Effect of topical upper airway anesthesia on apnea duration through the night in obstructive sleep apnea

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Effect of topical upper airway anesthesia on apnea duration through the night in obstructive sleep apnea. J. Appl. Physiol. 81(6): 2618–2626, 1996.—It has previously been reported that the duration of obstructive apneas increases from the beginning to the end of the night (M. Charbonneau, J. M. Marin, A. Olya, R. J. Kimoff, D. Levy, and M. Cosio. Chest 106: 1695–1701, 1994). The purpose of this study was to test the hypothesis that stimulation of upper airway (UA) sensory receptors during obstructed inspiratory efforts contributes to arousal and apnea termination and that a progressive attenuation of this mechanism through the night contributes to apnea lengthening. We studied seven patients (six men, one woman) with severe obstructive sleep apnea (apnea-hypopnea index = 93 ± 26 events/h) during two consecutive nights of polysomnographic monitoring. On one night (random order), we performed topical UA anesthesia with 0.2% tetracaine and on the control night, sham anesthesia. We measured apnea duration, esophageal pressure (Pes) during apneas, and apneic O2 desaturation. Consistent with previous findings, apnea duration, number of efforts per apnea, and peak Pes at end apnea increased from the beginning to the end of the control nights. UA anesthesia produced a significant increase in apnea duration at the beginning of the night but no change in apnea length at the end of the night. Peak Pes and the rate of increase in Pes during the anesthesia nights were greater than during control nights, but the rate of increase in Pes was similar for the beginning and end of the control and anesthesia nights. These findings suggest that UA sensory receptors play a role in mediating apnea termination at the beginning of the night but that the contribution of these receptors diminishes as the night progresses such that greater inspiratory efforts are required to trigger arousal, leading to apnea prolongation.

METHODS

One female and six male subjects with untreated OSA confirmed by polysomnography were recruited from the Royal Victoria Hospital Sleep Clinic (Montreal). All subjects underwent routine testing of pulmonary function in the department’s laboratory. The subjects were taking no regular medications and had no other active medical problems. The study was approved by the Human Ethics Committee of the Royal Victoria Hospital, and written informed consent was obtained from all subjects. There were eight other subjects enrolled in the study whose results were incomplete or could not be used in the final analysis. Three subjects were unable to tolerate the esophageal catheter, and four subjects could not maintain a constant posture throughout both nights. In addition, one subject failed to return for a second night’s study.

Each subject underwent two consecutive nights of full overnight polysomnography. A balloon-tipped esophageal catheter was placed for pleural pressure (measured as esophageal pressure [Pes]) measurements. The catheter was connected to a differential pressure transducer (Validyne P300D). The balloon volume (0.6 ml) was repeatedly verified throughout the night. Insertion of the catheter was assisted by 1–2 ml of 4% lidocaine viscous solution. Catheter placement was performed before the polysomnographic instrumentation to allow the maximum time for the effects of the lidocaine to diminish before stage 2 sleep on the control night. The time elapsed between catheter placement and lights out ranged from 70 to 90 min. Rib cage and abdominal motion were monitored by respiratory inductance plethysmography (Respi-
After spraying was completed, the subjects were asked to modified slightly from those described by Horner et al. (11). tetracaine or sham anesthesia was assessed by methods spraying with 10 ml of water in an identical pattern to that saliva accumulated during the procedure to minimize systemic absorption of the dose. Sham anesthesia consisted of spraying with 10 ml of water in an identical pattern to that used during anesthesia. Sensation in the oropharynx after tetracaine or sham anesthesia was assessed by methods modified slightly from those described by Horner et al. (11). After spraying was completed, the subjects were asked to scale the sensation elicited by a “soft” (cotton wool)-ended probe applied to each of the following: 1) floor of the mouth; 2) anterior dorsum of the tongue; 3) posterior dorsum of the tongue; 4) tonsillar fossae; 5) soft palate; and 6) posterior pharyngeal wall. After spraying was completed, subjects were asked to scale their sensations on a scale from 0 to 5 (5 = normal sensation; 0 = no sensation). In addition to this sensory scaling, note was taken of the presence/absence of the gag reflex elicited by a hard wooden probe applied to the posterior pharyngeal wall.

Study protocol. The sequence of the studies is summarized in schematic form in Fig. 1. On the control night, sham anesthesia (10 ml of water) was administered by an atomizer, and on the anesthesia night tetracaine was administered. Applications of sham anesthesia or tetracaine were made just before lights out at the beginning of the night (C1, An1) and then again after 2.5–3 h of sleep (C2, An2). When the subject was awakened, sham anesthesia or tetracaine was readministered as previously. The sensation was then reassessed, and the subject was allowed to return to sleep. The interruption of sleep was no more than 15 min. Data collection continued for a further 2- to 3-h period or until the patient woke spontaneously. Sham and true anesthesia nights were performed in random order, resulting in four patients undergoing sham anesthesia on the first night and three patients undergoing true anesthesia on the first night.

Data analysis. A given sleep period was eligible for analysis if it met the following criteria: 1) it was within the first hour after lights out; 2) it was during established stage 2 non-rapid-eye-movement (NREM) sleep (allowing for end-apneic microarousals) at least 10 min before or after a rapid-eye-movement (REM) period; and 3) the subject was in the same posture (supine or side lying) for all recording periods. These criteria were chosen to assess the effect of tetracaine anesthesia during its expected peak activity and to avoid spurious changes in apnea characteristics because of changes in posture and sleep stage. In addition, to minimize the risk of postural changes occurring after the 1-h period of data acquisition influencing the subsequent recordings, we required subjects to remain in the same position all night, resulting in the exclusion of four subjects because of difficulties in maintaining posture. Although data were acquired for 1 h after lights out during the first (C1, An1) and second (C2, An2) periods of the night, we also required that the subjects sleep continuously throughout, except for being awakened at C2 and An2 by the operator and spontaneously at night’s end. The latter was required in view of the hypothesis that any changes in the measured parameters from the beginning to the end of the night were associated with the effects of continuous sleep. Ten consecutive apneas were analyzed within each period by a single operator blinded to the experimental condition. The following measurements were made: 1) apnea duration (Dt), defined as the time between the start of the first obstructed effort to the resumption of airflow; 2) number of apneic efforts; 3) baseline and end-apneic oxyhemoglobin O2 saturation (SaO2); 4) rate of O2 desaturation (ΔSaO2/Δt); and 5) peak Pes just before arousal (Pespeak). We also calculated the rate of increase of effort (ΔPes/Δt) during apneas, as previously described (15, 21). In this study we also calculated the mean increase in the peak inspiratory pressure per effort (ΔPes/efforts) and the rate of apneic efforts (efforts/Δt). Finally, we also calculated an apnea-hypopnea index (AHI; events/h) for the four analysis periods that were used to compare apnea severity between the diagnostic polysomnography night and the control and anesthesia nights.

Statistical analysis. We used a two-way analysis of variance (ANOVA) based on 10 apneas/subject to test for statistical significance of differences in the number of apneic efforts, Pespeak, and peak and nadir SaO2 among C1, C2, An1, and An2. Because ΔPes/Δt, ΔPes/efforts, efforts/Δt, and ΔSaO2/Δt were derived and results for Δt were not normally distributed, to test for differences in these values we used Friedman’s test for multiple comparisons and Wilcoxon’s signed-rank test for post hoc paired comparisons (with adjustment of the level of significance by the Bonferroni correction for multiple comparisons). A P < 0.05 was accepted as significant.

RESULTS

Subject characteristics. The subjects’ anthropometric characteristics, with results of pulmonary function testing and initial polysomnography, are listed on Table 1. As a group, the patients were markedly obese and all had severe OSA. Where pulmonary dysfunction was documented, it was explainable by the effects of obesity and/or mild airflow limitation. The values for AHI shown in Table 1 are those obtained during NREM.
Although the gag reflex was intact in all subjects sites tested and a score of 1 for an intact gag reflex). The mean score was 4.5 (i.e., score of 5/5 for each of the 7 sensory testing are shown in Table 2. The highest possible mean score was 4.5 (i.e., score of 5/5 for each of the 7 sites tested for one site to be scored less than the others or for a gradient in sensation between regions on control nights). Although the gag reflex was intact in all subjects during both periods of control nights, the mean score for both portions of the control nights was consistently less than maximal (P = 0.0001). No trend was evident for one site to be scored less than the others or for a gradient in sensation between regions on control nights. At both the beginning and end of the night, tetracaine resulted in abolition of the gag reflex in all subjects, and, compared with control, there was a substantial decrease in the mean sensory score (P = 0.0001). In keeping with posterior pharyngeal application of anesthesia, there was a progressive decrease in the sensory score from the anterior tongue to the posterior pharynx.

Apnea characteristics. All subjects slept continuously between the first and second study periods on both control and anesthesia nights. Sleep consisted predominantly of NREM and apnea-related arousals, with only occasional brief intervals of REM sleep. There was no difference in the relative proportion of NREM to REM sleep between control and anesthesia nights. In addition, the period-specific AHI was not different among the four study periods and the whole-night AHI during the diagnostic night (P > 0.5).

Representative results in one subject of typical apneas in the four experimental periods are shown in Fig. 2. Under all conditions, as the apnea progresses the deflections in Pes gradually increase and become maximal on the last obstructed breath before arousal. During the anesthesia night, because the rate of increase in inspiratory effort is greater and apnea duration is increased, maximal effort at end apnea is substantially greater.

The group mean data for apnea duration are shown in Fig. 3. Apnea duration increased by 31 ± 5 (SE) % from C1 to C2 (P = 0.0001; Table 3) and by 105 ± 15% at An1 and C2 were not significantly different, P > 0.4). In contrast, UA anesthesia at the end of the night produced little effect on apnea duration (i.e., An2 was not significantly different from An1 or C2).

The data for inspiratory effort during apneas are summarized in Table 3. During control nights, the number of efforts per apnea increased from C1 to C2 (P = 0.001; Table 3). At An1, although there was a trend for an increase in the number of efforts per apnea compared with C1, during the anesthesia night this failed to reach statistical significance (P = 0.08). The maximal apneic effort increased by 42 ± 8% at C2 relative to C1 (P = 0.0001; Fig. 3), similar to previous findings (6, 21). At the beginning of the night, oropharyngeal anesthesia resulted in apnea lengthening (An1 25 ± 5% > C1, P < 0.001), the extent of which was comparable to the lengthening of events across the control nights (An1 and C2 were not significantly different, P > 0.4). In contrast, UA anesthesia at the end of the night produced little effect on apnea duration (i.e., An2 was not significantly different from An1 or C2).

The group mean data for apnea duration are shown in Fig. 3. Apnea duration increased by 31 ± 5 (SE) % from C1 to C2 (P = 0.0001; Table 3). At An1, although there was a trend for an increase in the number of efforts per apnea compared with C1, during the anesthesia night this failed to reach statistical significance (P = 0.08). The maximal apneic effort increased by 42 ± 8% at C2 relative to C1 (P = 0.0001; Table 3) and by 105 ± 15% at An1 (P = 0.0001) compared with C1. When compared with that at C2, maximal apneic effort at An2 was 42 ± 6% greater (P = 0.0001) but was not different from that at An1 (P = 0.8). The rate of change of inspiratory effort (ΔPes/Δt) was substantially increased during both An1 and An2 compared with C1 and C2 (P = 0.001). The increase in the rate of change of inspiratory effort between control and anesthesia periods was entirely explained by an increase in ΔPes/efforts with no change in efforts/Δt (P = 0.09).

The mean preapneic SaO2 results were similar for the four study periods (Table 4). The SaO2 at end-apnea was lower and the ΔSaO2/Δt was higher during An1 (P = 0.001) compared with other conditions. No difference was detectable for end-apneic SaO2 or ΔSaO2/Δt between

### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>FEV1, %Pred</th>
<th>FVC, %Pred</th>
<th>AHI, events/h*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>51</td>
<td>170</td>
<td>143</td>
<td>49.5</td>
<td>112</td>
<td>93</td>
<td>75.6</td>
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<td>2</td>
<td>F</td>
<td>45</td>
<td>150</td>
<td>148</td>
<td>65.8</td>
<td>93</td>
<td>86</td>
<td>105.6</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>41</td>
<td>178</td>
<td>130</td>
<td>41.0</td>
<td>82</td>
<td>87</td>
<td>106.0</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>43</td>
<td>178</td>
<td>110</td>
<td>34.7</td>
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<td>93</td>
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<tr>
<td>5</td>
<td>M</td>
<td>57</td>
<td>170</td>
<td>92</td>
<td>31.8</td>
<td>114</td>
<td>120</td>
<td>41.5</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>41</td>
<td>182</td>
<td>130</td>
<td>39.2</td>
<td>108</td>
<td>108</td>
<td>105.0</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>39</td>
<td>178</td>
<td>118</td>
<td>37.2</td>
<td>57</td>
<td>63</td>
<td>110.4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>6 M/1 F</td>
<td>45.3 ± 6.5</td>
<td>172.3 ± 10.8</td>
<td>124.4 ± 19.4</td>
<td>42.8 ± 11.6</td>
<td>94.3 ± 22.1</td>
<td>92.8 ± 19.7</td>
</tr>
</tbody>
</table>

M, male; F, female; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Pred, predicted; AHI, apnea-hypopnea index. *Values from baseline diagnostic polysomnogram.

### Table 2. Upper airway sensation

<table>
<thead>
<tr>
<th>Site</th>
<th>C1</th>
<th>C2</th>
<th>An1</th>
<th>An2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior tongue</td>
<td>4.4</td>
<td>4.4</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Underneath tongue</td>
<td>4.1</td>
<td>4.3</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Posterior tongue</td>
<td>4.3</td>
<td>4.4</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Right tonsillar fossa</td>
<td>4.5</td>
<td>4.6</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Left tonsillar fossa</td>
<td>4.6</td>
<td>4.6</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Soft palate</td>
<td>4.1</td>
<td>4.5</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Posterior pharynx</td>
<td>4.6</td>
<td>4.8</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Gag reflex</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>3.9</td>
<td>4.1</td>
<td>1.7</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Values are means (n = 7 subjects) of sensory score for light-touch sensation for each region. Scoring was by methods of Horner et al. (11), i.e., response between 0 (no response) and 5 (normal response). Gag sensation was assessed by operator as absent (0) or present (1). C1 and C2, application of 10 ml water (sham anesthesia) at beginning of control night and after 2.5–3 h of sleep, respectively; An1, and An2, application of anesthesia (tetracaine) at beginning of anesthesia night and after 2.5–3 h of sleep, respectively.
the control periods or the end of the study nights ($P > 0.6$).

**DISCUSSION**

In this study, consistent with previous work (6, 21), we found that apnea duration increased from C1 to C2. On the intervention night, compared with the same periods on the control night, topical UA anesthesia led to an increase in apnea duration at An1 but produced no change in apnea duration at An2.

Methodological issues. Before a discussion of the implications of these results, several methodological issues need to be addressed. The order of the control and anesthesia nights was randomized to reduce the risk that acclimatization to the laboratory could have resulted in spurious differences between the two nights. Because of the taste and rapid onset of action of the tetracaine, it was not possible for the subjects to be blinded to the intervention. However, there was no difference in sleep latency between the study and control nights, and none of the subjects complained afterward of adverse effects of the tetracaine. Furthermore, it seems unlikely that once sleep was established, knowledge by the patient of UA anesthesia would have influenced the measured parameters.

The esophageal catheter could theoretically have decreased arousal time compared with a noncatheter study because of UA stimulation. As was found previously (15), however, mean apnea duration was similar between the original diagnostic and control nights. Therefore, it seems unlikely that the pleural pressure catheter had any independent effect on our results. To minimize the possibility that the lidocaine used to assist passage of the catheter influenced OSA, we required that 1 hour elapse between catheter insertion and lights out. As well, the minimal amount of lidocaine necessary was used (<2 ml of a 4% viscous preparation). However, even in the unlikely event that the lidocaine used on control nights influenced the results, this would have had the effect of reducing the differences between control and anesthesia nights.

We selected tetracaine (onset of action of 3–8 min and peak action of 30–60 min) because of concern that...
lidocaine would not provide a sufficiently long period of anesthesia during sleep. To avoid the confounding effects of declining efficacy, we restricted our analysis to within 1 h after lights out. Systemic absorption of drug was minimized by encouraging the subjects to expectorate rather than swallow excess saliva during anesthesia. Direct application of an anesthetic mixture containing 0.5% tetracaine to laceraions in children resulted in unmeasurable serum levels up to 1 h later (32), and doses of topical lidocaine comparable to that used in this study have not resulted in detectable side effects (1, 2, 7, 20). Hence we believe it is highly unlikely that the effects of topical airway anesthesia were due to central effects of tetracaine due to systemic absorption. Furthermore, administration of the same dose of tetracaine altered apnea duration at the beginning but not at the end of the night.

Mechanisms of apnea termination in OSA. The termination of obstructive apnea is thought to require a brief arousal at or just before airway reopening (23, 26, 30). During apneas there is a progressive increase in inspiratory efforts, accompanied by progressive hypoxia and hypercapnia (30). Although arousal may be provoked by stimulation of peripheral (4) and/or central (3) chemoreceptors, recent work in animals and humans suggests that this may be mediated indirectly through an effect on ventilatory output, in that arousal appears to be more closely linked to the level of inspiratory effort (1, 2, 7, 20). Hence we believe it is highly unlikely that the effects of topical airway anesthesia were due to central effects of tetracaine due to systemic absorption. Furthermore, administration of the same dose of tetracaine altered apnea duration at the beginning but not at the end of the night.

Study rationale and hypothesis. We have recently shown that apnea duration increases through the night in severe OSA (6, 21) and that this prolongation is associated with an increased level of inspiratory effort at end-apnea (21). We have argued that our findings were most consistent with an increase in the arousal threshold to effort-related stimuli through the night, thus leading to delayed end-apneic arousal and apnea prolongation (21). This could result from either a decrease over the course of the night in central arousal responsiveness to peripheral stimuli or to a progressive decline in peripheral-receptor sensitivity such that increased stimulus intensity is required to provide a level of afferent input sufficient to provoke arousal. The present study aimed to address the latter possibility.

The peripheral receptors that may contribute to effort-mediated arousal have not been precisely identified, although evidence suggests that mechanoreceptors in the respiratory muscles and/or chest wall play a role (15, 21). In addition, UA mucosa has a rich sensory innervation, including mechanoreceptors responsive to fluctuations in transmural pressure (12, 13, 22, 28). Previous studies have indicated that such receptors may mediate feedback of inspiratory effort and the arousal response to airway occlusion (1, 13, 14, 19, 24, 28). For example, Issa et al. (14) compared time to arousal in response to face mask vs. tracheal occlusion in dogs and found that apnea duration was prolonged with tracheal occlusion. Basner et al. (1) reported that during induced face mask occlusion in normal subjects, topical UA anesthesia significantly increased the time to arousal and suction pressure at arousal from NREM sleep. As well, low-frequency vibration of the UA simulating snoring is a potent arousal stimulus in dogs (24). Thus UA mechanoreceptor stimuli may contribute to effort-related arousal in normal subjects. It seems probable that such a mechanism would also contribute to end-apneic arousal in OSA, in that intense stimulation of pressure-sensitive UA receptors would be expected during obstructed inspiratory efforts. This would result from both forceful suction collapse of the pharyngeal walls due to the highly negative intraluminal pressures (26) as well as caudal traction on pharyngeal structures due to transmission of negative intrathoracic pressure via the trachea and soft tissues of the neck.

If UA sensory receptors do contribute to the arousal response to airway occlusion in OSA, are there data to suggest a possible mechanism by which impairment of this function could develop over the course of a night? UA events during sleep in subjects with OSA include vigorous snoring-related vibration (35) and repeated forceful suction collapse of the pharynx (26). These events could be traumatic to the UA mucosa and result in inflammation, edema, and possibly neural damage analogous to peripheral nerve injury resulting from low-frequency vibration (31). In support of this, UA mucosal edema has been demonstrated both in uvulopalatopharyngoplasty surgical specimens (35) and by using magnetic resonance imaging (27) in severe OSA patients. Of note, in the latter study, these changes reversed after treatment with nasal continuous positive airway pressure. Furthermore, palatopharyngeal muscle biopsies of OSA patients receiving uvulopalatopharyngoplasty were also consistent with neurogenic damage (9). As well, Larsson et al. (16) demonstrated impaired oropharyngeal mucosal temperature sensation in OSA patients compared with age-matched non-snoring controls, suggesting the development of a pharyngeal sensory neuropathy. Thus sensory abnormalities may be associated with the chronic effects of OSA. If this is indeed the basis of UA trauma during sleep (7, 17, 35), it seemed possible to us that sensory dysfunction, which may be chronically depressed compared with normal subjects, could worsen

|                | Baseline | Nadir | ∆SaO2 /At, %
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>92.7 ± 0.5</td>
<td>81.6 ± 0.9</td>
<td>0.56 ± 0.04</td>
</tr>
<tr>
<td>C2</td>
<td>93.2 ± 0.5</td>
<td>80.8 ± 1.0</td>
<td>0.53 ± 0.04</td>
</tr>
<tr>
<td>An1</td>
<td>93.9 ± 0.5</td>
<td>77.6 ± 0.7*</td>
<td>0.79 ± 0.05*</td>
</tr>
<tr>
<td>An2</td>
<td>94.0 ± 0.6</td>
<td>82.6 ± 0.8</td>
<td>0.50 ± 0.03</td>
</tr>
</tbody>
</table>

Results are means ± SE (n = 7 subjects) for 10 apneas. SaO2, O2 saturation; ∆SaO2 /At, rate of desaturation. *P < 0.01, significantly different relative to C1, C2, and An2.
further over the course of a night due to the physical events in the UA during sleep.

On the basis of the foregoing, we therefore hypothesized in the present study that 1) UA sensory receptors contribute to the arousal response to UA obstruction in OSA, particularly at the beginning of the night; and 2) there is an attenuation of UA sensory receptor function through the night, which necessitates an increase in inspiratory effort to produce arousal, thereby resulting in apnea prolongation. On the basis of these hypotheses, we predicted that UA mechanoreceptor blockade by using topical anesthesia would produce an increase in apnea duration at the beginning of the night compared with a time-matched control period but would produce little or no change in apnea duration at the end of the night.

Interpretation of findings. We found that apnea duration and the number of apneic efforts increased from C1 to C2 by an amount comparable to those reported previously (6, 21). Consistent with our hypotheses, we found that apnea duration was increased at An1 compared with C1, this increase being comparable to that occurring spontaneously from C1 to C2. In contrast, UA anesthesia produced no further lengthening of apneas at the end of the night (Fig. 3). These findings are, therefore, consistent with a role for UA sensory receptors in mediating end-apneic arousal at the beginning of the night and with an attenuation of this function over the course of the night such that UA sensory inhibition by topical anesthesia no longer demonstrably affects apnea duration at the end of the night.

Since we performed the studies reported here, two reports on the effects of UA anesthesia on apnea duration as well as other OSA-severity measures have appeared (2, 7). Berry et al. (2) assessed apnea duration and inspiratory effort at arousal during two consecutive 2-h periods on separate control and anesthesia nights. Nasooropharyngeal anesthesia with lidocaine was performed during the second 2-h period on the anesthesia night. Apnea length was unchanged in the second relative to the first 2 h of the control night but increased during UA anesthesia by a similar extent to that shown at the beginning of the night in the present study. The lack of apnea lengthening from periods 1 to 2 of the control nights was probably due to differences in timing and duration of the two periods compared with our study (and possibly related also to the insertion of extended nasal canulas during the second 2-h period, which may have been disruptive to sleep and promoted earlier arousal). Overall, however, period 2 of these investigators appears to have been virtually identical to our C1 and An1 periods in terms of apnea duration and inspiratory effort at arousal on the control night and the effects of UA anesthesia on these variables. These findings, therefore, also support a role for UA sensory receptors in apnea termination. We speculate that the lack of an effect of UA anesthesia in our later period was not identified by these investigators due to the inclusion of data from earlier in the night in their period 2.

In another recent study, Deegan et al. (7) assessed the effects on OSA of oropharyngeal anesthesia maintained through the entire night, compared with a control night. For the night overall, there was a nonsignificant tendency for apnea/hypopnea duration to increase with UA anesthesia. However, these workers did not assess changes in variables at successive time periods through the night. If the data from the beginning and end of the night in our study were pooled, it would have been difficult to detect lengthening of apnea duration with anesthesia. Hence the results of Deegan et al. are not directly comparable to our own but are not necessarily conflicting. These time-of-night considerations may also account for the apparent discrepancies between these two previous studies (2, 7) in terms of the effects of UA anesthesia in subjects with OSA.

Although previous work is available that supports, or at least does not directly conflict with, our findings, this study is, therefore, unique in evaluating the effects of UA anesthesia on a time-of-night basis and in providing evidence of attenuated UA sensory function through the night. Further evidence for this needs to be established by direct testing of UA sensory function at the beginning and end of the night in OSA patients compared with normal subjects.

An alternate explanation for an attenuated role for UA sensory receptors at the end of the night could be that central arousal responsiveness to peripheral stimuli declines at the end of the night, due either to specific habituation or to nonspecific circadian factors (6, 21). However, if responses to UA stimuli decrease on this basis, it would be expected that responses to other respiratory stimuli such as those arising in the chest wall/respiratory muscles should also be reduced. Thus even when UA receptors were inhibited on the anesthesia night, and these latter stimuli probably made a greater contribution to end-apneic arousal, apnea duration and inspiratory effort at arousal (measured as $P_{es/peak}$) should still have increased through the night, which was not the case. Thus our findings provide indirect evidence against impaired central responsiveness to respiratory arousal stimuli as the mechanism for apnea's lengthening through the night. $Sa_{O2}$ data through the night. On the control nights, as in our previous studies (6, 21), end-apneic $Sa_{O2}$ showed no significant change from C1 to C2 (Table 4). In contrast, on the anesthesia nights, end-apneic $Sa_{O2}$ was significantly decreased at An1 compared with control but was no different at An2 from control and was therefore significantly higher than at An1. In that apnea duration was unchanged from An1 to An2, the $\Delta Sa_{O2}/\Delta t$ was greater at An1 than at An2 (Table 4). The reason for the difference is unclear. There may have been a decline in $O_2$ consumption ($V_{O2}$) through the night due to circadian metabolic changes. We also assume that increased inspiratory effort generation during apneas results in a higher $V_{O2}$. On control nights, because of a trend to a greater $\Delta P_{es/\Delta t}$ at C2, the opposing effects on $Sa_{O2}$ may have cancelled out. In contrast, because $\Delta P_{es/\Delta t}$ was increased at An1 when
\( V_O^2 \) was also likely to be higher, we speculate the combined effects led to a higher rate of \( V_O^2 \) and therefore \( \Delta S_O^2/\Delta t \).

The consistency of end-apneic \( S_O^2 \), through the control night raises the possibility of a primary role for peripheral chemoreceptor stimuli in mediating end-apneic arousal (15, 21). Arguments have previously been provided against this possibility (15, 21), and although these will not be reiterated here, the results of the present study further support this contention. Specifically, if arousal were triggered by a critical level of \( S_O^2 \), at An1 apnea duration should have decreased, not increased, due to the more rapid \( \Delta S_O^2/\Delta t \). By the same argument, apnea duration would have been expected to be increased at A2 compared with An1 in view of the slower \( \Delta S_O^2/\Delta t \), which was not the case. A systemic central or peripheral chemoreceptor effect of topical UA anesthesia cannot account for these findings in that such an effect would have been expected to be observed at both times of the night.

Inspiratory effort during apneas: influence of time of night and anesthesia. We had not initially anticipated the significantly greater \( \Delta P_{es}/\Delta t \) during apneas and higher \( P_{es_{peak}} \) observed on the UA anesthesia compared with control nights (Table 3). With respect to \( \Delta P_{es}/\Delta t \), the greater \( \Delta S_O^2/\Delta t \) observed at the beginning of the study nights (Table 4) may have contributed to the increased \( \Delta P_{es}/\Delta t \) during this period. However, this mechanism cannot account for the comparable \( \Delta P_{es}/\Delta t \) at An2, when \( \Delta S_O^2/\Delta t \) was considerably less. Another possibility is that UA sensory receptors play a role in the defense of UA patency, in that UA anesthesia increases pharyngeal airflow resistance (8) and can induce or increase apneas and hypopneas in normal subjects (20) and snorers (24). Although we observed no systematic differences on the flow channel between the anesthesia and control nights for the apneas analyzed, the oronasal thermistor (chosen over other flow measurement devices to minimize patient discomfort and sleep disruption) (15) may not reliably detect low levels of airflow. Thus we cannot discount the possibility that our UA anesthesia may have increased UA collapsibility and led to “more complete” UA obstruction during events and thereby a reflex increase in effort during apneas.

The evidence that UA mechanoreceptors provide central feedback of inspiratory effort has been discussed. The increased \( \Delta P_{es}/\Delta t \) during apneas with UA anesthesia would appear to indicate that UA mechanoreceptor feedback has an inhibitory influence on inspiratory drive such that the marked attenuation of UA sensation with tetracaine resulted in increased inspiratory drive and effort. In support of this, afferent impulses from other respiratory mechanoreceptors, e.g., in the chest wall and respiratory muscles, may be inhibitory to inspiratory drive (29). Thus sensory feedback from the UA may have also an inhibitory modulating influence on ventilatory output, with the loss of this with UA anesthesia thus leading to increased effort during apneas.

What might account for the greater \( P_{es_{peak}} \) on the anesthesia relative to control nights? We propose that the increase in \( P_{es_{peak}} \) from the C1 to C2 is due to a loss of afferent feedback from UA mechanoreceptors due to attenuated receptor function through the night. This leads to a requirement for greater activation (i.e., by a more intense effort) of other respiratory afferents, such as those in chest wall and respiratory muscles (15, 21), to produce a level of afferent stimulus sufficient to provoke arousal and apnea termination. The extent of inhibition of UA sensory receptors with topical UA anesthesia was presumably greater than that which we propose occurred spontaneously across the control night. Thus a greater level of effort again would be required to activate other afferents to an extent sufficient to provoke arousal, accounting for the greater \( P_{es_{peak}} \) on anesthesia nights. The lack of change in \( P_{es_{peak}} \) from An1 to An2 (Table 3) is also consistent with these proposals, in that no cross-the-night attenuation of UA contribution as on control nights would be anticipated in the face of similarly potent inhibition of UA receptors at both times of the night with topical anesthesia.

One of the predictions from the data summarized above, indicating that UA mucosal edema and sensory dysfunction may be present as chronic effects of OSA (9, 17, 35), is that even at baseline, i.e., the beginning of the night, UA sensation in OSA patients should be impaired relative to normal subjects (and then become further attenuated over the course of the night). Such a chronic defect, if present, could account, in part, for the apparent impairment in arousal responsiveness in OSA patients relative to normal subjects. That is, it has previously been pointed out (15) that there is a marked difference between normal subjects and OSA patients in time to arousal (15–20 vs. 25–30 s, respectively) and the level of inspiratory effort at arousal (\( P_{es_{peak}} = 15 \) to \( 17 \) cmH\(_2\)O vs. \( \geq 50 \) cmH\(_2\)O, respectively) in response to airflow occlusion during stage 2 sleep (15). These differences are analogous to the effects of UA anesthesia at the beginning of the night (C1 vs. An1, Table 3), which supports the concept that impaired UA sensory function accounts for the reduced arousal responsiveness in OSA patients relative to normal subjects. However, this possibility needs to be documented by objective sensory testing in both groups.

Finally, the interpretation of previous studies on effort-mediated arousal has been problematic, in that it has not been possible to definitively distinguish between afferent feedback related to a given level of effort or the central drive responsible for producing that effort as the primary stimulus for arousal. The results of the present study demonstrate clearly that at the beginning of the night, interruption of an afferent feedback mechanism, i.e., sensory stimuli arising in the UA mucosa, leads to an impairment of the arousal response and prolonged apnea duration. This therefore provides strong support for the concept that effort-related afferent stimuli arising in peripheral receptors play a determining role in the arousal response to airflow occlusion. The findings at the end of the night are also in
keeping with this mechanism, in that if the level of drive were the determining stimulus for arousal, apneic duration should have been shorter at the end of the anesthesia compared with control nights, given the more rapid increase in inspiratory drive and effort during apneas, which was not the case.

In summary, our findings confirm previous observations that, in OSA, apneic duration lengths through the night and that apneic prolongation is associated with an increased level of inspiratory effort at end-apneic. The important new contribution of this study is that apneic lengthening can also be produced by topical anesthesia-induced UA mechanoreceptor blockade at the beginning of the night, whereas at the end of the night the time-dependent increase and topical anesthesia-related increase in apneic duration are not different. We believe these findings are most consistent with the conclusion that UA mechanoreceptors provide important feedback of inspiratory effort during apnea, but this function becomes less effective as the night progresses so that arousal requires greater effort and is consequently delayed. We speculate that attenuation of UA mechanoreceptor function through the night in OSA is caused by repeated trauma to pharyngeal tissues as a consequence of UA vibration and closure. The extent to which changes in sleep events during the course of a single night may resemble the increase in severity of UA obstruction over a longer period is speculative. However, it is possible that further study of these processes may serve as a useful model for, and provide new insights into, the natural evolution of this disease.

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