Upper Airway Sensation in Snoring and Obstructive Sleep Apnea

R. JOHN KIMOFF, EMILIA SFORZA, VICTORIA CHAMPAGNE, LINDA OFIARA, and DANIEL GENDRON

Respiratory Division, Royal Victoria Hospital Site and Department of Neurology, McGill University Health Centre, Montreal, Quebec, Canada

Previous studies indicate that upper airway (UA) sensory receptors play a role in the maintenance of UA patency and contribute to arousal in response to airway occlusion. An impairment of UA sensory function could therefore predispose to UA obstruction during sleep. We hypothesized that UA sensation is impaired in obstructive sleep apnea (OSA), and that sensation improves after treatment with nasal continuous positive airway pressure (CPAP). We measured two-point discrimination (2PD) and vibratory sensation thresholds (VT) in 37 patients with OSA (mean [± SE] apnea–hypopnea index [AHI] = 39 ± 5 events/h), 12 nonapneic snorers (SN), and 15 control subjects (CL). Sensory thresholds were determined in the UA and on the lip and hand as control sites. Both 2PD and VT were similar among the three groups at the lip and hand sites but were significantly reduced in the UA of OSA and SN subjects versus CL ($p < 0.05$). Values for 2PD and VT in the UA of OSA versus SN were not significantly different. Sensory measures were repeated after 6 mo in 23 OSA patients treated with CPAP as well as in 18 untreated patients. Thresholds for 2PD and VT at control sites remained identical in both groups, as did 2PD for the UA. However, VT in the UA showed a significant improvement in treated (4.4 ± 0.2 pre-CPAP versus 3.8 ± 0.2 mm post-CPAP, $p < 0.05$) but not untreated patients. These findings indicate the presence of a selective impairment in the detection of mechanical stimuli in the UA of patients with OSA and SN, which is partially reversible after treatment with nasal CPAP in patients with OSA.

Apneic episodes in obstructive sleep apnea (OSA) are initiated by collapse of the upper airway (UA) during sleep, and resolve when stimuli generated during apneas provoke a brief arousal and lead to reopening of the airway. Whereas anatomic and neuromuscular factors clearly contribute to the increased tendency for UA collapse during sleep in OSA (1), there is evidence that UA mucosal sensory receptors may also play a role. Previous studies have shown that interfering with UA mucosal sensory function by topical anesthesia increases the tendency to airway collapse. For example, UA anesthesia can increase pharyngeal airflow resistance during wakefulness and sleep in normals (2). Furthermore, UA anesthesia also induces apneas and hypopneas during sleep in normals (3) and increases the frequency of obstructive events in snorers (4). These observations suggest that an impairment of UA mucosal sensory function could contribute to UA collapse during sleep.

There are also data indicating that UA sensory receptors contribute to end-apneic arousal and apnea termination (5–8). For example, in normal humans and dogs arousal in response to induced apneas occurs more rapidly when UA sensory receptors are exposed to pressure fluctuations than when they are not (5, 6). Furthermore, we and others have demonstrated that topical UA anesthesia delays end-apneic arousal and increases apnea duration (9, 10). Thus an impairment of UA sensory function could also contribute to delayed end-apneic arousal and increased apnea duration.

Larsson and colleagues (11) previously reported an impairment of thermal sensitivity in the oropharynx of patients with OSA compared with nonsnoring age-matched control subjects. These investigators postulated that snoring-related vibration or deformation of UA structures during apneas could lead to a sensory neuropathy which could contribute to UA dysfunction during sleep. The aim of the present study was to determine if a similar impairment is present in the detection of mechanical stimuli which may be of more proximate relevance for responses to changes in UA pressure and caliber (7, 8). We also studied snorers, and assessed the potential reversibility of changes in UA sensation in patients with OSA after treatment with nasal continuous positive airway pressure (CPAP), which has not previously been done (11). We therefore developed testing techniques for vibratory sensation and two-point discrimination (2PD) in the UA and applied these to patients with OSA and age-matched snorers and nonsnoring control subjects. We hypothesized that there is a selective impairment of UA mechanical sensory detection in OSA, and that this impairment is reversible after treatment of OSA patients with nasal CPAP.

METHODS

Study Population

OSA and snoring subjects were recruited from the Sleep Disorders Clinic of the Royal Victoria Hospital, and control subjects were recruited through advertisements. The study protocol was approved by the Human Ethics Committees of the Royal Victoria Hospital and Montreal Chest Institute. All subjects provided written informed consent to participation in the study.

OSA subjects were individuals with a history of snoring, symptoms compatible with sleep apnea, and an apnea–hypopnea index (AHI) > 10 events/h at overnight diagnostic polysomnography (PSG). Snorers (SN) were individuals with a history of long-standing snoring, no major symptoms of sleep apnea syndrome and snoring during > 25% of sleep epochs, and an AHI < 10 events/h on overnight PSG. Controls (CL) were individuals of similar age with a history of only rare or no snoring, no other symptoms of sleep apnea syndrome, and no snoring and a respiratory disturbance index of < 5 events/h on overnight PSG or home recording with an Edentrace II recorder (Mallinckrodt, Ottawa, Canada) (12). The subjects included in the between-groups analysis were all males between 25 and 55 yr of age. Age matching was thought to be important as sensory thresholds may change with age (13) and this was the range within which subjects could be matched for the three groups. Sensory testing was also performed on some older patients with OSA (56–74 yr), however, and data from these subjects were used for the repeat sensory testing post-CPAP described subsequently.

Exclusion criteria were any previous treatment for snoring or OSA, previous UA surgery excluding remote tonsillectomy, previous cerebrovascular accident, diabetes, any neuropathy or active neuro-

(*Received in original form October 4, 2000 and in revised form April 12, 2001*)

Funded by l'Association Pulmonaire du Québec.

Dr. Kimoff is a Clinical Research Scholar of the Fonds de la Recherche en Santé du Québec.

Dr. Sforza is currently affiliated with Centres Hospitaliers de l'Université de Genève, Switzerland.

Correspondence and requests for reprints should be addressed to Dr. R. John Kimoff, Respiratory Division, Rm L4.08, Royal Victoria Site, McGill University Health Centre, 687 Pine Ave. W., Montreal, PQ, H3A 1A1 Canada. E-mail: john.kimoff@muhc.mcgill.ca

Am J Respir Crit Care Med Vol 164. pp 250–255, 2001
Internet address: www.atsjournals.org

logic disease, and at the time of proposed testing, recent upper respiratory tract infection, excessive gag reflex, or very small oropharyngeal cavity which precluded sensory testing.

Protocol

Sensory testing was carried out in the late afternoon or early evening, typically on the day of the initial diagnostic polysomnogram, but was performed in all subjects within 4 wk of the diagnostic sleep study. The subjects were informed that the aim of the study was to test the possibility that changes in sensory function are related to the problem of sleep apnea, but the nature of the change or relationship to OSA pathophysiology were not detailed further. Testing of all subjects was conducted by the same individual (V.C.) who was unaware of the OSA status of the subjects at the time of testing. The subjects were blindfolded and seated on a chair at a table in front of the investigator. Wakefulness was confirmed continuously throughout the testing procedure by verbal interaction with the patient and assessment of responses during testing. Testing of 2PD and vibratory sensation threshold (VT) was performed in random order in the UA and at two control sites on the lower lip and the hand. All sensory tests were performed during the same session.

Within several weeks after PSG and sensory testing, a decision regarding treatment was made with OSA and SN patients in the Sleep Disorders Clinic. Patients with OSA who opted for CPAP treatment underwent an overnight titration polysomnogram during which CPAP was adjusted manually to alleviate apneas, hypopneas, and snoring during both non-REM and REM sleep with the patient in the supine and lateral decubitus positions. Patients with OSA treated with nasal CPAP were asked to undergo repeat UA sensory testing after approximately 6 mo of home CPAP treatment. Compliance with treatment was required to be $>$ 4 h/night documented by a microprocessor incorporated in the CPAP unit (Sullivan V Elite; ResMed, San Diego, CA) or by chronometer, and the patient had to have used CPAP throughout the night before retesting. Repeat testing was conducted in the identical manner and at the same time of day as the initial testing. Another group of patients with OSA who either chose to remain untreated or were still awaiting initiation of treatment underwent repeat sensory testing after a similar time period.

A group of eight subjects also underwent sensory testing with topical oropharyngeal anesthesia using 10% lidocaine delivered via metered-dose cannister, and with sham anesthesia using fine aerosolized saline. Testing under the two conditions was performed on the same day in random order, with 1 h between testing sessions. This was to confirm inhibition of the sensory modalities being tested through topical UA anesthesia.

Measurements

2PD was measured using standard techniques (13–15) on the dorsum of the hand on the skin overlying the first interosseous muscle, on the lower lip, and in the oropharynx along the margin of the soft palate lateral to the uvula on both the right and left sides. A series of two-point probes with fixed interprobe distances ranging from 2 to 28 mm were used for testing. The smaller probes (2 to 15 mm) were constructed by disassembling a commercial plastic disk (Disk-Criminator, Baltimore, MD) (14, 15) with a series of protruding pairs of metal rods around its circumference. As previously described (15), the disk was divided into multiple triangles, the bases of which were attached to thin rigid plastic handles. The larger probes (16 to 28 mm interprobe distance) were constructed using metal posts similar to those used in the Disk-Criminator embedded in a molding clay and attached to a handle.

At the beginning of the session there was an orientation procedure during which the subject was told when one or two prongs were being applied. Testing was then begun by applying the largest interprong distance for the given site, which were chosen to be suprathreshold for the hand (28 mm) and the lip (5 mm), or the largest probe that could consistently be used owing to spatial constraints in the oropharynx (14 mm). The probe was applied to the surface being tested for 2 s with enough pressure to slightly indent the skin or mucosal lining. Testing in the oropharynx was performed under direct visualization with the aid of a bright headlamp with the patient actively opening the mouth and protruding the tongue. Care was taken to contact only the testing surface along the soft palate and no other oropharyngeal structures. The testing stimulus was randomly alternated between one and two points and the subject was required to indicate one versus two points either verbally or by holding up fingers. If the subject correctly reported one versus two points on at least three of five trials, the next smaller interprobe distance was used. The smallest interprobe distance at which the subject correctly identified one versus two points in three of five trials was taken as the 2PD threshold for that site. A mean value was obtained for the right and left sides to yield the 2PD threshold for the soft palate. Some OSA and SN patients were unable to correctly identify one versus two points even at the largest interprobe distance in the UA. In this case a maximal value of 14 mm was assigned as the threshold value. (In that we ultimately found no significant differences between right and left sides in our analysis, subsequent studies could potentially use testing across the midline to allow greater interprobe distances and perhaps overcome this plateau effect at 14 mm, but this has not yet been done.)

Vibration testing was performed using standard techniques (13, 16, 17) on the pulp of the fingertip and the lower lip and using an adaptation of these techniques in the oropharynx on the upper portion of the anterior tonsillar pillar just below the palatal arch on both the right and left sides. Vibration testing was performed with a widely used clinical testing device (Vibratron II; Physitemp, Clifton, NJ) (17). This unit consists of a controller with two identical tranducers which deliver a vibrating stimulus at 120 Hz using a 1.5-cm plastic post. The amplitude of vibration is determined by varying the voltage at the controller unit. The controller provides a digital display of stimulus intensity in "vibration units," which are related to peak-to-peak displacement in microns by the following formula: $\mu = k \cdot (\text{vibration units})^2$ (17).

For testing at the hand, the subject rested the finger lightly on the post of one transducer, which sat on a tabletop as previously described (17). For testing at the lip and oropharynx, the other transducer was modified by attaching a rigid metal probe 8 cm long and 2 mm in diameter to the plastic post. The transducer was then fixed to a stand of adjustable height which was placed in front of the patient for testing. The position of the stand was adjusted so that the probe was applied against the lower lip or pharyngeal mucosa with sufficient pressure to produce a slight (1-mm) indentation and was maintained in this position throughout testing. As for 2PD, VT testing in the oropharynx was done under continuous direct visualization with a headlamp to ensure that the vibrating probe was always in proper position, applied with the appropriate pressure, and not in contact any other oral structures. The tonsillar pillar was selected rather than the margin of the soft palate used for 2PD testing, because of greater stability of the tissue in this area, and thus an improved ability to maintain constant position and pressure of the testing probe.

VT was determined using the method of limits (16, 17). Once the probe was in contact with the testing site, the intensity of vibration was increased progressively at a rate of 0.1 vibration units/s from zero until the patient detected the vibration. The stimulus was then increased to a suprathreshold value and decreased progressively at the same rate to a point at which the patient no longer detected the vibration. The subject reported the initial detection or extinction of vibration verbally or by holding up a finger. The process was repeated such that five trials were conducted at each site. Three ascending and two descending trials were performed at the finger and lip and five ascending trials only were performed in the oropharynx (as suprathreshold vibration was found too often in preliminary trials to produce gagging or other unpleasant sensations and require withdrawal of the probe). The mean of the five vibration unit values for the points of detection and extinction was obtained to yield the vibratory detection threshold for that site (17). In the UA there were no significant side-to-side differences for VT and the threshold values given are the means of right and left sides.

Overnight PSG included recording of standard electroencephalographic (EEG) leads (C4-A1/C3-A2), bilateral electrooculogram, chin and anterior tibialis electromyograms, airflow via nasal pressure cannula (18), thoracoabdominal movements via inductive plethysmography (Respitrace Systems, Ardsley, NY) or piezo bands (EPM Systems, Midlothian, VA), body position via infrared video or position sensor (EPM), sound via a microphone suspended above the patient's head, and arterial oxyhemoglobin saturation via finger pulse

oximetry (Ohmeda Biox 3700; Ohmeda Corp., Boulder, CO). All signals were acquired on a digital data management system (Sandman; Mallinkrodt, Ottawa, ON, Canada). Studies were scored manually by trained, experienced polysomnographic technologists. Sleep–wake state was defined according to standard criteria (19). Snoring was identified as typical inspiratory bursts of activity on the microphone channel. Segments of snoring (two or more consecutive snoring breaths) were tagged in the analysis software with total snoring time calculated as the sum length of snoring tags. An obstructive apnea was defined as an episode of cessation of airflow lasting at least 10 s with persistent respiratory effort, and a hypopnea as a discrete episode of reduction in airflow or inspiratory flow limitation on the nasal cannula pressure signal (18) lasting $>$ 10 s with associated desaturation $>$ 2% or arousal defined according to American Sleep Disorders Association (ASDA) criteria (20).

The data from Edentrace II studies, which include thermistor airflow, Sa_{O_2}, respiratory effort via electrocardiogram electrode impedance, heart rate, body position, and snoring via tracheal microphone, were downloaded to a personal computer and scored manually using the same Sandman analysis software as for PSG. Snoring was assessed as for PSG. Scoring criteria for respiratory events were similar to those used during PSG except that hypopneas were scored only when there was a greater than 50% reduction in flow with desaturation of at least 2% (12).

Data Analysis

Values for sensory thresholds at each site were compared between the three experimental groups using one-way analysis of variance (ANOVA). Values for 2PD were non-normally distributed and were compared using Kruskal-Wallis ANOVA on ranks and Dunn's test for post-ANOVA comparisons. Values for VT were normally distributed and were compared using standard one-way ANOVA with Student-Newman-Keuls test for post-ANOVA comparisons. Values for baseline and repeat sensory testing within subject groups were compared using the Mann-Whitney rank sum test for 2PD data and paired *t* tests for VT data (21). The reproducibility of baseline and repeat testing was assessed using intraclass correlation. A value of $p < 0.05$ was used for statistical significance.

Correlations were also determined between sensory threshold values and anthropometric data and measurements of the severity of sleep and respiratory disturbance on the diagnostic polysomnogram, using Spearman rank correlation for 2PD and Pearson product moment correlation for VT. Specific measures of sleep disturbance on the polysomnogram included total sleep time; sleep efficiency (total sleep time/total recording time); number of stage changes; number of awakenings; arousal index; percentage of each of stage 1, 2, 3/4, and REM sleep; and duration of each of these stages. Respiratory measures included AHI, apnea index, hypopnea index, total number of apneas and hypopneas, mean apnea duration, baseline Sa_{O_2}, nadir Sa_{O_2} for the night, mean end-apneic Sa_{O_2}, and mean change in Sa_{O_2} with apneas.

RESULTS

The subject characteristics of the three experimental groups are shown in Table 1. The groups were of similar mean age; body mass index (BMI) was significantly higher for the OSA and SN groups than for CL.

The values for sensory thresholds at the UA and control sites in the three experimental groups for both 2PD and VT are shown in Table 2. As previously indicated, values for 2PD were non-normally distributed so the data were analyzed using nonparametric methods and group values are shown as medians, whereas VT values were normally distributed, and were compared using parametric methods with group values shown as means. The median values for 2PD threshold were not significantly different among the three experimental groups at either the hand or lip control sites. However, there was a marked impairment of 2PD in the oropharynx of OSA and SN patients compared with CL. Although this is reflected in part by the higher median values for OSA and SN, it should be recalled that the maximal interprobe distance that could be used in the oropharynx was 14 mm Hg, and when there was a failure of detection at this level a value of 14 mm Hg was assigned. A total of 19 of 38 OSA and 5 of 12 SN subjects were assigned a value of 14, and in only 5 of the 19 OSA and 2 of the 5 SN subjects did these values represent true detection of one versus two points at 14 mm, whereas the other subjects completely failed detection of this interprobe distance. Thus, a substantial number of OSA and SN subjects were completely unable to discriminate at 14 mm in the UA whereas this never occurred in CL. Although median values for 2PD tended to be slightly lower in SN compared with OSA subjects, there was no statistically significant difference between the two groups.

As for 2PD, mean VT values were not significantly different between the three experimental groups at either the finger or lower lip control sites, whereas there were substantially higher values in the oropharynx of both OSA and SN compared with CL (Table 2). Individual values for VT for the lip and UA are shown in Figure 1. This figure illustrates the very similar clustering of threshold values over a relatively narrow range in all three groups on the lip, and over a comparable range in the UA of CL. However VT values were markedly dispersed in the UA of OSA and SN subjects with many subjects well beyond the upper limits of the CL group. Again, although there was a tendency for values to be slightly lower among SN than OSA subjects, this was not statistically significant. There were no statistically significant correlations between either 2PD or VT and measures of sleep disturbance or apnea severity on the diagnostic polysomnogram for either OSA or SN subjects.

Sensory testing was repeated in patients with OSA a mean of 5.9 $\pm$ 0.5 (SE) and 5.0 $\pm$ 0.5 mo after initial testing in 23 CPAP-treated and 18 untreated patients, respectively. Not all of the original 38 subjects were available for retesting, whereas some OSA subjects $>$ 55 yr old not included in the original group because of a lack of age-matched control subjects were available for retesting (six treated, five untreated subjects 56 to 74 yr old) and were included in the follow-up assessment. Treated patients had been on CPAP for a mean of 3.6 $\pm$ 0.4 mo before retesting and were objectively documented to have used treatment 6.1 $\pm$ 0.4 h per night during this period. There

TABLE 1. SUBJECT CHARACTERISTICS*

	OSA	SN	CL
n	38	12	15
Age, yr	40.6 $\pm$ 1.3	42.6 $\pm$ 2.8	37.8 $\pm$ 1.8
BMI, kg/m^2	33.2 $\pm$ 13†	32.1 $\pm$ 1.6†	24.8 $\pm$ 1.0
AHI, events/h	47.5 $\pm$ 6.6†	6.1 $\pm$ 0.9†‡	0.8 $\pm$ 0.3

* Values are mean $\pm$ SE.
† $p < 0.05$ versus CL.
‡ $p < 0.05$ versus OSA.

TABLE 2. SENSORY DETECTION THRESHOLDS*

	OSA (*n* = 38)	SN (*n* = 12)	CL (*n* = 15)
2PD Hand	19.0 (17.0–22.0)	17.5 (16.0–21.0)	18.0 (17.0–20.0)
2PD Lip	3.0 (2.0 –3.0)	3.0 (2.0–4.0)	3.0 (2.0–3.0)
2PD UA	14.0 (11.5–14.0)†	13.3 (12.5–14.0)†	10.5 (8.5–11.0)
VT Hand	1.3 $\pm$ 0.1	1.3 $\pm$ 0.1	1.1 $\pm$ 0.1
VT Lip	1.8 $\pm$ 0.1	2.1 $\pm$ 0.2	1.6 $\pm$ 0.1
VT UA	4.0 $\pm$ 0.2†	3.8 $\pm$ 0.4†	2.2 $\pm$ 0.1

* Values are median (95% confidence interval) for 2PD (mm) and mean $\pm$ SE for VT (vibration units).
† $p < 0.05$ versus CL.

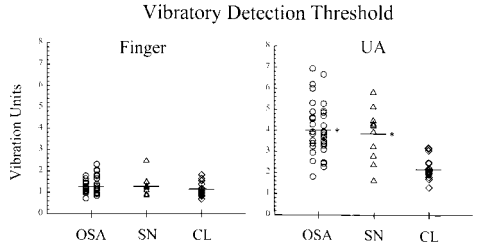

Figure 1. VT values for individual subjects in the three experimental groups for the finger control site (*left panel*) and the UA (*right panel*). Values for OSA subjects are shown in two columns because of the greater number of subjects. Note the similar grouping of values over a 2 vibration unit range for each of the three experimental groups at the control site, and a similar grouping of values in the UA of CL, contrasting with the considerably higher and much more widely dispersed values in the UA of snorers and patients with OSA. The distribution of values about the mean at the lip control site (not shown) was similar to the finger data for all three groups (Table 2). Group mean values are indicated by the *horizontal bars*. *$p < 0.05$ versus CL.

were small differences between the treated and untreated groups in age (54.0 ± 2.4 versus 44.9 ± 2.8 yr, respectively, $p > 0.05$) and diagnostic AHI (66.9 ± 6.3 versus 33.9 ± 4.4, respectively, $p < 0.01$) but no significant difference in BMI.

The results of repeat testing are shown in Table 3 and Figure 2. The values for both 2PD and VT at control sites on the hand and the lip were virtually identical at baseline and repeat testing for both the treated and untreated groups. Similarly, values for 2PD and for VT (Figure 2) in the UA of untreated patients showed no significant change from baseline to repeat testing. The similar median and mean values for baseline and repeat testing, together with generally strong intraclass correlation coefficients clearly demonstrate the reproducibility of our measurement techniques. For CPAP-treated patients, there was a tendency for an improvement in UA 2PD post-CPAP but this did not achieve statistical significance (Table 3). However, there was a significant improvement in UA VT values after CPAP treatment, with a decrease in mean VT value equivalent to approximately one-third of the difference between mean values for OSA subjects and CL at baseline testing (Table 2).

The effects of topical oropharyngeal anesthesia on 2PD and VT are shown in Table 4. There was no effect of topical UA anesthesia on sensory measures at control sites, arguing against any systemic effect of this intervention. However, anesthesia completely abolished 2PD in all patients and produced a severe attenuation of vibratory sensation in the oropharynx.

DISCUSSION

In this study we have shown that the sensory detection thresholds for both 2PD and VT were significantly higher in the UA of OSA and SN compared with CL, whereas sensory thresholds at control sites on the hand and the lip were similar among the three groups. We conclude that these findings demonstrate the presence of a selective impairment in UA mucosal sensory function in patients with OSA and SN. Our findings are consistent with those of Larsson and colleagues (11) who reported impaired thermal sensitivity in the UA of OSA subjects compared with nonsnoring control subjects. We have extended these observations to mechanical sensory modalities which likely play a role in mediating responses to changes in UA patency (7, 8). Furthermore, we assessed snorers and found a similar level of impairment in this group. We also found evidence for partial reversibility of the sensory changes after CPAP treatment in patients with OSA, although a significant impairment persisted.

There are several factors that could have accounted for the difference in sensory values between the experimental groups. The neural changes associated with obstructive sleep-disordered breathing leading to excessive sleepiness or cognitive impairment could have led to impaired central processing and detection of sensory stimuli. However, the lack of differences between the two groups at either the hand or lip control sites for both 2PD and VT suggest that a nonspecific mechanism such as excessive sleepiness does not account for the selective differences at the UA site. Similarly, although the CL were significantly less obese than patients with OSA and SN, it seems unlikely that obesity would produce a selective impairment in the UA with no evidence of any difference at either of the two control sites.

The reliability of our testing procedure should also be considered. Whereas mechanical sensory threshold testing in the UA has not to our knowledge previously been reported, we adapted standard, well-established techniques for testing at peripheral sites to the UA (13–17). The data shown in Tables 3 and 4 and Figure 2 clearly demonstrate the reproducibility of our techniques at all sites in OSA subjects. We have also performed repeat testing in a group of eight control subjects after 2 mo and found no difference in median or mean threshold values at any of the three sites and intraclass correlation coefficients > 0.7 for all comparisons. We are therefore confident of the reproducibility of our testing techniques. Given these considerations, we believe that our findings reliably demonstrate the presence of a selective impairment in sensory function in the UA of patients with OSA and snorers.

A very small number of subjects (1 to 2 per experimental group) were unable to be tested because of intense gag responses (i.e., gagging simply upon opening the mouth fully or with minimal intraoral stimulation). Such individuals might have relatively low sensory thresholds so that their exclusion from the sample could bias in favor of higher sensory thresholds. However, there was a very small number of such subjects, in similar proportion in the three groups, so that a major

TABLE 3. REPEAT SENSORY TESTING: OSA PATIENTS

	Treated ($n = 23$)			Untreated ($n = 18$)		
	Baseline	Post-CPAP	r	Baseline	Repeat	r
2PD Hand	21.0 (19.3–23.0)	21.0 (18.3–23.8)	0.81	20.0 (16.0–23.0)	18.0 (16.0–23.0)	0.90
2PD Lip	3.0 (2.0–4.8)	3.0 (2.0–4.0)	0.64	2.0 (2.0–3.0)	3.0 (2.0–3.0)	0.58
2PD UA	12.3 (9.8–14.0)	11.3 (10.3–13.5)	0.84	13.5 (12.0–14.0)	13.0 (11.4–14.0)	0.56
VT Finger	1.6 ± 0.1	1.5 ± 0.1	0.83	1.3 ± 0.1	1.3 ± 0.1	0.74
VT Lip	1.9 ± 0.1	1.8 ± 0.1	0.71	1.8 ± 0.1	1.6 ± 0.1	0.62
VT UA	4.4 ± 0.2	3.8 ± 0.2*	0.63	3.6 ± 0.3	3.9 ± 0.3	0.74

* $p < 0.05$ versus baseline. Values as in Table 2; r: rho for correlation between test and retest values, all r values $p < 0.05$.

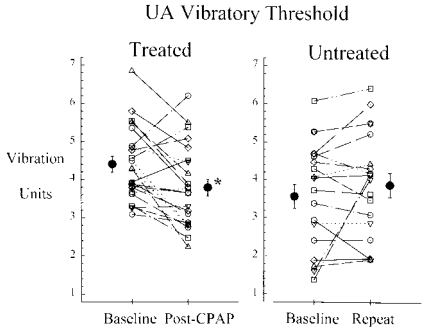

Figure 2. Individual UA vibratory detection threshold values at baseline and follow-up for CPAP-treated and untreated patients with OSA. Note the improvement in sensory detection in the UA in the majority of treated subjects, which contrasts with the stable values for a majority of untreated subjects. Group mean values ± SE are indicated by the *filled symbols with error bars*. *$p < 0.05$ versus baseline.

TABLE 4. EFFECT OF TOPICAL UA ANESTHESIA ($n = 8$)

	Sham	Anesthesia
2PD Hand	17.0 (16.0–19.0)	17.5 (16.0–19.0)
2PD Lip	3.0 (2.0–3.5)	3.0 (2.5–3.5)
2PD UA	12.5 (10.0–13.8)	14.0 (14.0–14.0)*
VT Finger	1.1 ± 0.1	1.2 ± 0.1
VT Lip	1.7 ± 0.2	1.9 ± 0.3
VT UA	2.8 ± 0.4	6.5 ± 0.3†

Values as in Table 2.
* $p < 0.05$.
† $p < 0.0001$ versus sham.

bias due to this factor seems very unlikely. A minority of patients with OSA (approximately 10% of otherwise eligible subjects; typically patients with severe OSA) could not be tested owing to small UA caliber and an inability to place the testing probes without contacting other structures. The UA sensory acuity of such subjects therefore remains unknown, and we cannot exclude the possibility that the inability to test these subjects caused a true difference between, for example, OSA and SN groups to be missed. However, the number of such subjects was small, and we were able to perform sensory testing from a large number of OSA subjects with a broad range of disease severity. We therefore doubt that any major bias or influence on the conclusions of the study is present as a result of this factor. Overall, we believe that our samples of SN and OSA subjects were representative of a broad population of individuals with obstructive sleep-disordered breathing.

There is morphologic evidence to support the presence of a sensory neuropathy in the UA in obstructive sleep-disordered breathing. Friberg and coworkers (22) described a proliferation of nerve endings in biopsy specimens from the oropharyngeal mucosa of snorers and OSA subjects, in a pattern suggestive of nerve injury. Woodson and coworkers (23) also described focal degeneration of myelinated nerve fibers and axons by electron microscopy in uvulopalatopharyngoplasty specimens from patients with OSA. Other studies have also provided evidence of denervation-type changes in UA dilator muscles, suggesting that efferent neural involvement may also occur (24). These observations have led to the suggestion that the progression from mild snoring to heavy habitual snoring and then OSA may represent a progressive local neuropathy (25).

There are several potential mechanisms which could lead to nerve or sensory receptor damage in the UA. Previous studies have demonstrated the presence of mucosal edema in the UA of patients with OSA, which improves with chronic CPAP treatment (26). The factors responsible for the edema are unknown, but presumably relate to repeated trauma to UA tissues from snoring-associated vibration and forceful suction collapse of the airway during apneas. Accumulation of fluid owing to mechanical effects, vascular changes, or release of inflammatory mediators could potentially interfere with the function of nerve endings in the mucosa. The improvement in edema post-CPAP (26) could also potentially account for the partial improvement in UA sensory function after chronic CPAP use in OSA subjects. Alternatively, there could be direct vibration-related injury to nerve endings analogous to that observed in the upper extremities of vibrating equipment operators (25, 27). Another possibility for OSA subjects is that Mayer and colleagues (28) have provided evidence for peripheral neuropathy in patients with OSA, the severity of which is related to the severity of nocturnal hypoxemia. However, it is not known whether this represents a sensory neuropathy, and our OSA subjects did not show evidence of impaired sensation in the upper extremity.

The similarity of the impairment in snorers and OSA subjects and the lack of correlation between the degree of sensory impairment and the measures of apnea severity suggest either that the UA sensory impairment develops early on in the development and progression of snoring or OSA (25), or that it represents some underlying susceptibility to the development of UA obstruction during sleep. The repeat sensory testing in OSA subjects showed that there was a selective improvement in the UA VT with nasal CPAP treatment. A trend to improvement was also seen for 2PD but this did not achieve statistical significance. Although the improvement in VT was significant, the mean value was still well above those seen for control subjects (Tables 2 and 3). The CPAP treatment period, while relatively long for follow-up assessment, may have been inadequate to allow the full extent of potential reversibility. We also cannot rule out the possibility that CPAP itself could perpetuate neural dysfunction, although this seems unlikely. Overall we believe our findings are consistent with the UA sensory impairment developing as a consequence of snoring and while remaining partially reversible, representing a largely permanent injury. Alternatively, these findings are also consistent with the possibility that the impairment may be caused by underlying genetic factors governing sensory function.

The impairment of UA sensory function demonstrated here could represent an important mechanism in the pathophysiology of obstructive sleep-disordered breathing. As discussed, previous studies have shown that application of topical UA anesthesia increases the propensity to UA collapse during sleep (2–4). Numerous studies have described protective UA dilator reflex responses to pulses of negative airway pressure, which act to maintain airway patency (29–31). These reflexes are attenuated during sleep in normals (29, 30), and are also attenuated during wakefulness in patients with OSA (31). The UA sensory impairment could potentially represent a defect in the afferent limb of such protective reflexes, thereby contributing to impaired defense of UA patency during sleep. Indeed recent work has shown that topical UA anesthesia impairs genioglossus dilator responses to negative pressure during wakefulness (32), and reduces phasic activity of this muscle during sleep (33).

We and others have also shown that interfering with UA sensory receptor function delays end-apneic arousal and apnea termination (5, 6, 9, 10). Furthermore, we have provided indirect evidence that dysfunction of UA sensory receptors may worsen over the course of a single night and contribute to lengthening of apneas from the beginning to the end of the

night (9). Further studies will be required to investigate specifically the possible contribution of altered UA sensory function to the initiation of UA obstruction during sleep as well as to impaired arousal responses to airway occlusion.

In summary, the findings of this study indicate the presence of a selective impairment of UA mucosal sensation in patients with OSA and snorers. This impairment may be an early change in the progression of UA obstruction during sleep, possibly developing as a consequence of vibration-related edema or neural damage during snoring or apneas, but may also represent an underlying factor contributing to susceptibility to snoring and apnea. Further studies will be required to more clearly establish the mechanisms of this impairment and to evaluate its contribution to the pathophysiology of obstructive sleep-disordered breathing.

Acknowledgment: The authors wish to thank Dr. John Stewart for the use of his Vibratron II testing device. They also acknowledge the expert contribution of the sleep laboratory technologists at the Royal Victoria Hospital.

References

1. Cistulli PA, Sullivan CE. Pathophysiology of sleep apnea. In: Saunders NA, Sullivan CE, editors. Sleep and breathing, 2nd ed. New York: Marcel Dekker; 1994. p. 405–448.
2. DeWeese EL, Sullivan TY. Effects of upper airway anesthesia on pharyngeal patency during sleep. *J Appl Physiol* 1988;64:1346–1353.
3. McNicholas WT, Coffey M, McDonnell T, O'Regan R, Fitzgerald MX. Upper airway obstruction during sleep in normal subjects after selective topical oropharyngeal anesthesia. *Am Rev Respir Dis* 1987;135:1316–1319.
4. Chadwick GA, Crowley P, Fitzgerald MX, O'Regan RG, McNicholas WT. Obstructive sleep apnea following topical anesthesia in loud snorers. *Am Rev Respir Dis* 1991;143:810–813.
5. Basner RC, Ringler J, Garpestad E, Schwartzstein RM, Sparrow D, Weinberger SE, Lilly J, Weiss JW. Upper airway anesthesia delays arousal from airway occlusion induced during human NREM sleep. *J Appl Physiol* 1992;73:642–648.
6. Issa FG, McNamara SG, Sullivan CE. Arousal responses to airway occlusion in sleeping dogs: comparison of nasal and tracheal occlusions. *J Appl Physiol* 1987;62:1832–1836.
7. Sant'Ambrogio G, Tsubone H, Sant'Ambrogio FB. Sensory information from the upper airway: role in the control of breathing. *Respir Physiol* 1995;102:1–16.
8. Widdicombe J. Upper airway reflexes. *Curr Opinion Pulmon Med* 1998; 4:376–382.
9. Cala SJ, Sliwinski P, Cosio MG, Kimoff RJ. Effect of topical upper airway anesthesia on apnea duration through the night in obstructive sleep apnea. *J Appl Physiol* 1996;81:2618–2626.
10. Berry RB, Kouchi KG, Bower JL, Light RW. Effect of upper airway anesthesia on obstructive sleep apnea. *Am J Respir Crit Care Med* 1995; 151:1857–1861.
11. Larsson H. Carlsson-Nordlander B, Lindblad LE, Norbeck O, Svanborg E. Temperature thresholds in the oropharynx of patients with obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1992;146:1246–1249.
12. Redline S, Tosteson T, Boucher MA, Millman RP. Measurement of sleep-related breathing disturbances in epidemiologic studies: assessment of the validity and reproducibility of a portable monitoring device. *Chest* 1991;100:1281–1286.
13. Calhoun KH, Gibson B, Hartley L, Minton J, Hokanson JA. Oral sensation and aging. In: Kuna ST, editor. Sleep and respiration in aging adults. New York: Elsevier Science; 1991. p. 215–225.
14. Crosby PM, Dellon AL. Comparison of two-point discrimination testing devices. *Microsurgery* 1989;10:134–137.
15. Aviv JE, Hecht C, Weinberg H, Dalton JF, Urken ML. Surface sensibility of the floor of the mouth and tongue in healthy controls and in radiated patients. *Otolaryngol Head Neck Surg* 1992;107:418–423.
16. Goldberg JM, Lindblöm U. Standardized method of determining vibratory perception thresholds for diagnosis and screening in neurological investigation. *J Neurol Neurosurg Psychiatr* 1979;42:793–803.
17. Gerr FE, Letz R. Reliability of a widely used test of peripheral cutaneous vibration sensitivity and a comparison of two testing protocols. *Br J Ind Med* 1988;45:635–639.
18. Montserrat JM, Farre R, Ballester E, Felez MA, Pasto M, Navajas D. Evaluation of nasal prongs for estimating nasal flow. *Am J Respir Crit Care Med* 1997;155:211–215.
19. Rechtschaffen A, Kales A. A manual of standardized terminology, technique and scoring system for sleep stages of human sleep. Los Angeles Brain Information Service. Brain Information Institute, UCLA, 1968.
20. ASDA Sleep Disorders Atlas Task Force. EEG arousals: scoring rules and examples. *Sleep* 1992;15:174–184.
21. Colton T. Statistics in medicine. Boston: Little, Brown; 1974. p. 189–227.
22. Friberg D, Gazelius B, Hokfelt T, Nordlander B. Abnormal afferent nerve endings in the soft palatal mucosa of sleep apnoics and habitual snorers. *Regul Pept* 1997;71:29–36.
23. Woodson BT, Garancis JC, Toohill RJ. Histopathologic changes in snoring and obstructive sleep apnea syndrome. *Laryngoscope* 1991;101: 1318–1322.
24. Edstrom L, Larsson H, Larsson L. Neurogenic effects on the palatopharyngeal muscle in patients with obstructive sleep apnoea: a muscle biopsy study. *J Neurol Neurosurg Psychiatry* 1992;55:916–920.
25. Friberg D. Heavy snorer's disease: a progressive local neuropathy. *Acta Otolaryngol (Stockh)* 1999;119:925–933.
26. Ryan CF, Lowe A, Li D, Fleetham JA. Magnetic resonance imaging of the upper airway in obstructive sleep apnea before and after chronic nasal continuous positive airway pressure therapy. *Am Rev Respir Dis* 1991;144:939–944.
27. Lundborg G, Dahlin L, Hansson HA, Kanje M, Necking LE. Vibration exposure and peripheral nerve fiber damage. *J Hand Surg* 1990;15: 346–351.
28. Mayer P, Dematteis M, Pepin JL, Wuyam B, Veale D, Vila A, Levy P. Peripheral neuropathy in sleep apnea: a tissue marker of the severity of nocturnal desaturation. *Am J Respir Crit Care Med* 1999;159:213–219.
29. Horner RL, Innes JA, Morrell MJ, Shea SA, Guz A. The effect of sleep on reflex genioglossus muscle activiation by stimuli of negative airway pressure in humans. *J Physiol* 1993;476:141–151.
30. Wheatley JR, Mezzanotte WS, Tangel DJ, White DP. Influence of sleep on genioglossus muscle activation by negative pressure in normal men. *Am Rev Respir Dis* 1993;148:597–605.
31. Mortimore IL, Douglas NJ. Palatal muscle EMG response to negative pressure in awake sleep apneic and control subjects. *Am J Respir Crit Care Med* 1997;156:867–873.
32. Fogel RB, Malhotra A, Shea SA, Edwards JK, White DP. Reduced genioglossal activity with upper airway anesthesia in awake patients with OSA. *J Appl Physiol* 2000;88:1346–1354.
33. Berry RB, McNellis MI, Kouchi K, Light RW. Upper airway anesthesia reduces phasic genioglossus activity during sleep apnea. *Am J Respir Crit Care Med* 1997;156:127–132.