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QUANTITATIVE SENSORY TESTING, OBSTRUCTIVE SLEEP APNEA AND PERIPHERAL NERVOUS LESIONS

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Stockholm 2006
To Bengt
and to our children
Carl Wilhelm, Philip, Richard and Mathilde
with love
ABSTRACT

In diagnosis of peripheral neuropathies, quantitative sensory testing (QST) is used to assess thermal and vibration sensitivity. QST is a psychophysical method susceptible to the influence of several factors. It is important to standardize the test. Vibrations may cause peripheral nerve lesions. Snoring induces oropharyngeal vibrations which could cause nervous lesions and consequent obstructive sleep apnea (OSA).

Objectives: to study the effect of anatomical site, applied pressure and local skin temperature on QST. To develop methodology for QST and EMG in oropharynx. To evaluate the presence of oropharyngeal nerve lesions in patients with OSA and snoring. Methods: Thermal and vibration thresholds were tested in 47 normal subjects at different sites in hand and foot. The effect of different local pressures on vibration thresholds and of different skin temperatures on thermal thresholds was studied. In 14 habitual snorers and 31 OSA-patients vibration detection thresholds (VDT) and cold detection thresholds (CDT) were tested intra-orally. Comparison was made to 23 non-snoring individuals. Concentric needle EMG was performed in m. palatoglossus in OSA patients, habitual snorers and normal subjects. Results: In general, the hand was more sensitive than the foot to QST. Thenar was most sensitive to warmth. There were no other significant differences between any of the sites within the hand or foot for thermal or vibration stimuli. Warm and cool thresholds were independent of local skin temperature. Different applied pressures did not change VDT. In OSA-patients, both VDT and CDT were elevated at the tonsillar pillars compared to non-snorers. VDT were not significantly different between snorers and normals, but this was true for CDT (p=0.001). In 10/11OSA patients, palatoglossus EMG showed signs of motor neuropathy. 11/22 habitual snorers showed moderate pathology. Conclusion: In the hand, the preferred site for thermal testing is the thenar eminence and for VDT the pulp of the index finger. Warming or cooling of the skin is unnecessary. Low pressure differences did not influence the results of VDT. Signs of palatal motor and sensory nervous lesions were present in most OSAS-patients and some snorers, supporting the hypothesis of a progressive nervous lesion. CDT and EMG could be used to evaluate structural damage, which might be important to identify snorers at risk and in choice of therapy.
List of Publications

I. **Hagander, L. G.**, Midani, H. A., Kuskowski, M. A., Parry, G. J.
   

II. **Hagander, L. G.**, Midani, H. A., Kuskowski, M. A., Parry, G. J.
   

III. **Hagander, L.**, Harlid, R., Svanborg, E. Oropharyngeal vibration and thermal sensitivity in patients with obstructive sleep apnea and snoring. Manuscript (Submitted)

IV. Svanborg E., **Hagander L.**, Haraldsson P.O., Harder L., Hultcrantz E.
   
   Electromyographic findings in upper airway muscles of patients with obstructive sleep apnea and snoring. Manuscript (Submitted)
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1 INTRODUCTION

1.1 QUANTITATIVE SENSORY TESTING

1.1.1 Introduction

Sensory impairment is a common symptom in neuropathies as well as in other neurological disorders. Evaluation of sensation is, thus, an important clinical examination. The bedside evaluation of thermal and vibratory sensation, usually using mirrors of different temperature or a tuning fork is a valuable test. However, the results are not reproducible, since stimuli are variable, and since examination is not standardized. QST is a logical extension of the clinical neurological evaluation. QST has the advantage of standardizing the stimuli and the test algorithm in a reproducible way in order to quantitative the results. QST can be useful to detect and validate abnormalities of sensation in neurological disease, to detect subclinical sensory impairment in persons at risk for developing certain neuropathies as well as in persons at risk from new medications or from industrial toxins, and in the follow-up of a patients to determine the natural course of a disorder or to evaluate therapy [1].

QST by means of vibration and thermal thresholds is an easy to perform, non-invasive method, which evaluates the entire sensory pathway form the distal receptor to the sensory cortex. Thresholds are therefore dependent on the peripheral as well as the central nervous system. Thus, an abnormal threshold cannot localize the nervous lesion to any specific level of the afferent somatosensory system, but a peripheral sensory nervous lesion would give rise to abnormal QST thresholds. An abnormal threshold may be found in a variety of neurological disorders. Thus, QST will not per
se be diagnostic for neither the level of the lesion nor for specific disease or etiology. However in spite of this lack of diagnostic specificity certain QST findings may characterize particular conditions and support differential diagnosis in neuropathies for instance.

It is a psychophysical method, dependent on patient cooperation as patients are required to indicate perception of a given stimuli verbally or by pressing a button. Thresholds are, thus, a measure of sensory function influenced by non-sensory factors such as the subject’s expectations and attitudes. It is therefore of uttermost importance to perform the test in a standardized way, with a well informed, motivated, subject who can participate and cooperate. In the literature, several authors have found QST in the extremities by means of vibration [2-9] and thermal testing reliable [5, 10, 11] and reproducible under standardized conditions. Therefore QST in the extremities is increasingly used for the assessment and follow up of peripheral neuropathies in clinical routine and research, testing vibration [6-9, 12-18] as well as thermal thresholds [2, 19, 20].

1.1.2 Psychophysics and sensory physiology

The human sensory modalities include the somatic senses such as touch, proprioception, vibration, temperature, and pain, as well as the other senses, including vision, hearing, balance, taste, and smell. All sensory modalities share three common steps: a psychical stimulus, a set of events transforming the stimulus to nerve impulses, and a response to the stimulus as perception or conscious experience of the sensation. The field of psychophysics focuses on the relationship between the
characteristics of the stimuli and the sensory experience of perception in the individual. Our perception of a certain stimulus depends on for instance previous experience, attention, and situation. Sensory physiology, on the other hand, focuses on neurophysiological mechanisms, i.e. how the stimulus is transduced by the sensory receptors, and the primary afferents and how it is processed in the brain [21]. QST is a psychophysical method, merging these two approaches. Thus, in order to get reproducible QST thresholds, standardizing of stimuli as well as psychological settings are crucial.

1.1.3 Neurophysiological mechanisms of somatic sensation

Sensory information is sent to the brain in the form of trains of electrical action potentials in individual afferent neurons as well as by populations of such afferents acting together. To maintain the specificity of each modality within the nervous system, receptor axons are segregated into different anatomical pathways and different central processing areas. Somatic sensation has four major modalities: discriminative touch, proprioception (sense of position and movement in limbs), nociception (sense of pain) and thermal sense (sense of warm and cold).

1.1.3.1 Sensory receptors

The sensory receptor is the distal part of first cell in the sensory pathway. It is capable of stimulus transduction, i.e. converting stimulus energy into electrical energy and hereby establishing a signalling mechanism, common in all sensory systems. The electrical signal produced by the receptor is called the receptor potential.
Humans have four classes of receptors, according to their sensitivity to physical energy: mechanical, chemical, thermal, or electromagnetic (the photoreceptors in the retina) [21]. They all transduce their specific type of stimulus energy into electrical signals. Mechanoreceptors, for instance, sense physical deformation of the tissue, which opens up stretch-sensitive ion channels, thereby giving rise to a depolarizing receptor potential. The amplitude or the receptor potential is proportional to stimulus intensity, since strong pressure open more ion channels for a longer time, producing a greater depolarization than does a weak pressure. Removal of the stimulus causes the stretch-sensitive channels to close.

The receptor potential is translated into a frequency code, which codes for the stimulus intensity [21]. The duration of the stimulus is determined by the adaptation of receptors. Although the continuous firing of a sensory neuron encodes the intensity of the stimulus, if the stimulus persists constantly for several minutes, the sensation is lost, i.e. adaptation of the receptor has occurred. There are two kinds of sensory receptors, slowly adapting and rapidly adapting. Slowly adapting receptors signal stimulus magnitude for several minutes, while rapidly adapting receptors respond only at the beginning and the end of a stimulus, conveying information about the change in sensory environment to the CNS. Thus, slowly adapting receptors signal pressure and shape of an object against the skin or the mucosa, while rapid adapting receptors signal motion of objects against the skin or the mucosa. Under normal circumstances each sensory neuron is sensitive primarily to one type of stimulus. However, if the stimulus is strong enough several kinds of nerve fibres can be activated.
1.1.3.1.1 **Receptive fields**

The receptive field of a sensory neuron is the region directly innervated by the terminals of the receptor neuron. Each receptor responds only to stimulation within its receptive field. A stimulus affecting an area larger than the receptive field will activate adjacent receptors. The density of receptors determines the spatial resolution of the stimulus and differs in different parts of the body. For example, spatial distribution is very high in the hand and perioral area, where sensory receptors are plentiful and the receptive fields are small, while other regions, such as the trunk, possess fewer receptors with larger receptive fields. These differences in receptor density are reflected in the CNS, as seen in the “sensory homunculus”, i.e. the topographical map of afferent input to the primary somatosensory cortex from different parts of the body, where the hand and perioral area have large parts.

1.1.3.1.2 **Somatosensory receptor types**

The receptor may be either bare nerve endings or nerve endings encapsulated by non-neural structure. The latter mediate the somatic modalities of touch (including vibration) and proprioception. Encapsulated receptors are mechanoreceptors such as Meissner’s corpuscle, Merkel disk receptor and Ruffini-endings mediating touch, and Pacinian corpuscles mediating vibration, but also muscular and skeletal mechanoreceptors mediating proprioception. Bare nerve endings mediate pain and thermal sensations.
1.1.3.2 Primary afferents

All somatosensory information from the limbs and the trunk is sent by dorsal root ganglion neurones. Somatosensory information from cranial structures is transmitted by cranial nerve sensory neurones, mainly from the trigeminal sensory neurones. These are functionally and morphologically homologous to dorsal root ganglion neurones [21]. The cell body in the dorsal root of the spinal cord has two branches of the axon projecting to CNS and to the periphery, respectively. The terminal of the peripheral branch is the receptor. The remainder is termed the primary afferent fibre, transmitting the encoded stimulus information to the spinal cord and the brainstem.

Mechanoreceptors and proprioceptors send their action potential in large-diameter, myelinated primary afferent fibres, conducting the action potential rapidly. The consist of relatively large Aβ sensory fibres, transmitting impulses from touch receptors to the central nervous system being 6-12 µm in diameter, with conduction velocities of 36-72 m/s. Thermal receptors and nociceptors have small-diameter axons that are either unmyelinated or thinly myelinated, conducting the impulses slowly. The afferents for cold are small myelinated Aδ and unmyelinated C fibres. Aδ sensory fibres are 1-6 µm in diameter and have conduction velocities of 4-36 m/s. C fibres are slow, unmyelinated fibres, with 0.2-1.5 µm in fibre diameter and conduction velocities of 0.4-2 m/s. The afferents for warmth are C fibres. Pain impulses are transmitted to the CNS by two fibre systems. One nociceptor system consists of small myelinated Aδ fibres. The other consists of unmyelinated C fibres. These different systems with their different conduction velocities explain the so-called double pain phenomena, i.e. the sensation of acute pain in two sessions: first
intense pain of short duration, then a free interval, followed by dull pain of long
duration [22].

1.1.3.3 Central pathways

There is a topographic arrangement in central pathways of sensory information in
dermatomes. Dermatomes are areas of the skin innervated from the fibres from one
dorsal root. They are distributed in a caudal-rostral fashion. The sensory
specialization of dorsal root ganglion neurones for the different modalities is
preserved in the CNS through distinct ascending pathways via thalamus to the
primary somatosensory cortex, located in the parietal lobe in the postcentral gyrus.
Touch and proprioception are transmitted directly to the medulla through the
ipsilateral dorsal columns. Temperature and pain are transmitted via synapses in the
spinal cord to the contralateral spinothalamic tract, ascending to the brainstem and
thalamus.

1.1.3.4 Temperature

Thermal sense is uniquely somatosensory, as it is not affected by other sensory input
such as vision. Humans recognize four different thermal modalities: cold, warm, cold
pain and hot pain. The thermal sensation results from the difference in temperature
compared to the actual temperature at the site of stimulation. Mapping experiments
show that the skin has discrete cold-sensitive and heat-sensitive spots. There are four
to ten times as many cold-sensitive as heat-sensitive spots [23]. Thermal receptors,
unlike mechanoreceptors, fire continuously at low rates when skin temperature is
within normal range. The firing does not rise or fall monotonically in case of
temperature change. Instead, each class of receptor show peak firing at a preferred temperature, which for cold receptors is 25 ºC and for warm receptors is 45 ºC. Temperatures above and below evoke progressive weaker responses in warm and cold receptors and activate thermal pain nociceptors for cold pain and hot pain, respectively. Thermal nociceptors include nociceptors for noxious heat (above 45 ºC), noxious cold (below 5 ºC), and polymodal nociceptors responding to a variety of destructive mechanical, thermal, and chemical stimuli. Thus, the code for skin temperature involves comparing the relative activity in these different thermal receptors and nociceptors. The temperature of the subcutaneous tissues determines the responses to thermal stimuli. Cool metal objects feel colder than wooden objects of the same temperature because the metal conducts heat away from the skin more rapidly, cooling the subcutaneous tissues to a greater degree [23].

1.1.3.5  *Vibration*

Vibration is the sensation produced by sinusoidal oscillation of objects placed against the skin. The sensation is most marked over bones, but it can be felt in other locations as well [23]. Mechanoreceptors respond to the oscillations, transducting them to action potentials coded as a pulse train. The vibratory frequency is signalled by the frequency of action potentials in the primary afferent. The intensity of vibration is signalled by the total number of primary afferents. With increasing stimulus intensity more distant receptors are activated. Humans are most sensitive to frequencies of 200-250 Hz.
1.1.4 History

The first, and for many years only, quantified somatosensory modality was vibration, in 1959 used in studies by Kugelberg and Lindblom for analysis of pain mechanism in trigeminal neuralgia [24, 25]. In 1976 Fruhstorfer, Lindblom, and Schmidt introduced a quantitative method for the examination of thermal sensibility. The stimulation technique, called Marstock because of the collaboration between Marbourg and Stockholm, resembled Bekesy audiometry: the patient reversed the direction of the temperature change of a thermode whenever warm, cold, or thermal pain thresholds were reached. The resulting temperature curve enabled a quantitative description of the subject's thermal sensibility and of the degree of impairment displayed by neurological patients [26]. Three years later, in 1979, Goldberg and Lindblom published a quantitative method for vibration threshold determinations, by means of an electromagnetic vibrator. Because of the vast variation demonstrated for both vibrator output and tissue damping, the thresholds were expressed in terms of amplitude of stimulator movement measured by means of an accelerometer, instead of applied voltage. They showed that the variance of the vibration detection threshold was less than that of the vibration disappearance threshold, and thus recommend the detection threshold alone [27]. In 1978, Dyck et al introduced automated systems to detect thresholds, using stimuli which were quantified and reproducible [1]. Since then several authors have reported development of different instruments for QST [28-34]. In a consensus development conference on standardized measures in diabetic neuropathy in 1992, QST was recommended to assess peripheral nerve function [35].
1.1.5 Psychophysical algorithm

Algorithms for threshold determination can be divided into those that involve reaction time in the measurement, and those that do not [7, 13, 17-19].

1.1.5.1 Reaction time inclusive algorithms

In the method of limits the subject is requested to stop a stimulus at the moment of detection while the stimulus intensity is increasing [10, 17, 36]. This is a reaction time inclusive method. The reaction time is the time required for transmission of the impulse from the peripheral tested site to the brain, processing, and transmission of the command from the brain to the signalling hand to halt the stimulus. During the reaction time, stimulus intensity keeps increasing resulting in an increase in the threshold value [36, 37].

1.1.5.2 Reaction time exclusive algorithms

In the reaction time exclusive methods, a stimulus of predetermined intensity, is given, and the subject is requested to indicate whether perception occurred or not after stimulus termination. Subsequent stimuli are changed according to the response by the specific algorithm used. The method of levels, as described by Yarnitsky and colleagues is a reaction time exclusive method, not more time consuming than the method of limits [10, 17, 36]. An initial stimulus step is given with the stimulus returning to adaptation immediately upon stimulus termination. Subjects are requested to give a “yes” or “no” response depending on whether or not the stimulus is perceived. A “yes” always causes the following stimulus to be smaller and vice
versa. Step size is halved at turns, or unchanged for no change of direction. This is continued until the step size reaches a preset final step.

Other reaction time exclusive methods include:

- the staircase method
- two alternative “forced choice” method
- “4, 2, and 1 stepping algorithm”

In the staircase method an initial stimulus step is given, subjects are asked to say whether or not they feel it [33]. The two alternate “forced choice” method requires the subject to choose which of two posts is actually vibrating during any given trial. The subject is forced to make a choice, i.e. the subject is required to guess which post is vibrating, when uncertain [11, 38]. The time consumption of the test might affect thresholds by drowsiness or boredom. Therefore the method of levels was introduced by Yarnitsky in 1991 [36], and the “4, 2, and 1 stepping algorithm” by Dyck in 1993 [39] as a quicker reaction time exclusive methods.

1.1.5.3 Which algorithm to use

Threshold values are of smaller absolute values when measured with reaction time exclusive methods compared to when measured with reaction time inclusive methods [7, 10]. It has been suggested that the difference in thresholds between the method of limits and the method of levels, explained by the reaction time, is age dependent [7]. The false high thresholds seen with the method of limits would, thus, have a tendency to become even higher with increased age. This suggests that when testing patients in
older age groups, such as OSAS patients (OSAS is a disease of increasing age [40-45]), the method of levels is preferred.

Most authors agree that the use of a reaction time exclusive method is advantageous in all age groups [20, 33]. The method of levels has been found less time consuming than other reaction time exclusive algorithms. In addition in the method of levels, random null stimuli can be used to assess quality of performance [46].

1.1.6 Factors affecting QST thresholds

1.1.6.1 Psychophysical factors

Since QST is psychophysical method, patient cooperation and patient alertness is of great importance. In order to get reliable thresholds optimal cooperation of the subject is required and loss of attention, fatigue and noise can induce variations in the thresholds obtained.

1.1.6.1.1 Attention

The method of limits is very sensitive to loss of attention, fatigue, and distraction and higher thresholds are obtained, as stimulus continues to rise until the subject signals detection. The slightest suspicion of reduced alertness or cooperation nullifies the value of the results. In OSAS patients, where EDS is a major symptom, alertness is presumably reduced, due to the sleepiness. The use of a reaction time exclusive method, such as the method of levels, would therefore be preferred in this patient group.

1.1.6.1.2 Learning

Like all psychophysical methods QST is subject to learning and practice effect. These are, however, generally limited to the first few minutes [47]. Therefore a practice trial
run is usually given in QST testing, and those practice trials are generally discarded. Variance in thresholds have been found to be markedly better when the first reading is omitted [46]. It has been suggested by Yarnitsky and Sprecher that the learning effect is more prominent in the method of limits [48], since the nature of the task is such that with repeated tests, performance can improve and thresholds decrease. The technique of performance is less critical in measurement in reaction time exclusive methods.

1.1.6.1.3 Feigning normal subjects

In order to judge the objectivity of QST test results in search of a way to discriminate between feigned and trustworthy results, Yarnitsky et al, studied OST in normal subjects feigning a neurological deficit [46]. They examined twenty-two healthy hospital employed volunteers unfamiliar with thermal testing. Following a standard explanation by the technician, subjects were acquainted with the testing procedure. WDT and CDT were tested in the arm using the method of limits. Subsequently they were asked to pretend a painfully injured arm with decreased sensitivity and produce suitable sensory evaluations. The results were compared with those from the laboratory files of twenty-one diabetic patients, whose thresholds matched those of the feigners. They found that feigned thresholds were markedly higher than corresponding normal thresholds, and that the variance for the real tests in normal subjects and diabetic patients was much smaller than for the feigned tests in normal subjects. The study confirmed the author’s basic assumption that variance between tests is low for a normal reading in a trustworthy subject, since the sensory processing is fairly stable during the short period of the test. In neuropathic conditions, the variance is somewhat larger, due to the impaired sensory system and possibly
distracting ongoing pain. When attempt is made to “invent” pathological results, an even larger variance is seen due to the inability to consistently repeat the feigned results [46]. Threshold variance can, thus, be a useful tool for the interpretation of test results, where a large variance signals inattentive or feigning test performance.

1.1.6.2 Subject conditions

1.1.6.2.1 Age

Vibration thresholds increase with age [2, 4-7, 12, 27, 31, 32, 49-58]. The age effect has been reported to be more pronounced in the lower parts of the body [7, 31]. Vibration sensitivity at the lip when tested with tuning fork is also lower at higher age [59]. Since OSA increases with age [40-45], the effect of age on VDT could be a confounding factor in oropharyngel testing, and even more so when using the method of limits, as the reaction time artifact has been suggested to increase with age [7].

Several studies have discussed the effect on age on thermal thresholds. Some investigators could not find a decline in thermal cutaneous sensation with age [30, 32, 54, 60], while others did [5, 7, 61, 62]. The studies are hard to compare, since different devices and different algorithms have been used. Some authors found impaired thermal discrimination thresholds with increased age in the foot, but not in the hand [2, 28]. Jamal et al found a trend for hot and cold thresholds to increase with age at the ankle, however, many older subject were found to be as sensitive as younger subjects [29]. Kenshalo et al found no significant difference in thresholds to thermal stimuli (warm or cold) between elderly and young at neither hands nor feet,
except that elderly feet were significantly less sensitive to warmth than young feet [32]. Fowler et al found statistically significant effect of age on warm thresholds at all tested sites (hand, foot, and face), while the effect of age on cold threshold was significant for hand and foot only [33]. Levy et al compared the age effect on thermal threshold using two different devices using different algorithms and found a small but statistically significant deterioration in thermal (warm and cold) thresholds with age using one method (Marstock, Somedic) but not using the other (Sensortek) [60].

Thus, it seems generally accepted that vibration thresholds increase with age, while it is more unclear regarding thermal thresholds. The age-effect seems to depend on method and algorithm, the foot seems to be more sensitive than the hand to the effect of age on thermal thresholds, and age seems to affect warm sensitivity differently than cool sensitivity. The age effect may be due to an age-related decline in receptor sensitivity, or may reflect a central decrease in neuronal fibers, or a slowing of central processing time.

1.1.6.2.2 Gender

Several studies have addressed the effect of gender on thermal and vibration sensitivity. Some authors could not find an effect of gender on sensory thresholds [2, 7, 12, 32], while others did [5]. Kenshalo compared thermal and vibration thresholds in the hand and in the foot in young and elderly subjects and found only one gender difference statistically significant; young male feet were less sensitive to warm than young female feet. This was, however, not the tendency in the young male subject group, where seven out of 10 young men had warm thresholds in their feet
comparable with those of the young women [32]. de Neeling et al demonstrated that healthy women had higher vibration thresholds than men in the feet when controlling for age and height, but found no effect of gender on thermal thresholds [5].

1.1.6.2.3 Height and Body Mass Index

A relationship between vibration perception and height has been shown in diabetic patients [34, 53] as well as in normal subjects [2, 31, 55, 56] were taller individuals tend to have higher thresholds regardless of age when tested in the feet. This relationship is more uncertain when tested in the hands. The relationship between thermal thresholds and height is less clear. Most authors have not found a relation between thermal thresholds and height [34, 53]. Lin et al did not find any association between body height and vibratory or cold threshold, but they found a statistically significant correlation between body height and warm threshold [7].

There is a discrepancy in the reports in the literature whether there is a relationship between sensory thresholds and BMI or not. Gerr and Letz, have found BMI to be significantly associated with VDT in finger and toe, when testing 4,462 male Vietnam-era veterans. The effect was, however, small and clinically negligible [56]. This finding was not confirmed by Bartlett et al, who did not find any significant association between BMI and sensory thresholds, including VDT [2].
1.1.6.3 Testing conditions

1.1.6.3.1 Anatomical site tested

It is well known that tested site affects QST thresholds. Sensitivity is lower in the foot than in the hand for vibration [2, 7, 12, 32, 50, 51, 63-65] as well as for temperature [7, 10, 11, 20, 29, 32, 33, 61, 65-67].

The difference between anatomical sites can be explained at different levels along the somatosensory pathway from the distal receptor to the primary somatosensory cortex in the postcentral gyrus. Different anatomical sites have different receptor density and different size of receptive fields, as well as different representation in the somatosensory cortex [68]. The difference in QST thresholds between sites would therefore be expected. A considerable variation in the density of thermal receptors from one region of the skin to another has been reported [69]. If receptors are present at lower density distally, this might explain the higher thresholds in the foot compared to the hand. It is also possible that central processing influence thermal and vibration sensitivity at different sites.

1.1.6.3.2 Probe size

QST thresholds are susceptible to the effect of the probe size, VDT [63, 64], as well as thermal thresholds [20, 33, 70-72]. The larger the stimulation area, the lower the thresholds. The increased sensitivity seen with larger stimulation area can be explained by spatial summation (the process by which potentials generated in different sites of the neurons are added together), and by the fact that a larger stimulation area might stimulate more receptors in an area with high receptor density.
1.1.6.3.3 **Stimulus rising time**

The stimulus rising time affects QST threshold, when testing with the method of limits [20, 36, 37, 52, 66, 73]. The faster the increase in stimulus intensity is, the higher the thresholds. This was studied regarding thermal thresholds by Swerup and Nilsson [73]. They studied the influence of the rate of the stimulus change on warm detection threshold (WDT) and cold detection thresholds (CDT) using the method of limits and found elevated WDT and lowered CDT with an increase in the rate of temperature change. The subjects, thus, felt warmth at a higher temperature and cold at a lower temperature when tested with higher rate of temperature change compared to when tested with a lower rate of temperature change. The reaction time artefact can explain this effect of stimulus rising time on thresholds. Reaction time can be considered almost constant. With an increased rate of stimulus change the threshold is reached faster but a higher stimulus is reached before the subject reacts. A similar mechanism can be suspected for VDT resulting in elevated VDT at higher stimulus rising time, when using the method of limits. The logarithmic ratio, i.e., the ratio between the intensity of a stimulus and the intensity of the sensation it evokes in the organism, has often been taken into account by using logarithmic scales in QST testing of VDT [31]. A logarithmic stimulus rise would give rise to a greater effect of the reaction time artefact on thresholds, in areas and/or patients with low sensitivity to vibration, since the reaction time artefact gets even greater when the stimulus intensity rises rapidly.
1.1.6.3.4 Local temperature at the site of stimulation

Local skin temperature at the site of stimulation does not clearly affect thermal or vibration thresholds.

Regarding vibration sensitivity, several authors have not seen any association between local skin temperature and VDT [2, 6, 64, 74]. Sosenko et al [53], however, found a significant relation between local skin temperature and vibration thresholds and Gerr and Letz [56] found slightly higher VDT in subjects with higher local skin temperature, when testing 4,462 male Vietnam-era veterans but this effect was small, and clinically negligible. VDT-testing can, thus, be performed regardless of local skin temperature in clinical practice.

Similarly, several authors have reported no effect of local skin temperature on thermal thresholds [7, 12, 33, 53]. Hilz et al [71] reported no effect of local skin temperature on warm and cold thresholds at skin temperature above 26 °C in children under the age of 10 years and found it unnecessary to warm up the skin at local skin temperatures above 26 °C. Gerr and Letz, however, in a large study of 4462 subjects, reported a moderate positive effect of skin temperature on the index finger on cold thresholds (higher temperature associated with poorer thresholds), but no such effect was found at the toe [56]. Bartlett et al reported that higher initial skin temperature was significantly associated with a decrease in cool thresholds in the hand but this effect was below the detectable level of the equipment [2]. In children and juvenile subjects, Hilz et al found that local skin temperature did not affect warm thresholds and had only poor correlation with cold thresholds [72].
1.1.6.3.5 Adaptation temperature on thermal thresholds

The adaptation temperature is the starting temperature of the probe before and between all stimuli. Kojo et Pertovaara [70] studied the effect of adaptation temperature on thermal thresholds and found that warm thresholds were elevated with increasing adaptation temperature. Thresholds were, however, measured as the absolute detection temperature and not as the difference between absolute detection temperature and adapting temperature, which, at least partly may explain the finding.

1.1.6.3.6 Application pressure at the site of stimulation

Vibration and touch receptors are both mechanoreceptors and deformation is their adequate stimulus. Therefore several reviews and studies have addressed the effects on VDT of application pressure at the site of stimulation [63, 64, 75, 76]. Cohen and Lindley [63] as early as in 1938 found that the greater the pressure, the lower the vibratory threshold. This was confirmed by Lowenthal and Hockaday in 1987 [76], who found that vibration threshold decreases as the pressure of the applied stimulus is increased and that this effect appears to be more marked in peripheral neuropathy. Gregg, on the other hand, in 1951 stated that the influence of the vibrator-holding pressure on the threshold was found to be negligible as long as too little pressure for adequate test-button contact, and excessive (almost painful) pressure was avoided [64].
Thermal receptors are free nerve endings not reacting on deformation and touch. A thermode with Peltier elements can be gently adapted with appropriate skin contact in most body regions. This ensures a modality-selective thermal stimulation and thermal stimuli may be given, without the mechanical cues of touch and pressure a bedside test would give by application of warm and cold objects [25]. To minimize the variation of probe application pressure Yarnitsky et al have recommended attaching the probe on the test site, considering limb curvatures in order to get good contact between probe and tested surface, using an elastic Velcro tape, always stretched in the same manner, e.g. 2 cm [48].

1.1.6.3.7 Hardness of the tested surface on VDT

Different anatomical sites also present different hardness of the tested surface, where skin overlying bone is a harder surface than skin overlying soft tissue. Hardness of the tested surface affects VDT, with lower thresholds on hard surface [27, 75]. It has been proposed that bone magnifies applied vibration [59]. Most VDT tests in clinical routine are made on skin closely overlying bone.

Depending on how the vibrating amplitude is measured by the device, hardness of the surface might also affect how the device calculates the thresholds. There are devices where the amplitude is calculated from applied voltage or current. In these cases the actual amplitude depends on the hardness of the surface, with high actual amplitude in air, less hard on bone and least high in soft tissue [27] but the threshold presented is in these devices the same calculated amplitude, regardless of the hardness of the surface and, thereby, the actual amplitude. The Vibrameter®, used to measure VDT
in this study, uses an electro-optical transducer to measure and display the actual peak-to-peak value of the vibration amplitude, and this disadvantage is avoided.

1.1.6.3.8 Frequency of vibration on VDT

Differences in thresholds at different frequencies of vibration have been demonstrated, with the highest sensitivity to vibration when testing with a frequency of 100 Hz, and lower sensitivity at higher (250Hz) or lower (50 Hz) frequencies [31, 52, 75, 77]. Differences between the thresholds at different frequencies of vibration have been explained as due to the frequency-specific characteristics of the mechanoreceptors and afferent fibres [31]. The mechanical response of the tissue is most pronounced at near the natural frequency of the tissue and becomes lower at both higher and lower frequencies [75, 77].

1.1.7 General principles in interpreting QST results

Vibration sensation is relatively easy to quantify and study, since increasing stimuli intensity evokes an increasing sensation of vibration. Temperature and thermal pain, on the other hand, are more complicated as four different sensations, cold pain, cold, warm, and hot pain, are evoked along the stimulus continuum, each of these mediated through different neural pathways, with overlapping ranges of sensitivity. This overlapping sensitivity may result in difficulties when interpreting QST results, i.e., when trying to determine which neural pathways are affected.
For evaluation of QST data comparison with data from normal subjects in general is recommended. Since QST is susceptible to many factors, this normal data must have been obtained using the same device, algorithm, and settings as well as with the same instructions to the patients. In clinical trials it is recommended that QST-testing is performed by a single investigator [25]. Further, in each patient with unilateral symptoms it is recommended to test the unaffected side as an intra-patient control [25].

1.1.8 OST in the oropharyngeal area

QST in the oral cavity is not in use in clinical routine, but has been reported in clinical research. QST evaluating thermal detection thresholds have previously been reported in the oral cavity following molar extraction in the territory of lingual and inferior alveolar nerves [78], and in patients with Burning Mouth syndrome [79]. In patients with OSA, thermal detection thresholds in the oropharynx have been evaluated by Larsson et al, who found significantly higher thresholds for warm and cold detection thresholds at the tonsillar pillars in OSA patients compared to normal, non-snoring controls [80]. Vibration thresholds have been evaluated in natural teeth and dental implants [81]. There is to our knowledge only one study where VDT have been tested in the oral mucosa, the study by Kimoff et al who evaluated VDT in the oro-pharynx in patients with OSA and snorers [82]. Vibration sensitivity using a tuning fork at the lower lip has shown diminished vibration at lower lip with increased age [59]. QST testing of thermal and vibratory thresholds in mucosal areas, other than the oral cavity, have been studied in the vagina by Vardi et al, reporting the method clinically feasible, valid, and repeatable [83].
1.2 OBSTRUCTIVE SLEEP APNEA SYNDROME

1.2.1 Introduction

Obstructive sleep apneas (OSA) are due to transient collapse and closure of the upper airway during sleep. Apneas often end with an arousal, thereby restoring pharyngeal patency through increased muscle tone. Pharyngeal dilator muscle function in combination with the change in pharyngeal muscle activation with onset of sleep is essential for the development if OSA in individuals susceptible to pharyngeal collapse. The recurrent arousals from sleep lead to activation of the sympathetic nervous system and fragmentation of sleep [84, 85]. OSA is a major health problem associated with increased mortality and morbidity in hypertension, cardiovascular disorders and accidents as well as reduced neurocognitive function and quality of life as will be discussed below. Nasal CPAP, the first treatment of choice in most OSA patients, has been shown to improve neurocognitive performance and blood pressure in randomised trials [86-89]. however it is considered that most patients remain undiagnosed and untreated [90, 91]. The rising number of people with obesity will probably make OSA an increasingly important public-health problem, especially in view of the neurocognitive and cardiovascular sequelae associated with this disorder.

The pathogenesis is not fully understood. We have proposed the hypothesis that snoring induced vibration may cause local peripheral nervous lesions in the oropharynx. A local nervous lesion would give rise to oropharyngeal muscle hypotonia, thus contributing to pharyngeal collapse in OSA, in two different ways; an efferent
nervous lesion causing motor impairment, and an afferent nervous lesion causing sensory impairment.

1.2.2 Definitions

Obstructive apneas are defined as cessation of airflow with duration of at least 10 seconds, with persistence of respiratory effort against the occluded airway [94]. Hypopneas refer to respiratory events when the airflow is reduced but not completely abolished. There is no world wide consensus on the exact definition of hypopneas. The most common definition is a reduction of airflow by at least 50% for 10 seconds or more accompanied by a physiological effect, such as an oxygen desaturation, pulse frequency change, EEG-arousal, etc. The laboratory findings of recurrent events (obstructive apneas, hypopneas and oxygen desaturations) during sleep are expressed as frequency indices, where **apnea index (AI)** is defined as the average number of apneas per hour of sleep, **apnea-hypopnea index (AHI)** is defined as average number of apneas plus hypopneas per hour of sleep, and **oxygen desaturation index (ODI)** is defined as average number of oxygen desaturations (of usually 2% or 4%) per hour of sleep.

OSA can be graded according to the severity criteria based on outcomes from the American Academy of Sleep Medicine [92] into **mild OSA** (5 – 15 events per hour of sleep), **moderate OSA** (15-30 events per hour of sleep, and **severe OSA** (greater than 30 events per hour of sleep). The term **Obstructive Sleep Apnea Syndrome (OSAS)** describes the presence of symptoms in addition to laboratory findings. It has been defined as “Intermittent, complete or partial, upper airway obstruction during
sleep causing mental and/or physical effects” [93]. The most common effect is excessive daytime sleepiness (EDS). Other symptoms include memory deficits, concentration difficulties, mood disturbances, night sweat, nycturia, impotence and decreased sexual drive, morning headache and heart burn [93]. Results of sleep disordered breathing (SDB) include snoring, OSA and OSAS, as well as Upper Airway Resistance Syndrome (UARS) [94, 95]. UARS is characterized by complaints of daytime fatigue and/or sleepiness, increased upper airway resistance during sleep, frequent transient arousals, and no significant hypoxemia or apneas [96]. The diagnosis is made on basis of respiratory events, referred to as RERA, respiratory effort related arousals. It is not clear whether this diagnosis may be made without oesophagal pressure monitoring. It has been discussed whether UARS is a distinct syndrome [97] or whether it is a mild end of the spectrum of abnormality in SDB [98].

1.2.3 Snoring

A useful working definition of snoring is the production of sound by of the upper airways during sleep. Snoring is characterized by increased inspiratory effort and increased endo thoracic negative pressure due to narrowing of the upper airways. The snoring sound is caused by the vibration of the structures in the oral cavity and oropharynx—the soft palate, uvula, tonsils, base of tongue, epiglottis, and pharyngeal walls. Snoring can last throughout the whole night or part of it and is favoured by the supine position [99].
The prevalence of habitual snoring is high and has been reported to be roughly 40% in men and 20% in women in USA [43, 100, 101]. In Sweden, 20% of men 50-60 years old, are affected [102]. Snoring has historically been considered a nuisance and an objectionable social problem. However, snoring is important because it may represent an alarm to alert one to the possibility of a sleep disorder [103].

Simple snoring is characterized by periods of snoring during the night which may be interrupted by sporadic apneas or hypopneas, but without arousals and without daytime symptoms. Simple snoring represents the preclinical condition of the wide spectrum of SDB [104]. The diagnosis of simple snoring is one of exclusion. It requires that the presence of any other nocturnal respiratory pathology be excluded [105].

There is unresolved debate as to whether snoring alone, without significant OSA, can interfere with daytime functioning. It is now known that in some individuals the resistance to inspiration increases repetitively, leading to brief arousals without any significant arterial hypoxaemia, UARS. When UARS patients are identified and excluded from the population of nonapnoeic snorers, it becomes even less clear whether snoring itself has any fragmentary effect on sleep. It has not been clearly shown that there is any significant long-term medical effect from snoring, as it is still not clear if the association with hypertension and cardiovascular disorders reported in heavy snorers is due to snoring itself or to the presence of obstructive apneas [104]. However, the fragmentation of sleep that may be caused, both by the snoring and by the bed partner's attempts to stop it, has the potential to result in EDS affecting daytime functioning.
1.2.4 History

Much of what we have learned about sleep-disordered breathing has occurred in the very recent past. In 1956 Burwell and colleagues published the first medical description of OSA [106]. They described a case of a sleepy, obese patient and used the term Pickwickian syndrome. The term “Pickwickian” was derived from *The Posthumous Studys of the Pickwick Club* written by Charles Dickens, in which the fat boy Joe resembles “modern” patients with obstructive sleep apnea. He was excessively fat, a heavy snorer, red faced, and sleepy during the day [107].

The first medical description of obstructive sleep apnea (OSA) that recognized that intermittent upper airway obstruction was the major pathogenic mechanism was in 1965. Jung and Kuhlo then described the characteristic repetitive interruptions of breathing during sleep in these patients and showed that carbon dioxide narcosis was not the cause of hypersomnia [108].

In studies published in the early seventies in the Bulletin de Physiopathologie Respiratoire, Lugaresi and colleagues described the dramatic hemodynamic and respiratory consequences of sleep apnea using invasive monitoring of blood pressure in sleeping Pickwickian patients [109, 110] and in subsequent studies, the same authors highlighted the pathophysiological link between snoring and obstructive apneas, indicating the existence of a continuum of clinical conditions between trivial snoring and the severest forms of OSAS. They coined the expression “heavy snorer’s disease” [99].
Much of what we have learned about sleep-disordered breathing has occurred in the last 20 years. It has been argued that two important findings have driven the development in this field. First, the work of Sullivan and colleagues [111], introducing nasal continuous positive airway pressure (CPAP) as a therapy. Since then treatment with tracheostomy, i.e., bypassing the pharyngeal obstruction, previously utilized in the severest sleep apnea patients, was almost discarded. Second, the work of Young and colleagues [43], who performed population-based studies with robust epidemiologic methods, and brought to realization that OSA was far from rare but was, indeed, very common. OSA was now recognized as a major public health issue.

Over the past 20 years it has become clear that OSA is a common disorder with disabling symptoms and substantial associated morbidity and mortality, which has had a profound impact on the field of sleep medicine. Despite this increased recognition of OSA, it is estimated that more than 80% of men and more than 90% of women with moderate to severe OSA remain undiagnosed [112].

1.2.5 Epidemiology

OSAS is a major public health problem. The true frequency of OSAS is not known with certainty since prevalence studies in the literature differ in sampling, study methodology, and definitions of respiratory events [113]. The most cited study is the Wisconsin Sleep Cohort Study [43], where 602 subjects randomly selected from 3,513 responses to questionnaires sent out to 4,284 persons in Wisconsin. The subjects were aged 30 to 60, and pregnant women and subjects with previous cardio-
respiratory history were excluded. This study reports that 24% of men and 9% of women had SDB defined as AHI>5, and that at least 2% of women and 4% of men in this middle-aged population met the minimal diagnostic criteria for OSAS (AHI >5 and daytime hypersomnolence). This estimation can be considered low as it concerns an active, non-pregnant, population without cardio-respiratory history. Gislason et al have estimated the prevalence of OSAS to a minimum figure of 1.3 % in Swedish men (ages 30-69) [114]. Thus, the prevalence of undiagnosed OSAS and OSA in the working population is high. It is estimated that up to 93% of women and 82% of men with moderate to severe OSA remain undiagnosed [112].

1.2.5.1 Risk factors

The most important risk factors for developing OSA include obesity and narrow upper airways, male gender, and older age. Upper airway muscle hypotonia, alcohol and smoking as well as ethnicity are other risk factors.

1.2.5.1.1 Obesity and narrow upper airways

Obesity is the most important risk factor for OSA because it is present in roughly 70% of patients with this disorder; it is reaching epidemic proportions, and it is the only major reversible risk factor [115-117]. Obesity, BMI, waist circumference, and neck circumference have been shown to be strong predictors of SDB [43, 118].

Subjects with narrow upper airways for any other reason than obesity are also at risk for OSA. Craniofacial skeletal abnormalities such as retrognathia/ micrognathia have been demonstrated in OSAS-populations [119-126]. OSAS is more prevalent in disorders such as acromegaly, hypothyroidism, rheumatoid arthritis, and Down’s
syndrome. In acromegaly the airway is narrowed by changes in craniofacial skeletal dimensions, overgrowth of the tongue, and diffuse thickening of the upper airway including the larynx narrow the airway [127]. In hypothyroidism the upper airway is narrowed by thickening of laryngeal tissue, oedema and obesity, but also myopathy in upper airway muscles contribute to the increased risk for OSAS [128]. In rheumatoid arthritis the upper airways might be narrowed by retrognathia due to temporo-mandibular joint destruction [129, 130]. Down’s syndrome is associated with mid-face hypoplasia, narrow nasal airway, large tongue, large tonsils and adenoids, and obesity, all contributing to narrow upper airway. Down’s syndrome is also associated with muscle hypotonia and autonomic dysfunction contributing to the development of OSA [131].

OSAS is also more prevalent in patients with enlarged tonsils and/or adenoids, and in patients with nasal obstruction. Enlargement of the tonsils and adenoids may be temporary during infections, but chronic enlargement is the most important cause of OSA in children [131]. Nasal obstruction can be due to nasal polyps, rhinitis and deviated nasal septum. Complete nasal obstruction leads to mouth breathing, which may predispose to OSA. Partial nasal obstruction leads to a more negative pharyngeal pressure during inspiration to overcome the obstruction, and this predisposes to OSA [131].

1.2.5.1.2 Gender

Gender is strongly associated with SDB. In community based studies it has been reported that men are 2.0 to 3.7 times as likely as women to have SDB [43, 132,
Sleep laboratory data, however, suggest a five to six-fold increased risk for OSA in men [115]. This discrepancy might be due to an underrating of OSAS-related symptoms in patients as well as physicians. It has also been suggested that sleep apnea is underestimated in women, relative to men. One possible explanation for this gender bias is that the clinical guidelines for the evaluation and diagnosis of sleep apnea, established primarily on men, are not valid for women. Young et al [134], however, did not find any significant gender differences when comparing the reported symptoms of 338 women and 551 men. They found that regardless of severity level, women with sleep apnea did not report symptoms that differed significantly from those of men with the same level of sleep apnea. They reported that in men as well as women snoring was the most sensitive and strongest predictor of sleep apnea. The gender related protective effect in females against OSA decreases post menopause (unless on hormone replacement therapy) with a prevalence of SDB approaching that seen in men [133, 135]. Young et al found a 2-fold increase in prevalence of sleep apnea in peri- and post-menopausal women compared to pre-menopausal women in the same age, as well as with the same BMI [136]. Bixler et al found a 5-fold increased risk to develop OSAS (AHI>15) in post-menopausal women without hormone replacement therapy compared to pre-menopausal women [133].

Snoring and OSA are more common in pregnant women. A study of normal pregnant women observed during pregnancy [137] has shown that snoring may be present during pregnancy alone and, despite the fact that blood pressure may stay within normal range, systolic pressure may increase more in women who snore loudly than in those who do not. Snoring was more common in women with pre-eclampsia. There were also indications that heavy snoring at night in pregnant women may be an independent factor for poor infant outcome.
This difference in OSAS prevalence suggests that the female gender (before menopause but not pregnant) may reduce the risk of sleep breathing disorders in adults. Kapsimalis et al have suggested several factors that might explain this gender protective effect including differences in obesity and the distribution of adipose tissue, upper-airway anatomy, upper-airway muscle function, control of ventilation, the effect of sex hormones, and leptin [135]. In post-menopausal women, hormone replacement therapy has been shown to be associated with lower prevalence of sleep apnea [133, 138]. This association has been reported to be more pronounced at younger ages, and is significant also after adjusting for obesity [138].

1.2.5.1.3 Age

OSA may occur at any age but typically peaks in certain age groups. It has been suggested that there are two types of sleep apnea [113]. The first type typical of the symptomatic OSAS patient peaking around 55 years of age [114, 139] and the second type age dependent, increasing in the elderly, but only vaguely associated with clinical symptoms and consequences. This was studied by Bixler et al [139] in a two-stage general random sample of men (aged 20 to 100 yr), consisting of a telephone survey (n = 4,364) and a sleep laboratory evaluation of a survey sub sample (n = 741). They report that OSAS, defined as AHI ≥ 10 and the presence of daytime symptoms, has its maximum prevalence in the middle age group (45 to 64 yr) while the prevalence of sleep apnea tends to increase with age but that the severity of sleep apnea, as indicated by both number of events and minimum oxygen saturation, decreased with age (controlling for BMI).
OSAS is also present in children. The true frequency is not known, but it appears to be high. The lower limit of the sleep apnea syndrome prevalence in Icelandic children has been reported to be 2.9% [140]. Stradling et al in 1990 [141] demonstrated sleep hypoxaemia and abnormally disturbed sleep in more than 60% of children listed for adenotonsillectomy for other reasons than sleep disorders.

1.2.5.1.4 Muscle hypotonia in upper airway muscles

Pharyngeal dilator muscle function is of importance for the patency of the upper airways. Muscle hypotonia in upper airway muscles leads to impaired upper airway muscle dilator function and increased upper airway collapsibility. An increased tendency to develop OSA after intake of alcohol has been shown as increase in numbers of apneas and duration of apneas. The decrease in arousability is thought to prolong the apneas and the upper airway muscle hypotonia contribute to obstruction of the upper airways [131, 142]. Benzodiazepines increase the degree of muscle relaxation of the upper airways, and it has been demonstrated that drug-induced coma involving benzodiazepines is characterized by snoring with flow limitation and obstructive apneas [143]. Upper airway obstruction is common during general anaesthesia caused by loss of muscle tone [144]. During general anaesthesia, central control of the upper airway is altered so that the muscles loose their activity. Obstructive “anaesthetic” apneas occurs both during the anaesthesia and in the recovery phase [131]. SDB is common in patients with neuromuscular disorders [145-147], where interference with neuromuscular control of ventilation by diffusely weakening of the upper airway dilator muscles is thought to contribute to OSAS.
1.2.5.1.5 Alcohol and smoking

Although an increased tendency to develop OSA after intake of alcohol has been shown [142] epidemiological studies analyzing the relationship between alcohol and SDB are not conclusive. Some authors have found an association, while others have not. This discrepancy might be reflecting the difficulties in finding reliable instruments for estimating alcohol use in epidemiological studies [113]. Smoking is associated with an increased risk of SDB [113, 148-150]. It has been proposed that it can be due to diffuse mucosal inflammation in the oropharynx as well as altered respiratory control because of pharmacological effects of nicotine [131].

1.2.5.1.6 Ethnic background

Several authors have studied the prevalence in SDB in different ethnic groups and higher prevalence has been found in Hispanics and non-whites compared to Caucasians and Chinese, independent of BMI, gender and age [151-153]. There are indications that this difference is age-dependent, since Redline et al reported that ethnical difference only was found in lower ages, and decreased with increasing age [153].

1.2.6 Signs and symptoms

Symptoms of OSA include snoring, choking at night, witnessed apneic episodes, nocturia, and frequent arousals. Daytime manifestations are excessive daytime somnolence, poor concentration, poor memory, mood changes, and irritability. The strongest signs and symptoms suggestive of OSA are measures of obesity, witnessed apneas, and prominent snoring. OSA should also be suspected in individuals
presenting with hypertension, excessive daytime sleepiness, and a family history of OSA and snoring [104, 115]. The symptoms in children differ from adults. Apart from adult symptoms and signs such as snoring, choking at night, witnessed apneic episodes, and frequent arousals, symptoms in children also include hyperactivity [141], oral breathing [154], growth retardation [155], bed wetting [156], cor pulmonale [155] and hypertrophy of tonsils and adenoids [141].

1.2.7 Consequences of OSAS – increased morbidity

1.2.7.1 Disturbed sleep and EDS, cognitive deficits and quality of life

OSA is a risk factor for excessive daytime sleepiness (EDS). In PSG studies of patients with SDB it is well known that apneas and snoring are capable of inducing arousals (an abrupt shift in EEG frequency lasting for > 3 seconds [157]). Such respiratory arousals repeated throughout the night give rise to sleep fragmentation and reduction in the total amount of SWS, resulting in EDS, the most important symptom in OSAS.

A wide range of cognitive deficits have been associated with OSAS, including decreases in general intellectual functioning, attention, memory and learning abilities, executive functions, and motor performance [158, 159]. Oxygen desaturations due to apneas may also contribute to these chronic neuropsychological deficits [158]. The possibility of anoxic brain damage as a pathogenic factor in severe OSAS has been discussed, since CPAP-treatment in some cases failed to normalize executive function, while EDS as well as impaired attention was reversed [159].
A considerable decrease in quality of life has been shown in patients with OSAS, most likely due to EDS [88, 160-162] as well as in their bed-partners, most likely due to sleep deprivation due to the noisy surrounding [163]. Grunstein et al have shown that OSA or frequent sleepiness or both are independent predictors of amount of sick leave, worse self-rated general health, impaired work performance and divorce rate in obese subjects [164]. Treatment with CPAP has been shown to return patients to a quality of life similar to the normal population [88, 160-162].

1.2.7.2 Cardiovascular consequences

A large number of studies report convincing evidence for an association between OSA and cardiovascular risk, as discussed below. To determine the role of OSA as an independent risk factor for cardiovascular disease is, however, a challenging task. First, since obesity is a major risk factor for OSA and also for cardiovascular disease. Thus, controlling for obesity as a co-variate is of major importance when determining cardiovascular risks seen in OSA, and large studies are therefore requested. Second, because the level of evidence in the literature for the role of OSA in causing cardiovascular disease is highly suggestive but not considered definitely proofed. It is debatable whether the definite proof of the connection between OSA and cardiovascular disorder has been presented [165, 166]. Studies showing reduction in cardiovascular disorder events after treatment of OSAS in large-scale randomized trials are still lacking. It has therefore been argued that although the hypothesis of OSA as a risk factor for cardiovascular disorders is highly attractive and plausible, treatment of patients to reduce cardiovascular risk is not yet evidence based [165]. In my opinion the strong association between OSA and cardiovascular disease, whether
causal or not, is a strong reason to find and diagnose OSAS patients and snorers at risk.

1.2.7.2.1 Hypertension

Data for the cardiovascular risks of OSA are most convincing for hypertension. It is now highly probable that OSA contributes to the development of hypertension independent of other relevant risk factors [167-170]. A study from the Wisconsin cohort of Young et al found a 2-3 fold increased risk to develop hypertension within four years depending on the degree of OSA in an initial sleep study (after controlling for confounding factors such as age, gender, obesity, alcohol and smoking) [170]. Grote et al found an increased risk for hypertension in OSA patients under 50 years of age [168]. Davies et al found elevated systolic and diastolic blood pressure in OSA patients compared to normal controls. Data were significant for 24 hours a day but particularly significant for the period of sleep [171]. Sjöström et al have shown an increased prevalence of SDB in 102 hypertensive men compared to normotensive controls [172].

In 2001, Faccenda et al [86] were the first to show causal links between short-term changes in blood pressure and CPAP treatment in OSA patients. They conducted a randomized placebo-controlled cross-over study of the effects of CPAP or oral placebo on 24-hour blood pressure in 68 OSAS patients not receiving hypotensive medication and showed that CPAP can reduce blood pressure in patients with OSAS. This effect of CPAP on blood pressure in OSAS patients has been confirmed in recent studies [87, 173, 174]. Heitmann et al in 2004 [174] demonstrated that CPAP caused a decrease in heart rate, associated with a decrease in mean arterial blood
pressure and noradrenaline plasma levels. CPAP lowered blood pressure mainly in hypertensive OSA patients, whereas the effect was small in normotensive patients.

1.2.7.2.2 Cardiovascular disease

It has been suggested that SDB is a risk factor for ischemic heart disease, and may be associated with increased morbidity and mortality due to cardiovascular disease [175-177]. There is, however, an ongoing controversy regarding the causal vs. co-morbid relationship between OSA and cardiovascular disease [165].

In a 7-year follow up of patients treated with advise of weight-loss vs. patients treated with tracheostomy, Partinen and Guilleminault found a significantly increased risk for cardiovascular morbidity in the conservatively treated group [178]. Shahar et al [179] showed a 2-fold increased risk for cardiovascular disease including myocardial infarction in patients with AHI ≥11 compared with normal subjects when examining the cross-sectional association between sleep-disordered breathing and self-reported cardiovascular disease in 6,424 individuals who underwent overnight PSG. Peker et al have shown that OSA is a risk factor for myocardial infarction and unstable angina when compared to control subjects with similar levels of obesity [180]. Hayashi et al [181] showed that the severity of coronary atherosclerosis showed a significant positive correlation with the ODI in all patients and multiple regression analysis showed that the ODI was the most significant, independent determinant of severity of coronary atherosclerosis among the coronary risk factors tested, and explained 13.4% of the variance. Franklin et al have reported an association between OSA and nocturnal angina, and the improvement of nocturnal angina with CPAP treatment in
OSAS patients [182]. Kaneko et al have reported an association between OSA and cardiac failure and have shown that treatment of coexisting OSA with CPAP improves cardiac function in medically treated patients with heart failure [183].

1.2.7.2.3 Cerebrovascular disease

Studies of OSA and its relation to stroke have shown an association [179, 184, 185]. Sleep apneas and hypopnoea are common after stroke; however, patients are often asymptomatic and do not use or respond to CPAP [186, 187]. It has been argued that stroke patients might have OSA as a consequence of cerebrovascular disease. This is supported by the study of McArdle et al, who explored the relationship between OSA and ischemic cerebrovascular disease in patients with transient ischemic attack (TIA), since TIA patients are less likely than stroke patients to have OSA as a consequence of cerebrovascular disease. They reported no increase in OSA in patients with TIA [188].

1.2.7.2.4 Pathophysiology underlying co morbidity between OSAS and cardiovascular disorders

The pathophysiology underlying the association between cardiovascular morbidity and OSA is unknown, but several possible mechanisms have been suggested in the literature. One is increased sympathetic activity, as high sympathetic activity has been reported in patients with OSA [84, 189] and that these increases are attenuated by treatment with CPAP [85]. Other proposed mechanisms are increased vasoconstrictor sensitivity [190] as well as an association with the pathogenesis of atherosclerosis. The latter supported by an the study of Ogha et al and Dyugovskaya et al, who have reported activation of adhesion molecules, known to be associated to the pathogenesis
of atherosclerosis in cardiovascular disorders, in OSAS- patients, and by the studies of Vgontzas et al and Yokoe et al, who have reported elevated levels of the inflammatory cytokines interleukin-6 (IL-6) [191, 192], and tumour necrosis factor-alpha (TNF-alpha) [191], as well as increased C-reactive protein (CRP) [192], an important risk factor for atherosclerosis and coronary heart disease. Yokoe et al have showed a decrease in levels of CRP and IL-6 with CPAP-therapy [192].

1.2.7.3 Insulin resistance and diabetes

It is estimated that more than half of the adult population in the United States is overweight or obese. The dramatic increase in the prevalence of obesity over the last two decades has occurred in men and women across all ages and in various racial and ethnic groups [193]. Although the prevalence of obesity in Sweden still is low in an international perspective, the development during the last decades is alarming [194].

It is well known that obesity in adults is associated with increased incidence of hypertension, cardiovascular disease, stroke, and altered glucose metabolism seen as Type 2 diabetes mellitus [195, 196]. It is also well known that OSA in adults is associated with increased incidence of hypertension, cardiovascular disease, and stroke. A number of studies have reported that OSA also is associated with glucose metabolism independent of obesity [197-203].

Ip et al [197] have shown that OSA is independently associated with insulin resistance and that insulin resistance is present even in non obese OSA patients. They examined 270 consecutive non-diabetic subjects with a range of SDB from absent to
severe (out of whom 185 had AHI ≥ 5) in a sleep lab. Fasting glucose and fasting insulin were measured and insulin resistance was calculated. They report an association between OSA and insulin resistance in obese as well as non-obese subjects. Punjabi et al [198] found that insulin resistance is present even in mild forms of OSA. They showed an almost dose-response relationship between impaired glucose metabolism and AHI when studying a community-based large sample of 150 men over the age of 45 years with BMI of 120-160% of their ideal body weight, exclusive of those with cardiopulmonary or cardiovascular disease, hypertension, diabetes or hyperlipidemia. Elmasry et al reported the prevalence of severe OSA, defined as AHI >20 was significantly higher in diabetic patients than in normoglycaemic subjects [201].

In a controlled study Vgontzas et al have shown that insulin resistance was associated with OSA independently of obesity, and that visceral fat, which is strongly associated with insulin resistance, was the primary parameter linked with OSA [202]. The same group have found increased incidence of SDB in women with polycystic ovary syndrome, a common endocrine disorder in pre-menopausal women associated with insulin resistance [199]. Thus, it seems like OSA is increased in disorders in which insulin resistance is a primary pathophysiologic abnormality.

Even snoring without apneas has been reported to affect glucose metabolism. Al-Delaimy et al have reported an elevated risk of developing Type II Diabetes in snorers [203] and Elmasry et al have reported an increased incidence of diabetes within 10 years in habitually snoring males aged 30-69 years [200].
However, it has been shown that sleep disturbance per se is a risk factor for weight gain, insulin resistance, and Type 2 diabetes [204].

All these studies indicate that OSA is associated with impaired glucose metabolism independent of obesity, perhaps as a consequence of its associated sleep disturbance. Since insulin resistance is a known risk factor for atherosclerosis, this may be the link between OSA and cardiovascular disease.

In 1988 Reaven proposed the existence of a syndrome X, a cluster of independent risk factors for diabetes and cardiovascular disease, being comprised of hyperinsulinemia, glucose intolerance, dyslipidemia, central obesity, and hypertension [205]. Since then there have been other names attributed to this syndrome, the most common being the metabolic syndrome and the insulin-resistance syndrome [206]. A multitude of epidemiological studies have shown that obesity, hypertension and insulin resistance are indeed all inter-correlated, that they correlate with other cardiovascular disease risk factors and that the syndrome is predictive of cardiovascular events [207, 208]. It is also recognized that many subjects with OSAS have central obesity and other features of the metabolic syndrome [191, 209, 210] and that snoring without apneas may be a predictor for metabolic syndrome [211]. Due to this association between OSA and the metabolic syndrome, a syndrome Z has been suggested, defined as syndrome X with the addition of OSA (unpublished suggestion, Thorarinn Gislason).
1.2.7.4 Accidents

OSAS patients have been shown to have a 2-4-fold risk for car accidents compared to healthy drivers [212-216]. George et al reported decreased performance skills in laboratory driving in OSAS patients compared to normal control subjects and also to control subjects after intake of alcohol [217]. The increased risk of traffic accidents due to OSA is removed when patients are treated with CPAP [218, 219].

OSAS patients have also been shown an increased risk for occupational accidents. Lindberg et al report that sleepy snorers have an increased risk of occupational accidents [220], while no increased risk was found for non-sleepy snorers or sleepy non-snorers. They studied the influence of snoring and EDS on the risk of occupational accidents in a population-based, prospective questionnaire study of 2,874 men. Ten years later 2,009 (73.8% of the survivors) responded to a follow-up questionnaire including questions on work and potential confounders. Data were compared to national register data on occupational accidents during the ten year period. An increased risk of occupational accidents was found in sleepy snorers after adjusting for confounders such as age, body mass index, smoking, alcohol dependence, years at work, blue-collar job, shift work, and exposure to noise, organic solvents, exhaust fumes, and whole-body vibrations.

1.2.8 Consequences of OSAS – increased mortality

Several authors have addressed the association between SDB and increased mortality. Though there is a debate in the literature regarding OSAS causing cerebrovascular
sequels, there are several studies confirming an association between OSAS and cardiovascular mortality.

Partinen et al have reported higher mortality rate at five-year follow up for 127 OSAS patients conservatively treated (recommendation of weight loss) compared to 71 tracheostomy treated OSAS patients, who had more severe OSAS at the start of the study. During the study period 14 deaths occurred, all in the conservatively treated group, with cardiovascular disease the cause of death in 8/14 patients [221]. Lavie et al have reported a significantly increased mortality risk in lung and heart disease in OSAS patients in the fourth and fifth decades of life. After multivariate analysis they suggested that OSAS affects death indirectly, most probably by being a risk factor for hypertension [222]. Lindberg et al have found a doubled risk of cardiovascular death among men aged 30-59 years suffering from snoring and EDS, the two major symptoms of OSA, but no increased mortality in men aged 60 or above [223]. This confirms the findings of other groups who have not found any increased mortality risk for elderly subjects with SDB [224, 225]. The association between snoring and sudden cardiovascular death was studied in autopsies of 460 consecutive cases of sudden death among 35 to 76-year-old Finnish men [226]. Snoring history was obtained from cohabiting individuals. Cardiovascular cause of death was more common among those who snored habitually than among those who snored occasionally or never. Habitual snorers died more often while sleeping and habitual snoring was found to be a risk factor for morning death. The authors concluded that the possibility of OSAS as a cause of sudden death should at least be considered in habitual snorers.
Marin et al [227] have reported a positive effect of CPAP treatment on mortality in OSAS. They showed a significantly increased risk of fatal and non-fatal cardiovascular events over a 10 year period in untreated male patients with severe OSAS compared to control subjects with similar degree of obesity. Treatment with CPAP in severe OSAS reduced this risk to the control level.

1.2.9 Consequences of OSAS - costs

The increases in our knowledge about OSAS in the last decades has led to rapidly growing demand for services, but most health care delivery systems are not able to meet this demand. Except for the medical benefits in diagnosing and treating OSAS, there are also studies showing benefits regarding cost-efficacy in diagnosing and treating OSAS and meeting these demands.

Ronald et al [228] have shown that OSAS patients are heavy consumers of health care resources for several years prior to diagnosis. They compared health service utilization for a 10-year interval prior to diagnosis of 181 OSAS patients to those of randomly selected age-, gender-, and geographically matched controls from the general population. In OSAS patients they reported increased physician claims every year for a ten years period before diagnosis, and the last three years before diagnosis it was 2-3 folded compared to controls. They also reported more overnight hospitalizations in OSAS patients than for controls in the decade prior to diagnosis. Thus, by the time patients are finally diagnosed as OSAS, they have already been heavy users of health services for several years.
In other American studies, comparing untreated OSAS patients with matched controls, it has been shown that untreated OSAS patients have doubled physician costs [229], hospitalization days doubled to tripled [229], and a doubled mean annual medical cost per patient [230] compared to controls. In treated OSAS patients, however, physician costs have been shown to fall 33% and hospitalization to decrease from 1.27 to 0.54 days per patient and year [231].

In a retrospective Swedish study [232], the total number of in-hospital days due to cardiovascular or pulmonary disease was investigated in CPAP-treated OSAS patients 2 years before and 2 years after CPAP-prescription and compared to those of OSAS patients not using their prescribed CPAP. They found a decrease in the total number of in-hospital days due to cardiovascular or pulmonary disease in the CPAP users (n = 19) from 413 days before prescription to 54 days after. In the non-compliant group (n = 12), however, they found an increase from 137 days before to 188 days after CPAP prescription. The authors conclude that CPAP treatment reduces the need for acute hospital admission due to cerebrovascular and pulmonary disease in OSAS-patients, and that this reduction of concomitant health care consumption should be taken into consideration when assessing the cost-benefit evaluation of CPAP therapy.

Douglas and George have estimated the accident reduction after OSAS treatment and calculated that every pound spent on OSAS treatment would give 12.3 fold return in savings [233].
Thus, it seems important that health service planners recognize these benefits and the cost- efficacy of diagnosing and treating OSAS. OSAS services should get high priority in health budgets.

1.2.10 Treatment

As described above, OSAS is a major public health problem associated with increased morbidity and mortality in cardiovascular disorders, including hypertension and accidents. Effective treatment is, however, available.

Nasal CPAP is the first choice of treatment in patients with moderate and severe OSAS [234]. The positive pressure prevents upper airway occlusion. CPAP-treatment improves EDS, the major OSAS symptom [88], sleep in moderate and severe OSAS patients [235, 236], self-reported health status [88], cognition [237], and quality of life to a level similar to the normal population [88, 160-162]. CPAP-treatment in OSAS patients also reduces blood pressure in hypertensive patients [174], reduces nocturnal angina [182], removes the increased risk of traffic accidents [218], improves cardiac function in medically treated OSAS patients with heart failure [183], and reduces the risk of fatal- and non-fatal cardiovascular events [227].

Other available therapies include mandibular protrusion devices [238-241], surgical treatment such as uvulopalatopharyngoplasty (UPPP) [242-244], and conservative treatment such as weight loss advice [132, 245-247], sleeping position training [248, 249], and hormone replacement therapy in post-menopausal women [138].
Adenotonsillectomy is the most common therapy for OSAS in children. Nasal continuous positive airway pressure can be an effective treatment option, but it entails cooperation and training of the child and the family. A valid but often overlooked alternative, orthodontic treatment, may complement adenotonsillectomy [250].

1.2.11 Diagnosis

1.2.11.1 Diagnostic criteria

In 1999 the American Academy of Sleep Medicine Task Force [92] proposed the following criteria for diagnosis of OSAS: 5 or more respiratory events (AHI, ODI or RERA) per hour during sleep associated with excessive daytime sleepiness not explained by other factors or at least 2 of the following signs and symptoms: choking or gasping during sleep, recurrent awakening during sleep, unrefreshing sleep, daytime fatigue, and/or impaired concentration. Based on the number of respiratory events OSAS can be graded as follows; Mild: 5 to 15 events per hour of sleep. Moderate: 16-30 events per hour of sleep. Severe: >30 events per hour during sleep.

For EDS three levels of severity have been proposed [104]. Mild: occurs during activities that require little attention (e.g. watching television, reading). Moderate: occurs during activities that require some attention (e.g. movies, concerts, meetings). Severe: occurs during activities that require an elevated degree of attention (e.g. during meals, conversation, driving). EDS is often diagnosed using the Epworth Sleepiness Scale (ESS), a simple questionnaire measuring the general level of daytime sleepiness. ESS is a measure of the probability of falling asleep in a variety of situations, which scores significantly different in patients with primary snoring
from those with OSAS Furthermore, ESS scores increase with the severity of OSAS [251].

**1.2.11.2 Diagnostic levels**

The objective assessment of patients with a suspected OSA has primarily used attended polysomnographic studies, which is considered “Gold Standard”. The growing demand for diagnostic services, technologic advances and issues of availability, convenience and cost have led to a rapid increase in the use of portable recording devices. Many approaches yield satisfactory diagnostic information. The available diagnostic methods can be divided into four levels [252].

1.2.11.2.1 **Level I: Complete cardiorespiratory PSG in sleep lab**

Level I is defined as PSG with minimum 7 channels, including EEG, EOG, chin EMG, heart rate or ECG, respiratory flow, effort, and oxygen saturation. Level I, PSG is performed with attending personal, which make it possible with interventions. According to the recommendations from the Standards of Practice Committee and approved by the Board of Directors of the American Sleep Disorders Association. PSG is routinely indicated for the diagnosis of sleep-related breathing disorders [253].

1.2.11.2.2 **Level II: Unattended PSG at home**

Level II is defined as PSG as in Level I, but with a portable PSG device for use in the patient’s home, thus without attending personnel. It is very expensive in terms of cost
and experience, is more prone to artefacts than Level I, and does, thus, not always yield reliable diagnosis. It is, however, very useful for research purposes.

1.2.1.2.3 Level III: Portable sleep apnea diagnosing devices

Level III is defined as a portable device dedicated for sleep apnea diagnosis, with minimum 4 channels, including respiratory flow or effort, heart rate or ECG and oxygen saturation.

Several devices are available on the market, and several authors have validated these against PSG. A recent study by Dingli et al [254] have evaluated a portable device measuring nasal air flow, thoraco-abdominal movement, finger pulse oximeter, and body position, the Embletta (Flaga, Reykjavik, Iceland) against PSG. Using the diagnostic cut of AHI ≥ 15, the AHI-level where there is robust evidence for the benefits of CPAP therapy, they found that all nine patients categorised as not OSAS had AHI < 15 slept on PSG and all 23 with OSAS on Embletta had an AHI ≥15 on PSG. 18 patients, however, fell into the possible OSAS category potentially requiring further investigation and 11 home studies failed. Thus, in this study most patients were satisfactorily classified by home Embletta recordings, but 29 out of 61 required further investigation.

The authors recommend the use of both nasal pressure and the thoraco-abdominal movement as indicators of hypopneas, as well as the use of manual scoring as the automatic software did not relate closely to the manually scored results.
In 1990, Svanborg et al [255] reported a validation study of a simplified device consisting of combined oximetry and respiration and body movement monitoring against conventional PSG. The authors concluded that a combination of respiration movement and oximetry recording seemed to give sufficient information to confirm or negate a diagnosis of OSAS in a majority of patients with clinical symptoms, but that further investigations were needed in border-line patients.

It thus seems that Level III is capable of diagnosing SDB with high sensitivity and specificity. Level III is usually considered first choice for CPAP therapy control, and is used for primary diagnosis in many parts of the world including the Scandinavian countries.

1.2.11.2.4 Level IV: One- or two channel sleep apnea screening devices

Level IV is defined as continuous recording of one or two channels, i.e., reduced systems such as holter-ECG, ambulatory blood pressure monitoring, portable oximetry, actigraphy, and wrist worn peripheral artery tonometry (watch-PAT), [256]:

- **Holter-ECG** has been shown to have morphologic changes characteristic for sleep apnea, with cyclical variation of heart rate in different sleep stages as well as during apneas [257].
- **Ambulatory blood pressure** monitoring can be used since it has been shown that OSAS patients lose the normally expected morning dip in arterial blood
pressure and in general have higher blood pressure during sleep, probably at least partially caused by the nocturnal apneas and hypoxemia [258].

- **Portable oximetry** alone is used as a screening tool for SDB by many clinicians. According to several authors, it has a limited diagnostic value owing mainly to a low sensitivity for moderate to mild cases of OSAS [259-261].

- **Actigraphy** implies the detection of movements as a measure of sleep and wake cycles. It is mainly used as a supplement to the clinical interview and sleep diary in circadian rhythm disorders. The method can be useful in OSAS together with other systems to estimate sleep wake pattern, as it indicates arousals. The method can however not detect whether movements are due to apneas or not, and misses the arousals that are not associated with movements [262].

- The Wrist worn peripheral artery tonometry, **Watch-PAT**, has been used to detect OSAS. The PAT technology represents a unique and relatively new concept of non-invasive measurement of sympathetic activation levels that appears to be very accurate for detecting SDB events. The Watch-PAT measures peripheral arterial tone, heart rate, oxygen saturation, and actigraphy for automatic analysis of respiratory disturbance index (RDI). The method has been validated against PSG [263].

In conclusion, Level IV systems can give good indications for SDB and other sleep disorders, but have low sensitivity and specificity.
1.2.11.3 Which level to use. Pros and cons.

The American Academy of Sleep Medicine, American College of Chest Physicians, and the American Thoracic Society recommended in 2003 that for patients strongly suspected of having OSAS, a full comprehensive, attended overnight PSG is required [253]. Although Level I is considered the gold standard for diagnosis of OSA, several screening devices evolving, since the full attended PSG, is cumbersome, expensive, labour-intensive, and requires expertise.

The rapidly growing demand for diagnosis and treatment, have resulted in long waiting lists. Pack [264] has written that it seems inconceivable that we should tell a patient “You are highly likely to have a severe sleep apnea, a disorder associated with an increased risk of car crashes, high blood pressure, and probably heart attack and stroke. We have an effective treatment for this disorder. We will arrange a study for you in 14 months’ time to access this.” He concludes that the major issue now in this field is access. How to solve this access is still debated. In some regions, including the Scandinavian countries, level III, home diagnosis, is the standard, whereas in others, including large parts of the USA, level I remains the preferred approach.

In 1999 Chevrin et al published a cost-utility analysis in favour of Level I diagnosis [265]. Cost-utility of three approaches to the diagnosis of OSA was analyzed:

1) Attended PSG, 2) home studies, and 3) simple clinical investigations (interview, without any recording). Level I was found expensive (1190 USD, but gave the smallest diagnostic error (0-5%). Home studies were less expensive (440 USD) but resulted in a higher diagnostic error (5-30%) and the simple clinical investigation was again less expensive (210 USD) but had the largest diagnostic error (5-65%). The
authors propose that if the costs of consequently correctly or falsely prescribed CPAP equipments are calculated, including the resulting costs and utility for the health care system, then a diagnostic procedure with PSG is the priciest procedure, despite the high initial cost. Douglas [266], on the other hand, states that home studies may be used to diagnose OSAS and that they can represent a cost-effective option in the attempt to meet the increasing diagnostic demand. Douglas et al have estimated that in comparison to performing Level I diagnostics in all patients, the use of home Embletta recordings (Level IV) reduce costs by 42% [254]. For the future, they suggest further studies, where home diagnostic systems are validated against clinical outcome rather than against in-lab PSG [266]. One such study of Whittle et al in 1997 [267], demonstrated that Level III diagnosis rendered similar CPAP outcomes and use as Level I diagnosis.

Level III diagnostics is used as routine in the Scandinavian countries. The Swedish consensus report regarding diagnosis and management of OSAS from 1994 [93] states that the minimal requirements for simplified recordings are as follows: monitoring of pulse oximetry, breathing pattern and body position, all combined. The minimal recording time should be 6 hours performed during the subject’s normal sleeping time, and should contain at least 4 hours of estimated sleep. Automated scoring must not be relied on solely. Interpretation needs to be performed by a physician trained in sleep medicine, and diagnostic decisions must be taken in conjunction with the patient’s symptoms. A negative study does not exclude the diagnosis. When significant discrepancy between the diagnostic study and clinical findings is seen, further examinations should be made.
1.2.12 Pathogenesis

Apneas are caused by repeated episodes of narrowing of the upper airway during sleep. The site of this narrowing is in the pharynx [268-272]. The pharynx is like a muscular tube, extending from the back of the nose to the epiglottis. It is vulnerable because it lacks substantial bony or rigid support. Thus, the patency of this segment of the airway is dependent on the activity of the pharyngeal dilator muscles as well as anatomical factors mediating upper airway narrowing. In OSA the upper airway dilating muscle activity is not sufficient to overcome the negative inspiratory pressure created by the thoracic pump. Consequently, the upper airway collapses.

The etiology of OSAS is only partly known. Why apneas occur, why only certain individuals are affected, and why it only occurs during sleep is only partially understood.

1.2.12.1 Proposed causative OSAS mechanisms

Two principally different possible mechanisms are usually mentioned as causative of OSAS, namely A. an anatomically narrow upper airway (overweight with fat deposits in the larynx, considered the most common cause; an aberrant facial skeleton or soft tissue enlargement) or B. muscular hypotonia in upper airway muscles (neuromuscular diseases or toxic reactions, e.g., alcohol) [273]

1.2.12.1.1 Anatomically narrow upper airway and obesity

Much work has been done to address the hypothesis that abnormal anatomy underlies SDB. It has been discussed whether anatomy alone explains OSA, or whether
abnormal neuromuscular control of the pharyngeal dilator muscles is the cause of the collapse. According to this hypothesis the presence of narrow upper airways in combination with changes in airway physiology produced by sleep leads to SDB events and OSAS [274].

It seems clear that most patients with OSA have small pharyngeal airways [275], since CT and MR imaging studies have shown more narrow upper airways during wakefulness in OSA-patients compared to normals [276-281]. Schwab et al [282] in an MRI case-control study found enlarged tissue structures surrounding the upper airways in patients with sleep apnea. They calculated odds-ratio and found that enlarged soft tissue volume of lateral pharyngeal walls, tongue an total soft tissue had an Odds Ratio for Sleep Apnea of > 6 when adjusted for gender, ethnicity, age, craniofacial size and visceral neck fat. Furthermore, increase in the size of the upper airway soft tissues, such as the soft palate, tongue, parapharyngeal fat pads and lateral pharyngeal walls, have been demonstrated with CT and MR imaging in patients with OSA [277, 281, 283-285]. Upper airway oedema contributes to the enlargement of these soft tissue structures, and CPAP is thought to reduce this oedema. Obesity also contributes to the enlargement of upper airway soft tissue.

Shneerson has stated that we are unaware of any disease or disorder with narrowing of the upper airway where an increased risk of OSAS has not been reported [131].

**Obesity** is the most important risk factor for OSA [116, 117]. Obesity and neck circumference has been shown to be a strong predictor of SDB [43], indicating that fat deposition around the upper airway contributes to OSA. This has been confirmed
in upper airway imaging studies, where enlarged fat pads have been found in the lateral pharyngeal walls in obese patients with OSA [276, 277, 286, 287]. Grunstein et al, however, reported that waist circumference is a better predictor for OSA than neck circumference or BMI, suggesting that the link between obesity and sleep apnoea cannot be explained solely by neck fat deposition [118].

**Narrow upper airways for other reasons than obesity** are also risk factors for OSA. Craniofacial skeletal abnormalities, endocrine disorders, Downs syndrome, enlargement of the tonsils and/or adenoids, and nasal obstruction, all have narrow upper airways in common and are all associated with increased risk for developing OSA (as discussed above). Sleep position affects narrowing of the upper airways. In the supine sleep position, the weight of the tongue and mandible is not counteracted by tonic muscle activity and tends to fall back into the pharynx and contribute to the narrowing and obstruction. This is more marked in REM sleep when muscle hypotonia is greater [131].

1.2.12.1.2 Muscle hypotonia in upper airway muscles

Several studies have shown that oropharyngeal upper airway muscle hypotonia contributes to the development of OSA whether induced by alcohol, benzodiazepines, general anaesthesia or neuromuscular disease (as discussed above under risk factors for developing OSA). Disorders in the central nervous system giving rise to upper airway muscle hypotonia have also been discussed. Increasing evidence demonstrates that OSAS is an
independent risk factor for stroke. However, in some cases, especially when located
in the brainstem, stroke might be the cause rather than a consequence of OSAS [288].
Indications of central nervous system lesions in OSAS patients are given in MRI
studies, which have shown evidence of gray matter loss correlated to the severity of
OSA [289]. Brain changes in OSA patients have previously been considered
consequences of OSA, as apneas give rise to hypoxia, hypercapnia and increase in
blood pressure, which might induce a central nervous lesion. There are, however,
signs of early nervous lesions as well and it is speculated whether such an early
central nervous lesion might contribute to the development as well as maintenance
and progress of OSA [290].

1.2.12.2 Natural progression

Elio Lugaresi, who was one of the first researchers to study and describe OSAS, has
coincided the expression “heavy snorers disease” [41]. He described the natural history
of the OSAS based on interviews with 118 patients. Typically, there was a
development from continuous snoring in the early twenties to intermittent snoring in
the early forties, followed by addition of day-time somnolence in the mid forties. Not
until around age 50 would the patient seek medical help and get diagnosed. The
concept of a “heavy snorer’s disease” is corroborated by the fact that OSAS is a less
common diagnosis before middle age. The progressive nature of OSAS has later been
demonstrated in several studies, with objective recordings of indices of respiratory
distress, particularly in patients with a mild - moderate disease [40, 291, 292]. An
increase of OSA severity has been demonstrated in untreated patients, which partly
could be explained by increase in BMI, but BMI increase was not the case in many
patient groups [291]. In the Wisconsin Sleep Study the mean apnea-hypopnea index
(AHI) increased from 2.6 to 5.1 events per hour over 8 years [292]. The increase in AHI was substantially greater in obese individuals and in those who reported habitual snoring at baseline. However, weight increase does not always provoke impairment of obstructive respiration. In one study where this relationship was prospectively studied, there was no certain correlation between increases in AHI and body weight [40].

It has been demonstrated that the progressive nature of OSAS remains despite surgical therapy [242, 293] or weight loss. Several studies have reported progress of SDB despite weight loss. Pillar et al have seen return of OSA despite obesity surgery [294] and Lindberg et al have found that BMI-changes do not explain changes in obstructive respiration over time [40] although weight loss has been demonstrated to decrease the severity of OSA [117, 295, 296]. Svanborg and Larsson found marked worsening of obstructive breathing in some patients despite weight loss [291].

The progressiveness despite surgical therapy or weight loss indicates that anatomical factors such as obesity and narrow upper airways cannot fully explain the pathogenesis of OSA. Other anatomical factors often do not progress, after adolescence, the tonsils gradually decrease in relative size, and skeletal aberrations as a rule do not worsen in adulthood. Concomitant clinical neuromuscular disorders are rare in OSAS-cases. Anatomical factors can therefore not explain the progressive nature of OSA.

Some other factor than anatomic predisposition could therefore also be responsible for progression!
1.2.12.3 *Local oropharyngeal peripheral nervous lesion*

Such a factor could be a local peripheral nervous lesion.

Long standing snoring transmit vibrations to the oro-pharyngeal structures [297, 298]. It is well known from occupational medicine that long-term use of hand-held vibrating tools may induce local peripheral nerve lesions in the hands, the so-called Hand Arm Vibration Syndrome (HAVS) [299-313].

We have proposed the hypothesis that snoring induced vibration may cause local peripheral nerve lesions in the oro-pharynx [273, 314-317]. A local nervous lesion would give rise to oropharyngeal muscle hypotonia, thus contributing to pharyngeal collapse in OSA, in two different ways; an efferent nervous lesion causing motor impairment, and an afferent nervous lesion causing sensory impairment.

The progressive nature, despite surgery or weight loss, would be explained by existence of the irreversible nervous lesion. Thus, after surgical reduction of pharyngeal tissue, or weight loss resulting in less narrow upper airways the underlying nervous lesion would give rise to a gradually impaired airway flow, resulting in the return of snoring. The snoring induced vibration would result in continued peripheral nervous damage, giving rise to increased snoring and return of OSA. CPAP therapy on the other hand is not associated with progress of OSA. CPAP therapy eliminates the snoring, and the upper airways are, thus, not exposed to further vibration. The irreversible nervous lesion would not progress from the level when CPAP was prescribed.
1.3 PERIPHERAL NERVOUS LESIONS

1.3.1 Neurophysiological evaluation of peripheral nerve function

QST is a method used in clinical neurophysiological routine in the extremities, capable of investigating peripheral sensory nerve function in large myelinated (vibration) as well as thin unmyelinated (thermal and thermal pain) afferent nerve fibres. Other methods used to investigate peripheral nerve function are needle EMG studies and nerve conduction studies (ENeG). These electrophysiological studies are commonly used in clinical routine for evaluation and follow-up of suspected neuromuscular disorders.

1.3.1.1 Needle EMG

The needle EMG is a routine clinical procedure in which a small needle is inserted into a muscle to record the electrical activity of several neighbouring motor units. The findings are an expression of the physiological or pathophysiological state of muscles. Three types of observations are made: spontaneous electrical activity in a relaxed resting muscle, configuration of the motor unit potential (MUP) regarding phase, duration and amplitude with weak voluntary contraction, and the pattern of MUP recruitment with maximal voluntary contraction.

Using needle-EMG it is possible to grade a lesion, and also to follow a denervation-reinnervation process by repeated investigations, since the procedure is not harmful and is generally well tolerated by adults. EMG is mostly performed in limb muscles, but may also be used when examining laryngeal muscles, diaphragm, sphincters, etc.
It has, however, not previously been employed in the scientific study of the upper airway muscles. Muscle biopsy studies have demonstrated signs of denervation in upper airway muscles, as will be discussed below. Performing EMG in these muscles has several advantages compared to muscle biopsy, since EMG can be performed repeatedly and in different muscles or at different sites within a muscle without harm. Muscle biopsies, on the other hand, cannot be performed in humans without a medical indication for surgical tissue removal, due to ethical reasons. Muscle biopsies can also be performed only once in a muscle, i.e., it is not possible to screen for subclinical findings or follow the effect of treatment.

1.3.1.1.1 Anatomical and physiological background to EMG

The motor unit, the smallest functional unit of the motor system, consists of a motor neuron, its axon, and all the muscle fibres innervated by this axon. The motor units can be of different size. In postural muscles the motor units are usually large (containing several hundreds of muscle fibres), whereas in cranial nerve innervated muscles the units tend to be small (10-20 fibers) [21].

1.3.1.1.2 EMG findings in normal muscle

In normal muscle no spontaneous activity outside the endplate region is observed at rest. During a weak voluntary contraction a series of MUPs is recorded as different motor units become recruited. The size of individual MUPs, measured as duration and amplitude, varies between different muscles, facial muscles of smaller size than muscles in the extremities. Normal values have been established in most commonly studied muscles for the amplitude and duration of MUPs. The size is determined by the number of muscle fibres within the motor unit, and thus varies between different
muscles. Small MUPs are noticed in the facial muscles; the low amplitude reflects the low number of muscle fibres per motor unit, and the short duration reflects the conduction velocity and length of the axonal branch innervating these muscle fibres. On maximal contraction, MUP:s overlap in a full interference pattern with numerous recruitments of MUPs so that it is impossible to identify single potentials [318].

1.3.1.1.3  **EMG findings in denervated muscle**

Denervation refers to the situation when the muscle fibres in a motor unit have lost their innervating motor neuron. Denervation activity in EMG is noted at rest in denervated muscles and consists of abnormal spontaneous activity seen as fibrillations and positive sharp waves. Fibrillations and positive sharp waves are usually associated with an ongoing denervation process, but are not pathognomonic of a nervous lesion, since they are also observed in myopathic muscles. The configuration of the MUP in denervated muscle may vary. With partial denervation the duration and amplitude of the MUP is normal or increased depending on the chronicity of denervation. Usually the remaining adjacent, relatively normal axons give off small branches, collateral sprouting, that innervate the muscle fibres denervated by the loss of other axons. Accordingly, surviving motor units become larger, containing more than the normal number of muscle fibres. This results in MUPs of higher amplitude and longer duration. The new branches are thought to conduct impulses with lower velocity than normal axons, and presumably at longer distance than the original, thus requiring longer time, as reflected in the increased MUP duration. With total denervation no MUPs are observed even at attempts to maximal contraction. The functional loss of motor units in the denervated muscle results in reduced patterns or discrete activity on maximal contraction, depending on
the severity of the denervation. Reinnervation can be demonstrated in EMG as reinnervation potentials, i.e., polyphasic potentials of long duration. These pathological EMG-phenomena take place in all skeletal muscles, irrespective of location, motor unit size, etc, if a lesion to their innervating peripheral nerve has occurred [318].

1.3.1.2  Nerve conduction studies

The nerve conduction velocity is the speed at which an electrical impulse, an action potential, is conducted along a motor or sensory axon. It is an expression of the physiological or pathological state of the nerve studied and can be measured with great accuracy through electrical stimulation and recording. Routine nerve conduction studies objectively document the presence and severity of peripheral nerve dysfunction. ENeG is capable of determine the level of injury, i.e. neuronal cell body, root, plexus or peripheral nerve, the distribution of abnormality, i.e. focal, multifocal or diffuse, and the pathophysiology in terms of segmental demyelination versus axonal degeneration. Afferent as well as efferent nerves can be tested, thus, motor as well as sensory lesions can be diagnosed [318]. Many peripheral nerves can be studied, given an anatomical distribution suitable for electrode placement and nerve distances long enough to calculate nerve conduction velocities. ENeG is therefore well suited for studies in the extremities, and can be used in cranial nerves, such as the facial nerve (seventh cranial nerve, N. VII). ENeG studies only evaluate large myelinated nerve fibre function. ENeG cannot be performed intraorally or intrapharyngeally, due to anatomical reasons.
1.3.2 Hand and Arm Vibration Syndrome

HAVS is a condition associated with the use of vibrating tools, which occurs mainly in men. It consists of a vasospastic component, Raynauds disease or “white fingers”, and local digital sensory neuropathy with reduced sensory nerve conduction velocities in the digits. The HAVS diagnosis is sometimes difficult and can be misinterpreted as a nerve compressive disorder such as Carpal Tunnel Syndrome (CTS), which may also develop and can co exist with HAVS as vibration- induced sensory nerve impairments exits both in the digits and across the carpal tunnel [299, 302, 303, 305, 307, 312]. Vibration exposed patients present considerable impairment in hand function [306].

Neural damage in symptomatic vibration-exposed patients has been demonstrated [308, 319]. In animal experiments, continuous vibrations have been shown to cause peripheral nerve lesions after a couple of weeks [313]. These vibration-induced lesions appear to be caused by disrupted retrograde axoplasmatic transport, with a cumulative effect; i.e., the longer the vibration continued, the more pronounced changes were recorded [320]. Stromberg et al took biopsies of the dorsal interosseus nerve from 10 men exposed to vibrations from hand held tools and from 12 male age matched necropsy controls and found pathological changes in all 10 patients dominated by breakdown of myelin and by interstitial and perineurial fibrosis associated with incomplete regeneration or with organisation of oedema. All but one of the 12 controls were normal and the authors conclude that demyelination may be the primary lesion [308].
An exposure-effect relationship for vibration induced neuropathy has been suggested and different underlying mechanisms are likely to be involved in the pathogenesis of the neurological and vascular components of the hand-arm vibration syndrome [304].

Several studies have shown impaired thermal and vibration sensitivity tested by the means of QST in the hands in HAVS patients. Strömberg et al showed elevated thermal thresholds for both warm and cold and to a lesser degree increased vibrotactile and pain thresholds in HAVS patients [305]. Toibana et al showed that thermal thresholds were significantly correlated with pain thresholds, and the sensitivity of the thermal threshold testing tended to be greater than that of the pain threshold testing in vibration-induced neuropathy [321]. Sakakibara et al found thermal threshold testing useful in vibration-exposed subjects, and that it might be a sensitive indicator in vibration-exposed subject who may have slight or mild nerve impairments [322]. QST of thermal and vibration thresholds are, thus, useful in the evaluation of local vibration induced nervous lesions in the hands. Thermal thresholds of warm and cold sensation seem to be more impaired than vibration or pain thresholds.

1.3.3 HAVS and OSA, similarities

OSA is a condition associated with the exposure for snoring induced vibration in the oropharynx [297, 298] with men more commonly affected than women [43], while HAVS is a condition associated with the use of vibrating tools, with men more commonly affected than women [300, 302, 305]. The exposure-effect relationship for vibration induced neuropathy seen in HAVS [323] can be suspected in OSA considering the progressive nature of OSA over decades of snoring [41, 291].
Sensory nerves are more vulnerable to vibration induced neuropathy than motor nerves [305, 321, 322]. HAVS probably starts as a sensory neuropathy, but may later include motor symptoms. In analogy, sensory oropharyngeal nerves can be suspected to be more vulnerable to vibration induced neuropathy than oropharyngeal motor nerves. However, at the time for OSA diagnosis, the long duration of exposure to snoring vibrations might also induce a motor neuropathy. This could partly explain the discrepancy in the literature regarding reported signs of motor impairment in the pharyngeal muscles in OSA patients. Most studies report sings of motor denervation [315, 324-327], but some do not [328, 329].

In HAVS, avoidance of further vibration exposure is a critical part of treatment due to the dose-response-relationship of vibration exposure and local neuropathy. Redeployment recommendations, reducing the duration, frequency or intensity of exposure to vibration are part of treatment before symptoms become irreversible [302, 330, 331]. Miyashita et al have reported decrease of occurrence of vibration syndrome. They found a maximum in number and severity of HAVS in the late seventies. After that it decreased year by year. The occupational health care system, with limitations and avoidance of vibration exposure, is considered to have contributed to the decrease or prevention of occurrence of HAVS [332].

The available OSA treatments; CPAP, mandibular advancement device, and surgical treatment such as UPPP, all have in common that snoring is reduced. We hypothesize that avoidance of further vibration exposure, i.e. snoring, is a critical part of treatment of OSAS due to the probable dose-response-relationship of snoring and local
neuropathy, as seen in HAVS. Indeed, we speculate that early treatment of snoring in predisposed individuals would prevent OSA.

### 1.3.4 Inflammation

The presence of local mucosal oedema in OSA has been demonstrated. The factors responsible for the oedema are unclear but presumably relate to a local inflammation due to repeated trauma to upper airway tissue from the snoring-induced vibration and forceful suction collapse with pharyngeal pressure swings and muscle contractions against the occluded airway of the airway during apneas. Inflammatory cell infiltration has been found in the mucosa [326, 327, 333, 334], as well as the musculature [326] of the upper airways in OSA patients. The increased tendency to general inflammation in OSAS patients, demonstrated as elevation of morning plasma levels of the pro-inflammatory cytokines Interleukin-6 and Tumor Necrosis Factor-α [335], might also take part in the local inflammation. There are reports of local release of inflammatory mediators in the upper airways of OSAS patients [326, 336]. Boyd et al [326] have demonstrated a significant increase in inflammatory cell infiltration in the muscular and mucosal layers from the soft palate and tonsillar pillars after immunostaining with antibodies directed against inflammatory cells. Puig et al [336] have shown that epithelial cell vibration *per se* could trigger inflammatory signalling. They applied vibration, simulating snoring, to human upper airway epithelial cells and found release of the proinflammatory cytokine Interleukin-8.
1.3.5 Upper airway – normal conditions

1.3.5.1 Anatomy

1.3.5.1.1 The pharynx

The pharynx is like a muscular tube, extending from the back of the nose to the epiglottis. It has three major functions; respiration, swallowing, and speech. This muscular tube is vulnerable because it lacks substantial bony or rigid support. Most mammals have rigid skeletal support of the pharyngeal airway. The evolution of speech in humans is thought to have needed substantial laryngeal motility, leading to a hyoid bone without rigid support and a vulnerable airway in humans. Due to the lack of rigid structural support, the patency of the upper airway is dependent on soft tissue position, which can be affected by gravity. In the supine position the tongue and soft palate move posteriorly, reducing the pharyngeal area, thereby increasing supraglottic airway impedance and collapsibility, which is demonstrated by the clinical observation that snoring is much more prominent in the supine position. The minimum calibre of the upper airway in the wake state is the retropalatal oropharynx [277, 278], which makes it a site of interest as the potential location of collapse in OSA.

The wall of the pharynx has three layers: mucous, fibrous, and muscular. The mucous membrane, lined by ciliated columnar epithelium in the upper part and by stratified squamous epithelium in the lower part, is continuous with that of the nasal cavities, the mouth and the larynx. The fibrous layer lies between the mucous and muscular layers. The muscular layer of the pharynx consist of the constrictor muscles with fibres in a circular direction and the stylopharyngeus and salpingopharyngeus muscles with fibres in a longitudinal direction [337].
The pharynx may be divided into three parts. The nasopharynx – behind the nasal cavities, above the soft palate; the oropharynx – from the palate to the upper border of the epiglottis, where the retropalatal part, between the hard and soft palate sometimes is referred to as velopharynx; and the hypopharynx – from the base of the tongue to the larynx. The oropharynx, is located behind the mouth, and communicates with it through the oropharyngeal isthmus. The isthmus is formed by the palatoglossal fold or arch, formed by the underlying palatoglossus muscle. The palatopharyngeus muscle raises a ridge behind the palatoglossus, the two folds being separated by the tonsillar sinus. Both folds can usually be seen in the mouth and are often referred to as the “anterior or posterior tonsillar pillars” or the “palatoglossal and palatopharyngeal arches”. The palatine tonsils are two masses of lymphoid tissue located in the lateral walls of the oropharynx, in the sinus between the folds. They are present at birth; enlarge during childhood, but usually diminish in size from the age of puberty [274, 337].

1.3.5.1.2  The palate

The palate, forming the roof of the mouth, may be divided onto the hard and the soft palate. The hard palate is formed by the maxillae and palatine bones, lined by a mucous membrane covered by stratified squamous epithelium with numerous mucous glands posteriorly. The soft palate is a mobile fold attached to the posterior border of the hard palate. The soft palate has three layers; mucous, fibrous, and muscular. The mucous layer, covered by mainly stratified squamous epithelium, has mucous glands and lymphoid tissue in the sub mucosa. The fibrous layer, the palatine aponeurosis,
is situated between the mucosa and the muscle layer. The muscles of the soft palate are the tensor veli palatini, the levator veli palatini, the palatoglossus, and the palatopharyngeus and uvulae muscles [337].

1.3.5.2 Neuromuscular conditions in the upper airways

1.3.5.2.1 Oropharyngeal sensation

Accurate sensory feedback from the oropharynx is essential in normal swallowing and speech. There are receptors responding to touch, pressure, vibration, position, pain, temperature and taste located in the mucosa. Superficial receptors of pharynx are capable of initiating a variety of reflexes, such as swallowing, respiratory arrest [338], and reflexes to maintain upper airway patency, such as the negative pressure reflex [339] and other upper airway patency reflexes stimulated by stimuli, such as pCO₂ and pO₂ changes [340, 341], sensation of cold (inhaled air) or mechanical sensations [342] (as will be discussed below).

The main sensory nerve supply to the oropharyngeal mucosa, including most of the surface of the palatine tonsil, comes from sensory fibers of the glossopharyngeus nerve, (the ninth cranial nerve, N. IX), which together with the pharyngeal branch of the vagal nerve (the tenth cranial nerve, N. X), is the primary source of the sensory innervation of the pharynx. The tonsillar branch innervates tonsil, soft palate and the tonsillar pillars and the lingual branch innervates the tongue. The innervation is unilateral in the pharynx. The sensory innervation of the areas overlying the hard palate and the anterior part of the soft palate are, however, mediated by the maxillary branch of the trigeminal nerve (the fifth cranial nerve N.V.), like the nasopharynx.
The hypopharynx is innervated by the internal laryngeal branch of the vagus nerve (N. X). There is some overlap in the sensory innervation of the pharynx [337, 338].

Sensory receptors can be classified into four groups according to their morphology; corpuscular endings (including encapsulated receptors such as the rapidly adapting Meissner’s corpuscle, and smaller corpuscles), the slowly adapting Merkel neurite complexes, Ruffini-like endings, and free nerve endings. The receptors of the pharyngeal epithelium are predominantly free nerve endings, distributed in the oropharyngeal mucosa in a superficial plexus of the intraepithelial nerves and a deeper plexus in the lamina propria [338]. The epithelia of the pharyngeal mucosa is more richly innervated than the skin and the anterior oral cavity but deep receptors are fewer in number and are generally less complex. One cannot always attribute function to each morphological class of receptor. Some specialized endings process a degree of stimulus specificity, e.g. Meissner corpuscle and vibration or Merkel neurite complex and tactile sensation. Most morphologically identical nerve endings, however, represent a functionally heterogeneous population of fibers capable of transducing stimuli of different modalities. Each receptor is often maximally sensitive to a specific stimulus, but it also responds to other stimuli. Not all nerve endings are multimodal, but free nerve endings representing one modality are morphologically indistinguishable from those responding to other modalities. One single primary afferent neuron terminates in a variable number of receptor endings, all of the same morphological type but of different function. Many of these receptors produce a frequency coded response in the afferent fibers to code stimulus intensity [59, 338].
The sensory innervation density, i.e., the amount of receptors per unit area, varies in different parts of the body. In the skin, for example, it is well known that cutaneous surface innervation density varies from area to area, with the lip and perioral area most densely, and the back less densely innervated. This is reflected in the CNS by greater central representation of certain body parts, such as the perioral area. Almost 1/3 of the entire central sensory field located in the postcentral gyrus serves the face and mouth, with the tongue having a particularly large representation compared to its actual size, as is usually demonstrated in the figure of the so-called "sensory homunculus". This is true within the oral cavity as well, with tactile sensitivity varying in different parts of the oral cavity, with the greatest sensitivity to light touch at tip of the tongue and hard palate and the greatest two point discrimination (2PD) sensitivity at the tip of the tongue followed by lips and hard palate. 2 PD tests the ability to discriminate between the touch of one or two points using standard techniques, where a series of two-point probes with a fixed inter-probe distance ranging from small to large are used for testing. High receptor density as well as large central representation is probably the reason for the excellent 2PD sensation in this area, where the anterior tongue, upper lip, and anterior part of hard palate are more sensitive than the fingertip to light touch and 2PD [59].

One mapping study determined the areas of relative heat and cold sensitivity in the mouth: The lip mucocutaneous junction was very sensitive to cold and moderately sensitive to heat. The palate was relatively heat-insensitive, except for a small area next to the second molar. The tongue tip was very cold sensitive and the tongue dorsum was most heat sensitive [59].
The entire sensory pathway includes the distal receptor, the primary sensory efferent nerve fiber, the brainstem, the thalamus and the somatosensory cortex located in the gyrus postcentralis.

1.3.5.2.2 Upper airway muscles

Because of the physiological importance of maintaining pharyngeal patency (and other tasks required of this portion of the airway such as speech and swallowing) a sophisticated motor control system has evolved, with more than 20 upper airway muscles playing a part. These muscles surround the upper airway and actively constrict and dilate the upper airway lumen, interacting in a complex fashion to maintain its patency [273, 343, 344].

The most important striated upper airway muscles involved in respiration are the muscles of the soft palate (the tensor veli palatini, the levator veli palatini, the palatoglossus, and the palatopharyngeus muscles) and the muscles in the floor of the oral cavity (the genioglossus and the geniohyoideus muscles) [273].

The palatoglossus muscle, also referred to as the anterior tonsillar pillar, moves the palate downwards-forwards, thus promoting nasal airflow. It has mainly inspiratory phasic muscle function, with reduced activity during expiration. The nerve supply comes from the pharyngeal plexus, from accessory nerve (N. XI) and vagus nerve (N. X) [273, 337].
The palatopharyngeus muscle, also referred to as the posterior tonsillar pillar, moves the palate downwards. It has mainly inspiratory phasic muscle function. It is innervated by the pharyngeal branch of the vagal nerve (N. X) via the pharyngeal plexus [273, 337].

The tensor and levator veli palatini muscles elevate and tighten the soft palate, promoting oral respiration. These muscles are tonically active during the whole respiratory cycle, thus, the have mainly tonic or postural muscle function. Their function is important for airway patency during both inspiration and expiration. Their activity diminishes during sleep. The levator veli palatini is innervated by pharyngeal plexus from motor branches the accessory nerve (N. XI), and the vagus nerve (N. X). The tensor veli palatini muscle is innervated by the mandibular branch of the trigeminal nerve (fifth cranial nerve, N. V) [273, 337].

The genioglossus muscle protrudes the tongue. It contracts with each inspiration, and thus, exhibits phasic muscle function. Its function remains essentially the same during wakefulness and the different sleep stages. This muscle is considered the most powerful pharyngeal dilator. It is innervated by the hypoglossal nerve (twelfth cranial nerve, N. XII), a pure motor nerve innervating the muscles of the tongue [273, 337].

The geniohyoideus muscle elevates and protrudes the hyoid bone, and is active at inspiration in the same manner as the genioglossus muscle, and thus exhibits mainly inspiratory phasic muscle function. It is also innervated by the hypoglossal nerve (N. XII) [273, 337].
Other muscles in this area are those in the muscular layer of the pharynx, i.e. the constrictor muscles with fibres in a circular direction and the stylopharyngeus and salpingopharyngeus muscles with fibres in a longitudinal direction. They get their nerve supply, from motor branches of the cranial part of the accessory nerve (eleventh cranial nerve, N. XI), which via the branch of the vagus nerve (tenth cranial nerve, N. X) to the pharyngeal plexus supplies all the muscles of the pharynx except the stylopharyngeus, supplied by the glossopharyngeal nerve (ninth cranial nerve, N. IX) [337].

1.3.5.3 Upper airway respiratory physiology

1.3.5.3.1 In the wake state

At inspiration, the negative pharyngeal pressure caused by the inflation of the lungs tends to suck the upper airway closed. This is counteracted by activation of the dilating muscles surrounding the upper airway [345].

The inspiratory phasic upper airway muscles include the palatoglossus, the palatopharyngeus, the genioglossus, and the geniohyoidus muscles. Out of those, the genioglossus muscle is the one most studied. These muscles increase their activity during inspiration, thus stiffening and dilating the upper airway and counteracting the collapsing influence of negative airway pressure. This has been shown in normal awake subjects, especially in the palatoglossus, the palatopharyngeus and the levator palatini muscles. An increased activity has also been demonstrated in the palatoglossus and palatopharyngeus muscles in the supine position, when gravity is negatively influencing the width of the upper airway [346, 347].
During expiration, however, when pressure inside the airway becomes positive and the tendency for collapse is decreased, the activity of these muscles is substantially reduced (although not eliminated, tonic activation).

The tonic or postural muscles, such as the tensor and levator veli palatini, are also thought to play a role in the maintenance of the patency of the upper airways. They do not consistently have inspiratory phasic activity but instead maintain a relatively constant level of activity throughout the respiratory cycle [115].

A "wakefulness" drive to the upper airway muscles has been described. The inspiratory phasic and tonic or postural upper airway muscles are probably controlled by groups of neurones within the brainstem that have different firing patterns relative to the respiratory cycle. The hypoglossal motor system in the medulla, which controls efferent traffic to the genioglossus muscle, is the best studied and can be affected by many variables [115]. The activity of the pharyngeal dilator muscles is increased by several stimuli. Negative pressure is considered the strongest stimulus [348-351]. Other stimuli include increase in pCO₂, decrease in pO₂ [340, 341] and the sensation of cold (inhaled air) as well as and input from local mechanoreceptors in the upper airway enhances the activity in the pharyngeal dilators[342].

1.3.5.3.2 In the sleep state

OSA patients only have airway impairments during sleep. Also in severe OSA no significant airway impairment is seen during wakefulness. The onset of sleep, thus seems to play an essential part in the pathophysiology. The transition from wake to sleep is associated with change in upper airway muscle activity in normal control subjects.
The inspiratory phasic upper airway muscles such as the genioglossus, maintain their activity [352, 353], while muscles with a primarily tonic activation pattern (such as the tensor veli palatini) lose activity at sleep onset which continues to fall as sleep deepens, reaching levels of 20–30% of waking values during stage IV sleep [354]. These activity patterns could be explained by different activity in the brainstem neurones controlling their activity. Orem et al [355] have shown that neurones with activity closely related to the respiratory cycle (phasic neurones) largely maintain their activity during sleep, while neurones whose activity pattern is not clearly related to the respiratory cycle (tonic neurones) have large decrements in activity. This could also explain why sleep is always associated with a significant rise in upper airway resistance, also in normal subjects [356, 357]. Sleep deprivation has also been shown to decrease activation of the genioglossus muscle in response to increased CO₂ in normal subjects [358]. Thus, the efferent motor activity to the upper airway muscles can be precisely modulated to meet the physical demands of the upper airway, and is also substantially affected by changing state between sleep and wake.

1.3.5.3.3 Airway reflexes

Substantial evidence in animals [350] and humans [351] supports the presence of a reflex responsible for the response in pharyngeal dilator muscles to negative pressure. Application of negative pressure to the pharyngeal airway leads to a substantial increase in the activity of the genioglossus as well as other upper airway muscles [342, 359]. It has been shown that loss of this reflex during sleep leads to decrements in pharyngeal dilator muscle activity in OSA patients [360, 361]. This reflex is probably mediated via sensory neurons in the pharyngeal mucosa, since these muscles appear to lack muscle spindles [324]. It has been shown that the afferent signal for
this reflex to the genioglossus muscle is carried mainly in the trigeminal and superior laryngeal nerves with the glossopharyngeal nerve playing a less important role [350, 362].

1.3.5.4 Upper airway muscle fiber characteristics

Skeletal muscles are composed of fibres of different types, each type being identified by the isoform of myosin heavy chain. They are divided into slow fibres (Type I fibres) and fast fibres (Type IIA, II, and IIB fibres). Slow type I fibres are resistant to fatigue due to their highly oxidative metabolism. They present small fibre size, abundance of capillaries, and a high aerobic oxidative enzyme activity and their resistance to fatigue is required for muscles with continuous activity. Fast fibres type II and IIB are easily fatigable, while fast fibres type IIA exhibit intermediate fatigue resistance. The upper airway muscles as a rule have less fast type IIB fibres and more slow type I and intermediate IIA than limb muscles, and also present a smaller fiber size [273], indicating high resistance to fatigue. This is a convenient arrangement in order to meet the demands of continuous activity required in the upper airway muscles to maintain patency of the upper airway and participate in respiration.

1.4 IS OSAS A NEUROLOGICAL DISORDER?

As mentioned above, it is apparent from the patient histories that a majority have been habitual snorers for years before apneas become apparent. Snoring implies vibration of the tissues that produce the sound. In occupational medicine, it has been shown that longstanding vibration of tissues may cause local nerve lesions [299, 308, 363]. It therefore seems possible, that snoring vibrations, repeated every night for
several years, might cause neuronal lesions in the upper airway. This, in turn, could result in a gradual collapse of the pharyngeal tube due to weakness, i.e. partial paresis of the dilating muscles. Another possible cause of collapse could be an impaired contracting reflex, since the sensation of negative pressure and relatively cold air is what triggers the dilating muscles to contract at inspiration.

1.4.1 Sensory nervous lesions in the upper airway

A sensory nervous lesion affecting thermal sensitivity would induce an impaired dilatation reflex in the upper airways. The impaired reflex would in turn induce weakness in the oropharyngeal muscles.

Evidence for sensory nervous lesions in the upper airways of patients with OSA has previously been presented. Larsson et al found pathologically increased thresholds for temperature sensitivity on the tonsillar pillars in patients with OSAS [80]. Kimoff et al [82] showed decreased sensitivity to vibrations in the upper airway of both snorers and OSAS-patients, in comparison to non-snoring subjects, furthermore with a significant improvement after CPAP-treatment. Gulleminault et al [364, 365] and Kimoff et al [82] have shown reduced sensibility to two-point discrimination in OSAS patients and snorers. Friberg et al have demonstrated abnormal efferent nerve endings in the mucosa of the soft palate OSAS patients and snorers [316]. Furthermore, evidence for impaired mucosal sensory function at multiple sites in the upper airway have been shown by Nguyen et al, who tested OSA patients regarding mucosal sensitivity to air pulses at different sites in the upper airway, from the oropharynx to the larynx using an endoscopic method [366].
There is also indirect evidence that sensory function in the upper airway mucosa contributes to the collapsibility seen in OSA. Local anesthesia in the upper airway mucosa increases the tendency to airway collapse, and has been found to increase pharyngeal airflow resistance during wakefulness and sleep in normal subjects [367]. Local anesthesia has also been shown to induce apneas and hypopneas during sleep in normals [368] and to increase the frequency of obstructive events in snorers [369]. Swallowing, another main function of the pharynx, is dependent on normal pharyngeal sensation. The swallowing reflex is delayed in OSA [370]. Surgery, i.e., UPPP, has often been thought to cause dysphagia seen in OSAS patients, but in fact swallowing dysfunction has been shown to be present in a majority of patients with OSAS or habitual snoring before any form of treatment had been given and that snoring patients run an increased risk of developing subclinical pharyngeal swallowing dysfunction independent of concomitant sleep apnea [371]

### 1.4.2 Motor nervous lesions in the upper airway

A motor neuron dysfunction would induce a partial oropharyngeal muscle denervation, and thus, hypotonia, contributing to the upper airway collapsibility seen in OSAS.

#### 1.4.2.1 Changes in muscle activity

In OSA, the combined forces of the upper airway dilating muscles are not sufficient to overcome the negative inspiratory pressure created by the thoracic pump. Consequently, the upper airway collapses [269, 360]. The negative pressure in the
upper airway is greater (i.e., more negative) in OSAS patients than in controls, probably an effect of the narrow upper airway [115].

1.4.2.1.1 In the wake state

Several studies have shown greater EMG-activity of both the genioglossus and tensor palatini during wakefulness in patients with OSA compared to normal subjects [339, 372]. A source of confusion is the EMG method used in these studies, by which genioglossus activity was measured. The EMG signal was obtained by a pair of unipolar intramuscular electrodes referenced to a single ground. This differs from needle EMG used in clinical routine. Since a direct comparison between individuals of the actual genioglossus EMG signal is not possible with this method, relative amplitude was calculated. The amplitude was expressed as 0 to 100% of maximal genioglossal EMG activity. The highest EMG signal, obtained using a variety of maneuvers (most often maximal tongue protrusion or maximal inspiratory effort against an occluded airway) was defined as 100% [339]. It might seem contradictory that augmented EMG-activity of the genioglossus muscle is recorded in awake OSAS patients in comparison to normal subjects, since augmented EMG-activity sometimes is interpreted as increased muscle strength [373], and a peripheral nervous lesion by definition gives rise to less muscle strength. The increased relative amplitude of EMG activity does not reflect strength, it is rather a reflection of how much of the maximal muscle capacity that is needed to preserve patency of the upper airways. In the presence of a nervous lesion, the maximal muscle capacity is reduced, and, thus, a higher percentage of maximal capacity is needed to preserve upper airway patency during wakefulness.
The increased muscle activity in OSAS-patients has been interpreted as a neuromuscular compensation mechanism for a narrow pharyngeal airway, lost during sleep secondary to the physiological muscle hypotonia in that state, i.e. to overcome compromised pharyngeal anatomy, the upper airway dilator muscles of a patient with apnoea must be much more active during wakefulness than those of healthy controls [115, 361, 374]. Augmented genioglossal EMG-activity could, however, be compensation, not only for anatomical factors, but also for partial paresis of other dilating or stabilizing muscles.

1.4.2.1.2 In the sleep state

During sleep, genioglossus EMG-activity is markedly diminished. The difference in EMG activity between wake and sleep is greater in OSAS patients than in normal subjects [269, 339]. Apnea patients have substantially greater decrement in both genioglossal and tensor palatine EMG following sleep onset than normal controls [360]. Thus, tonic as well as phasic upper airway dilating muscles are affected. During an apnea, pharyngeal occlusion is associated with decreased tone in the genioglossus muscle [269] and as a consequence the tongue is pulled backwards-downwards. Towards the end of an apnea, the activity increases again [375, 376]. Pharyngeal reopening often coincides with arousal and always with increased activity in the genioglossus muscle. Apnea resolution does not occur until inspiratory EMG activity reaches its peak in all dilating muscles, irrespective of whether arousal occurs or not [377]. Reduction in upper airway tone is thought to account for the emergence of airway occlusion during sleep, particularly if airway size is restricted [378].
1.4.2.2 Changes in muscle fiber characteristics in OSA

OSAS patients present more fast type II fibres and less slow type I fibres in upper airway muscles compared to normal subjects. Several studies have addressed this issue. More type IIA and less type IIB and type I have been demonstrated in OSAS patients than non-apneic snorers in the medial pharyngeal constrictor muscle [328], and also in the genioglossus and uvulae muscles [379]. In the uvula greater glycolytic, glycogenolytic and anaerobic enzymatic activity has been demonstrated in OSAS patients compared to normal subjects [379]. In the uvula, Sériès et al have demonstrated that patients with the most easily collapsible upper airway also showed the greatest increases in EMG activity, type IIa fiber prevalence, anaerobic metabolism, and susceptibility to muscle fatigue [380]. In the medial constrictor pharyngeus muscle a dominance of type II fibres and non-specific myopathic changes (fibrosis, central nuclei) have been demonstrated in OSAS patients compared to normal subjects, while no difference was found in biopsies taken from the calves [381]. Carrera et al [382] confirmed previous findings of higher percentage of type II fibres in untreated OSAS patients compared to normals, independently of obesity and not seen in patients on CPAP treatment.

Transformation between slow and fast fiber types can occur in response to changes in the muscle activation [383]. It must therefore be considered that heavy-resistance training may produce preferential type II hypertrophy [384]. Myofiber hypertrophy also occurs in several neurogenic disorders, perhaps as a result of overuse of remaining healthy motor units [385]. The changes described above in OSAS may thus result from increased use of the partly denervated upper airway dilator muscles to maintain airway patency. To counteract the increased intraluminal pressure caused by
a narrow upper airway (the Bernoulli effect), these muscles simply have to work harder than those in a non-apneic person without nervous lesions. This might also account for an increased fatigability during sleep.

1.4.2.3 Histopathological changes in OSA

1.4.2.3.1 Striated muscle histopathology and denervation in general

Degeneration of motor neurons leads to a lack of electromechanical activity in muscle fibres and a lack of trophic factors from motor nerves to muscle fibres. The principal morphological change in a denervated muscle fiber is shrinking in diameter. All muscle fibres belonging to the same motor unit are of the same histochemical type. In a normal muscle, they are evenly distributed over a rather large area, creating a mosaic pattern of fibres from different units. A reinnervation process will create a pattern known as “type grouping”, since a regenerating axon tends to innervate all muscle fibres it comes close to, implying that fibres adjacent to each other will now be activated by the same axon [386].

If there is no regeneration of the axon, the whole motor-unit will degenerate; causing a histological picture termed “grouped atrophy”. When a lesion to a peripheral nerve occurs over an extended period of time, the rule is that there will be parallel processes of reinnervation and denervation, creating patterns of both type grouping and grouped atrophy in histological sections from the same muscle. Since those muscle fibres still functioning have to carry the load of the atrophied ones, the rule is also that a number of hypertrophic fibres will be seen. This is simply the effect of these fibres working harder. Thus, a typical histological finding of a partly denervated muscle is increased number of both atrophied and hypertrophied muscle fibres. In a normal muscle, the
fibre-size distribution is unimodal or near-Gaussian, whereas it tends to be bi-modal or polymodal in a denervated muscle [386].

1.4.2.3.2 Histopathological findings

In muscle histology studies evidence has been found for motor neuron lesions in patients with OSAS.

In 1992, Edström L et al. [325] published the first study showing typical histological signs of peripheral nervous lesions in OSAS patients, the majority with a severe form of the disease. Muscle biopsies were performed in the palatopharyngeus muscle. Histopathological findings typical for slowly progressive motor neuron lesions, such as type grouping, grouped atrophy and great variability of muscle fiber size (simultaneous atrophy and hypertrophy) were found in all patients, but not in normal control subjects. Friberg et al [315] applied the same technique and found similar histological pictures as Edström et al, i.e. signs specific for neurogenic lesions such as type grouping, and fascicular and/ or grouped atrophy in OSAS patients and snorers. Since this study also included heavy snorers with minor degree of obstruction, comparison could be made to clear OSAS-cases and normals. The findings did indicate a progressive lesion in the palatopharyngeus muscle. Some degree of pathology was present in a majority of snorers, but these findings were much more pronounced in the OSAS- patients.

Lindman and Ståhl [324] corroborated these findings in biopsies from the palatopharyngeus muscle and the uvula in patients with long-standing sleep-disordered breathing. They analyzed muscle morphology, fibre type and myosin
heavy chain compositions with enzyme-histochemical, immunohistochemical and biochemical techniques, comparing them to reference samples obtained at autopsy from previously healthy subjects. The muscle samples from the patients, and especially those from the palatopharyngeus, showed several morphological abnormalities, the most striking being abnormal variability in fibre size, increased proportion of small-sized fibres, and increased frequency of fibres containing developmental MyHC isoforms. These findings indicate denervation and degeneration processes and thus suggest a neuromuscular disorder of the soft palate in SDB patients. Boyd et al [326] in a histopathological study of upper airway muscles in OSA patients, showed signs of denervation based on positive immunostaining of the muscle fiber sarcolemmal membrane for the neural cell adhesion molecule. They simultaneously showed signs of reinnervation by immunoreactivity for a neuronal marker presenting a increase in intramuscular nerve fibers in OSA patients compared with control subjects. They also demonstrated an increased number of inflammatory cells in soft palate muscle tissue of patients with OSAS. Woodson et al [327] found atrophied and hypertrophied muscle fibers in the soft palate of patients with sleep apnea or severe snoring, but not in non-snoring controls. They also performed electron microscopy studies, which showed frequent focal degeneration of myelinated nerve fibers in severely apnoic patients.

Together all these data indicate that local motor and sensory nervous lesions are quite common in the oropharynx of OSAS patients. This would contribute to the pathogenesis of the disease. We hypothesize that this is a vibration induced lesion analogous with the vibration induced nervous lesion seen in hands and fingers in patients with HAVS.
2 AIMS OF THE STUDY

The general aims of this study are to determine the effect of certain variables on vibration and thermal thresholds tested with the method QST and to evaluate the presence of local oropharyngeal nervous lesions by means of QST and EMG in patients with OSAS and habitual snoring. The specific aims are:

I. To compare thermal thresholds of CDT, WDT, CPT and HPT at different sites at the hand, wrist, and foot to determine if there are any significant differences, and in that case to identify a preferred site of testing. To evaluate the effect of local skin temperature on CDT and WDT.

II. To compare VDT at different sites at the hand, and foot to determine if there are any significant differences, and in that case to identify a preferred site of testing. To evaluate the effect of different applied local pressure on VDT.

III. To develop a methodology for QST of thermal and vibration thresholds in the oropharynx. To use this method to test oropharyngeal sensitivity in patients with OSAS and habitual snoring in comparison to normal subjects.

IV. To study whether concentric needle EMG is suitable for examining oropharyngeal muscles. To compare EMG-findings of patients with OSAS and habitual snoring to normal subjects.
3 MATERIAL AND METHODS

3.1 QST TESTING IN THE EXTREMITIES (STUDY I AND II)

Subjects: When studying thermal and thermal pain thresholds, forty-six healthy volunteers (13 males and 33 females) aged 20–58 years (mean age 33.3 years, SD 9.6 years) were studied. We tested the effect of tested site on cool (45 subjects) and warm (46 subjects) detection thresholds and cold (44 subjects) and heat (45 subjects) pain thresholds. Twenty-seven subjects (9 males and 18 females) aged 21–61 years (mean age 33.6 years, SD 11.7 years) were tested to evaluate the effect of pre-test regional skin temperature near the site of testing on cool and warm thresholds. All the subjects were interviewed and examined by one of the investigators (L.H.). All the enrolled subjects were free of neurological illnesses, did not have any medical condition that may cause peripheral neuropathy, have had no exposure to neurotoxic substances, were not taking any prescription medications and had normal neurological examination. When studying vibration thresholds forty-seven healthy volunteers (13 males and 34 females) the effect of tested site on VDT was evaluated. In 41 of the same group (11 males and 30 females) the effect of local pressure on VDT was evaluated. In both measurements the mean age was 35 years (SD=10), and age range was 20–58 years.

Testing conditions. All the tests were performed in a quiet, air-conditioned room with the subject sitting in a comfortable recliner. Standardized instructions were given and a training session of every test was performed. All the tests were performed under the supervision of one of the authors (L.H.). Total testing time of each session did not exceed one hour to prevent loss of concentration.
Tested sites. The effect of site on thermal thresholds was tested at the thenar eminence (TE), volar surface of the wrist (VW), dorsum of the hand (DH) at the first metacarpal space, and the dorsum of the foot (DF) of the non-dominant side. The effect of local skin temperature on thermal thresholds was tested at the TE of the non-dominant side. Only one side was tested in order to limit the duration of the test. The effect of site on VDT was evaluated at three sites of the index finger (pulp, dorsum of the middle phalanx and the nail) and at two sites of the great toe (dorsum of the proximal phalanx and the nail) under the effect of 30 g/1.22 cm² of pressure. The effect of pressure on VDT was evaluated at the dorsum of the middle phalanx of the index finger and the proximal phalanx of the great toe using pressure of 30 g/1.22 cm² (24.59 g/cm²), 50 g/1.22 cm² (40.98 g/cm²) and 100 g/1.22 cm² (81.96/cm²).

Equipment and test algorithms. Thermal tests were performed with a Medoc TSA 2001 device (Medoc Ltd, Minneapolis, MN). A Peltier thermode was secured at the tested site with an elastic Velcro band as previously described [48]. To avoid tactile or pressure stimulation the probe was kept in contact with the skin for the entire duration of the test. The thermode size was 46×29 mm for the evaluation of effect of site, and 30×30 mm for the evaluation of effect of regional skin temperature on thermal thresholds. The starting temperature (adaptation temperature) was 32 °C. We used the method of levels [48] to test CDT and WDT, and the method of limits [387] to test CPT and HPT. The rate of temperature change was 1 °C/s in all of the tests. For CDT and WDT, the first search step was 3 °C and the final search step was 0.1 °C. Random dummy stimuli were used. For CPT and HPT, 6 stimuli were given at intervals of at least 10 s.
Vibration tests were performed with a Medoc VSA 3000 device (Medoc LTD, Minneapolis, MN). The vibration frequency was 100 Hz and the area of stimulation was 1.22 cm² (0.2 sq. inch). A special holder was designed at the University of Minnesota to hold the vibrator in a standardized way (Fig. 3.1.1). The vibrator pin was adjusted vertically in equilibrium in contact with the surface of the stimulated site. A predetermined weight (30, 50 and 100 g) was added over the vibrating pin. The vibration threshold was electronically calculated by the device depending on the amount of electrical current supplied to the vibrating coil and reported as µm of displacement of the vibrating pin. The method of levels was used [10]. The starting level was 0 µm of displacement. The rate of vibration amplitude increase was 0.2 µm/s and the return rate was 9 µm/s. The interval between stimuli was 4 s. The first search step was 1 µm and the final search step was 0.1 µm. Random 0 µm stimuli were incorporated in the test.

Fig. 3.1.1. Design of the vibrator holder. (A) Pivotal axis with minimal friction. (B) Equilibrium rod. (C) Adjustable weight to assure equilibrium. (D) Additional weights. (E) Flexible wire that does not interfere with equilibrium. (F) Sliding piece to adjust the height of the device.
Control of local skin temperature: The regional skin temperature was constantly monitored using a thermistor that was applied to the surface of the skin and secured with adhesive tape about 2 cm away from the thermode. During the evaluation of the effect of tested site, the skin temperature was kept at or above 32 °C. A heating lamp (positioned over the hand and the forearm or over the foot) was turned on when local skin temperature dropped below 32 °C, and turned off when the local skin temperature rose up to 34 °C. While the test was proceeding, the heating lamp was turned off. For the evaluation of the effect of regional skin temperature on CDT and WDT, the subject was initially exposed to cold environment until the skin temperature of the hands dropped below 27 °C, the test was done while local skin was gradually warming up in the following order: 27 °C (±0.7), 29 °C (±0.7), 31 °C (±0.4) and 32 °C (±0.4). Then the hand and forearm were warmed up to 37 °C and the test was done while the local skin was gradually cooling down in the following order: 37 °C (±0.7), 35 °C (±0.7), and 33 °C (±0.4). For practical considerations a range of regional temperature variation was allowed (shown in parentheses). A heating lamp or a latex examination glove filled with ice water was used to slow down the rate of skin temperature change between stimuli when necessary. During heating or cooling, the thermode was kept in contact with the skin of the tested site.

Statistical analysis. The data was first analyzed with Kolmogorov-Smirnov test to determine normality of distribution. Since significant non-normality was found, median, fifth, 25th, 75th and 95th percentiles were calculated. Statistical significance was assessed with a Wilcoxon matched-pairs signed-rank test after adjustment with Bonferroni correction for multiple comparisons. Correlation between the local skin temperature and the thermal detection thresholds for cool and warm was tested by
measuring Spearman (rho) correlation coefficient as well as coefficient of reliability (rho²).

Ethical consent to the studies was given by the Human Subjects Committee at the University of Minnesota. All patients and control subjects gave informed consent.

3.2 OST TESTING IN THE OROPHARYNX (STUDY III)

All study patients sought medical attention at a sleep disorders clinic due to habitual snoring and/or excessive daytime sleepiness. Included patients were free from neurological illness or any medical condition that might cause peripheral neuropathy, previous upper airway surgery, and smoking. At the time of testing, none had any recent upper respiratory tract infection. None of them had previously been treated for snoring or OSAS. The night before QST testing all patients underwent a whole-night sleep respiratory recording including respiratory movements, airflow (cannula), body position and pulse oximetry. The QST testing investigator (LH) was unaware of the results of the sleep recordings, which were all scored by the same investigator (RH). Inclusion criterion for OSAS-patients was an apnea-hypopnea index (AHI) of at least 20. For habitual snoring AHI < 11 was required. Normal subjects were included if co-habiting persons denied habitual snoring.

31 patients with OSAS (27 men and 4 women, mean age 52 years, range 23-72 years), 14 habitual snorers (11 men and 3 women, mean age 49 years, range 26-81 years) and 23 normal subjects (15 men and 8 women, mean age 39 years, range 15-64 years) were included.
All the tests of vibration and thermal detection thresholds were performed in a quiet room with the subject sitting in a comfortable recliner. No drinking or eating was allowed one hour previous to the testing. Standardized instructions were given and a training session of every test was performed. All tests were performed by one of the investigators (LH). Total testing time of each session did not exceed 45 minutes to prevent loss of concentration.

**Vibration Detection Thresholds** (VDT) were examined on the tonsillar pillars bilaterally, on the lower lip and over the pulp of the index finger of the non-dominant hand.

A vibrameter® Type IV (Somedic Inc, Sollentuna, Sweden), producing 100 Hz vibrations, with a custom made intra-oral probe, consisting of a 10 cm long vibrating pin with a stimulating surface area of 6 mm in diameter was used (Fig 3.2.1). The Vibrameter® uses an electro-optical transducer to display the static application force. This was used when testing the finger. When testing the lower lip or the pharyngeal mucosa, a constant application pressure was visually ensured by the investigator, making sure that the probe was applied against the lower lip or the pharyngeal mucosa with sufficient pressure to produce a slight indentation of approx 1 mm, and that the probed stayed in the same stable position throughout the test. VDT was determined by the method of limits, i.e., by increasing the stimulus intensity from zero to the point where vibration is first detected. Five stimuli were given at each site and the mean was calculated as the threshold. Vibration thresholds were expressed as micrometer displacement (µm).
Thermal thresholds were measured using the device Medoc 2000 TSA (Medoc Inc., Israel) with a custom-made intra-oral probe (Fig. 3.2.2), with a 9 mm in diameter circular stimulating surface. Cold and Warm Detection Thresholds (CDT and WDT) were tested separately. CDT was examined on the tonsillar pillars bilaterally, on the tip of the tongue and on the lower lip. WDT was examined on the tonsillar pillars bilaterally, and on the tip of the tongue. Thermal thresholds were determined by the Method of levels. The starting temperature (adaptation temperature) was 32°C when testing the lower lip, 34°C when testing the tip of the tongue, and 36°C when testing the tonsillar pillars. The rate of temperature change was 1°C/s in all thermal tests. The first search step was 3°C and the final search step was 0.1°C. Random dummy stimuli were used. Thermal thresholds were expressed as the calculated difference between detection temperature and adaptation temperature in °C. A constant application
pressure was visually ensured by the investigator, making sure that the probe was applied against the site tested without making any indentation, and that the probed stayed in the same stable position throughout the test.

![Image](image1.png)

**Fig 3.2.2.** The custom made intra-oral probe for CDT-testing.

**Statistical analysis:** Statistical analysis was made by calculation of means, medians, SD and confidence intervals Threshold values from the three subject groups were compared with the non-parametric Mann-Whitney U-test. Statistical significance value was p<0.05. Regression analysis was performed to compare matched data.

Ethical consent to the study was given by the ethical committee at Karolinska Institute, Stockholm. All patients and control subjects gave informed consent.
Fourteen OSAS patients (all male, AHI 27-80, mean age 50 years), 24 habitual snorers (5 women, 19 men, AHI < 15, mean age 46 years) and 4 normal subjects (all women, mean age 37 years) were investigated. EMG was performed in *m. palatoglossus* bilaterally and in *m. uvulae*. All patients had undergone at least one whole-night sleep respiratory recording previous to this investigation, comprising at least pulse oximetry, respiration movements, airflow, snoring vibrations, body position and ECG. All normal subjects were declared non-snorers by their partners.

For EMG, a disposable concentric bipolar needle was used (Medtronic Functional Diagnostics Inc., 75 cm length, recording tip 0.64 mm). The subject was sitting up straight with a firm head rest. Local anesthesia by means of Xylocain spray was used in most subjects, since the patients were going to receive treatment (UPPP-surgery or radiofrequency ablation) in the same session. Needle insertion was made at 2-4 points; 1-2 cm to the left and right of the uvula. The EMG-needle was inserted by an ear-nose-and throat surgeon, while the electromyographer (ES or LoHa) recorded the signals on an EMG-machine. The subjects were asked to 1) relax the palate during scoring occurrence of spontaneous activity; 2) to contract the palate maximally (yawning, vocalizing) to determine interference pattern; and 3) to breath normally and maintain a slight contraction of the palate, so that individual motor units could be discerned. The electromyographer was unaware of the result of the sleep respiratory recording of the investigated patient, i.e., whether the patient was a habitual snorer or suffered from sleep apnea syndrome.
The following findings were always regarded as pathological:

- Spontaneous activity (fibrillation potentials, positive sharp waves) at rest
- Motor-unit potentials which were polyphasic and/or with increased amplitudes (>2 mV) and duration.
- Reduced interference pattern despite high firing frequency at maximal voluntary contraction.

If only polyphasic and/or amplitude-increased motor-unit potentials were present, the degree of pathology was scored as mild. If both changes in motor-unit potential configuration and a reduced maximal amount of voluntary activity (reduced interference pattern) were recorded, the degree of pathology was scored as moderate. If spontaneous denervation activity was present together with any of the other signs, or if maximal voluntary activity was reduced to the point that only single units could be recorded, the degree of pathology was scored as high.

To exclude polyneuropathy, all investigated patients who had any type of pathology in the oropharyngeal EMG-investigation later underwent recording of conduction velocities in the ulnar, peroneal and sural nerves (non-dominant side), and EMG of the anterior tibial muscle.

**Statistical analysis** was made by calculation of means, medians, SD and confidence intervals. Comparisons between the different groups of subjects were made by the non-parametric Mann-Whitney U-test.

Ethical consent to the study was given by the local ethical committees at Karolinska Hospital, Stockholm, and Linköping University Hospital. All patients and control subjects gave informed consent.
4 RESULTS

4.1 THERMAL THRESHOLDS IN THE EXTREMITIES (STUDY I)

4.1.1 Cool and warm detection thresholds
The hand was significantly more sensitive than the foot for CDT and WDT ($P<0.001$).
In the hand, no significant difference was found for CDT at the different sites. For WDT the thenar eminence was more sensitive than the volar surface of the wrist ($P<0.001$) and the dorsum of the hand ($P=0.0035$), but no significant difference was found between the volar surface of the wrist and the dorsum of the hand (Table 4.1.2).
The range of 5th to 95th percentile was the narrowest at the thenar eminence followed by the volar surface of the wrist followed by the dorsum of the hand, but the medians and 5th percentiles were nearly identical at these sites, and most of the differences were accounted for by the 95th percentiles (Fig. 4.1.1, Table 4.1.1).

Fig. 4.1.1. Warm (white) and cool (gray) thresholds at different sites. Rectangles represent median, 25th and 75th percentiles, and error bars represent 5th and 95th percentiles.
Table 4.1.1. Thermal thresholds at the different sites for the different modalities presented as median and 5th–95th percentiles (in parentheses)

<table>
<thead>
<tr>
<th>Site</th>
<th>Cool-DT</th>
<th>Volar wrist</th>
<th>Dorsum hand</th>
<th>Dorsum foot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thenar</td>
<td>31.5</td>
<td>31.5</td>
<td>31.5</td>
<td>31.4</td>
</tr>
<tr>
<td>(31.0–31.7)</td>
<td>(30.6–31.8)</td>
<td>(29.6–31.9)</td>
<td>(28.2–31.8)</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>32.5</td>
<td>32.6</td>
<td>32.6</td>
<td>34.3</td>
</tr>
<tr>
<td>(32.2–33.3)</td>
<td>(32.2–34.1)</td>
<td>(32.3–35.3)</td>
<td>(32.3–39.7)</td>
<td></td>
</tr>
<tr>
<td>Foot</td>
<td>9.8</td>
<td>14.2</td>
<td>16.2</td>
<td>11.7</td>
</tr>
<tr>
<td>(1.2–24.5)</td>
<td>(1.3–27.6)</td>
<td>(0.5–27.0)</td>
<td>(0.5–25.1)</td>
<td></td>
</tr>
<tr>
<td>Volar wrist/dorsum foot</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Thenar/dorsum hand</td>
<td>P = 0.0001</td>
<td>P = 0.0008</td>
<td>P = 0.0075</td>
<td>NS</td>
</tr>
<tr>
<td>Dorsum hand/dorsum hand</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4.1.2. Statistical significance of thermal thresholds differences between different sites (NS, not significant)

<table>
<thead>
<tr>
<th>Site</th>
<th>Cool</th>
<th>Warm</th>
<th>Cold</th>
<th>Hot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thenar/volar wrist</td>
<td>NS</td>
<td>P &lt; 0.0001</td>
<td>P = 0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Thenar/dorsum hand</td>
<td>NS</td>
<td>P = 0.0035</td>
<td>P = 0.0008</td>
<td>NS</td>
</tr>
<tr>
<td>Thenar/dorsum foot</td>
<td>P = 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Volar wrist/dorsum foot</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Dorsum hand/dorsum hand</td>
<td>P = 0.0002</td>
<td>P &lt; 0.0001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Volar wrist/dorsum hand</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

4.1.2 Cold and heat pain thresholds

For HPT, all the sites at the hand and the foot were equally sensitive (Fig. 4.1.2, Table 4.1.1). One subject reached 50 °C at thenar eminence without reporting pain. For CPT, the thenar eminence was the least sensitive site compared to other sites at the hand and the foot (P<0.008) (Table 2). No significant differences were found otherwise. One subject reached 0 °C at all sites and another reached 0 °C at the foot without reporting pain.
4.1.3 Effect of regional skin temperature on cool and warm detection thresholds

We found no significant effect of local skin temperature on WDT (Spearman correlation coefficient rhea (83)=0.2, \( P = 0.64 \)). Weak but statistically significant correlation was found for CDT (Spearman correlation coefficient rho (83)=0.25, \( P = 0.03 \)) (Fig. 3). However, coefficient of reliability was very low and accounted for only 6% of the variance (rho²=0.06) methods. Cooler local skin temperature was correlated with detection of temperature change at slightly lower values. The maximum difference caused by varying skin temperatures did not exceed 0.2 °C for median, and 0.1 °C for 5th and 95th percentiles. (Fig. 4.1.3)
Fig. 4.1.3. Warm (open squares) and cool (closed squares) detection thresholds at different local skin temperatures. Represented in median, 5th and 95th percentiles

4.2 VIBRATION THRESHOLDS IN THE EXTREMITIES (STUDY II)

4.2.1 Effect of tested site on vibration detection thresholds

The index finger was significantly more sensitive than the great toe ($P<0.0001$). With 30 g of added weight (24.59 g/cm$^2$), the pulp was more sensitive than the nail ($P=0.007$), but no significant difference was found between the dorsum of the phalanx and the pulp or the nail. The narrowest range of 5th–95th percentile was found at the pulp followed by the dorsum of the phalanx followed by the nail. At the great toe, there was no significant difference of vibr-DT between the dorsum of the phalanx and the nail Fig. 4.2.2.
4.2.2 Effect of applied pressure on vibration detection thresholds

VDT was measured at the dorsum of the phalanx at the index finger and the great toe with different added weights; 30 g (24.59 g/cm²), 50 g (40.98 g/cm²) and 100 g (81.96 g/cm²). At the index finger, VDT was significantly lower with 30 g compared with 100 g ($P=0.004$ and 0.013, respectively), but similar with 30 and 50 g. The range of 5th–95th percentile was narrowest with 30 g followed by 50 g followed by 100 g. At the great toe, no significant difference of VDT was found using the different weights. Some individuals complained of discomfort when tested with 100 g (Fig. 4.2.3)
Fig. 4.2.3. Vibration thresholds at dorsum of the index finger and the great toe with different weights. Represented as median, 5th and 95th percentiles.

4.3 OROPHARYNGEAL QST FINDINGS IN OSAS PATIENTS AND SNORERS (STUDY III)

In normal subjects, the vibration thresholds at the lip were in average 3.5 µm (range 0.4 – 9.6, 95% CI 2.3 – 4.7) and at dig II 1.3 µm (range 0.5 – 7.4, 95% CI 0.6 – 2.0). Cold detection thresholds were expressed as difference between the threshold and the adaptation temperature, and were at the tip of the tongue in average 1.2 ºC (range 0.4 – 3.0, 95% CI 1.0 – 1.6). At the lower lip they were in average 0.6 ºC (range 0.1 – 1.2, 95% CI 0.5 – 0.8). The results of the habitual snorers and the OSAS-patients did not show any significant differences from the normal subjects at any of these sites.

In some subjects with strong gag reflexes oropharyngeal testing was not possible. One normal subject and 2 OSAS-patients could therefore not go through with any of the tests in the upper airway. Another normal subject could not endure CDT. VDT was not possible in one additional OSAS-patient due to a large tongue. Seven out of seven normal subjects did not experience the sensation of warmth at the tonsillar pillars, despite testing at the maximal temperature level (50 ºC), why this type of
testing was discontinued. Warmth detection testing was therefore not performed in any patient.

The results of testing at the tonsillar pillars are summarized in Table 4.3.1 A and B. At the tonsillar pillars, vibration thresholds were in average 18.3 µm (95% CI 8.2 – 28.3) in normal subjects, 21.9 µm (95% CI 9.3 – 34.4) in snorers and 30.6 µm (95% CI 23.5 – 37.6) in OSAS-patients (Fig. 4.3.3). These results were significantly different between normal subjects vs. OSAS-patients (p=0.003), but not vs. snorers, and neither between snorers and OSAS-patients. Two normal subjects, 1 snorer and 2 OSAS-patients did not experience vibration sensations at this site at all. Two snorers and 13 OSAS-patients had values exceeding the upper 95% CI for normal subjects.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>95% CI</th>
<th>SD</th>
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<tr>
<td>Normals</td>
<td>19</td>
<td>18.3</td>
<td>9.9</td>
<td>8.2-28.3</td>
<td>20.8</td>
</tr>
<tr>
<td>Snorers</td>
<td>12</td>
<td>21.9</td>
<td>19.0</td>
<td>9.3-34.4</td>
<td>18.7</td>
</tr>
<tr>
<td>OSAS</td>
<td>23</td>
<td>30.6</td>
<td>31.0</td>
<td>23.5-37.6</td>
<td>16.4</td>
</tr>
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</table>

Table 4.3.1 A. Oropharyngeal vibration detection thresholds (amplitude displacement in µm)

<table>
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<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>95% CI</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>16</td>
<td>2.0</td>
<td>2.1</td>
<td>1.6-2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Snorers</td>
<td>13</td>
<td>6.1</td>
<td>3.8</td>
<td>1.8-10.4</td>
<td>5.6</td>
</tr>
<tr>
<td>OSAS</td>
<td>28</td>
<td>8.2</td>
<td>6.7</td>
<td>6.0-10.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Table 4.3.1 B. Oropharyngeal cold detection thresholds (calculated difference between detection temperature and adaptation temperature in ºC)
Oropharyngeal vibration thresholds

Mean ±SE ±SD Outliers Extremes
1 = OSAS  2= snorers  3= normals

CDT at the tonsillar pillars were in average 2.0 °C (95% CI 1.6 – 2.5, max. 3.5 °C.) in normal subjects, 6.1 °C (95% CI 1.8-10.4) in habitual snorers and 8.2 °C (95% CI 6.0-10.3) in OSAS-patients (Fig 4.3.4). These results were significantly different between normal subjects vs. OSAS-patients (p<0.001), and also between normal subjects and habitual snorers (p=0.001). There was no significant difference between snorers and OSAS-patients.

Fig 4.3.3 Vibration detection thresholds at tonsillar pillars: Comparison between OSAS-patients, habitual snorers and normal subjects.
Fig 4.3.4 Cold detection thresholds at tonsillar pillars: Comparison between OSAS-patients, habitual snorers and normal subjects.

5/9 snorers and 21/27 OSAS-patients had values exceeding maximum values for normal subjects. Seven OSAS-patients and one snorer did not perceive the sensation of cold at the lowest tested temperature (19 °C).

Twenty-two OSAS patients and 11 snorers successfully completed both WDT and CDT. Pathology was defined as thresholds exceeding the upper 95% CI for WDT and the maximum value for CDT in the normal group. 11/22 OSAS-patients had pathological values in both tests; 5 had values within normal limits in both tests, 3 had pathological CDT but normal WDT, and one patient had pathological WDT but normal CDT. No snorer had pathological values in both tests; 3 had values within normal limits in both tests, 6 had pathological CDT but normal WDT, and 2 patients had pathological WDT but normal CDT. Thus, CDT was more commonly affected in
those who had one pathological test, both concerning OSAS-patients and snorers. In
the OSAS-patients, 75% had pathological CDT and 57% pathological WDT. In
snorers, 54% had pathological CDT and 17% pathological WDT.

Both WDT and CDT in the oropharynx were significantly higher in normal men
(n=15) compared to women (n=8), p=0.006 and p=0.02, respectively (Fig 4.3.5A and
B). Such differences were not present in any other tested site.

**Fig 4.3.5 A** Gender difference in vibration detection thresholds at tonsillar pillars
**Oropharyngeal cold thresholds in non-snoring women and men**

- **p = 0.02**

**Median**

<table>
<thead>
<tr>
<th>Gender</th>
<th>1 = women</th>
<th>2 = men</th>
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<tr>
<th>Min-Max</th>
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**Cold thresholds**

**Fig 4.3.5 B.** Gender difference in cold detection thresholds at tonsillar pillars

There was no significant correlation between the degree of sensory impairment in terms of CDT or WDT vs. the measures of apnea severity. Neither were there any correlations between CDT and WDT vs. number of snoring years, as reported by the patients, or WDT and CDT vs. age in normal subjects.

### 4.4 EMG FINDINGS IN UPPER AIRWAYS MUSCLES IN OSAS PATIENTS AND SNORERS (STUDY IV)

In five patients, three with OSAS-diagnosis and two snorers, the examination had to be discontinued due to patient discomfort, i.e., only 1-2 needle insertions were made with a small number of identified motor units. They have not been included in this analysis.
Ten out of 11 successfully examined OSAS patients showed signs of motor neuron lesion in at least one of the examination points. These signs were spontaneous denervation activity (4 cases), polyphasic potentials of increased duration (10 cases), high amplitude potentials (3 cases) and reduced interference pattern (7 cases; in 3 of these very few recorded units). An example of a high-amplitude MU-potential is given in Fig. 4.4.1 A, and a normal MU-potential from the palatoglossus muscle is shown in Fig. 4.4.1 B for comparison.

![Motor-unit potential of increased amplitude and duration, indicating peripheral neurogenic lesion. Sample from EMG of palatoglossus muscle from patient S3.](image)

**Fig 4.4.1A.** Motor-unit potential of increased amplitude and duration, indicating peripheral neurogenic lesion. Sample from EMG of palatoglossus muscle from patient S3.
An example of markedly reduced activity at maximal voluntary effort, and several polyphasic potentials, is given in Fig. 4.4.2 A. In this patient a muscle biopsy was also performed, and a histological section is shown in Fig 4.4.2 B for comparison. The only patient with a completely normal result (nr 8) had a short history of snoring and apneas (<2 years); his problems had started after a severe tonsillitis.
Fig 4.4.2 A EMG-recording from a patient with severe OSAS (pat nr 9, AH1 =60). At maximal voluntary effort, only a few mostly polyphasic motor-unit potentials are recorded.

Fig 4.4.2 B Cross-section from m. palatopharyngeus of the same patient, stained with myofibrillar ATPase, after acid preincubation with pH 4.6. Type I fibers stain black, type IIA light, and type IIB grey. The thick white arrow points to a fascicle with atrophic type II fibers. This is an example of the phenomenon of 

**fascicular or grouped atrophy**, which is typical of a neurogenic lesion.
Of the 22 successfully investigated snorers, 7 had minor changes (mostly polyphasic potentials of increased duration) and 4 moderate EMG-changes. None had spontaneous denervation activity. The remaining 11 subjects were judged to have normal EMG-recordings.

All patients with pathological oropharyngeal EMG-findings were later investigated with ENeG in the extremities and EMG of the tibialis anterior muscle. None had pathological findings in this subsequent investigation. Thus, there was no case with signs of polyneuropathy.

EMG was scored as normal in all 4 non-snoring subjects. The motor unit potentials in these cases were generally of low amplitude, in average 350 µV. The maximum-recorded amplitude in single units was 1290 µV. The duration was short (3-8 ms). This indicates that the motor units in these muscles normally comprise relatively few muscle fibers.

A summary of the EMG-findings in OSAS-patients and snorers in comparison to normal subjects is given in Fig.4.4.3.
Fig 4.4.3. Degree of pathology in oropharyngeal EMG from normal subjects, habitual snorers and OSAS-patients. 1=normal EMG; 2= slight pathology; 3= moderate pathology; 4= grave pathology.
5 DISCUSSION

5.1 STUDY I
In this study we compared thermal thresholds in 46 normal volunteers at 3 sites at the hand and wrist and one site at the foot. Our goal was to determine if there is a significant difference in thresholds at the tested sites and to identify if there is a preferred site of testing for each thermal modality.

We found the hand to be significantly more sensitive than the foot for CDT and WDT. Several authors have reported thermal thresholds values at the hand and foot using a variety of methods. Warm detection thresholds have been found significantly lower at the volar forearm and dorsum of the hand compared to the foot [20]. Considerable between-subjects variation has been found at the foot in contrast to very little variation at the thenar eminence for CDT and WDT [2]. Several studies have reported lower thermal perception thresholds at the hand compared to the foot and larger range of inter-individual variation at the foot, but without reporting statistical significance [11, 15, 26, 28, 32, 61, 65, 67, 71, 72, 388]. Others have found no difference for cool thresholds between the hand and the foot [12, 26, 33].

Our measurement of WDT at the hand and wrist showed that the thenar eminence was significantly more sensitive than the dorsum of the hand and the volar surface the wrist. The difference was of small absolute value and barely above the detectable level of the equipment (0.1 °C) in most cases. No significant difference was found between the dorsum of the hand and the volar surface the wrist. Other authors reported no significant difference of warm thresholds between the volar forearm and dorsum of the hand [20]. When the thenar and volar surface of the forearm were compared, the thenar was found to be more sensitive to warmth but statistical significance was not reported [71, 72, 388].
We found no significant difference of the CDT between the three tested sites at the upper extremity. Small differences in cool thresholds have been reported between different sites in the hand but they were not statistically significant. It has been reported that cool threshold at the volar forearm is lower compared to the thenar eminence [72]. Cool threshold was also reported to be lower at the thenar eminence compared to hypothenar eminence [67]. In both reports, it is not clear if the observed differences are statistically significant.

Our findings and the literature data suggest that any site at the hand or wrist is practically suitable for the evaluation of cool and warm detection thresholds. However, we found that the narrowest range of 5th to 95th percentile was recorded at the thenar eminence for cool and warm thermal modalities indicating the smallest inter-individual variability. Therefore, the thenar eminence may be a preferred site of testing.

In this study, comparison of CPT at different sites at the hand and the foot showed that the thenar eminence is the least sensitive ($P<0.008$). No significant difference was found between the dorsum of the hand, volar surface of the wrist and the dorsum of the foot. Measurement HPT showed no significant difference between all the sites at the hand and the foot. Several authors found no difference between the hand and the foot for CPT [67] and HPT [1, 11, 32, 65, 67]. Significant but small difference of HPT was reported at the upper extremity where the volar surface of the forearm was found slightly more sensitive than the dorsum of the hand in 8 healthy subjects [20]. The hypothenar eminence was found slightly less sensitive to cold pain than the thenar eminence, but no statistical analysis was performed [67]. Some of our subjects did not report pain at 0 °C (one at all sites and another at the foot) and at 50 °C (one at the thenar eminence) which are the technical limits of the used device. In 61 normal subjects, pain was not felt by some subjects at 5 °C (3 at the hypothenar
eminence and 8 at the tarsal region) and at 50 °C (two at the hypothenar eminence and two at the tarsal region) [67]. In our subjects the thenar eminence was the least sensitive site to cold induced pain, therefore, this site may be the most suitable for detecting hyperalgesia.

We also evaluated the effect of local skin temperature on thermal detection thresholds in 27 normal volunteers. We found that local skin temperature within a range of 27 °C to 37 °C did not cause a significant effect on WDT and only had a minor effect on cool-DT. This finding reconfirms the findings of several previous studies that have addressed this issue. Several authors reported no effect of local skin temperature on thermal detection [12, 33, 53]. Similarly, in children under the age of 10 years, no effect of local skin temperature was found on warm and cold thresholds if the skin temperature is above 26 °C [71]. The authors suggested that it is unnecessary to warm the skin when the local skin temperature is above 26 °C. In a large study of 4462 subjects, a moderately positive effect of skin temperature was found on the index finger thermal discrimination threshold for cool (higher temperature associated with poorer thresholds), but no such effect was found at the toe [56]. Others found that higher initial skin temperature was significantly associated with a decrease in cool thresholds at the hand, however, this effect was below the detectable level of the equipment [2]. In a more recent study in 225 children and juvenile subjects, local skin temperature did not affect warm thresholds and had only poor correlation with cold thresholds ($r^2=0.06–0.26$ in subjects younger than 12 years old and $0.06–0.55$ in subjects 12–17.9 years old, $P<0.01$) [72]. In our study, we kept the thermal plate of the thermode in contact with the examined skin for the entire duration of the test. This is expected to keep the skin temperature similar to the adaptation temperature of the thermode (32 °C) when no stimulus is being delivered disregarding the regional skin temperature. We believe that this technique further reduces the effect of local skin
temperature on CDT and WDT, making it unnecessary to warm or cool the skin if it is within the range of 27–37 °C.

This study indicates that thermal detection threshold is a robust measure and therefore appropriate for use in clinical practice and clinical trials. It is not influenced by underlying skin temperature, at least within the range used in this study (27–37 °C), which would normally be encountered. The hand is consistently more sensitive than the foot for warm and cool thresholds but equally sensitive for thermal pain, with the exception of the thenar eminence which is less sensitive for cold pain than all other sites. Within the hand and wrist, there are no clinically relevant differences between different sites. However, the thenar surface has the narrowest 5th–95th percentile ranges for cool and WDT which reflects the least inter-individual variations. Therefore the thenar eminence may be the preferred site for longitudinal evaluation of patients with sensory loss, either in experimental studies or while following patients clinically.

5.2 STUDY II

In this study we found that the index finger is more sensitive to vibration than the great toe which has been reported by several authors [64, 65]. This difference between the hand and the foot was found to become more pronounced with advancing age [2, 32, 51] as well as in patients with chronic renal failure [50]. At the index finger we found significantly lower VDT at the pulp compared to the nail but no significant differences were found between the dorsum of the middle phalanx and the pulp or nail. The range of 5th–95th percentile was narrowest at the pulp compared to the other sites at the index finger. Hardness of the tested surface can exert a dampening effect and mechanically impede the amplitude of vibration for a given
electrical current that is supplied to the coil of the vibrator. This has been demonstrated by several authors who showed more impedance of vibration and higher vibration thresholds when testing was conducted on a harder surface [27, 389], but this dampening effect disappeared at higher frequencies of 250–500 Hz [75]. This dampening effect could account for our finding of lower VDT at the pulp compared with the nail, which was clinically negligible.

Pressure applied to the vibrating pin is expected to increase the dampening effect. Several investigators have evaluated the effect of pressure at the stimulation site. In 1938, Cohen and Lindley [389] measured vibration threshold using weights of 50–100 g over surface of 0.2–0.8 cm² (pressure of 62.5–500 g/cm²) and found it to be lower under higher pressure. Similarly, Lowenthat and Hockaday [76] found considerable reduction in vibration thresholds as pressure applied to the stimulator increases from 200 to 800 g/1.33 cm² (150–600 g/cm²). Using much lower pressure, Greg et al in 1951 [64] measured vibration thresholds using ‘(negligible) load to the vibrating system’ and concluded that the effect of vibrator-holding pressure was not significant. Similarly, Era and Hänninen in 1987 [75] found no significant effect of static load of 1–3 N on 1.33 cm² (0.75–2.26 g/cm²) on vibration thresholds measured at different frequencies (50–500 Hz). We compared the effect of small weights applied to the site of testing on VDT using 30 g (24.59 g/cm²), 50 g (40.98 g/cm²) and 100 g (81.96 g/cm²) at the index finger and the great toe. At the index finger VDT was significantly lower at pressures of 30 and 50 g compared with 100 g but there was no difference between 30 and 50 g. At the great toe no difference of VDT was found with all the different weights. All the differences were at or barely above the detection resolution of the device (minimum 0.1 µm), and as a result were clinically negligible. Some subjects complained of discomfort when using 100 g.
This study indicates that measurement of VDT is a robust method of testing and therefore appropriate for use in clinical and research settings. The hand is clearly more sensitive than the foot but there are no or negligible differences between different sites at the index finger and at the great toe disregarding the hardness of the tested surface. Testing can be done appropriately under low weights preferably in the range of 30–50 g to minimize discomfort. The used device should be pre-calibrated to operate under a specified pressure.

5.3 STUDY III

In the present study, there were significantly increased oropharyngeal thresholds for both the sensations of vibration and cold in OSAS-patients compared to the normal subjects. In snorers such a difference was present for CDT but not VDT. The snorers had, as a group, less pathology in all tests, and a much greater variability was found. Certain snorers had thresholds well within the range of those in the group of normal subjects, whereas three could not perceive either cold or vibrations. There were, however, no statistically significant differences between snorers and OSAS-patients in VDT or CDT, but there was a trend, as seen in Fig 1 and 2.

Our findings regarding vibration sensitivity confirm the findings of Kimoff and colleagues [82], who found impaired vibration sensitivity in OSAS-patients and snorers compared to non-snoring controls of similar age, but not between snorers and OSAS-patients. Concerning the function in large myelinated sensory fibres, Guilleminault et al have also reported reduced sensitivity to 2-point discrimination in the upper airways in OSAS patients and snorers compared to normal non-snoring
individuals [364, 365]. Nguyen et al have reported reduced sensitivity to touch of air pulses at different sites in the upper and lower airways [366].

Our findings of reduced thermal sensitivity in OSAS-patients and habitual snorers compared to normal subjects confirm the findings of Larsson et al [80], who found reduced thermal sensitivity in the oropharynx of OSAS patients compared to normal subjects, but who never tested snorers. In that study, all the tested subjects except four OSAS-patients experienced the sensation of warmth in the palate at test-temperatures below 50 °C. There could be several reasons for this discrepancy between Larsson et al:s study and the present. It is well known that several factors affect sensory testing, such as probe size, type of equipment, etc. In the study of Larsson et al, the employed equipment was not commercially available. One important factor is the algorithm for testing, and this differed. In the present study, the method of levels [10] in which testing of cold and warmth is done separately. Larsson et al used the Marstock method [26], in which alternating cold and warm stimuli are given. The Marstock method has been criticized, since cooling will influence the ensuing warm perception and vice versa [73].

In the present study, both the function of thin myelinated, unmyelinated (cold sensation), and large myelinated (vibration sensation) fibres has been tested in the same subjects, which has not previously been done in the oropharynx. In most OSAS-cases, there was a good concordance between VDT and CDT. However, in habitual snorers, most subjects had discordant results. CDT was more commonly affected in those who had one pathological test, both concerning OSAS-patients and snorers. Thus, CDT gave more discriminative results.
In general terms, VDT and CDT were much higher at the tonsillar pillars than at any other site, including the tongue and the lip. Also, it should be noted that none of the tested normal subjects experienced warmth at this site, despite testing with 50 °C, the maximum output temperature of the equipment (at higher temperatures, there is a risk of burn injury). The tongue was very cold sensitive. Our findings are in concordance with previous findings [59]. We thus found the palate to be relatively insensitive to both cold and vibration stimuli, but this was particularly true for VDT. Two normal subjects did not experience vibration at this site at all, and the normal variability was much greater for VDT than for CDT. Another source of confusion was that we found that the sensation of vibration at the palate differed from that in the fingers. A number of subjects, both normal and patients, had difficulties in defining the sensation as vibration; more like touch, pressure or pain. In clinical routine, VDT is usually performed with application of the probe against skin closely overlying bone. If application is made against soft tissue, such as the tonsillar pillars, the thresholds will be higher and the sensation will have a different quality [27]. Age can be a confounding factor when testing VDT, as they are increased with age [5], while this is not as pronounced concerning CDT. Data are conflicting whether they are at all affected [7, 32, 53]. Fowler et al. compared the age-effect on thermal thresholds in hand, foot and face, and found no significant effect of age on CDT in the face [33]. In the present study, there was no significant correlation in normal individuals between increasing age and CDT and VDT, respectively, which could be due to the limited sample size. All these facts (low sensitivity to vibrations, soft tissue, and the confounding age factor) make VDT a less suitable test method in the soft palate.
A new finding in this study is the gender difference in oropharyngeal VDT and CDT, with significantly higher thresholds in men. Such a difference was not found in any other tested site. Several previous studies have addressed this issue in testing of hand and foot, and in most studies no gender differences were found [2, 7]. One reason for this could be that normal men are more likely to snore occasionally than normal women.

The findings in the present study support the previously formed hypothesis [317], that the inability of the dilating upper airway muscles to maintain airway patency during sleep is due to peripheral nerve lesions, causing partial paresis and/or impaired dilating reflexes at inspiration, worsening over time. Snoring vibrations, repeated every night for several years, might cause progressive, local nervous lesions in the oropharynx as part of the pathogenesis of OSAS. There were no signs of impaired sensitivity in any other location in the patient groups. The habitual snorers showed less pronounced pathology in both VDT and CDT than the OSAS-patients. However, there was no significant correlation between the degree of sensory impairment vs. the measures of apnea severity.

5.4 STUDY IV

There is convincing evidence that peripheral nervous lesions are common in the upper airway muscles in patients with OSAS. Such lesions may also be found in habitual snorers, but they are less common and less pronounced. The present study gave evidence of muscle pathology in almost all patients with OSAS, and to a lesser degree in 11/22 patients with habitual snoring. The pathology revealed in the EMG only
rarely consisted of denervation activity; such a picture would indicate an ongoing
denervation. Instead, the most common findings were reduced maximal voluntary
activity and motor-unit potentials of increased amplitude and/or duration
(polyphasia). Polyphasia indicates a reinnervation process, and motor-unit potentials
with increased amplitude and duration are typical of long-standing, chronic nervous
lesions. This supports the previously formed hypothesis [317] that the inability of the
dilating upper airway muscles to maintain airway patency during sleep could be due
to peripheral nerve lesions, causing partial paresis and/or impaired dilating reflexes at
inspiration, worsening over time. Snoring vibrations, repeated every night for several
years, might cause progressive neuronal lesions in the upper airway.

During an apnea, pharyngeal occlusion is associated with decreased muscle tone
[269]. However, augmented activity of the genioglossus muscle has been recorded in
awake patients with OSAS in comparison to normal subjects [373], which might
seem contradictory. This activity is markedly diminished during sleep, the difference
being greater than in normal subjects [269, 339]. The increased muscle activity during
the awake state has been interpreted as a neuromuscular compensation mechanism for
a narrow pharyngeal airway, lost during sleep [374], but it could, however, represent
compensation, not only for anatomical factors, but also for weakness of other dilating
or stabilizing muscles. Another source of confusion is the method by which the
muscle activity has been measured in the previous studies. This has been done by
means of so-called hooked wire-electromyography. Pairs of wire electrodes have
been inserted in the muscle, with the signals rectified and integrated by a resistance-
capacitance circuit on a moving time average basis. Since this type of signal cannot
be directly compared between different individuals, electromyographic activity has
been expressed as a percentage of maximum activity i.e., a relative measure. Even in
absolute terms, the amplitude of the EMG signals does not necessarily reflect strength; certainly there is no linear relationship. Also, pathological changes of the type described above cannot be discerned. However, with concentric bipolar EMG, direct comparison can be made and normal values for amplitude and duration be given. Different muscles will vary in these respects, due to different average numbers of muscle fibers per motor unit, in turn depending on the principal function of the muscle in question (finely graded movements of short duration or a more postural function). Pathological findings do, however, remain the same, irrespective of the type of muscle examined. One drawback concerning this type of EMG procedure is that the examination in the oropharynx must be performed by an experienced electromyographer, since the examination needs to be performed very quickly due to patient discomfort.

There is currently no way of predicting whether a person with habitual snoring will develop OSAS or not, nor are there any studies showing the usual rate of progress. Future studies could be performed prospectively on patients with habitual snoring to show whether the degree of pathology in the EMG increases over time. Repeated investigations after CPAP treatment could also show whether the degree of muscular pathology decreases, i.e., whether an effective reinnervation could take place. If snorers without significant apneas but with some indications of nervous dysfunction are at risk for developing OSAS, early treatment should be given.
6 CONCLUSION

I. Testing of thermal thresholds in normal subjects can be adequately conducted at several sites at the hand. However, the thenar eminence (TE) is preferred given the small inter-individual variability. TE may be preferred for evaluating hyperalgesia to cold given its higher threshold. Warming or cooling of the skin is unnecessary within the range normally encountered in routine clinical evaluation.

II. Testing of vibration thresholds in normal subjects can be adequately conducted at several sites of the index finger and the great toe. The thresholds were not affected by different application pressures within 30–100 g/1.22 cm².

III. Testing of vibration (VDT) and cold detection thresholds (CDT) could be performed in the oropharynx. Warm detection could not be performed. CDT gave more discriminative results. CDT could become a useful clinical method to evaluate the degree of oropharyngeal structural damage, which might be important in choice of therapy. Signs of sensory nervous lesions were present in the oropharynx of most OSAS-patients and some snorers, indicating progressive oropharyngeal sensory nervous lesions. These findings support the hypothesis that OSAS could be attributed to local peripheral neurogenic lesions.

IV. Concentric needle EMG is a method that may be employed in clinical practice to evaluate the extent of damage in upper airway muscles. This study also supports the hypothesis that progression
from habitual snoring to the clinical disease of OSAS could be attributed to a local oropharyngeal neuropathy, since it demonstrates motor nervous lesions.
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