Two-Point Palatal Discrimination in Patients With Upper Airway Resistance Syndrome, Obstructive Sleep Apnea Syndrome, and Normal Control Subjects*

Christian Guilleminault, MD, BiolD; Kasey Li, MD, DDS; Ning-Hung Chen, MD; and Dalva Poyares, MD

Study objective: To compare the results of a two-point palatal discrimination response in normal subjects (n = 15), patients with obstructive sleep apnea syndrome (OSAS) [n = 15], and patients with upper airway resistance syndrome (UARS) [n = 15] matched for age, sex, and body mass index.

Design: Comparison study of three subject groups.

Setting: A sleep-disorders clinic.

Subjects: Participants were selected based on clinical questionnaire, clinical evaluation, and polysomnography.

Intervention: Polysomnography involving measurement of flow limitation with a nasal cannula pressure transducer system and of respiratory effort with esophageal pressure was performed in order to recognize the presence, absence, and types of sleep-disordered breathing. The 45 subjects were submitted to a two-point palatal discrimination study during wakefulness performed by an investigator blinded to the polysomnogram results.

Results: Patients with OSAS had a clear impairment of their palatal sensory input with a significant decrement in two-point discrimination, but patients with UARS and normal control subjects had similar responses. Patients with UARS exhibited at least intermittent snoring in most cases.

Conclusion: The normal responses seen in patients with UARS indicate that these patients are more capable of transmitting sensory inputs than patients with OSAS. This may be one element explaining the difference in arousal response previously documented in UARS compared to OSAS.

(CHEST 2002; 122:866–870)

Key words: neurologic lesion; obstructive sleep apnea syndrome; palatal sensation; snoring; two-point discrimination test; upper airway resistance syndrome

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; OSAS = obstructive sleep apnea syndrome; PES = esophageal pressure; RDI = respiratory disturbance index; RERA = respiratory event-related arousal; UARS = upper airway resistance syndrome

Patients with upper airway resistance syndrome (UARS) have very few, if any, obstructive apneas; their normal breathing pattern consists mostly of hypopneas and breaths with increased respiratory effort. These patients present with respiratory effort-related arousals (RERAs) and have an important increase in the 7-Hz to 9-Hz EEG power spectrum of the central leads compared to normal subjects.1–3 Patients with obstructive sleep apnea syndrome (OSAS) have obstructive apneas and hypopneas that lead to oxygen desaturations, and their sleep EEG is very different from that of patients with UARS and control subjects. They have a delayed arousal response, despite the fact that increased respiratory effort is seen during the obstructive phase, as confirmed by the difference in patterns of EEG spectrum analysis in the central leads.4 We hypothesized that a difference in sensory input may be responsible for the divergent responses to the abnormal breathing patterns that may exist between patients with UARS and patients with OSAS. Friberg et al4,5

*From the Stanford University Sleep Disorders Clinic, Stanford, CA.

Dr. Guilleminault is the recipient of an Academic Award from The Sleep Research Center of the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Dr. Poyares was supported by a fellowship from FASEP, Sao-Paulo, Brazil.

Manuscript received November 9, 2001; revision accepted March 1, 2002.

Correspondence to: Christian Guilleminault, MD, BiolD, Stanford University Sleep Disorders Clinic, 401 Quarry Rd, Suite 3301, Stanford CA 94305; e-mail: cguil@stanford.edu
performed various histologic analyses on biopsy specimens obtained from patients with OSAS. They showed that patients with OSAS had evidence of morphologic abnormalities, including signs of neurogenic lesions in the palatopharyngeal muscles obtained during uvulopalatopharyngoplasty, compared to normal control subjects. These patients also presented an increased number of various nerve endings in the mucosal epithelium, as shown by histochemical techniques, additionally supporting the hypothesis that patients with OSAS have a neurogenic disorder involving afferent fibers located in the palatal mucosa. Some of their histologic findings are similar to those obtained by Edstrom et al. We hypothesized that patients with OSAS have different afferent inputs during sleep compared to UARS, due to the neurogenic lesions previously described and that the palatal neurogenic lesions play a role in the delayed responses to abnormal respiratory effort during sleep. Our first investigation analyzed the response to two-point discrimination test applied to the palatal mucosa on control subjects, patients with UARS, and patients with OSAS during wakefulness.

**Materials and Methods**

**Subject Population**

Subjects were evaluated in the sleep clinic or recruited from the community. Normal subjects were recruited based on response to an extensive sleep questionnaire, the sleep disorders questionnaire. After clinical interview and examination, subjects underwent a nocturnal polygraphic recording with measurement of esophageal pressure (PES). Several normal control subjects who were part of a larger study on measurement of respiratory efforts during sleep received payment for their participation.

**Inclusion/Exclusion Criteria**

Patients with sleep disorders and normal subjects fulfilled the following clinical and polysomnographic inclusion criteria: (1) clinical criteria, age between 35 years and 50 years (or premenopausal for women); body mass index (BMI) between 23 and 26; absence of neurologic, cardiovascular, pulmonary, or other chronic illness; no prior surgery on the nose and palate; no current drug intake; and no prior treatment of sleep-disordered breathing; (2) polysomnographic recording criteria, patients with OSAS must have an apnea-hypopnea index (AHI) > 15/h of sleep; patients with UARS must have an AHI < 5/h of sleep; normal control subjects must have an AHI ≤ 1/h of sleep, and must not have evidence of abnormally increased effort during sleep as described for UARS; and (3) subjects must have provided informed consent.

**Polysomnography**

All subjects with an initial evaluation who met inclusion criteria underwent nocturnal polysomnography. The following variables were monitored: EEG, electro-occulogram, chin electromyogram, leg electromyogram, heart rate (modified V̇̇E lead), and body position. Respiration was evaluated with nasal cannula pressure transducer system, PES transducer, thoracic bands, abdominal bands, pulse oximetry, and neck microphone. Recordings were scored following the international criteria for sleep/wake with identification of short (≥ 3 s) arousals; tabulation of apneas, hypopneas, and RERAs; and obstructive, mixed events, and central events following the criteria of the American Academy of Sleep Medicine. The tabulation of apneas, hypopneas, and RERAs lead to a respiratory disturbance index (RDI). There was also scoring of short visual arousals (≥ 3 s) secondary to “abnormal breathing efforts.” This scoring is performed using PES recording with recognition of “PES crescendos” and “sustained abnormal respiratory effort” as previously described, in addition to the nasal cannula pressure transducer system with recognition of respiratory events of < 10 s duration but terminated by a visual EEG arousal of ≥ 3 s (arousal with abnormal breathing effort).

**Palatal Test**

Forty-six subjects fulfilling inclusion criteria were submitted to a palatal test that was performed between 10:30 AM and 1:00 PM. The different categories of subjects (OSAS, UARS, and control) were matched for age (± 2 years) as well as BMI (± 1.5). An investigator blinded to the polysomnographic results and the subject’s clinical classification obtained measurements.

All subjects were comfortably seated with jaws kept open with a speculum to more easily evaluate palatal sensation. As a first step, a 25-gauge needle was placed on a 1-mL tuberculin syringe. The point of the needle had been cut off to present a smooth top. A small plastic collar was placed on the needle at a distance of 0.5 mm, 1 mm, and 2 mm from the tip of the modified needle. During the first two measurements, the needle was placed in contact with the mucosa of the right and left lateral walls of the palate in the quadrant located on the same line as the base of the uvula, and the third measurement was made at the base of the uvula. There was a 2-min interruption between each measurement, and the order of measurement (right, left, central) was determined based on a randomization table. If the patient did not recognize the tactile stimulus with the collar placed at 0.5 mm and without pressure applied, a syringe with the collar placed at 1-mm or 2-mm distance from the tip was used after a 2-min break, and the pressure applied was increased until the mucosa was impressed to contact the plastic collar. The pressure was, however, light enough to avoid any lesion of the mucosa. This semiquantitative approach was used to ensure that there was a sensory response to pressure. This preliminary phase also allowed the subject to acclimate to the procedure and learn to avoid triggering a gag reflex.

Once the single-point pressure resulting in a positive response was determined, the two-point distinction study was performed. A special compass-like device was built (Fig 1). When the two branches were in close contact, the distance was 0.4 mm in diameter. A screw system allowed opening the two branches to keep the two branches fixed at the selected distance. The same collars as those used to determine response to pressure were placed on each branch of the device. The amount of pressure exerted on the equipment to obtain a one-point tactile response was again determined and corresponded with the initial results found with the modified needle and syringe. The amount of pressure applied was similar to the pressure determined with the one-point palatal tactile test. The two-point detection measurement was obtained twice in three selected palatal locations (Fig 2) in a random fashion. The best result of the six measurement trials is presented in Table 1.
Statistical Analysis

As the data are not normally distributed, the values obtained for the two-point discrimination measurements (i.e., the first interval when subject could distinguish two points) were compared for the three experimental groups using a Kruskal-Wallis analysis of variance on ranks and a Dunn test for postanalysis of variance comparison.

Results

The forty-five individuals, 15 in each group, involved in the study analysis are presented in Table 1. One subject with OSAS was removed: an outlier with a two-point distinction of 15-mm distance, a much higher distance than everyone else in the study. Review of clinical history and esophageal pH study revealed that he had reflux in association with OSAS. None of the other subjects studied had clinical symptoms or suspicion of esophageal reflux with OSAS. RDI and snoring data are presented in Table 1. The frequency of arousals with abnormal breathing efforts (defined as number of visual arousals of ≥ 3 s noted at the end of normal breathing patterns that do not fit the definition of apnea, hypopnea, or RERAs) was a mean of 3 ± 2/h in patients with OSAS, 17.9 ± 4/h in patients with UARS, and 2 ± 1.5/h in control subjects. The scoring of these short events showed that patients with UARS responded very quickly with an arousal to breathing abnormalities, such as an abnormal increase in breathing effort or minor flow limitation without development of apnea or hypopnea. All subjects responded to pressure with the syringe test, except for five patients with OSAS requiring the 1-mm marker to recognize the one-point response and four patients with OSAS requiring pressure applied up to the 2-mm marker.

Two-Point Distinction Measurements Study

There was a significant difference between patients with OSAS and the two other groups. Table 1 presents the data when taking the best response of the six measurement trials. There were similarly significant differences if all trials were included. The mean ± SD values were 3.86 ± 0.58, 1.66 ± 1.0, and 1.63 ± 0.29 for OSAS, UARS, and control subjects (mean rank, 38.0, 15.9, and 15.1, respectively; p = 0.0001; Table 1). As subjects were matched for age and BMI, there was no significant difference between these variables.

Discussion

Axonal degeneration and segmental demyelination in afferent neurons, such as in A fibers, cause sensory impairment. These lesions are associated with a slowing of impulse conduction.9 Friberg et al.4,5,10 accumulated data providing evidence for local neurogenic lesions in OSAS and heavy snorers. Their data are in accordance with those shown by Woodson et al.11 and by Series et al.12 Recently, Kimoff et al.13 performed a study closely related to ours with investigation of two-point discrimination in OSAS and snorers. Most of these authors hypothesized that snoring was responsible for the histologic alterations reported. Kimoff et al.13 found abnormal responses in their snorers. This finding was similar to the abnormal response found by Friberg et al.10 when using a heated probe to investigate palatal response not only in OSAS but also in snorers. Clearly, snoring is not the only factor that may lead to the histologic impairment. Esophageal reflux may be a component in the development of local impairment of the palatal mucosa and, likely, its local afferent nerve fibers.
In contrast to the snorers reported by Friberg et al.\(^4\) and Kimoff et al.\(^1,3\) and despite the fact that nearly all (13 of 15 patients) of our patients with UARS presented intermittent snoring as documented by the polygraphic recordings, our patients did not differ significantly from our control subjects when two-point discrimination was studied. Several elements could explain this discrepancy: (1) There was not enough snoring during the night and/or the number of years spent snoring was insufficient in

| Control | Age, yr | Sex | BMI | RDI | Two-Point Discrimination | Snoring
|---------|---------|-----|-----|-----|--------------------------|-------
| 1       | 38      | Female | 23.6 | 0.0 | 1.5 | 0
| 2       | 40      | Female | 23.4 | 0.0 | 1.5 | 0
| 3       | 42      | Male | 24.4 | 0.2 | 1.5 | 0
| 4       | 41      | Male | 25.2 | 0.4 | 1.5 | 0
| 5       | 36      | Male | 24.5 | 0.1 | 2.0 | <50 Mild
| 6       | 48      | Male | 24.1 | 0.2 | 1.5 | 0
| 7       | 43      | Male | 24.9 | 0.1 | 1.5 | 0
| 8       | 40      | Male | 24.3 | 0.0 | 1.5 | 0
| 9       | 41      | Male | 24.6 | 0.4 | 2.0 | 0
| 10      | 39      | Male | 24.3 | 0.1 | 2.0 | <50 Moderate
| 11      | 37      | Male | 25.2 | 0.2 | 1.5 | 0
| 12      | 47      | Male | 25.2 | 0.4 | 1.5 | 0
| 13      | 44.2    | Male | 24.5 | 0.8 | 1.5 | <50 Mild
| 14      | 42      | Male | 24.7 | 0.3 | 1.5 | 0
| 15      | 40.6    | Male | 24.1 | 0.6 | 2.0 | 0

| OSAS | Age, yr | Sex | BMI | RDI | Two-Point Discrimination | Snoring
|------|---------|-----|-----|-----|--------------------------|-------
| 1    | 39.6    | Female | 24.1 | 21  | 3.5 | >50 Moderate
| 2    | 41.1    | Female | 23.9 | 28  | 3.0 | >50 Moderate
| 3    | 40.6    | Male | 25.1 | 35  | 3.5 | >50 Moderate
| 4    | 42.3    | Male | 25.7 | 39  | 4.0 | >50 Severe
| 5    | 37.0    | Male | 25.3 | 29  | 3.5 | >50 Severe
| 6    | 48.7    | Male | 24.8 | 33  | 3.0 | >50 Severe
| 7    | 42.2    | Male | 25.6 | 37  | 4.0 | >50 Moderate
| 8    | 39.3    | Male | 24.8 | 32  | 3.5 | >50 Severe
| 9    | 41.9    | Male | 25.2 | 38  | 4.5 | >50 Severe
| 10   | 38.9    | Male | 24.7 | 32  | 4.0 | >50 Moderate
| 11   | 38.1    | Male | 25.8 | 31  | 3.5 | >50 Severe
| 12   | 46.6    | Male | 25.9 | 32  | 4.0 | >50 Severe
| 13   | 44.2    | Male | 25.6 | 36  | 4.5 | >50 Severe
| 14   | 41.7    | Male | 25.5 | 39  | 5.0 | >50 Severe
| 15   | 41.9    | Male | 24.9 | 40  | 4.5 | >50 Severe

| UARS | Age, yr | Sex | BMI | RDI | Two-Point Discrimination | Snoring
|------|---------|-----|-----|-----|--------------------------|-------
| 1    | 39.1    | Female | 23.9 | 2.0 | 1.5 | <50 Mild
| 2    | 39.6    | Female | 23.7 | 1.3 | 1.0 | 0
| 3    | 43.0    | Male | 24.8 | 3.0 | 1.5 | <50 Mild
| 4    | 40.2    | Male | 25.1 | 3.1 | 2.0 | <50 Moderate
| 5    | 37.0    | Male | 24.2 | 1.6 | 1.5 | <50 Mild
| 6    | 47.1    | Male | 24.4 | 3.3 | 2.0 | <50 Moderate
| 7    | 43.8    | Male | 24.8 | 2.3 | 2.0 | <50 Moderate
| 8    | 41.4    | Male | 24.6 | 1.8 | 2.5 | <50 Moderate
| 9    | 40.6    | Male | 24.7 | 2.1 | 1.5 | <50 Mild
| 10   | 40.1    | Male | 25.0 | 1.6 | 1.5 | <50 Mild
| 11   | 37.1    | Male | 24.7 | 2.9 | 1.5 | <50 Mild
| 12   | 47.1    | Male | 25.0 | 3.1 | 1.5 | 0
| 13   | 44.9    | Male | 24.9 | 2.4 | 1.0 | <50 Mild
| 14   | 42.1    | Male | 25.0 | 2.2 | 2.0 | <50 Moderate
| 15   | 40.2    | Male | 24.4 | 1.9 | 2.0 | <50 Mild

*The two-point discrimination measurements presented are the best result of the six measurement trials obtained at one of the three different palatal locations selected for the testing. Age and BMI were not significantly different. The RDI, defined as the number of abnormal respiratory events per hour of sleep, was significantly higher for patients with OSAS as per inclusion criteria. Snoring is subdivided by “duration”: absent, intermittent, and regular based on the presence of a microphone signal during 0%, <50%, or >50% of total sleep time. Snoring is further subdivided by “intensity”: absent, mild, moderate, and severe based on the width of the recorded microphone signal calibrated in power.*
patients with UARS to have induced the neurologic lesions. (2) There are different types of snoring. OSAS may cause more extensive vibrations at the palatal level while UARS may present more noise related to narrowing behind the base of the tongue. Impairment of the nose leads to vibration and snoring that is very different. Hoffstein et al\textsuperscript{14} showed in a large series of snorers that snoring is a very dubious symptom with various connotations. (3) Associated features such as covert reflux, importance of negative PES at end of inspiration, and others are different in OSAS and UARS, and the destruction of palatal mucosa occurs at a faster rate in OSAS than in UARS.

We believe that all three hypotheses are possible and may be seen in association. Some patients with UARS (2 of 15 patients) do not present with snoring but rather have sleep-disordered breathing. Also patients with UARS have a different character of snoring compared to patients with OSAS, most commonly lower pitched and appearing to occur behind the base of the tongue. The issue of the symptom duration is more difficult to judge, complicated by the fact that this is not a prospective study; however, some of the patients with UARS offered symptoms of tiredness and fatigue since their late teenage years and had evidence of a small mandible as indicated by the need for wisdom tooth extraction early in life as well as the development of hypertension.\textsuperscript{15} UARS is probably anatomically different from OSAS, and chronic snoring does not equate to UARS. The fact that some chronic snorers can have hypertension develop would support this subdivision. Other explanations may exist. For example, very loud palatal snorers may have intermittent presence of sleep-disordered breathing during nocturnal polysomnography with night-to-night variability. Furthermore, recording techniques (presence or absence of nasal cannula pressure transducer system or PES measurement) may identify more or less respiratory pathology during sleep. Compared to Kimoff et al,\textsuperscript{13} we have overall similar findings for OSAS patients (ie, these subjects are significantly different from control subjects). The results differ though, which is likely related to a divergence in the technique used, as we first determine a threshold for pressure to be applied and may have used a different approach. Moreover, we selected a population clearly less obese and less severe based on RDI compared to these authors. Kimoff et al\textsuperscript{13} reported an improvement in vibration sensation and a trend toward return of two-point discrimination with use of nasal continuous positive airway pressure (CPAP). These findings are of importance, as CPAP was not used for long. They could indicate reversibility of the lesions in some cases. This has previously been suggested by the disappearance of vascular endothelial abnormalities in some OSAS patients with CPAP treatment.\textsuperscript{16} The important finding, however, is the normal response at two-point discrimination in well-defined patients with UARS, emphasizing an additional difference between the two syndromes.

REFERENCES

7 Guilleminault C, Chowdhury S. Upper airway resistance syndrome is a distinct syndrome. Am J Respir Crit Care Med 2000; 161:1412–1413