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Soft Palate Sensory Neuropathy in the Pathogenesis of Obstructive Sleep Apnea

Ola Sunnergren, MD; Anders Broström, RN, PhD; Eva Svanborg, MD, PhD

Objectives/ Hypothesis: In general, obstructive sleep apnea (OSA) seems to be a progressive disorder whose pathogenesis is not fully understood. One hypothesis is that long-standing snoring vibrations cause a local neuropathy in the upper airway, which predisposes to obstructive events during sleep. The aim of this study was to investigate sensory function in the upper airway in a cohort of subjects comprising nonsnorers, snorers, and untreated subjects with OSA, and to correlate data to apnea–hypopnea index (AHI) and duration of snoring.

Study Design: Cross-sectional cohort study.

Methods: Subjects were recruited from primary care hypertension clinics. Whole-night respiratory recordings were performed to determine presence and degree of OSA. Three groups were formed based on AHI and snoring history: 1) nonsnorers (n = 25); 2) snorers, AHI < 10 (n = 32); 3) OSA subjects, AHI ≥ 10 (n = 33). Quantitative cold sensory testing of the soft palate and lip was used to assess neuropathy.

Results: There were no significant differences concerning lip sensory function between groups. Nonsnorers showed significantly lower thresholds for cold (i.e., better sensitivity) in the soft palate compared to both other groups ($P < .01$). Snorers had lower thresholds than OSA subjects ($P < .05$). There were significant correlations ($P < .01$) between decreased sensory function and AHI ($r_s = .41$) and to duration of snoring ($r_s = .47$).

Conclusions: The degree of sensory neuropathy in the upper airway correlates with degree of obstructive sleep disorder. Our results strengthen the hypothesis that snoring vibrations may cause a neuropathy in the upper airway, which contributes to the progression and development of OSA.

Key Words: Obstructive sleep apnea, snoring, cold thermal testing, soft palate, method of limits, quantitative sensory testing.

Level of evidence: 2b.

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INTRODUCTION

The pathogenesis of obstructive sleep apnea (OSA) and obstructive sleep apnea syndrome (OSAS) is not fully understood. In general, OSAS seems to be progressive over time and the prevalence increases with age.[1,2] Many patients report years of snoring before witnessed apneas and symptoms occur.[3] Anthropometric as well as anatomic factors compromising the size of the upper airway, such as excess body weight, maxillomandibular retrognathia, and enlarged tonsils, are well-known risk factors for snoring and OSA. However, because anatomic features in most cases remain unchanged in adulthood and excess body weight is not a prerequisite for OSA, other factors seem to be involved in the progression of OSA. It is well known from occupational medicine that long-standing vibrations may cause nervous lesions in tissues, with an exposure–effect relationship between vibration and neuronal damage.[4,5] In animals it has been shown that both unmyelinated and myelinated fibers in the hind leg are damaged after vibration exposure.[6] Based on these observations, the hypothesis was formed on the pathogenesis of OSA that long-standing snoring-induced vibrations cause neurogenic lesions in upper airway tissues, thereby damaging the reflex circuits responsible for keeping the upper airway open during inspiration. This would become critical during sleep, when the muscle tone is normally reduced. This hypothesis has been proposed and pursued by Svanborgs research group for several years, and several studies have been performed supporting this hypothesis by showing upper airway neuropathy in OSAS subjects.[7–9] Other research groups have also contributed with data supporting the hypothesis.[10–12] In these studies several different methods of measuring local sensory neuropathy have been used, such as vibration,[10] two-point discrimination,[11] and air-pressure pulses.[12] However, these previous studies included limited numbers of subjects, clear differentiations of patients with varying degrees of

From the The ENT Clinic (S.O.), Ryhov County Hospital, Jönköping, Sweden; Department of Clinical Neurophysiology (B.A., S.E.), University Hospital, Linköping, Sweden, School of Health Sciences (B.A.), Jönköping University, Jönköping, Sweden, Department of Clinical Neurophysiology/ IKE (S.E.), Linköping University, Sweden.

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Send correspondence to Dr. Ola Sunnergren, ENT Clinic, Ryhov County Hospital, 55185 Jönköping, Sweden.
E-mail: ola.sunnergren@lj.se

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TABLE I.
Subject Characteristics and Results.

Group	No. of Subjects			Age	AHI	Snoring Years	ESS	BMI	CDT (°C) Soft Palate	CDT (°C) Lip
	Total	Male	Female							
1. Nonsnorers	25	8	17	59 (51–65)	2 (0–5)	0	7 (0–17)	26 (21–38)	2.8 (1.0–5.0)	0.9 (0.4–1.4)
2. Snorers	32	14	18	60 (41–65)	4 (0–10)	13 (4–30)	8 (1–19)	28 (21–34)	5.1 (1.0–13.2)	1.1 (0.4–2.1)
3. OSA subjects	33	18	15	59 (42–66)	30 (10–82)	15 (4–40)	8 (1–16)	31 (22–43)	6.6 (1.7–16.6)	1.1 (0.5–2.2)

Values are given as means (maximum–minimum).
AHI = apnea–hypopnea index; ESS = Epworth sleepiness scale; CDT = Cold detection thresholds; OSA = Obstructive sleep apnea; BMI=body mass index.

obstructive breathing were not made, and there were no attempts to correlate the duration of snoring to degree of sensory deficit in the upper airway.

As preparation for the present study we have previously evaluated a cold thermal testing method for the assessment of local neuropathy in the soft palate with special reference to test–retest repeatability.[13] We have shown that measuring cold detection thresholds (CDT) with the noninvasive Method of Limits shows good test–retest repeatability and consequently is suitable for this task. The aim of the present study was therefore to use this method to compare sensory function in the upper airway in a cohort of subjects comprising nonsnorers, snorers, and untreated subjects with OSA, and to correlate these data to AHI and duration of snoring.

MATERIALS AND METHODS

Subjects were consecutively recruited from primary care hypertension clinics. None of the subjects had sought medical attention or been evaluated for OSA before the time of inclusion. All subjects underwent a full-night respiratory recording in their homes, which included nasal airflow, pulse oximetry, respiratory movements, and body position (recorded with the Embletta recording system, Somnologica software, ResMed Inc, Trollhättan, Sweden). Recordings were evaluated for apnea–hypopnea index (AHI), with apneas and hypopneas scored according to the 2007 recommendations of the American Academy for Sleep Medicine. A medical history, with special emphasis on snoring, was obtained from all subjects. All subjects underwent a clinical examination including assessments of tonsillar size and body mass index (BMI). Sleepiness was measured by the Epworth Sleepiness Scale (ESS). Subjects were grouped based on a combination of self reported snoring history and AHI as follows: 1) *Nonsnorers,* with partner-verified absence of past or present snoring and AHI $\leq$5; 2) *Snorers,* with partner-verified habitual snoring and AHI $<$10; 3) *OSA subjects,* with partner-verified habitual snoring and AHI $\geq$10. Exclusion criteria were previous tonsil or soft palatal surgery, central sleep apnea, medications known to affect peripheral nerves, as well as cases where snoring history could not be confirmed. Patients with position-dependent OSA were also excluded from further analysis, because their night-to-night AHI variability made it difficult to classify them as snorers or OSA subjects.

Sensory function in the upper airway was measured by CDT with a Medoc TSA–2001 apparatus (Medoc Ltd, Ramat Yishai, Israel). A thermode with a 6-mm diameter Peltier element at the tip was used at the soft palate and at the lip. CDTs were determined with the Method of Limits (MLI).[13] The apparatus was set at 36°C starting temperature for soft palate testing, and 32° C for lip testing. The MLI algorithm consisted of four continuously increasing stimuli. The subject was asked to press a hand-held computer mouse button as soon as they perceived a sensation of cold. The time intervals between the four stimuli were randomized to last between 4 and 6 seconds. The average of the four stimuli was taken as threshold value. A stimulus change rate of 1°C/sec was used. CDTs were calculated as the difference between starting temperature and mean detection temperature in °C. The soft palate was chosen as test site for two main reasons: first, this tissue is probably the site in the upper airway most subjected to the stretching and vibration that occurs during snoring, making it a suitable site to look for nervous lesions. Second, this site is easily accessible by mouth. The lip was chosen because it is not affected by snoring and therefore suitable as control site. The exact test locations were: centrally at the outer surface of the lower lip and centrally at the left side of the soft palate. All tests were performed by the first author, blinded to the results of the full-night respiratory recordings, at the ENT clinic, Ryhov County Hospital, Jönköping, Sweden. All participants gave informed consent. The study was approved by the ethical committee of the University Hospital in Linköping, Sweden (diary number M24-08).

Statistical Analysis

Descriptive statistics were used for population and group characteristics. Correlations between soft palate CDTs and age, AHI, and self-reported snoring years were evaluated with Spearman's rank correlation coefficient. Group analysis was performed using Mann-Whitney *U*-tests and Kruskal-Wallis test. Group analysis was used because Hagander et al.[9] did not find a significant correlation between sensory impairment and AHI on an individual level. All data were analyzed with SPSS statistical software version 15.0 (SPSS Inc, Chicago, IL). Statistical significance was set at $P < .05$.

RESULTS

A total of 101 subjects met inclusion criteria and underwent CDT testing. Eight subjects (three women, five men) could not participate in CDT testing due to strong gag reflexes, and three subjects (all men) had technically unsatisfying recordings. Characteristics of the remaining 25 nonsnorers, 32 snorers, and 33 OSA subjects included in the analysis are summarized in Table I.

There were no significant differences in tonsillar size, ESS score, or age between groups. BMI was significantly lower in the control group compared to the other groups, but BMI did not differ between the snorers and the OSA subjects. In the nonsnoring group neither soft palatal nor lip CDT was correlated to age. Neither were CDTs correlated to gender in the control group.

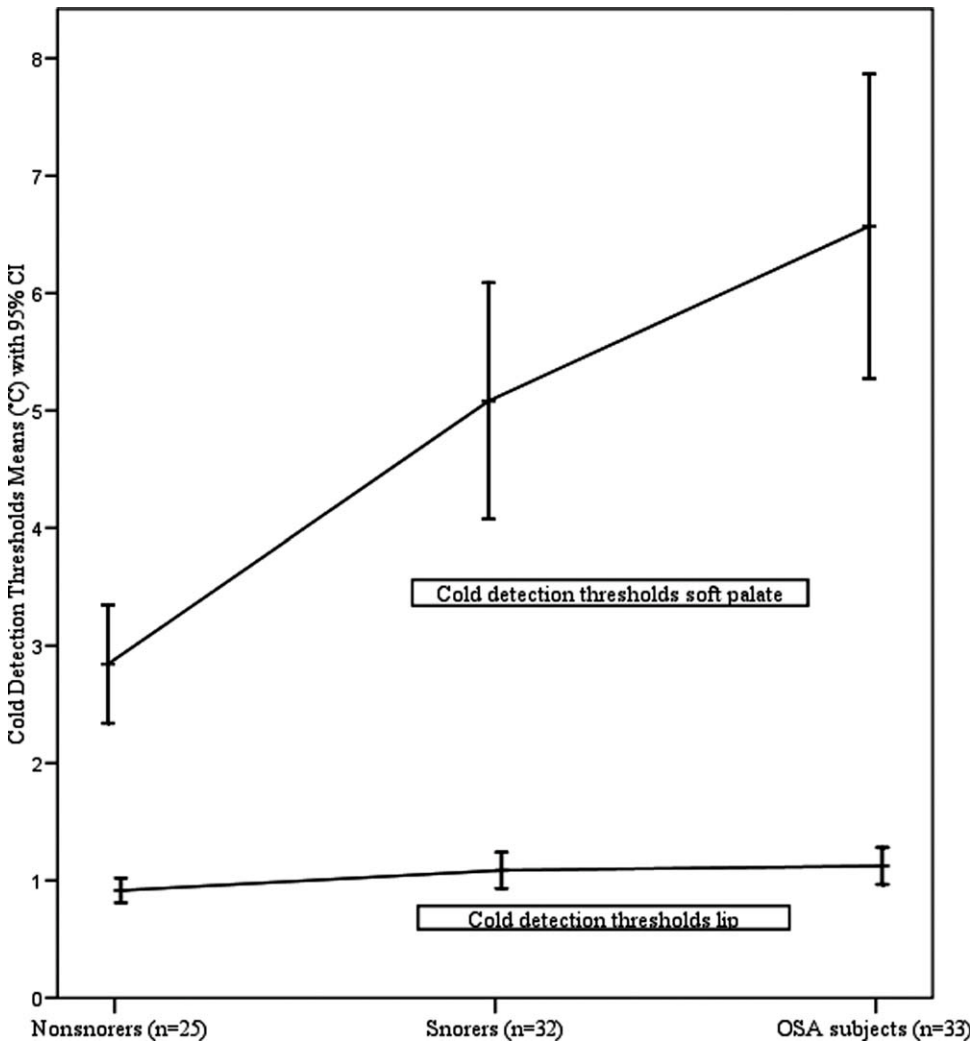

Fig. 1. Cold detection thresholds for the soft palate and lip by groups.

On group level, Kruskal-Wallis test showed significant difference between groups for soft palate CDTs ($P < .01$) but not for lip CDTs. Further, Mann-Whitney tests showed significant differences in soft palatal CDTs between nonsnorers compared to both snorers ($P < .01$) as well as OSA subjects ($P < .01$) (Fig. 1, Table I). There were also significant differences between snorers and OSA subjects ($P < .05$). Lip CDT did not differ between any of the groups.

In Figures 2 and 3 CDTs are plotted against AHI and self-reported snoring years. Although there is a considerable amount of scatter in both plots, the statistical analyses indicate that the degree of neuropathy increases with both AHI and duration of snoring. Correlation analyses show weak but significant ($P < .01$) correlations between both AHI and self-reported snoring years versus CDTs ($r_s = .41$ and $r_s = .47$, respectively).

DISCUSSION

The findings in the present study confirm and strengthen previous knowledge of the association between upper airway sensory neuropathy and OSA.[7–12] Snorers without significant OSA and subjects with OSA showed a gradual decrease in sensitivity to cold, compared to nonsnorers, indicating a progressive sensory nervous lesion.

Our data show a significant positive correlation between both estimated duration of snoring and objectively measured degree of sleep disordered breathing to degree of soft palatal neuropathy on the individual level, but these correlations are rather weak. This might be due to, for example, that self-estimated snoring years were not remembered correctly. There is also the possibility of a discrepancy between self- and partner reported data to objectively measured data on snoring so that objective measurements of snoring would have given a stronger correlation. One weakness of this study was that snoring was not recorded objectively. Concerning AHI, there is the possibility of night-to-night variability. Another methodologic aspect is whether snorers and OSA subjects performed worse than controls on CDT testing simply because they were sleepy or unfocused. CDT testing does require good cooperation from the tested person in order to obtain reliable data. However, there were no correlations either between duration of snoring or degree of

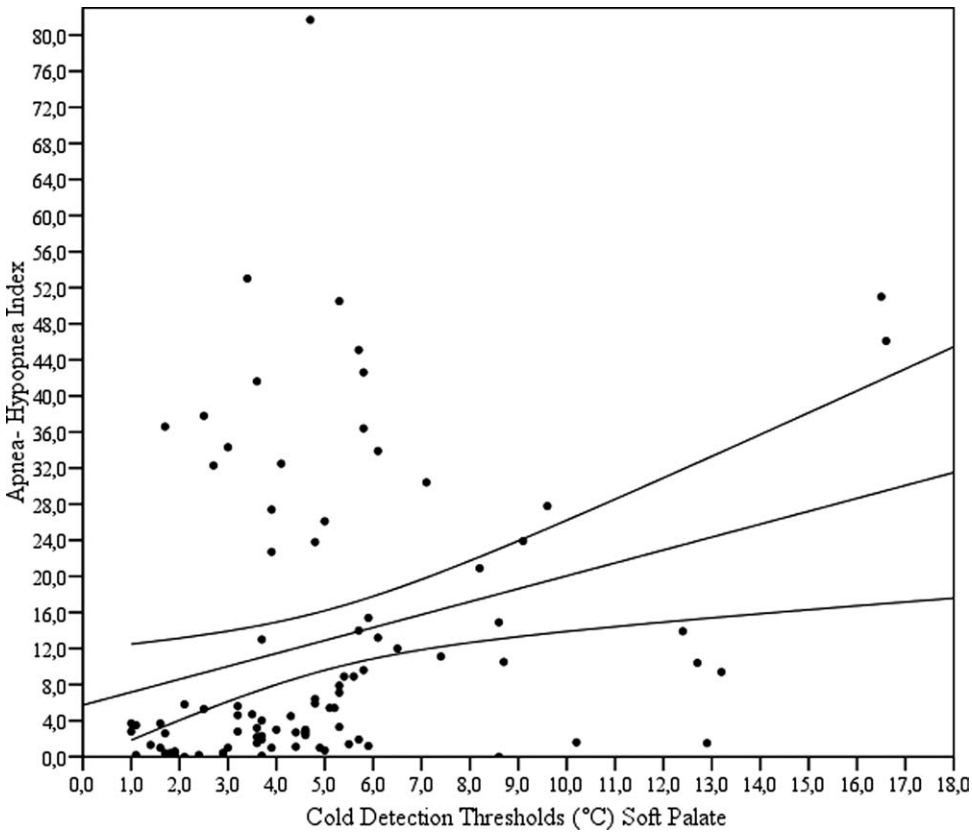

Fig. 2. Scatter plot showing a significant positive association of apnea–hypopnea index with soft palate cold detection thresholds (Spearman rank correlation = .41; $P < .01$). Regression line and lines for the 95% confidence interval (CI) are shown.

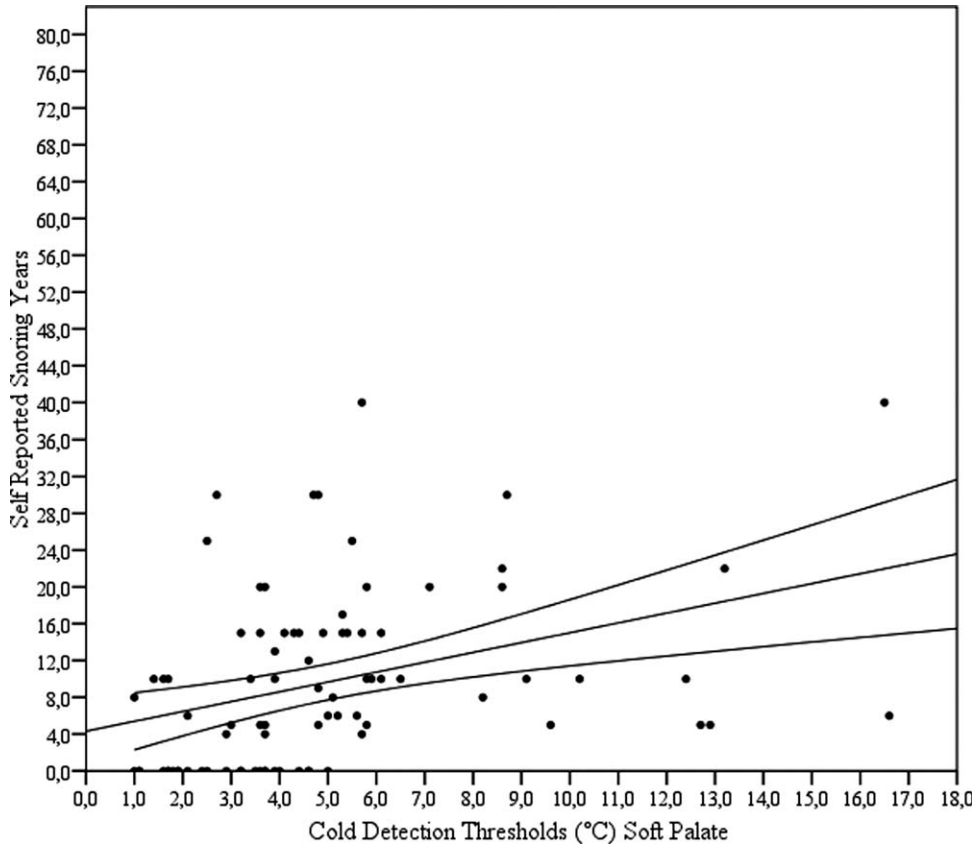

Fig. 3. Scatter plot showing a significant positive association of self-reported snoring years with soft palate cold detection thresholds (Spearman rank correlation .47; $P < .01$). Regression line and lines for the 95% confidence interval are shown.

OSA to lip CDT, which would have been expected if the subjects were sleepy or inattentive. Additionally, there were no differences between the groups concerning subjective sleepiness, as measured by ESS.

Our data strengthen the hypothesis that long-standing, snoring-induced vibrations can cause a local neuropathy in the soft palate, and that this neuropathy might be involved in the pathologic progression often seen in OSA. The upper airway in humans consists of a muscular tube lacking rigid support in the form of bone or cartilage. Therefore, its patency during wakefulness as well as in sleep is dependent on dilating muscular forces. This dependency is more pronounced during sleep due to the negative influence of gravity as well as with the natural decrease in muscular tone. During inspiration the negative pressure created in the thorax tends to collapse the upper airway due to the Bernoulli effect. Through the years, several studies (as rewieved by White[14]), have showed activation of the upper airway muscles in response to inspiratory negative pressure. Another important activating factor of this reflex circuit is the sensation of cold, as in inhaled air,[15,16] which activates sensory neurons in the upper airway mucosa.[17] With this in mind it seems logical that snoring-induced impaired sensation to cold could impair the reflex responsible for muscular dilatation of the upper airway during sleep. The theory is further supported by the findings of Horner et al.[18] that anesthesia of the upper airways reduces the activity in the dilating upper airway muscles as measured by electromyograms.

Long-standing vibrations does not only cause sensory neuropathy to thermal stimuli but also to mechanical stimuli.[4,5] As discussed above, the activation of upper airway dilating muscles include responses to both these types of sensory stimulus (thermal as in cold air and mechanical stimuli as in inspiratory negative pressure). Negative pressure is considered a stronger stimulus for pharyngeal dilation than cold, and therefore a sensory neuropathy concerning mechanical stimuli can be an even more important pathologic feature in OSA than cold sensory neuropathy. That this reflex is impaired in sleep apnea subjects have been shown in several studies.[14] Sensory nerves have a wide, highly specialized range of functions. Larger myelinated sensory fibers register vibration, touch, pressure, and position sense. Smaller myelinated sensory fibers (A δ) transmit temperature sensations and may be affected either exclusively or to a much greater degree than the large diameter myelinated fibers. It has been shown that the A δ fibers are more sensitive than the other fiber types to local anesthetics, but what effect vibrations have on the different fiber types is not known. However, disorders affecting the vasa nervorum, such as chronic arteriosclerotic ischemia, usually primarily cause small-fiber sensory and motor dysfunction, that is, temperature sensitivity will be affected before pressure. The effects of vibration on nerve blood flow are unknown, but vibration appears to activate vasoconstriction in arteries via the somatosympathetic pathway.[19] It is therefore possible that temperature sensitivity will be impaired before sensitivity to mechanical changes.

Long-standing vibrations in the upper airway may have other deleterious effects in the snoring patient than disturbed regulation of upper airway patency. In a study by Lee et al.,[20] snoring subjects had an increased risk of carotid atherosclerosis independent of other risk factors. One of the pathologic mechanisms proposed is that snoring-induced vibration transmits through the tissues to the carotid artery wall inducing a local endothelial injury. Most often "simple snoring" is looked upon as a harmless but unpleasant condition. However, untreated habitual snoring seems to be a risk not only for progression into OSA but also for the development of carotid artery atherosclerosis.

However, the main question remains to be answered: are these findings of local sensory neuropathy merely an insignificant consequence of snoring or the key to explain the progression from snoring to OSA? By following the subjects in the present study with repeated measurements of cold thresholds in the soft palate and nocturnal respiration, we hope to answer the question whether changes in local sensory neuropathy and AHI are related to each other, and also if termination of upper airway tissue vibration through CPAP treatment can hinder the progression or even regress the degree of local sensory neuropathy found in the soft palate. To shed light on this question the participants of this study will be followed longitudinally, which will give us a unique possibility to assess the pathogenic relationship between OSA and a local sensory neuropathy in the upper airway.

CONCLUSIONS

The degree of sensory neuropathy in the upper airway, as reflected by cold detection thresholds, correlates with the degree of obstructive sleep apnea disorder. Our results strengthen the hypothesis that snoring vibrations may cause a neuropathy in the upper airway, which contributes to the progression and development of OSA.

BIBLIOGRAPHY

1. Silva GE, An MW, Goodwin JL, et al. Longitudinal evaluation of sleep-disordered breathing and sleep symptoms with change in quality of life: The Sleep Heart Health Study (SHHS). *Sleep* 2009;32:1049–1057.
2. Berger G, Berger R, Oksenberg A. Progression of snoring and obstructive sleep apnoea: the role of increasing weight and time. *Eur Respir J* 2009; 33:338–345.
3. Lugaresi E, Plazzi G. Heavy snorers disease: from snoring to the sleep apnea syndrome—an overview. *Respiration* 1997;64:11–14.
4. Stromberg T, Dahlin LB, Lundborg G. Hand problems in 100 vibration-exposed symptomatic male workers. *J Hand Surg Br* 1996;21:315–319.
5. Virokannas H. Dose–response relation between exposure to two types of hand–arm vibration and sensorineural perception of vibration. *Occup Environ Med* 1995;52:332–336.
6. Lundborg G, Dahlin LB, Hansson HA, Kanje M, Necking LE. Vibration exposure and peripheral nerve fiber damage. *J Hand Surg Am* 1990;15: 346–351.
7. Friberg D, Ansved T, Borg K, Carlsson-Nordlander B, Larsson H, Svanborg E. Histological indications of a progressive snorers disease in an upper airway muscle. *Am J Respir Crit Care Med* 1998;157:586–593.
8. Svanborg E. Impact of obstructive apnea syndrome on upper airway respiratory muscles. *Respir Physiol Neurobiol* 2005;147:263–272.
9. Hagander L, Harlid R, Svanborg E. Quantitative sensory testing in the oropharynx: a means of showing nervous lesions in patients with obstructive sleep apnea and snoring. *Chest* 2009;136:481–489.
10. Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D. Upper airway sensation in snoring and obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;164:250–255.
11. Guilleminault C, Li K, Chen NH, Poyares D. Two-point palatal discrimination in patients with upper airway resistance syndrome, obstructive sleep apnea syndrome, and normal control subjects. *Chest* 2002;122:866–870.
12. Nguyen AT, Jobin V, Payne R, Beauregard J, Naor N, Kimoff RJ. Laryngeal and velopharyngeal sensory impairment in obstructive sleep apnea. *Sleep* 2005;28:585–593.

13. Sunnergren O, Broström A, Svanborg E. How should sensory function in the oropharynx be tested? Cold thermal testing; a comparison of the methods of levels and limits. *Clin Neurophysiol* 2010;121: 1886–1889.
14. White DP. The pathogenesis of obstructive sleep apnea. *Am J Respir Cell Mol Biol* 2006;34:1–6.
15. Mathew OP. Upper airway negative-pressure effects on respiratory activity of upper airway muscles. *J Appl Physiol* 1984;56:500–505.
16. Horner RL, Innes JA, Murphy K, Guz A. Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol* 1991;436:15–29.
17. Lindman R, Ståhl PS. Abnormal palatopharyngeal muscle morphology in sleep-disordered breathing. *J Neurol Sci* 2002;195:11–23.
18. Horner RL, Innes JA, Holden HB, Guz A. Afferent pathway(s) for pharyngeal dilator reflex to negative pressure in man: a study using upper airway anesthesia. *J Physiol* 1991;436:31–44.
19. Stoyneva Z, Lyapina M, Tzvetkov D, Vodenicharov E. Current pathophysiological views on vibration-induced Raynaud's phenomenon. *Cardiovasc Res* 2003;57:615–624.
20. Lee SA, Amis TC, Byth K, Larcos G, Kairaitis K, Robinson TD, Wheatley JR. Heavy snoring as a cause of carotid artery atherosclerosis. *Sleep* 2008;31:1207–1213.