Dynamic modulation of upper airway function during sleep: a novel single-breath method

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Dynamic modulation of upper airway function during sleep; a novel single-breath method. J Appl Physiol 101: 1489–1494, 2006. First published July 6, 2006; doi:10.1152/japplphysiol.00173.2006.—To examine the dynamic modulation of upper airway (UA) function during sleep, we devised a novel approach to measuring the critical pressure (Pcrit) within a single breath in tracheostomized sleep apnea patients. We hypothesized that the UA continuously modulates airflow dynamics during transtracheal insufflation. In this study, we examine tidal pressure-flow relationships throughout the respiratory cycle to compare phasic differences in UA collapsibility between closure and reopening. Five apneic subjects (with tracheostomy) were recruited (2 men, 3 women; 18–50 yr; 20–35 kg/m2; aapnea-hypopnea index >20) for this polysomnographic study. Outgoing airflow through the UA (face mask pneumotachograph) and tracheal pressure were recorded during brief transtracheal administration of insufflated airflow via a catheter. Pressure-flow relationships were generated from deflation (approaching Pcrit) and inflation (after Pcrit) of the UA during non-rapid eye movement sleep. During each breath, UA function was described by a pressure-flow relationship that defined the collapsibility (Pcrit) and upstream resistance (Rus). UA characteristics were examined in the presence and absence of complete UA occlusion. We demonstrated that Pcrit and Rus changed dynamically throughout the respiratory cycle. The UA closing pressure (4.4 ± 2.0 cmH2O) was significantly lower than the opening pressure (10.8 ± 2.4 cmH2O). Rus was higher for deflation (18.1 ± 2.4 cmH2O·L−1·s−1) than during inflation (7.5 ± 1.9 cmH2O·L−1·s−1) of the UA. Preventing occlusion decreases UA pressure-flow loop hysteresis by ∼4 cmH2O. These findings indicate that UA collapsibility varies dynamically throughout the respiratory cycle and that both local mechanical and neuromuscular factors may be responsible for this dynamic modulation of UA function during sleep.

sleep apnea; critical pressure; upper airway occlusion; pathophysiology

OBSURCTIVE SLEEP APNEA (OSA) is a common disorder associated with upper airway obstruction during sleep, leading to recurrent arousals and oxyhemoglobin desaturations. In previous studies, our laboratory has demonstrated that upper airway obstruction is related to increases in pharyngeal collapsibility during sleep, as determined by measurements of upper airway critical pressures (Pcrit) during sleep (6, 7, 19–22, 26). The Pcrit is established empirically by varying the upstream nasal pressure and by determining the pressure at which the upper airway occludes. Several protocols for determining Pcrit during inspiration have been utilized in spontaneously breathing sleeping (2), in anesthetized subjects (5, 11, 12), and in paralyzed subjects (9). These protocols, however, require monitoring pressure-flow relationships over multiple nasal pressure levels for an extended period of time to determine Pcrit.

In previous studies, investigators have evidence that Pcrit is not a static measure of upper airway function but rather that it can vary dynamically over the respiratory cycle. Employing an isolated upper airway preparation in animal, investigators have demonstrated marked increases in upper airway collapsibility during expiration compared with inspiration (4, 15, 16, 23–25, 28). In humans, a similar approach for assessing upper airway properties over multiple breaths and pressure (17) has demonstrated increases in upper airway collapsibility during expiration compared with inspiration. Nevertheless, appropriate methods for assessing the dynamic changes in upper airway function within a single respiratory cycle have not yet been developed for humans.

To examine the dynamic modulation of upper airway function during sleep, we devised a novel approach for measuring the Pcrit within a single breath in tracheostomized sleep apnea patients. Our approach was based on recent methods administering air directly into the trachea, which abolished OSA (18). During TTI, we found that the upper airway regulated the release of insufflated airflow from the trachea because airflow varied throughout the respiratory cycle. This finding led us to hypothesize that monitoring tidal pressure-flow relationships during TTI would provide a dynamic assessment of changes in upper airway function throughout the respiratory cycle. We further examined whether the development of pharyngeal occlusion within a breath influenced the dynamic modulation of upper airway flow during TTI in sleeping apneic patients.

METHODS

Subjects

Five tracheostomized patients with concomitant OSA referred to the Johns Hopkins Sleep Disorders Center were also recruited for this study if they had non-rapid eye movement (NREM) apnea-hypopnea index >20 episodes/h (with a capped tracheostomy) and were free of cardiorespiratory insufficiency (daytime hypercapnia or hypoxemia and evidence of right or left heart failure) and significant pulmonary disease. In these subjects, tracheostomy had been performed either because patients could not use nasal continuous positive airway pressure (CPAP; n = 4) or were refractory to treatment with nasal CPAP (n = 1). The demographic and anthropometric description of these subjects have been described previously (18). The protocol was

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approved by the Johns Hopkins Institutional Review Board, and
informed consent was obtained from each patient.

Conceptual Approach

In the present study, we employed a novel method to determine the inspiratory and expiratory upper airway properties in sleep apnea patients (with tracheostomy) within a single breath. Our approach was based on our previous findings that the upper airway remained in a flow-limited condition during TTI administration (18). Flow limitation was defined by the relationship between Pcrit and downstream pressure, such that the downstream pressure remained less than Pcrit. The sleep apnea patients in the present study also demonstrated a similar pressure regimen with the downstream nasal pressure (atmospheric) being less than the Pcrit (which was positive) throughout the respiratory cycle (18). Under these circumstances, the rate of flow leaking out the upper airway was not influenced by changes in the downstream (nasal) pressure, and it remained unchanged when subatmospheric nasal pressure was applied (18). Thus the upper airway remained in a flow-limited condition in these apneic patients throughout the respiratory cycle.

Under flow-limited conditions, airflow should be linearly related to the gradient between the upstream [tracheal pressure (Ptrach)] and Pcrit (6, 7, 20, 22, 26). In patients with sleep apnea, our laboratory has previously demonstrated that the upper airway can occlude when tracheal pressure is lower than Pcrit (18). During occlusion, tracheal insufflation will lead to a rise in tracheal pressure (see pressure-flow relationship; Fig. 1, segment A) and flow will not discharge out the upper airway until Pcrit exceeds a Pcrit (Fig. 1). Thereafter, airflow will increase linearly with the rise in Pcrit (Fig. 1, segment B) until the level of flow discharging out the upper airway (Vua) equals the insufflation flow rate (Vin). This point (Fig. 1, point E) represents the steady-state or equilibrium position for the respiratory system during tracheal insufflation. During tidal breathing, Pcrit will rise and fall above and below this equilibrium position. Because Pcrit varies throughout the respiratory cycle, Vua will also vary, as described by the pressure-flow relationship (Fig. 1, see inspiration and expiration, segments A, B, and C). This curve can be used to describe upper airway function in terms of its collapsibility (Pcrit) and upstream resistance (Rus), as previously described (26). Our major goal was to describe the dynamic modulation of upper airway function as the upper airway inflates and deflates throughout the respiratory cycle.

Experimental Apparatus

Polysomnography. Standard polysomnographic monitoring was performed during all study protocols, and it included monitoring of electroencephalograms (C3-A2, C3-O1), left and right electrooculograms, submental electromyogram (EMG), and electrocardiogram (modified V3 lead). Arterial oxygen saturation was also monitored (Biox 3700, Ohmeda, Boulder, CO). Body position was monitored visually with infrared video cameras so that patients could be maintained supine throughout the protocol.

Pressure upstream of collapse (Ptrach). In the tracheostomized sleep apnea patients, Pcrit was measured in the trachea via Shiley tracheostomy tube (Mallinckrodt, St. Louis, MO) inserted before the experimental protocol. An external cap was affixed to the tracheostomy tube, and sealed ports were made in the cap for inserting an insufflation cannula and a Luer stub adapter connected to a pressure transducer (Gould-Statham, Oxnard, CA).

Vua and nasal pressure. Nasal pressure was measured at an outlet of the tight-fitting face mask and monitored with pressure transducers. Nasal pressure was adjusted with a modified CPAP device (CPAP, Medizin fuer Arzt und Patient, Martiris-reid, Germany) that could be used to switch pressures from one level to the other over a range from 5 to 15 cmH2O, as previously described (20). Vua was monitored with a pneumotachometer (model 300A, Hans Rudolph, Kansas City, MO) affixed to a tight-fitting face mask (Respironics, Murryville, PA). The pneumotachometer was connected to a 2-cmH2O differential pressure transducer (model DP45–28, Validyne Engineering, Northridge, CA).

TTI. The apparatus employed for delivering TTI was previously described (18). In brief, an air compressor and flow regulator were used to insufflate air through an ~3-m length of oxygen extension tubing (Baxter, Valenica, CA) and a transtracheal catheter (SCOOP catheter, Transtracheal Systems, Denver, CO). A mass flowmeter (Matheson, Secaucus, NJ) and a solenoid were connected in series to monitor the level of Vin and to direct flow to the patient or atmosphere, respectively. Pcrit was continuously monitored, and the signal was digitized by a microcomputer. The computer controlled the direction of flow (Labview, National Instruments, Austin, TX) through the solenoid based on the Pcrit level. When this pressure remained below a threshold (<20 cmH2O), airflow was applied to the patient. When Pcrit exceeded this limit, the TTI flow was diverted by the solenoid to atmosphere.

Data acquisition. All physiological signals were amplified and recorded continuously on a polygraph recorder (Grass recorder, Astromed, Warwick, RI). Signals from the analog amplifiers were also digitized at 100 Hz and stored on optical disk for offline analysis (DI-200 A/D board and Windaq/200 software, Dataq Instruments, Akron, OH).

Experimental Protocols

Assessment of tidal pressure-flow loops. Sleep was initiated while nasal pressure was kept at atmospheric pressure. During periodic obstructive apneas, we administered TTI at flow rates between 9 and 16 l/min through a cuffed tracheostomy, as previously described (18). At this flow rate, a stable breathing pattern during stable stage 2 NREM sleep was obtained that was characterized by upper airway closure and reopening in each breath as previously demonstrated (18) and illustrated in Fig. 2. During this stable breathing pattern, five representative breaths were taken to determine upper airway properties.

Effect of upper airway occlusion on upper airway collapsibility. To assess whether differences in closing and opening were due to upper airway hysteresis, we increased the TTI flow rate by 0.5–5 l/min during tidal breathing. Vua rises and falls along the pressure-flow relationship throughout inspiration (B) and expiration (C).

Fig. 1. Schematic of the relationship between tracheal pressure (Ptrach) and upper airway flow (Vua). The upper airway is occluded (A) when Pcrit is lower than the critical closing pressure (Pcrit). When transtracheal insufflation (TTI) is applied at a constant flow rate (Vin), Pcrit reaches and equilibrium point (E) in the absence of respiration. As Pcrit changes during tidal breathing, Vua rises and falls along the pressure-flow relationship throughout inspiration (B) and expiration (C).
NREM sleep in all experimental conditions. Vin was utilized as a reference level for each individual. Upper airway function was characterized for each respiratory cycle by analyzing the relationship between Vua and Ptrach. Linear segments of the pressure-flow relationship were identified for the deflation and inflation segments of the pressure-flow loops. Least squares linear regression (Excel, Microsoft, Redmond, WA) was performed on pressure-flow data obtained from both the deflation and inflation segments (correlation coefficients ranged from 0.75 to 0.99 for inflation and deflation limbs). Regression equations were then used to derive Pclose, Popen, and Rus for the deflation and inflation segments (14), as previously described (22). Upper airway hysteresis was calculated as the difference between the mean end-expiratory and end-inspiratory pressures at the level of the insufflated flow. ANOVA (generalized linear model) with Tukey’s post hoc comparisons were utilized to test differences between Pclose, Popen, and Rus between the occluded upper airway and the unoccluded upper airway condition. A value of $P < 0.05$ was considered significant.

RESULTS

Effect of TTI on Breathing Pattern in OSA

In Fig. 2, the effects of TTI on breathing patterns are illustrated in a patient with OSA during NREM sleep. Baseline breathing patterns off TTI (Fig. 2, middle) during spontaneous breathing were characterized by periodic obstructive apneas (Fig. 2, Vua) with augmenting Ptrach swings, oxyhemoglobin desaturations, and arousals from sleep (not shown). In contrast, TTI at ~15 l/min (Fig. 2, right and left) stabilized the breathing pattern, diminished Ptrach pressure swings, and abolished oxyhemoglobin desaturations and arousals. In each subject, TTI was able to abolish periodic apneas and stabilize breathing patterns, as previously reported (18). During TTI, airflow discharged out the upper airway, and it fluctuated around the equilibrium TTI flow rate during tidal breathing. As Ptrach fluctuated during tidal breathing, Vua increased as Ptrach rose during expiration, and decreased as Ptrach fell during inspiration, consistent with the conceptual pressure-flow relationship shown in Fig. 1. Of note, while Vua fell to zero, it never became negative, despite further decreases in Ptrach during midinspiration, suggesting an occluded upper airway at this point in the respiratory cycle.

Upper Airway Pressure-Flow Relationships During TTI

Tidal fluctuations in Ptrach and Vua are further illustrated in an expanded recording from a single patient during TTI administration in Fig. 3. As Ptrach fell and approached atmospheric pressure during inspiration, the level of Vua discharging out the upper airway also fell. In fact, with further decreases in Ptrach during inspiration, upper airway flow ceased, indicating that the upper airway had closed (Pclose; Fig. 3) during this portion of the respiratory cycle. As Pclose began to rise again, airflow resumed out the upper airway (Popen; Fig. 3). As Ptrach varied throughout the respiratory cycle, exhaled airflow contributed to a rise in Vua above the TTI level during expiration, whereas inhalation from the TTI source accounted for a fall in Vua below the TTI level during inspiration.

In Fig. 4A, Ptrach vs. Vua loops are generated for the five-breath recording example in Fig. 3. Each breath in the
V˙ua-Ptrach relationship inscribed practically superimposable counterclockwise loops. During inspiration, V˙ua decreased linearly with the decline in Ptrach (see segment B), and it ultimately ceased despite further decreases in Ptrach below Pcrit (see segment A). As Ptrach rose in late inspiration, V˙ua remained zero (V˙ua = 0), indicating the upper airway remains closed for this portion of the respiratory cycle (see segment X) until V˙ua was reestablished as Ptrach exceeded Popen (Fig. 4A). The sloped portions of the V˙ua-Ptrach loops are represented by linear regression lines constructed from the V˙ua-Ptrach segments obtained for each breath. These regression lines were used to calculate Perit during phase 1 (Pclose) and phase 2 (Popen) of the V˙ua-Ptrach loops, as illustrated in Fig. 4B.

Upper Airway Tidal Pressure-Flow Loops

The data obtained from tidal pressure-flow loops are illustrated in Fig. 5 and summarized in Table 1 for TTI flow rates associated with the presence and absence of upper airway occlusion. Loops were analyzed from steady-state periods of breathing at a TTI flow rate of 11.9 ± 1.2 l/min for the occluded upper airway condition and at a TTI flow rate of 14.0 ± 1.2 l/min (P > 0.07) for the unoccluded upper airway condition. In the occluded upper airway condition, the range of V˙ua for the linear portions of the pressure-flow loops used was 2.4 ± 0.8 to 17.9 ± 3.8 l/min for the closing limb and 2.5 ± 0.8 to 17.3 ± 4.0 l/min for the opening limb. In the unoccluded upper airway condition, the V˙ua range was comparable to the occluded upper airway condition for the deflation segment (4.0 ± 2.1 to 18.3 ± 2.2 l/min; both P > 0.3 compared with the occluded upper airway conditions) and for the inflation segment (5.8 ± 3.1 to 18.3 ± 2.1 l/min; both P > 0.4 compared with the occluded upper airway conditions). Of note, in both the occluded and unoccluded conditions, Popen and Pclose the upper airway occurred at positive pressures in each subject (Fig. 5, conditions 1 and 2). These findings confirmed that the upper airway remained flow limited during TTI administration.

Table 1. Group mean data for TTI flow rates and breathing mechanics during occluded upper airway (condition 1) and unoccluded upper airway (condition 2) states

<table>
<thead>
<tr>
<th></th>
<th>Condition 1</th>
<th>Condition 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTI, l/min</td>
<td>11.9±1.2</td>
<td>14.0±1.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Closing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perit, cmH2O</td>
<td>4.4±2.0</td>
<td>4.6±2.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Rus, cmH2O·l⁻¹·s⁻¹</td>
<td>18.1±2.4</td>
<td>19.2±3.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Opening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perit, cmH2O</td>
<td>10.8±2.4*</td>
<td>7.1±2.6*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rus, cmH2O·l⁻¹·s⁻¹</td>
<td>7.5±1.9*</td>
<td>22.0±5.7*</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Hysteresis, cmH2O</td>
<td>4.3±0.6</td>
<td>3.0±0.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE. TTI, transtracheal insufflation; Perit, critical pressure; Rus, upstream resistance. *P < 0.05, upper airway opening vs. closing.
because the downstream pressure at the nose remained less than Pcrit throughout the respiratory cycle (see Conceptual Approach).

**Within-breath modulation of upper airway properties.** For both the occluded upper airway and unoccluded upper airway conditions, PClose was significantly lower than Popen (Table 1 and Fig. 6A). Similarly, there was a decrease in Rus from the deflation limb to the inflation limb of the upper airway pressure-flow relationship (Table 1, Fig. 6B).

**Effects of occlusion on upper airway pressure-flow hysteresis.** PClose did not differ between the occluded airway and unoccluded airway conditions (Fig. 6A). In contrast, Popen decreased by 3.7 ± 0.9 cmH2O from the occluded upper airway to the unoccluded upper airway condition (Fig. 6A). There was no difference in Rus for the deflation limb of the pressure-flow curve between the occluded upper airway and unoccluded upper airway conditions, whereas Rus for the inflation limb increased significantly by 14.5 ± 4.6 cm H2O·L·s⁻¹·cm⁻¹ in the unoccluded upper airway compared with the occluded upper airway condition (Table 1). At the TTI level, the inflation segment of pressure-flow loop was displaced further to the right in the occluded upper airway compared with the unoccluded upper airway condition (4.3 ± 0.6 vs. 3.0 ± 0.4 cmH2O in the occluded upper airway vs. the unoccluded upper airway condition; P < 0.05; Table 1).

**DISCUSSION**

This paper describes a novel method for assessing the physiological properties of the upper airway continuously on a breath-by-breath basis during tracheal insufflation. We found that the collapsibility was reduced and the Rus increased during upper airway deflation compared with inflation of tidal pressure-flow loops. Moreover, preventing upper airway occlusion did not alter the critical closing (upper airway deflation) properties. Rather, it led to a decrease in Popen and an increase in the Rus during reopening (upper airway inflation). Our findings indicate that upper airway properties change dynamically within a breath in sleeping apneic individuals as a function of the respiratory phase and the state of airway patency. These data suggest that the upper airway is more stable in the early compared with late phase of inspiration and that, once the upper airway has occluded during sleep, it is much harder to reopen.

**Mechanism for Within-Breath Changes in Upper Airway Properties**

Dynamic changes in upper airway function may be related to the mechanical changes in tracheal traction, lung inflation, and/or surface tension throughout the respiratory cycle. Reciprocal changes in Pcrit and Rus have previously been observed in the isolated feline upper airway with caudal traction on the trachea (15, 25, 28). Increases in inspiratory effort produce caudal traction on the trachea (29), which decreases Pcrit and increases Rus (15, 28). Consistent with animal studies, we found increasing effort (decreasing Pcrit) led to a decrease in Pcrit and increase in Rus, whereas decreasing effort lead to a increase in Pcrit and decrease in Rus. Mechanical effects of caudal tracheal traction can account for decreased Pcrit and increased Rus as effort increases in the early compared with the latter part of inspiration. The stabilizing effect of caudal tracheal traction is likely offset by lower lung volumes in early inspiration than late inspiration, which would increase therapeutic CPAP requirements (8). Thus dynamic changes in upper airway function within a single breath can be best attributed to alterations in tracheal traction rather than lung volume, and the effects of tracheal traction on upper airway collapsibility may be underestimated with this current method.

In addition to the stabilizing effect of tracheal traction during early inspiration, surface tension can account for hysteresis in opening and closing Pcrit within a breath. The development of upper airway occlusion within a breath was associated with substantial increase in Pcrit hysteresis (~4 cmH2O). This finding is best explained by surface forces that develop when mucosal surfaces are opposed and adhere to one another (10–12). In previous studies, our laboratory has shown that a 30% change in the surface tension of the liquid lining the upper airway decreases the difference between Popen and PClose by 2 cmH2O (11), consistent with observed differences between Popen and PClose pressures during sleep (1).Our present findings confirm that surface forces contribute an ~2-cmH2O increase in the Popen compared with PClose. Our within-breath method for determining Popen and PClose allows us to conclude that surface forces account for approximately one-half of the hysteresis between Popen and PClose.

In addition to mechanical effects, it is also possible that phasic neuromuscular activity may account for residual differences between Popen and PClose. Phasic EMG generally peaks in early inspiration (27, 30), has been associated with decreased upper airway collapsibility in animals and humans (23, 24). Although we do not assess upper airway EMG activity, current evidence suggests that phasic neuromuscular activity may account for the remaining decrease in the early inspiratory (closing) compared with late inspiratory (opening) Pcrit.

**Limitations**

There are three main limitations of our present study. First, our study lacked EMG monitoring of upper airway muscles; therefore, we did not examine the relationship between Pcrit and neuromuscular activity. Nevertheless, the phasic modulation of upper airway dilator activity is well documented, as is the relationship between early inspiratory activation and reductions in upper airway collapsibility. Of note, when tidal pressure-flow loops were generated during TTI administration in deeply anesthetized subjects, no significant hysteresis was observed (13),
which may have been due to the suppression of phasic upper airway neuromuscular activity (5). Second, our sample size is limited to a small number of sleep apnea subjects, making it difficult to extrapolate our findings to normal individuals who may also exhibit phasic modulation of upper airway properties. We acknowledge that to extend our approach to the study of normal subjects during sleep, air must be insufflated below a site of upper airway obstruction and subatmospheric pressure must be applied to the airway opening, such that the airway remains flow limited (i.e., nasal pressure remains below a negative Pcrit). Third, our findings indicate that mechanical and neuromuscular effects provide for a marked decrease in Pcrit in early inspiration, which stabilizes upper airway patency during this portion of the respiratory cycle.

Implications

The present findings have important physiological implications for investigating the control of upper airway function during sleep. Our method provides an approach for examining the acute modulation of upper airway flow dynamics within and between single breaths. Within-breath changes in upper airway properties can provide a dynamic assessment of the mechanical (late inspiratory) and neuromuscular (early inspiratory) components of upper airway collapsibility. Utilizing this approach, investigators can now partition the effects of these factors. In addition, our technique provides greater flexibility in assessing the acute effects of interventions on the dynamic modulation of upper airway function. Extending this method to nontracheostomized subjects would allow investigators to delineate effects of acute interventions such as surfactant instillation, changes in lung volume or mandibular position, and electrical or pharmacological stimulation of upper airway neuromuscular activity. Moreover, this approach can be adapted for studies of upper airway function in healthy apneic and nonapneic subjects.

GRANTS

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