation (6, 11, 13). Interestingly, repetitive hypoxia is followed by a sustained increase in ventilatory motor output, referred to as long-term facilitation (LTF) (20). This excitatory mechanism occurs after repetitive stimulation of the carotid bodies as ventilation returns to baseline over a long duration, up to several hours (10). LTF has been observed in several animal models (10, 12, 17, 18, 20, 21, 31) but not others (16). The critical contribution of episodic hypoxia to the genesis of LTF suggests potential relevance to sleep apnea syndrome. However, studies investigating the occurrence of LTF in humans have shown variable results. One study in awake humans demonstrated no evidence of LTF (19). Conversely, we have shown that LTF is elicited by repetitive hypoxia during sleep but only in subjects who snore regularly and who have evidence of inspiratory flow limitation (IFL) during sleep (2). In our model, LTF manifested as increased inspiratory minute ventilation (Vi) and alleviation of IFL lasting for 40–60 min during the recovery period after hypoxia. Conversely, repetitive hypoxia in sleep apnea patients resulted in decreased Rua during the recovery, albeit without corresponding increase in Vi (1). However, upper airway anatomy in sleep apnea patients may dampen ventilatory LTF despite upper airway dilatation. Therefore, we hypothesized that repetitive hypoxia during sleep is followed by a period of decreased Rua in normal subjects (including those who snore). The purpose of this study was to determine the after effects of episodic hypoxic on Rua and ventilation during stable non-rapid eye movement (NREM) sleep in humans.

METHODS

Subjects

The Human Investigation Committee of the Wayne State University School of Medicine and the Detroit Veterans Affairs Medical Center approved the experimental protocol. Informed written consent was obtained from 11 healthy subjects free of daytime sleepiness, sleep disordered-breathing, and who have evidence of inspiratory flow limitation (IFL) during sleep (2). In our model, LTF manifested as increased inspiratory minute ventilation (Vi) and alleviation of IFL lasting for 40–60 min during the recovery period after hypoxia. Conversely, repetitive hypoxia in sleep apnea patients resulted in decreased Rua during the recovery, albeit without corresponding increase in Vi (1). However, upper airway anatomy in sleep apnea patients may dampen ventilatory LTF despite upper airway dilatation. Therefore, we hypothesized that repetitive hypoxia during sleep is followed by a period of decreased Rua in normal subjects (including those who snore). The purpose of this study was to determine the after effects of episodic hypoxic on Rua and ventilation during stable non-rapid eye movement (NREM) sleep in humans.

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or other medical disorders. The absence of sleep-disordered breathing was confirmed by sham studies in nine subjects. There were five men and six women with a mean age of 29.3 ± 7.7 yr (range 22–46 yr) and body mass index of 26.6 ± 4.6 kg/m².

Breathing Circuit

The subject was connected to the circuit with an airtight silicone rubber mask strapped and glued to the face to prevent leaks. 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. Three cylinders containing 100% N₂, 8% O₂, or 100% O₂ were connected to the inspiratory line. To maintain isocapnia, supplemental CO₂ was added to the inspiratory line from an external source, and end-tidal Pco₂ (PetCO₂) was maintained at control levels.

Measurements

Electroencephalograms (EEG), electrooculograms (EOG), and chin electromyograms (EMG) were recorded by using the international 10–20 system of electrode placement (EEG: C3–A2 and C4–A1; EOG: F7–A1 and F8–A2). Inspiratory airflow was measured by a heated pneumotachometer (model 3700A, Hans Rudolph, Kansas City, MO) attached to a pressure transducer (Validyne, Northridge, CA). Tidal volume (VT) was obtained from the electronic integration of the flow signal (model FV156 Integrator, Validyne, Northridge, CA). Supraglottic airway pressure was measured by using a transducer-tipped pressure catheter (model TC-500XG, Millar Instruments, Houston, TX). The hypopharyngeal position was confirmed by advancing the catheter tip 2 cm after it disappeared behind the tongue. PetCO₂ was measured by using air sampled continuously from the nasal mask by an infrared analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Arterial O₂ saturation (SaO₂) was measured by pulse oximeter (Biox 3700, Ohmeda). All signals were displayed on a polygraph recorder (model 7-D, Grass, West Warwick, RI) and recorded by using Biobench data acquisition software (National Instruments, Austin, TX) for further analysis (see below). Surface diaphragmatic EMG (EMGdia) was recorded by using two surface electrodes (3M Red Dot, 3M, St. Paul, MN) placed 2–4 cm above the right costal margin in the anterior axillary line. One pair was positioned at the percutaneous dullness at total lung capacity, and another pair was positioned at the point of percutaneous dullness at functional residual capacity. The electrode pair with the best signal-to-noise ratio was selected for analysis.

Protocol

The study was conducted during regular sleep hours. Subjects lay in the supine position for the whole study. After reaching stable stage 2 or stage 3 sleep, the subjects breathed room air for 5 min (control period), followed by 3 min of hypoxic gas (8% O₂); this sequence was repeated 10 times. Hypoxia was rapidly induced by having the subject breathe one or two breaths of 100% N₂ followed by continuous 8% O₂ for 3 min to maintain hypoxia (SaO₂ 80–84%). Care was taken to ensure that isocapnia was maintained throughout the hypoxia period by measuring PetCO₂, and 5% CO₂ was supplemented as needed. Hypoxia was abruptly terminated with one breath of 100% O₂. The breathing pattern was monitored for 40 min of recovery after the 10th exposure to hypoxia (H₁₀). To ensure that changes in the recovery period were not time-dependent effects per se, nine of the subjects underwent a sham study on a different night with the identical measurements but no intervention. The other two subjects declined to participate in future studies.

Data Analysis

Sleep state. Wakefulness/sleep stage was scored according to standard criteria (22). The subjects were in stable stage 2 or stage 3 (slow wave % = 20–50%) sleep during the hypoxic exposures and data collection.

Selection of breaths. The control period consisted of 3 min immediately preceding the first hypoxic exposure. All breaths were used for determination of IFL. The last 20 breaths were used for measurement of Ru and V₁. A similar duration was selected for 20 min of recovery (R₂₀). All breaths were used for determination of IFL; the last 20 breaths were used for V₁ and Ru analysis. 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. Inspiratory VT, inspiratory time (Ti), total time for a breath (Tv), breathing frequency, PetCO₂, and SaO₂, were calculated breath by breath during stable sleep during the first normoxic period (control period) and at 20 min after the H₁₀ exposure (R₂₀). Breaths for analysis were selected during a period of stable sleep with no evidence of an arousal, as confirmed by an independent observer who matched the sleep stage precisely, without knowledge of breathing, between control and R₂₀. A mean value for each variable was computed from 20 consecutive breaths. For the sham study, no hypoxia was induced. Data were sampled after 80 min of sleep; this duration was equal to the total duration of the repetitive hypoxia trials in the night 1 protocol. Accordingly, for the sham study, the recovery period (R₂₀) was designated as 100 min from the beginning of the control period. All the data were normalized to the control period data for comparison.

Upper airway mechanics. To ascertain changes in upper airway mechanics, a pressure-flow loop was plotted for every breath in 20 breaths of the control period and 20 breaths each at R₂₀. All breaths were averaged, and composite pressure-flow loops were plotted for the control and R₂₀ periods for each subject. To generate a composite pressure-flow plot breaths with different duration, pressure and flow were sampled at equally distributed points in inspiration and expiration in each breath. Ru at a fixed flow (0.2 l/s) was computed from each loop as a numeric representation of the slope of the linear part of the pressure-flow loop. Pressure-flow loops were also utilized to determine the presence of IFL in each subject by using a flow loop of each breath. A 3-min segment of control was used to determine the presence of IFL on a breath-by-breath basis. Flow limitation was defined by the inspiratory flow reaching a plateau at a maximal level (Vmax) despite a ≥1-cmH₂O decrease in the supraglottic (downstream) pressure (5). Flow limitation was determined as a dichotomous variable. The development of IFL indicates dissociation between the driving downstream pressure and flow. Accordingly, the effect of repetitive hypoxia on the severity of IFL was determined by comparing the proportion of breaths with flow limitation and by comparing Vmax between the control and the recovery period in subjects with IFL. A change in Vmax can be used as a surrogate for changing collapsibility.
**EMG**dia. The raw EMG signal was amplified, filtered with a band pass filter of 100–10,000 Hz (model 7-D polygraph, Grass), and full wave rectified. ECG artifacts were “blanked” with an ECG blander (model SB-1, CWE). The processed signal was integrated with a moving-time averager with a time constant of 100 ms (model MA-821 RES, CWE). Phasic EMG activity was determined from the peak integrated activity of the moving time average and expressed in arbitrary units (au).

**Statistical analysis.** A commercially available computer statistical package was used to analyze the data (Sigma Stat 2.0, SPSS). $V_{\dot{I}}$ (as percentage of control) at 20 min of recovery ($V_{\dot{I}} R_{20}$) was chosen as the dependent variable because it represents the presence or absence of LTF. The level of significance was set at $P < 0.05$. Paired t-test was used to compare values of variables between control and $R_{20}$.

**RESULTS**

Figure 1 is a representative polygraph record showing ventilation and upper airway mechanics during control conditions (A), hypoxia (B), and at $R_{20}$ (C). Hypoxia resulted in increased flow and a reduction of the magnitude of negative supraglottic pressure; this effect persisted at $R_{20}$. A representative pressure-flow loop during control and posthypoxic recovery ($R_{20}$) is shown in Fig. 2. Note the change in slope and the amelioration of the inspiratory flow limitation. The x-axis shows $P_{sg}$ (in cmH$_2$O), and the y-axis shows flow (in l/s).

Data are reported only from subjects with stable sleep or only minimal fragmentation. During the hypoxic trials, arousal and wakefulness occurred for $2.7 \pm 2.6$ min (out of 30 min), and no periods of wakefulness were noted during the recovery period. Hypoxia resulted in increased $V_{t}$ from $0.42 \pm 0.13$ to $0.49 \pm 0.09$ liter (117% of control; $P < 0.05$) and $V_{t}/T_{I}$ from $0.26 \pm 0.09$ to $0.32 \pm 0.06$ l/s (123% of control; $P < 0.05$). However, inspiratory muscle activity did not increase because $EMG_{dia}$ was $16.1 \pm 6.9$ au during control and $15.3 \pm 4.9$ au during recovery (95% of control; $P > 0.05$). Similarly, the after effects of repetitive hypoxia on timing parameters were not remarkable, because there was no significant change in $T_{I}$, $T_{E}$, or $T_{I}/T_{T}$ (Table 1).

The ventilatory changes during the recovery period occurred in association with decreased $R_{ua}$ from $10.7 \pm 7.5$ to $8.2 \pm 4.4$ cmH$_2$O·l$^{-1}$·s$^{-1}$ (77% of control; $P < 0.05$). Similarly, $R_{ua}$ at $V_{max}$ decreased from $16.2 \pm 12.0$ to $12.3 \pm 7.9$ cmH$_2$O·l$^{-1}$·s$^{-1}$ (90% of control; $P = 0.07$). When analysis was repeated after removal of
one subject who demonstrated increased Rua at $V_{\text{max}}$, a statistically significant decrease was noted from $16.5 \pm 12.6$ to $11.8 \pm 8.2$ cmH$_2$O·l$^{-1}$·s (81% of control; $P = 0.02$).

Seven subjects showed flow limitation during the control period (89 ± 18% of the control breaths). The proportion of breaths with IFL did not change in the recovery period (71 ± 42% of R$_{20}$ breaths; $P > 0.05$); IFL was eliminated only in one subject. The remaining four subjects had no breaths that met the operational definition of IFL during the control or recovery periods. The proportion of breaths with IFL for the whole group was $57 \pm 47$ and $48 \pm 46$% during control and R$_{20}$, respectively ($P > 0.05$). Similarly, there was no change in $V_{\text{max}}$ for breaths with IFL between control ($0.34 \pm 0.03$ l/s) and R$_{20}$ ($0.36 \pm 0.03$ l/s) ($P > 0.05$).

The findings of the sham study differed from the repetitive hypoxia study (Fig. 4). $V_{\text{i}}$ and $V_{\text{T}}$ during the recovery period were 94 and 100% of control, respectively ($P > 0.05$). Similarly, there was no significant change in Rua 102% of control ($P > 0.05$) or the proportion of breaths with flow limitation (61 ± 41% during control and 62 ± 41% at R$_{20}$; $P > 0.05$). However, prolongation of $T_e$ occurred ($1.9 \pm 0.3$ s during the control period vs. $2.1 \pm 0.3$ s at R$_{20}$; $P < 0.05$). Therefore, respiratory frequency decreased ($17.4 \pm 1.7$ breaths/min during control vs. 16.21 ± 0.1 breaths/min at R$_{20}$; $P < 0.05$; Table 1).

**DISCUSSION**

We showed reduced Rua and increased $V_{\text{i}}$ in the recovery period after repetitive hypoxic exposure, confirming the development of LTF by repetitive hypoxia in sleeping humans.

**Effects of LTF on Upper Airway Mechanics**

We showed that repetitive hypoxia results in decreased Rua indicative of upper airway dilatation. One possible explanation for decreased Rua is passive dilatation secondary to increased thoracic inspiratory activity (32). Given that our data do not show increased diaphragmatic activity, passive upper airway dilatation requires LTF of the intercostal muscles with ensuing increased $V_{\text{T}}$ and increased caudal traction. This is consistent with data showing that intercostal muscles are more likely to demonstrate LTF after repetitive hypoxia than the diaphragm in cats (12). Accordingly, decreased Rua would be due to increase $V_{\text{T}}$.

Decreased Rua can also be explained by active upper airway dilatation as a result of LTF of ventilatory motor output to upper airway dilators (7, 8, 26). There is evidence in the literature that repetitive hypoxia elicits LTF of ventilatory motor output to upper airway dilators. Mateika and Fregosi (18) showed that repetitive hypoxia in vagotomized cats is followed by in-

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**Table 1. Ventilation and timing during control and Posthypoxic recovery**

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>R$_{20}$</th>
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<tr>
<td>Repetitive hypoxia (n = 11)</td>
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<tr>
<td>$T_i$, s</td>
<td>1.6 ± 0.24</td>
<td>1.6 ± 0.24</td>
</tr>
<tr>
<td>$T_e$, s</td>
<td>1.9 ± 0.47</td>
<td>2.1 ± 0.41</td>
</tr>
<tr>
<td>$T_i/T_e$</td>
<td>0.46 ± 0.06</td>
<td>0.43 ± 0.05</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>17.2 ± 2.7</td>
<td>16.8 ± 2.5</td>
</tr>
<tr>
<td>$V_{\text{T}}$, l</td>
<td>0.42 ± 0.13</td>
<td>0.49 ± 0.99$*$</td>
</tr>
<tr>
<td>$V_{\text{T}}/T_i$, l/s</td>
<td>0.26 ± 0.09</td>
<td>0.32 ± 0.06$*$</td>
</tr>
<tr>
<td>$V_{\text{i}}$, l/min</td>
<td>7.1 ± 1.8</td>
<td>8.3 ± 1.8$*$</td>
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<tr>
<td>Sham study (n = 9)</td>
<td></td>
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<tr>
<td>$T_i$, s</td>
<td>1.62 ± 0.15</td>
<td>1.66 ± 0.11</td>
</tr>
<tr>
<td>$T_e$, s</td>
<td>1.9 ± 0.29</td>
<td>2.1 ± 0.27$*$</td>
</tr>
<tr>
<td>$T_i/T_e$</td>
<td>0.47 ± 0.05</td>
<td>0.45 ± 0.05</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>17.4 ± 1.7</td>
<td>16.1 ± 1.1$*$</td>
</tr>
<tr>
<td>$V_{\text{T}}$, l</td>
<td>0.51 ± 0.06</td>
<td>0.51 ± 0.03</td>
</tr>
<tr>
<td>$V_{\text{T}}/T_i$, l/s</td>
<td>0.31 ± 0.03</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td>$V_{\text{i}}$, l/min</td>
<td>8.7 ± 0.7</td>
<td>8.2 ± 0.09</td>
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</table>

Values are means ± SE; n, no. of subjects. R$_{20}$, 20th min after last hypoxic exposure; $V_{\text{i}}$, inspired minute ventilation; $V_{\text{T}}$, tidal volume; f, breathing frequency; $T_i$, inspiratory time; $V_{\text{T}}/T_i$, mean inspiratory flow. $*$P < 0.05.
creased activity of the genioglossus and the alae nasae but not the diaphragm (18). Similarly, we showed that repetitive hypoxia in snorers results in amelioration of IFL for 40–60 min after termination of hypoxic exposure during NREM sleep (2). Accordingly, increased VT during the recovery period would be due to decreased Rua or “unloading” of the upper airway (14, 28). Previous studies showed that unloading of the upper airway in healthy individuals who snore, with the use of nasal continuous positive airway pressure (14) or He-O2 mixture during NREM sleep (28), results in reduced total pulmonary resistance and increased VT and Vi. This interpretation is also consistent with our previous finding (2) that ventilatory LTF manifests mostly in subjects with snoring and flow limitation. In summary, LTF of either intercostal muscles or upper airway dilators can explain decreased Rua; we cannot distinguish between these two possibilities on the basis of our findings.

The present study corroborates our previous work demonstrating LTF after episodic hypoxia in sleeping humans (2). There are, nevertheless, two differences that should be mentioned. 1) We found that decreased Rua was associated with ventilatory LTF for the whole group. In contrast, our previous study showed ventilatory LTF only in subjects with IFL. One likely explanation is that the majority of the subjects in the present study were snorers and had evidence of IFL during euepnic breathing. 2) We noted that flow limitation persisted during the recovery period despite decreased Rua and increased Vi. This disproves our previous suggestion (2), based on the flow profile only, that LTF is associated with amelioration of flow limitation and demonstrates dissociation between resistance and collapsibility (see below).

We were intrigued by the observation that decreased Rua was not associated with increased V\textsubscript{max}. The discrepancy between the two indexes of upper airway mechanics suggests dissociation between changes in caliber and changes in compliance. Several studies have demonstrated similar dissociation under similar experimental paradigms. First, Rowley et al. (24, 25) showed, in a feline preparation, that V\textsubscript{max} is increased during hypercapnia secondary to reduced critical closing pressure (Pcrit) despite increased Rua. Second, there is evidence that stimulation of pharyngeal dilators enlarges the lumen of the upper airway (26), whereas evidence that upper airway dilators “stiffen” the upper airway is still lacking. Third, our laboratory previously showed a similar dissociation during induced hypopcapnia in individuals who snore (4, 5); reduced ventilatory motor output resulted in decreased V\textsubscript{max} without change in Rua. Finally, Aboubakr et al. (1) studied obstructive sleep apnea patients during sleep using a repetitive hypoxia protocol similar to the present study. The upper airway was stabilized with nasal continuous positive airway pressure at a pressure level preventing apnea and hypopnea while allowing IFL. Repetitive hypoxia was followed by decreased Rua, indicative of upper airway-dilating muscle recruitment. However, no change in V\textsubscript{max} was noted.

The aforementioned studies demonstrate that resistance and collapsibility may be altered independently. Although the mechanism of the dissociation between Rua and V\textsubscript{max} cannot be ascertained from our data, we interpret our finding as further support of the notion that repetitive hypoxia elicits LTF of the pharyngeal dilators and not pump muscles. Thus stimulation of upper airway dilators may decrease Rua without necessarily increasing V\textsubscript{max} or collapsibility. We emphasize that our interpretation is speculative in the absence of direct measurement of pharyngeal collapsibility and upper airway-dilating muscle activity.

Limitations of Methods

Several limitations have to be considered for proper interpretation of our data. First, changes in sleep state might have caused a misinterpretation of the data. However, we analyzed data only when the sleep was in stable stage 2 or greater, with no evidence of changes in sleep state by Rechtschaffen and Kales criteria (23) or by transient arousals (29). The induction of hypoxia caused only a transient minimal change in the sleep state in 8 of 11 subjects, which lasted for <3 min of wakefulness for the whole duration of hypoxia. A subject who did not maintain sleep at stage 2 or deeper for the majority of the 140-min study was excluded from the study. The data reported here were from periods where there was no difference in sleep state.

Second, we measured Rua as an index of upper airway caliber and V\textsubscript{max} as a surrogate for Perit and hence pharyngeal collapsibility. According to the principles of flow in collapsible tubes, V\textsubscript{max} is a function of upstream pressure, upstream resistance, and Pcrit of the collapsible segment. Although Pcrit is not the sole determinant of V\textsubscript{max}, there is an inverse correlation between V\textsubscript{max} and Pcrit (higher V\textsubscript{max} = lower Pcrit = less collapsible upper airway) under most conditions. Therefore, we believe that reasonable inferences regarding upper airway collapsibility can be made from V\textsubscript{max}. This conclusion needs to be confirmed in the future by direct measurements of Pcrit under similar experimental conditions.

We measured surface EMG\textsubscript{dia} as a marker of EMG\textsubscript{dia} activity. However, the surface location of the electrodes precludes precise determination of the inspiratory muscle. Thus we presume, but cannot be certain, that we measured EMG\textsubscript{dia} signals. Conversely, we did not measure pharyngeal muscle activity; instead, we used Rua to ascertain the net effect of muscle recruitment on upper airway caliber. We believe that this approach provides a better assessment of the mechanical function of all upper airway muscles rather than the readily accessible dilators. However, measurement of specific upper airway dilators is needed to confirm the effect of episodic hypoxia on upper airway neural control and dilation.

We noted that Vi during the control period differed between the sham study and the repetitive hypoxia study. This variability was not due to differences in euepnic breathing because the proportion of breaths with IFL was similar between the sham study and the
repetitive hypoxia study. The main difference was a smaller number of subjects in the sham study. We interpret the difference in eupneic control as a manifestation of night-to-night variability. However, it had no impact on the recovery period given the marked difference between the repetitive hypoxia and the sham study. Therefore, we believe that the difference in response between the repetitive hypoxia nights and the sham nights represented a true physiological response to repetitive hypoxia per se and was not due to selection bias or variability in control respiration.

Finally, we noted increased Tc and reduced frequency during the sham study. This change seems to be a time-dependent phenomenon. Interestingly, this effect was less apparent (and not statistically significant) during repetitive hypoxia night. It is tempting to speculate that the preservation of respiratory frequency is another manifestation of LTF. However, this speculation requires experimental proof.

In summary, we have shown that episodic hypoxia during sleep in normal subjects elicits LTF of ventilatory motor output manifested by decreased Rua and increased Vt without increased EMGdia, suggesting that the thoracic pump does not demonstrate LTF.

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