Effects of topical anesthesia on upper airway resistance during wake-sleep transitions

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Doherty, Liam S., Philip Nolan, and Walter T. McNicholas. Effects of topical anesthesia on upper airway resistance during wake-sleep transitions. J Appl Physiol 99: 549–555, 2005. First published March 24, 2005; doi:10.1152/japplphysiol.01221.2004.—Deformation of the upper airway (UA) by negative transmural pressure alters the activity of UA mechanoreceptors, causing a reflex increase in UA muscle activity. Topical anesthesia of the UA mucosa, which greatly reduces this reflex response, causes an increase in UA resistance during stage 2 sleep. We hypothesized that topical anesthesia of the UA mucosa would predispose to UA instability at sleep onset and, therefore, examined the effect of UA anesthesia on pharyngeal resistance (Rph) in stage 1 sleep. Eleven normal, healthy volunteers were instrumented to record standard polysomnographic variables, respiratory airflow, and UA pressure at the nasal choanae and the epiglottis. Subjects were permitted to sleep until stable stage 2 sleep was reached and were then awoken. This procedure was repeated three times to obtain reproducible wake-sleep transitions. The UA mucosa was then anesthetized with 10% lidocaine to the oropharynx and laryngopharynx, and the pharyngeal mechanics were studied during the subsequent wake-sleep transition. Three subjects were excluded because of failure to resume sleep postanesthesia. Rph was significantly higher after anesthesia during stage 1 sleep [2.88 ± 0.77 cmH2O·1–1·s (mean ± SE)] compared with control [0.95 ± 0.35 cmH2O·1–1·s; P < 0.05], but there was no difference during wakefulness. Furthermore, there was a significant rise in Rph at wake-to-sleep transitions and a significant fall in Rph at sleep-to-wake transitions after anesthesia (P < 0.05) but not in the control condition. We conclude that sensory receptors in the UA mucosa contribute to the maintenance of UA patency at wake-sleep transition in normal humans.

Topical anesthesia; obstructive sleep apnea; pathophysiology

Pharyngeal patency is maintained by the tonic and phasic contraction of upper airway (UA) dilating muscles. During sleep, a progressive loss of UA muscle tone occurs, leaving the pharynx vulnerable to the negative collapsing pressures that occur during inspiration (27). This loss of tone is thought to contribute to the development of obstructive sleep apnea syndrome (OSAS). Sensory receptors in the UA mucosa are activated by negative transmural pressures during inspiration and cause a reflex increase in activity of UA dilating muscles. This reflex response likely plays a role in preventing UA narrowing or collapse during sleep (14).

The role of UA mucosal mechanoreceptors in the maintenance of UA patency in humans has been examined by reducing their activity using topical application of local anesthesia to the UA. Topical UA anesthesia causes a rise in UA resistance (UAR) in normal subjects during stable non-rapid eye movement (8). Furthermore, topical anesthesia applied to the UA causes an increase in obstructive apneic and hypopneic events in both normal subjects and snorers (6, 23), a delayed arousal from induced airway occlusion in normal subjects (1), and an increase in apnea duration during sleep in patients with OSAS (2, 5).

These data suggest that reflex responses to UA mechanoreceptors act to prevent pharyngeal narrowing during sleep and that defects in these reflexes may play a role in the pathophysiology of OSA by contributing to the development and prolongation of apneic events. We hypothesized that these reflex responses are of particular importance at sleep onset when state-related withdrawal of UA muscle activity should tend to increase UAR and promote UA occlusion. We tested this hypothesis by examining the behavior of pharyngeal resistance (Rph) during wake-sleep transitions, with and without topical anesthesia of the UA.

Methods

Subject selection. Eleven healthy volunteers [8 men, 3 women; median age 21 yr (range: 21–28 yr), body mass index 24.2 (range: 18.7–36.7)], from the student and medical staff of the hospital gave their informed consent to participate in the study. Three were later excluded as they failed to sleep during the study. The protocol was approved by the Ethics Committee of St. Vincent’s University Hospital. All subjects were nonsmokers with no history of respiratory, cardiac, sleep, or UA disorders, although two subjects admitted to occasional snoring. No subject had taken caffeine or alcohol on the day of the study.

Measurements. Sleep was recorded on a five-channel polygraph (Grass model 78E) using gold cup electrodes for the channels of electroencephalography (EEG; C3/A1 and O2/A1) and two channels of electrooculography (LOC/A1 and ROC/A1) and a submental electromyogram. Electrode location was determined according to established guidelines (16). The scalp was prepared by removal of dead skin with exfoliative cream. Electrodes were then glued into position with collodion and quickly set with the aid of an air compressor. Electrode gel was inserted within each electrode cup to lower impedance. An impedance reading in each electrode of <10 kΩ was deemed acceptable. Staging of sleep was determined by standard criteria (16). Ribcage and abdominal movements were monitored by respiratory inductance plethysmography (Respirance, Ambulatory Monitoring, Ardsley, NY), calibrated using the isovolume technique.

Simultaneous recordings of pressure measured at the nasal choanae and epiglottis and airflow were used to calculate Rph. Subjects breathed through a nasal continuous positive airway pressure (CPAP) mask (Ultra Mirage, ResMed, Abingdon, UK), and mask pressure (Pmask) was recorded by a differential pressure transducer (Validyne DP45–26, Northridge, CA) calibrated beforehand with a handheld micromanometer (Digitron P200 S, Radiometrics, Dublin, Ireland).

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which was checked regularly against a water manometer. Pmask was recorded only to confirm nasal rather than mouth breathing. Respiratory airflow was monitored by a heated pneumotachograph (Fleisch no. 2, Linton Instrumentation, Norfolk, UK) and differential pressure transducer (Validyne DP45–14). Pharyngeal pressures were measured using two transducer-tipped catheters (Gaelsec CTO-1, Isle of Skye, UK). The sensitivity of these catheters was 5 μV·V⁻¹·mmHg⁻¹ with a linear pressure range of 0–300 mmHg. Both flow and pressure signals were adjusted so that no amplitude or phase difference could be detected at up to 2 Hz. These catheters, the Pmask/mouthpiece pressure transducer, and the pneumotachograph were simultaneously calibrated before the experiment in vitro in a chamber that was subjected to oscillating pressures and flows at a variety of random speeds (−15 to +15 cmH2O, −3 to +3 l/s, 0–2 Hz) with a 3-liter syringe. One nostril was anesthetized using topical lidocaine (2%, Instillagel, Farco-Pharma, Cologne, France). One transducer-tipped catheter was passed via the anesthetized nostril until the tip lay in the region of the epiglottis, 17 cm from the external nares. The other catheter was advanced through the same nostril until it touched the posterior nasopharyngeal wall, and then it was withdrawn 5 mm so that it lay in the nasal choana. The catheters were fixed in place by taping them to the nose. No measurements were taken from these catheters until at least 30 min had elapsed, by which time the effect of topical anesthesia would have worn off. Catheter signals were recalibrated in vivo against the Pmask signal during occluded inspiratory efforts before and after the experiment.

The airflow and pressure catheter signals were amplified (CWE, Ardmore, PA), filtered (30 and 1,000 Hz), and recorded on computer for later analysis. The pressure catheters were believed to be susceptible to a degree of thermal drift, and this effect was eliminated or minimized using computer software by zeroing pressure at points of zero flow (end inspiration and end expiration). All signals (EEG, pressure, flow, etc.) were recorded using a computer-based data capture/signal averaging system (Spire 2; Cambridge Electronic Design, Cambridge, UK).

Protocol. Subjects were instructed to partially sleep deprive themselves the night before (≤6 h sleep) and to avoid caffeine and alcohol on the day of the study. Subjects reported to the Sleep Laboratory at 10:30 PM and were instrumented according to the methods outlined above. Subjects were instructed to lie supine, and the investigator noted any deviation from this position by directly viewing each subject’s posture through an adjoining window. When 5 min of stable stage 2 sleep had elapsed, they were woken. This procedure was repeated up to three times until the sleep latency period of two consecutive sleep trials agreed within 5 min of each other. The oropharynx and hypopharynx were then sprayed with 2 ml of lidocaine (10 mg/l) (AstraZeneca Pharmaceuticals, Hertfordshire, UK), and any remaining fluid was spat out into a container. Adequate anesthesia was defined when the gag reflex was abolished, and subjects reported difficulty swallowing. Subjects were then allowed to fall asleep until stable stage 2 sleep had been reached or 45 min had elapsed.

Analysis of wake-sleep transitions. The ratio of EEG power in the theta band to the EEG power in the alpha band was calculated offline for occipital and central EEG during each breath. Measurements of power were obtained from an averaged periodogram over the duration of the breath using the Welch technique (EEG sample rate 512 Hz, 1,024 point sliding Hanning window, advanced 512 points per iteration). The results of this analysis were used as an aid to identification of alpha-theta and theta-alpha transitions. If three out of five consecutive breaths occurred during alpha activity, this was labeled as wakefulness; if three out of five breaths occurred during theta activity, this was labeled as stage 1 sleep. Wake-sleep transitions were never defined visually, as this was thought to be less objective.

The first episode of stage 1 sleep was defined as beginning from the period from the first 15-s epoch dominated by theta activity and ending with 1) resumption of sustained alpha activity, 2) arousal, 3) onset of stage 2 sleep, or 4) 90 s of stable stage 1 sleep had elapsed. This was compared with a period of wakefulness of identical duration immediately preceding the first appearance of theta rhythm. Any breaths coinciding with a sigh, swallow, or generalized body movement was excluded from the analysis, as this interfered with Rph measurement.

Calculation of Rph. Rph was calculated as the difference in pressure measured at the epiglottis and nasal choanae divided by the rate of airflow. A computer-derived algorithm calculated Rph at peak inspiratory flow rates (PIFR) and at 0.25 l/s flow rates. Rph was then averaged for all breaths and for all subjects. The changes in Rph at sleep onset were assessed in the following ways.

1) The mean Rph for all breaths in the first episode of stage 1 sleep was calculated and compared with the mean Rph for an equal number of breaths in the preceding period of presleep wakefulness.

2) The Rph for each of five breaths preceding and five breaths following the first three alpha-theta and first three theta-alpha transitions was recorded.

Statistical analysis. Where data were normally distributed, they are expressed as either the mean ± SE or mean ± SD; otherwise the data are presented as median (range). Paired data were compared by using the Wilcoxon signed-ranks test. Nonparametric hypothesis testing was calculated using Friedman’s ANOVA and a nonparametric implementation of the Student-Newman-Keuls post hoc test (12).

RESULTS

Data from eight subjects were used in the analysis as three subjects failed to return to sleep after application of the topical anesthetic. There was a trend toward increased sleep latency after anesthesia [339.9 s (196–1,013 s); median (range)] compared with that measured before topical anesthesia [94.5 s (13–1,014 s)] (P = 0.12, Wilcoxon signed-ranks test). Airflow limitation was not observed in any subject. Figure 1 illustrates an example of the identification of a wake-sleep transition preanesthesia (Fig. 1A) and postanesthesia (Fig. 1B).

Of note, no significant relationship was found between changes in Rph and body mass index either pre- or postanesthesia or between wakefulness and stage 1 sleep. Nor was there any trend in Rph according to gender or whether or not the subject snored.

Each of the subjects underwent three sleep trials before anesthesia. Comparing each preanesthesia sleep trial, no significant differences in Rph measured at PIFRs during wake-sleep transitions were noted (Fig. 2). Before pharyngeal anesthesia, no significant change in Rph was seen when J) the mean Rph for all breaths in the first episode of stage 1 sleep was calculated (13 ± 3 breaths; mean ± SD) and compared with the mean Rph for an equal number of breaths in the preceding period of presleep wakefulness (Table 1), and 2) the Rph for each of five breaths preceding and five breaths following the first three alpha-theta and first three theta-alpha transitions was recorded (Figs. 3 and 4).

Fig. 1. An example of pressure and airflow changes measured at the epiglottis and nasal choanae and the identification of a wake-sleep transition in one subject preanesthesia (A) and postanesthesia (B). Wakefulness is defined as occurring when 3 out of 5 consecutive breaths have an alpha-to-theta ratio <1. Stage 1 sleep is defined when 3 out of 5 consecutive breaths have an alpha-to-theta ratio >1. Pepi, epiglottis pressure; Pchoa, nasal choanae pressure.
However, Rph during stage 1 sleep was significantly increased following pharyngeal anesthesia, although Rph during wakefulness was similar to the preanesthetic levels. This increase was evident whether compared with wakefulness after pharyngeal anesthesia, or with stage 1 sleep before anesthesia (Table 1). Furthermore, alpha-theta transitions were associated with a significant increase in Rph, and theta-alpha transitions were associated with a significant decrease in Rph when the breaths immediately before the transition were compared with those immediately after (Figs. 3 and 4).

**DISCUSSION**

Minimal changes in Rph occur at sleep onset in normal subjects (17). However, the present data indicate that topical anesthesia of the oropharynx exaggerates these changes and provide evidence that sensory mechanoreceptors in the UA mucosa contribute to the prevention of UA collapse, most likely via a reflex response to negative pressure in the UA generated by inspiration.

During wake-sleep transitions, there is an abrupt fall in ventilation accompanied by a slight rise in UAR (17, 36), a loss in UA muscle tone (24, 32), and an attenuation of UA reflexes (10). This rise in UAR is thought to be the result of a relaxation of UA muscle tone once wakefulness drive has been withdrawn (36). Sensory receptors in the UA are thought to be responsible for preventing airway collapse by activating a reflex increase in UA muscle activity in response to negative airway pressure generated by inspiration (14). During stable sleep, the negative pressure reflex of the genioglossus is impaired, although this phenomenon has not been demonstrated during wake-sleep transitions (31). To eliminate the contribution of the negative pressure reflex to UA muscle tone, Fogel et al. (9) applied CPAP to subjects during wake-sleep transitions yet still noted some drop in UA muscle activity, most likely attributable to the loss of “wakefulness” tone. Other factors besides negative pressure reflexes may also affect the UA at alpha-theta transitions. UAR has been shown to increase with age (9, 37), supine position during sleep more in the supine than lateral position. Thus we did not prevent subjects from changing position during sleep, and two of the eight subjects changed to a semirecumbent position during sleep. Malhotra and coauthors (21) reported a poor correlation between patterns seen during wake-sleep transitions. Henke and co-workers (13) have also reported a range of values reported in these studies.

The measured Rph values at PIFRs during wakefulness in our study (0.75 ± 0.23 cmH₂O·l⁻¹·s⁻¹; mean ± SE) are lower than those published by DeWeese and Sullivan (8) (2.19 ± 1.21 cmH₂O·l⁻¹·s⁻¹), Hudgel and Hendricks (15) (1.31 ± 0.4 cmH₂O·l⁻¹·s⁻¹), Fogel et al. (10) (1.63 ± 0.34 cmH₂O·l⁻¹·s⁻¹), and Malhotra et al. (21) (2.0 ± 3 cmH₂O·l⁻¹·s⁻¹; mean ± SD) but higher than reported by Wasicko et al. (35) (0.43 ± 0.03 cmH₂O·l⁻¹·s⁻¹). The range of values reported in these studies may reflect normal variation; e.g., Hudgel and Hendricks (15) reported a range of −0.42 to 3.09 cmH₂O·l⁻¹·s⁻¹ among their subjects. Alternatively, lower values in Rph have been reported to occur in younger compared with older subjects (9, 37). The age of subjects in this study was 22.3 ± 2.4 yr (mean ± SD), younger compared with the subjects in some of the above-mentioned studies [Hudgel and Hendricks (15), 28 ± 2 yr; Fogel et al. (10), 31 ± 2.3 yr; Malhotra et al. (21), 29.4 ± 8.2 yr; and DeWeese and Sullivan (8), age range: 25–35 yr]. Furthermore, in some of the other studies referred to in this paper (17, 18, 32, 36, 37), authors calculated total UAR values rather than Rph as measured in this protocol. UAR values are by nature larger than Rph values, and this makes comparison with other studies more difficult.

Rph values postanesthesia were higher at flow rates of 0.25 l/s than at PIFRs, which may reflect the variable breathing patterns seen during wake-sleep transitions. Henke and co-workers (13) have also reported a poor correlation between resistance values and flow rates. Subjects were requested to lie supine and with the neck in its anatomical resting position, but we did not prevent subjects from changing position during sleep, and two of the eight subjects changed to a semirecumbent position during sleep. Malhotra and coauthors (21) reported that negative pressure increased genioglossus activity during sleep more in the supine than lateral position. Thus we must consider the possibility that changing body position may have influenced our findings, but this was not the case since the readings were no different for the six subjects who remained supine throughout the study.

**Table 1. Pharyngeal resistance at peak inspiratory flow rates and 0.25 l/s measured during wakefulness and stage 1 sleep pre- and postapplication of topical anesthesia**

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Awake</th>
<th>Stage 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepi, cmH₂O</td>
<td>−1.74±0.35</td>
<td>−1.73±0.36</td>
</tr>
<tr>
<td>Rph₀.25, cmH₂O·l⁻¹·s⁻¹</td>
<td>0.79±0.28</td>
<td>0.89±0.22</td>
</tr>
<tr>
<td>Rphpeak, cmH₂O·l⁻¹·s⁻¹</td>
<td>0.75±0.23</td>
<td>0.95±0.35</td>
</tr>
<tr>
<td>Postanesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pepi, cmH₂O</td>
<td>−1.63±0.27</td>
<td>−1.86±0.36</td>
</tr>
<tr>
<td>Rph₀.25, cmH₂O·l⁻¹·s⁻¹</td>
<td>0.94±0.34</td>
<td>3.27±1.09†</td>
</tr>
<tr>
<td>Rphpeak, cmH₂O·l⁻¹·s⁻¹</td>
<td>0.79±0.29</td>
<td>2.88±0.77†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8. Pepi, epiglottis pressure; Rph₀.25, pharyngeal resistance at 0.25 l/s; Rphpeak, pharyngeal resistance at peak inspiratory flow rates. *P < 0.05 compared with immediately preceding period of wakefulness; †P < 0.05 compared with stage 1 sleep before topical pharyngeal anesthesia: Friedman’s ANOVA and Student-Newman-Keuls.
DeWeese and Sullivan (8) have previously demonstrated an increase in UAR after application of topical anesthesia to the UA during stage 2 sleep in normal subjects. However, these authors also demonstrated a significant increase in UAR after UA anesthesia during wakefulness, a finding not replicated in the present study. This difference may reflect intersubject variability in UAR (17) or methodological differences since DeWeese and Sullivan randomly selected 10–20 breaths during a 5- to 10-min wakefulness interval for analysis.

Sleep onset is not a clearly defined sleep stage, as there are often transient changes from alpha to theta and theta to alpha waveforms before a stable pattern emerges. Analyzing data at 30-s epochs according to the criteria of Rechtschaffen and Kales (26) can miss a wake-sleep transition if it lasts for <50% of the epoch and relies on a subjective description of sleep staging. We chose the objective automated approach described by Kay and colleagues (17), whereby sleep staging is defined according to the ratio of theta to alpha activity in the occipital EEG recording, with wakefulness identified as predominantly alpha activity and stage 1 sleep as predominantly theta activity. Episodes of periodic breathing are quite common during stage 1 sleep, and this may have an effect on recordings of UAR if breaths to be analyzed are chosen at random. To overcome this potential problem, we compared the mean Rph at PIFRs and at low flow rates (0.25 l/s) for all breaths in stage 1 sleep with an equal number of breaths during wakefulness. In addition, we compared the mean Rph at three wake-sleep transitions over 10 breaths for comparison with previously published reports (18).

Certain potential limitations in our study design should be addressed. First, we did not perform baseline sleep studies in our subjects to exclude an occult sleep-related breathing disturbance. However, none had any clinical evidence to suggest the presence of OSAS, only two subjects snored, and no apneic or hypopneic events were observed during the experiment. Second, sleep trials with anesthesia always occurred after sleep trials without anesthesia, potentially introducing an order bias. However, we do not believe an order bias to be likely as subjects underwent multiple sleep trials before anesthesia to establish a comparable sleep latency period between sleep trials pre- and postanesthesia. No significant difference in Rph was seen between any of the preanesthesia sleep trials (Fig. 2). Furthermore, randomizing subjects to anesthesia first followed by a control sleep trial could potentially expose the subject to remnant anesthetic agent and thus alter the control findings. Finally, subjects were asked to partially sleep deprive themselves before the experiment to facilitate sleep while instrumented. Sleep deprivation/fragmentation has been reported to adversely affect UA muscle activity, sleep drive, and restoration of UA patency in both animal and human studies (20, 25, 29, 30, 34). However, the degree of sleep deprivation among subjects was not measured but anecdotally meant subjects slept, on average, 1–2 h less than their usual pattern and thus was unlikely to significantly influence the findings. Furthermore, differences in Rph pre- and postanesthesia during wake/sleep transitions were examined under the same “sleep-deprived” conditions.

Although topical anesthesia was applied to the oropharynx and the hypopharynx until the gag reflex was eliminated, the nasopharynx was not anesthetized, and it is possible that areas of the UA may have remained unexposed to anesthetic. We believe that this effect would likely underestimate the importance of the sensory receptors as many of the mechanorecep-
tors are likely to lie in the nasopharynx (14). Some subjects may have inadvertently swallowed some of the topical anesthetics, thereby potentially exposing that individual to systemic effects of the drug. However, we believe that the resulting dose of swallowed drug would have been very small and would be expected to cause stimulation rather than depression of the central nervous system (28). It is only when excessive doses of these agents are administered that respiratory depression occurs.

Application of topical anesthesia to the UA also gave rise to unstable breathing patterns so that the wake-sleep transition was marked by more frequent arousals. This effect prolonged sleep latency and may have given time for the topical anesthesia to partially wear off. As the half-life of the topical anesthetic is ~10 min, the effect of topical anesthesia diminishes rapidly over time. Thus the present results likely underestimate rather than overestimate the role of UA mechanoreceptors in the maintenance of airway patency during wake-sleep transitions. A nasal CPAP mask was used to monitor airflow during sleep. While it is possible that some mouth breathing occurred during the experiments, we regard this as unlikely since we could readily identify any mouth breathing from an attenuation of the flow signal and a reversal of the epiglottic-choanal pressure relationship.

The present data provide further support for an important role for UA receptors in the maintenance of oropharyngeal patency during sleep and reinforce the findings of previous reports on this subject. A putative role for this mechanism in the pathophysiology of OSAS would likely involve a defect in UA reflexes, and there is some evidence of such a defect in patients with OSAS. UA sensation, assessed by two-point discrimination and vibratory sensation thresholds while awake, has been shown to be impaired in OSAS patients and nonapneic snorers compared with normal controls (19). Furthermore, vibratory sensation improved after 6 mo of CPAP therapy, suggesting that this is a secondary defect, probably as a result of the mechanical trauma of snoring. While these initial studies suggest a UA afferent nerve defect, others have implicated either a disorder of the UA muscles or of the associated efferent nerves. Pathological studies of biopsies taken from the palatopharyngeal muscle of patients with OSAS have demonstrated evidence of a progressive local neurogenic lesion, possibly caused by the trauma of snoring, which may be a contributory factor to UA collapsibility (11). More recently, indirect evidence of both nerve degeneration and muscle denervation in the UA of patients with OSAS has been reported (4). It seems that efferent as well as afferent nerve defects may contribute to the pathogenesis of OSAS.

Indirect evidence of a role for defective UA reflexes in the pathophysiology of OSAS comes from previous reports from this center that topical UA anesthesia was associated with an increased frequency of apneas and hypopneas during sleep in normal subjects (23) and heavy snorers (6) but not in patients with established OSAS (7), indicating a lesser effect of UA anesthesia in patients with OSAS, which might be explained by deficient UA reflexes in OSAS patients compared with normal subjects and nonapneic snorers. Further evidence comes from the finding that UA anesthesia reduces phasic genioglossus activity during sleep in patients with OSAS, supporting a role for UA receptors in modulating UA dilator muscle activity (3).

In conclusion, although UAR only increases slightly at wake-sleep transitions in normal humans (18), topical anesthesia significantly increases Rph during stage 1 sleep and causes a significant increase in Rph at the alpha-theta transition. This provides further supporting evidence for the role of mucosal mechanoreceptors in the maintenance of UA patency.

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**References**


