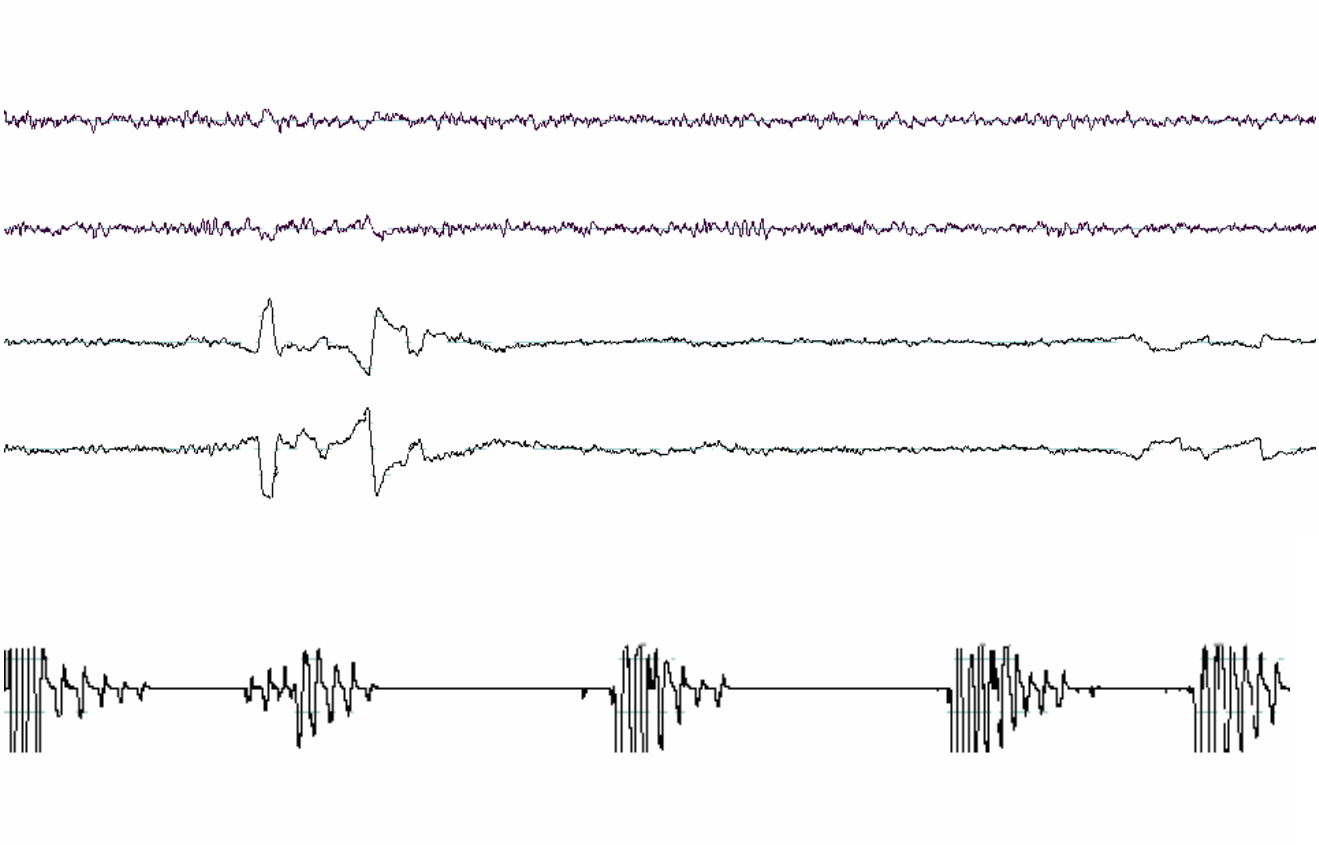

SLEEP APNEA AND SLEEP
Diagnostic aspects

Carin Sahlin

Department of Public Health and Clinical Medicine, Respiratory Medicine and Allergy, Umeå University, Sweden 2009

Umeå University Medical Dissertations
New Series No 1246 ISSN 0346-6612 ISBN 978-91-7264-702-2

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ABSTRACT

Background: Patients with sleep apnea have frequent apneas and hypopneas during sleep. Apneas can be either central or obstructive. The apnea-hypopnea index (AHI) is the mean number of apneas and hypopneas per hour of sleep.

Aims: 1) To evaluate the effect of a mandibular advancement device on obstructive apneas and sleep; 2) to evaluate the influence of body position on central apnea frequency; 3) to investigate whether obstructive or central apnea is related to mortality in patients with stroke; and 4) to investigate sleep and sleeping positions in women.

Methods: Subjects were investigated during whole-night sleep respiratory recordings, either polysomnography including continuous recordings of EEG, EOG, EMG, airflow, respiratory effort, ECG, pulse oximetry and body position, or simplified sleep apnea recordings without EEG, EOG and EMG.

Results: The frequency of obstructive apneas, hypopneas and arousals decreased and rapid eye movement (REM) sleep increased in patients with mild, moderate and severe sleep apnea during treatment with a mandibular advancement device.
Central apneas were more prevalent in the supine position compared with the non-supine position in patients with Cheyne-Stokes respiration. The mean ± SD central AHI was 41 ± 13 in the supine position and 26 ± 12 in the non-supine position, $p<0.001$.
Stroke patients with obstructive sleep apnea ran an increased risk of death during 10 ± 0.6 years of follow-up with an adjusted hazard ratio of 1.76 (95% CI 1.05-2.95) compared with controls, independent of hypertension, age, body mass index, gender, smoking, diabetes mellitus, atrial fibrillation, Mini-Mental State Examination and Barthel-ADL. Central apnea was not related to early death.
Total sleep time, sleep efficiency, rapid eye movement sleep, slow wave and time in the supine position decreased with age in women. Sleep quality in women was reduced with age, body mass index, obstructive sleep apnea, smoking, alcohol and hypertension.

Conclusions: Obstructive sleep apneas and arousals are reduced and REM sleep is increased using a mandibular advancement device in patients with mild, moderate and severe sleep apnea. The frequency of central apneas and hypopneas is increased in the supine position in patients with Cheyne-Stokes respiration. Stroke patients with obstructive sleep apnea run an increased risk of early death. Central sleep apnea was not related to early death among the present patients. Normal values for sleep stages and sleeping positions are presented in a population-based sample of women. Age, body mass index, obstructive sleep apnea, smoking, alcohol and hypertension reduce sleep quality in women.

Key words: Sleep apnea syndromes; Polysomnography; Sleep stages; Supine position; Women; Stroke; Prognosis; Cheyne-Stokes respiration

ORIGINAL PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. Marklund M, Franklin K A, Sahlin C, Lundgren R. The effect of Mandibular Advancement Device on Apneas and Sleep in Patients With Obstructive Sleep Apnea. Chest 1998; 113:707-13.

II. Sahlin C, Svanborg E, Stenlund H, Franklin KA. Cheyne-Stokes respiration and supine dependency. Eur Respir J 2005; 25: 829-833.

III. Sahlin C, Sandberg O, Gustafson Y, Bucht G, Carlberg B, Stenlund H, Franklin KA. Obstructive Sleep Apnea Is a Risk Factor for Death in Patients With Stroke -A 10 year follow up. Arch Intern Med 2008; 163: 297-301.

IV. Sahlin C, Franklin KA, Stenlund H, Lindberg E. Sleep in women-Normal values for sleep stages and position and the effect of age, obesity, sleep apnea, smoking, alcohol and hypertension. Sleep Medicine. In press

ABBREVIATIONS

AHI	Apnea-hypopnea Index
BMI	Body mass index
CAHI	Central apnea-hypopnea Index
CSA	Central sleep apnea
CSR	Cheyne-Stokes respiration
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
EOG	Electro-oculogram
EMG	Electromyogram
NREM	Non Rapid Eye Movement
OAHI	Obstructive apnea-hypopnea Index
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
RIP	Respiratory inductance plethysmography
REM	Rapid eye movement
SWS	Slow wave sleep

INTRODUCTION

There are increasing numbers of sleep laboratories and sleep investigations worldwide. One reason is the many subjects who are investigated because of sleep apnea and snoring.

The registration of sleep started with a German psychiatrist, Hans Berger, who made the first registration of brain activity during sleep in 1929 [1]. He found that EEG patterns changed during wakefulness and sleep. In 1953, Dr Kleitman and colleagues at the University of Chicago identified rapid eye movements (REM) [2]. Further research by Dr Kleitman and his colleague Dr WC Dement led to the discovery of cyclical variations in REM at about 90-minute intervals [3]. Sleep was then also classified into five stages, stage 1, 2, 3, 4 and REM.

Sleep apnea was identified by Gastaut and colleagues in France in 1965. They reported an association between breathing abnormalities, snoring and daytime sleepiness in patients during sleep [4]. The first sleep research center was established at Stanford University in the USA in 1970. In order better to understand and record sleep apnea and sleep, a method called "polysomnography" was introduced. These recordings included the registration of brain activity with EEG electrodes, eye movements and muscle tone. Respiration parameters, body position and pulse oximetry were then added. Sleep stages in polysomnography recordings today are based on the standard criteria specified by Rechtschafen and Kales [5]. Strict definitions of sleep apnea and EEG arousals were published by the American Academy of Sleep Medicine in 1999 [6]. Polysomnography is still the reference standard for sleep apnea recordings.

Polysomnography investigations are expensive and take a long time to perform and score. In the past, patients had to sleep at a sleep laboratory, but it is now also possible to perform unattended polysomnography with mobile equipment. In the USA, sleep studies must include the registration of sleep stages, otherwise patients do not qualify for US Medicare reimbursement [7]. Because the need for sleep apnea investigations was increasing worldwide, more simplified sleep apnea equipment was introduced. Technical developments with new simplified devices have been in progress for many years and equipment with only one or two channels is available. The American Academy of Sleep Medicine does not recommend the use of equipment with less than level III in sleep apnea recordings. This comprises unattended devices that measure at least four cardio-respiratory parameters; respiratory movements, airflow, oxygen saturation and heart rate or ECG [8]. This simplified equipment is frequently used for clinical investigations and is mobile, so there is no need

for patient beds at the sleep clinic. These investigations are less expensive because the recordings take a shorter time to evaluate and the procedure of applying the sensors takes a shorter time than monitoring a full polysomnography. Sleep time is often estimated as recording time or time in bed. Patients can sleep at home in their own beds. It is important to have specially trained personnel to work with this equipment and to score the registrations manually. These recordings are best when it comes to detecting severe sleep apnea [9]. Polysomnography is better than simplified recordings, especially in research and in the evaluation of treatment, as the apnea-hypopnea index is based on actual sleep time and not on an estimate of sleep time. It also includes sleep quality in the form of sleep stages and sleep efficiency. Furthermore, it is also important to score arousals that can be another measurement of disturbed sleep. Arousals result in non- continuous or fragmented sleep and are also associated with daytime sleepiness [10].

As time has passed, more systems for automatically scoring sleep apnea and sleep stages have been established. Sleep stage scoring is often based on frequency spectra analysis, but this automatically scoring is not reliable in the same way as manual scoring. It is important that trained personnel re-analyse these scores and that a manual estimation is made of both sleep stages and sleep apneas. Comparisons between automatic portable scoring devices and polysomnography reveal high sensitivity but low specificity [11]. Automatic scoring, using simplified portable devices has difficulty differentiating obstructive apneas from central apneas. This equipment may also have different rules for detecting apneas and hypopneas. It is therefore important that each laboratory is aware of the different measurements and their consequences.

Obstructive sleep apnea

Obstructive sleep apnea occurs when there are frequent obstructions in the upper airways. It is characterized as breathing efforts during apnea. Obstructive sleep apnea is classified when there are more than 5 apneas and hypopneas per hour of sleep (apnea-hypopnea index >5). Obstructive sleep apnea syndrome is defined when excessive daytime sleepiness also occurs.

The prevalence of an apnea-hypopnea index of > 5 in the North-American population was found by Young et al. to be 24% in men and 9% in women. Duran et al. reported an apnea-hypopnea index of > 5 in 26% of men and 28 % of women, while Bixler et al. reported a frequency of 17% in men [12-14].

The tongue and soft palate obstruct the upper airway, especially when patients lie in the supine position. Risk factors include obesity with increased fat surrounding the pharynx, mandibular retrognathia and large tonsils [15].

Patients with obstructive sleep apnea run an increased risk of cardiovascular disease and early death [11, 16-24]. Peppard et al. found a dose-dependent relationship between baseline AHI and the presence of hypertension 4 years later [22]. Valham et al. recently reported an increased risk of stroke in patients with coronary artery disease who had sleep apnea [24]. Patients with an obstructive AHI of > 5 ran an increased risk of stroke or death in an observational cohort study where patients were followed for a mean of 3.4 years by Yaggi et al. [19].

Continuous positive airway pressure (CPAP) is the most successful treatment for obstructive sleep apnea [25]. CPAP applied through a mask over the nose prevents the tongue and soft palate obstructing the upper airway when patients breathe against positive airway pressure. Another treatment involves the use of a mandibular advancement device. A mandibular advancement device advances the mandible and prevents the tongue from obstructing the upper airway. Sweden has been a forerunner in the development of mandibular advancement devices [26-30].

Central sleep apnea

No efforts to breathe are made during central apneas. Central apneas occur most commonly during Cheyne-Stokes respiration. This is a breathing pattern with repetitive increases and then decreases in tidal volume followed by a central apnea [6, 31]. Cheyne-Stokes respiration with central apneas occurs in 40-50% of patients with congestive heart failure and in some stroke patients [32-34].

Oxygen, CPAP, BiPAP, adaptive servo ventilation, theophylline and azetazolamide reduce central apneas [32, 35-42]. There is, however, no established treatment modality, as there is a lack of evidence relating to the effect on symptoms, quality of life or mortality [43].

DIAGNOSTIC PROCEDURES

Polysomnography (Figure 1)

Polysomnography includes the continuous recording of electroencephalograms (EEG), electromyograms (EMG) and electro-oculograms (EOG) to score sleep stages, sleep time and arousals. Oro-nasal thermistors or nasal pressure cannulae are used for the detection of airflow. Respiratory efforts to differentiate between obstructive and central apneas are measured with abdominal and chest piezo-electric belts, or respiratory inductive plethysmography (RIP) or esophageal pressure. Oxygen desaturation is measured with a pulse oximeter. An electrocardiogram (ECG) and a body position sensor are also included.

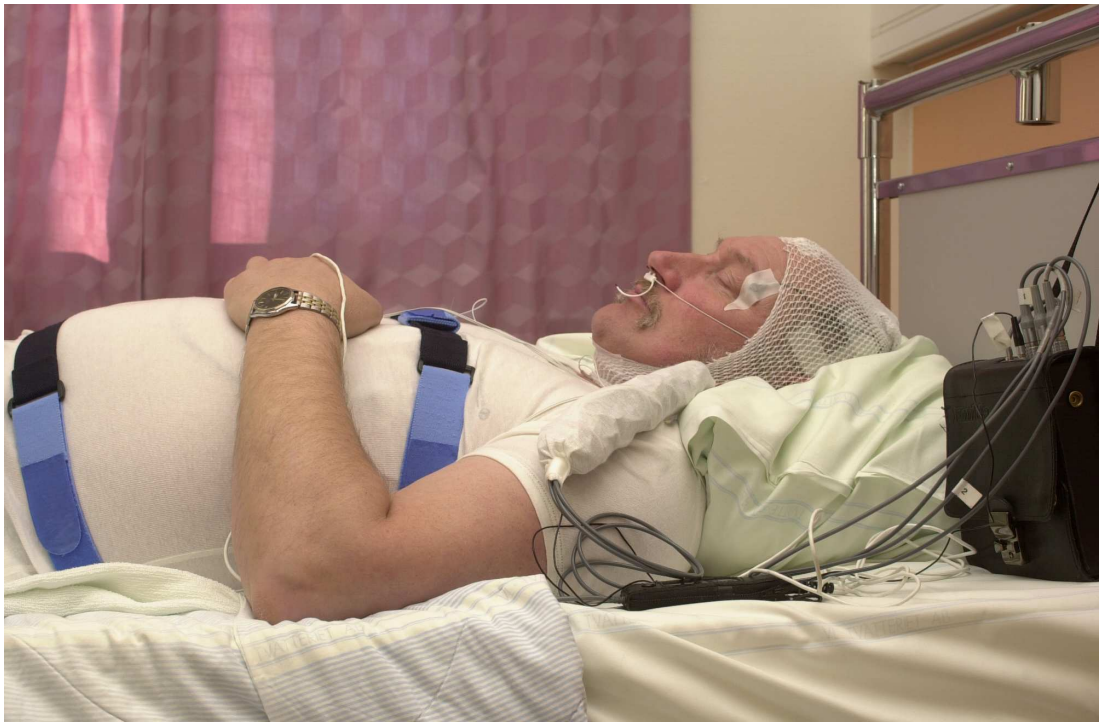

Figure 1. Polysomnography

Simplified sleep apnea recordings (Figure 2)
The exact sleep time cannot be determined, since no EEG has been recorded. Instead, sleep time is estimated from the respiratory patterns or as the recording time (time in bed). A number of different simplified sleep apnea recordings are available. So-called level 3 recordings are unattended devices that measure at least four cardio-respiratory parameters, including respiratory movements, airflow, oxygen saturation and heart rate or ECG [6].

Figure 2. Simplified sleep apnea recordings

Pneumotachograph (Figure 3)
This is an apparatus for recording the rate of airflow to and from the lungs. Pneumotachography is regarded as the golden standard for exact recordings of airflow. It measures the total volume of oro-nasal airflow using a snugly fitting mask and enables the quantitative measurement of airflow.

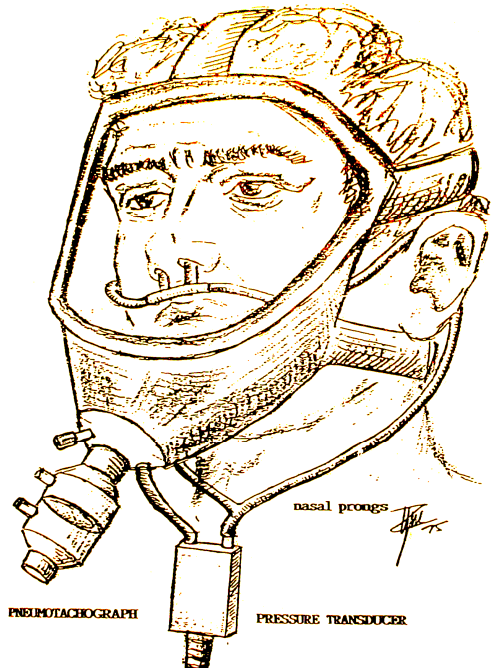

Figure 3. Pneumotachograph [44]

Oro-nasal thermistor (Figure 4)
An oro-nasal thermistor measures the temperature of inspired and expired airflow during respiration. The signals from thermal sensors are non-linearly related to actual airflow.

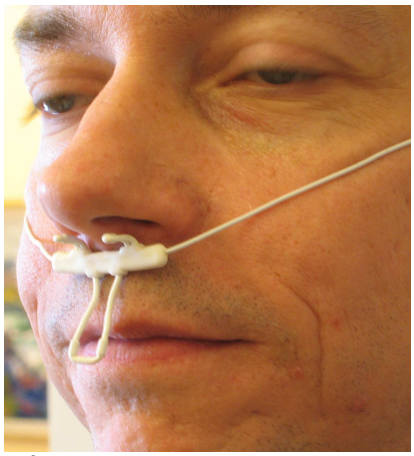
Figure 4. Oro-nasal thermistor

Nasal pressure cannula (Figure 5)
Nasal pressure cannulae measure changes in pressure in nasal airways. They are more accurate than thermistors when it comes to estimating airflow and changes in pressure are linear to airflow.
Many apneas and hypopneas are detected by nasal cannulae but are missed by thermistors. Norman et al. found that the nasal cannula detected 99% of events recorded by a thermistor, but the thermistor detected only 52% of events recorded by the nasal cannula[45].

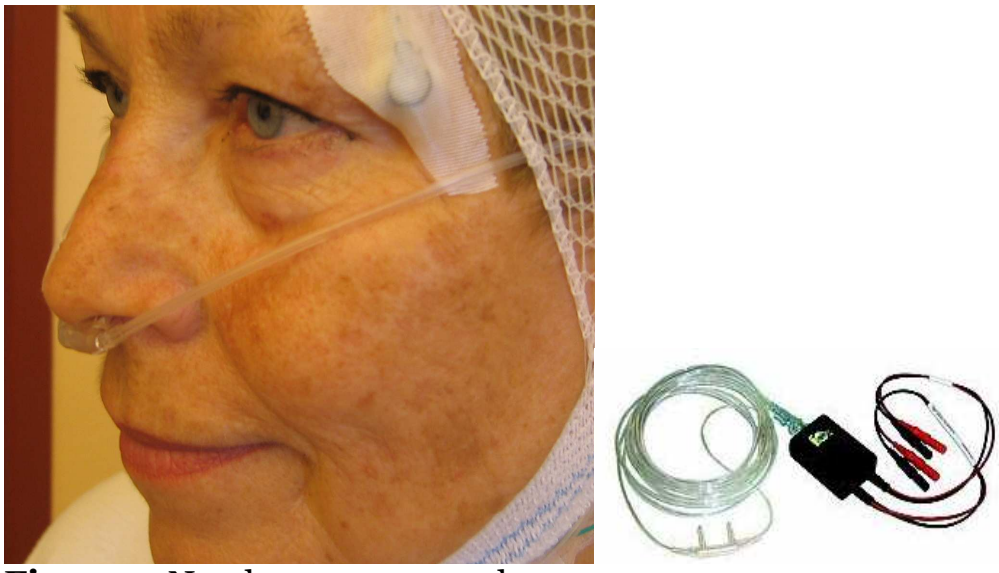

Figure 5. Nasal pressure cannula

Esophageal pressure catheter (Figure 6)
Esophageal pressure is the reference standard for measuring respiratory effort and differentiating between obstructive and central apneas [46].

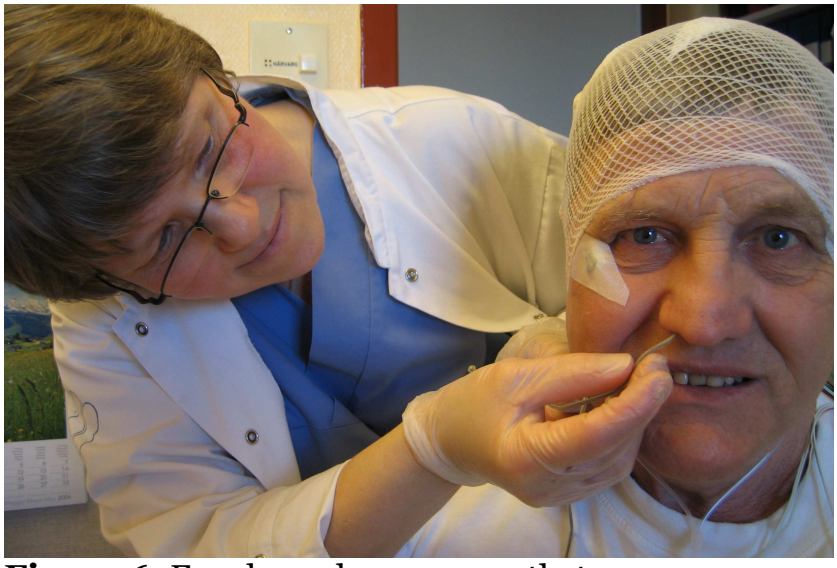

Figure 6. Esophageal pressure catheter

Piezo-electric belts for thorax and abdomen (Figure 7)
These belts are sensitive to changes in length. They provide only qualitative information on changes in ventilation or airflow.

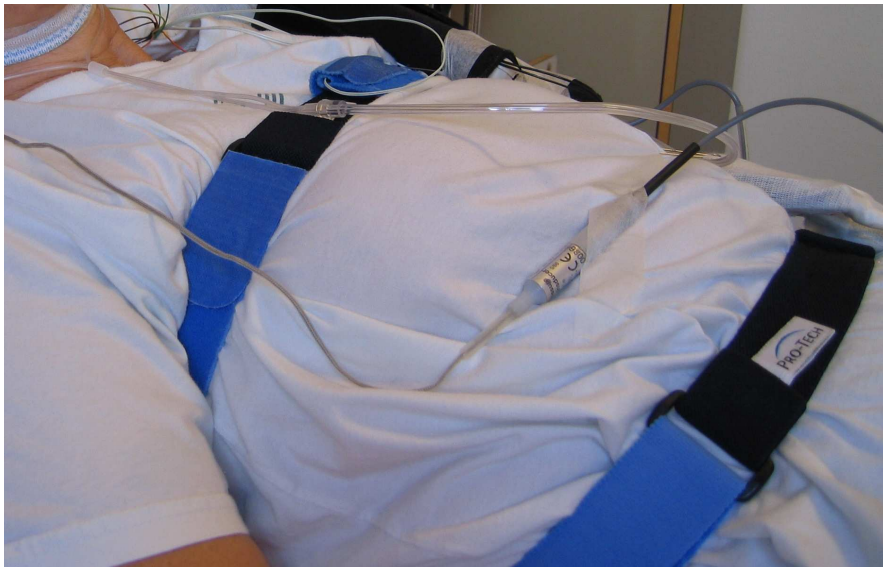

Figure 7. Piezo-electric belts thorax, abdomen

Induction plethysmography (Figure 8)
Induction plethysmography measures conductance around the complete circumference of the thorax and abdomen respectively. Changes in cross-sectional area proportional to airflow measured with pletysmography.

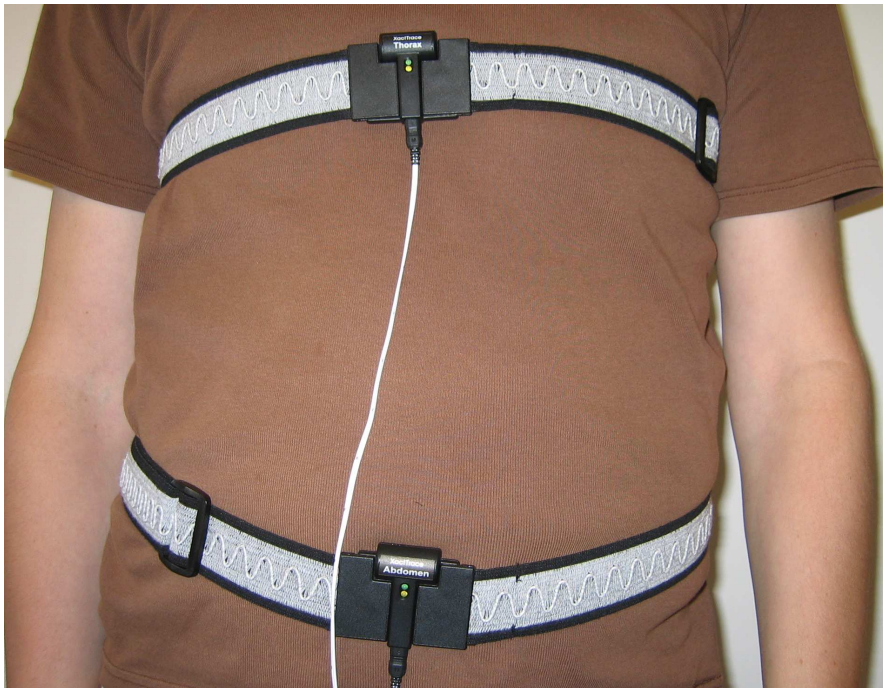

Figure 8. Induction plethysmography

Pulse oximetry (Figure 9)
The pulse oximeter determines arterial oxygen saturation and pulse by measuring the absorption of selected wavelengths of light. It can be attached to a finger or ear.

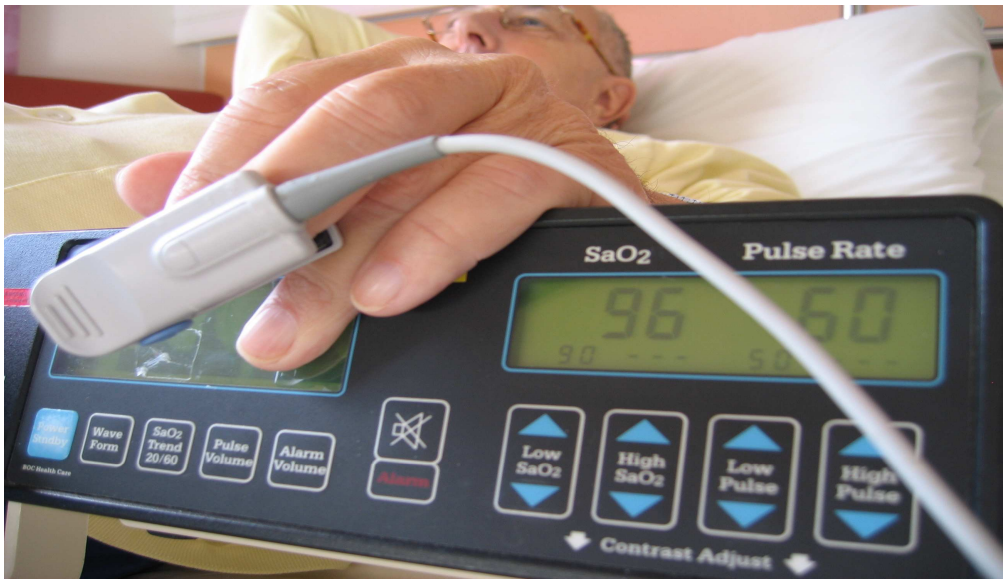

Figure 9. Pulse oximeter

Body position sensor (Figure 10)
Different body position sensors are available. One sensor generates output voltage levels corresponding to the following positions: supine, right, left and prone. The sensor can be attached to a thorax belt above the sternum.

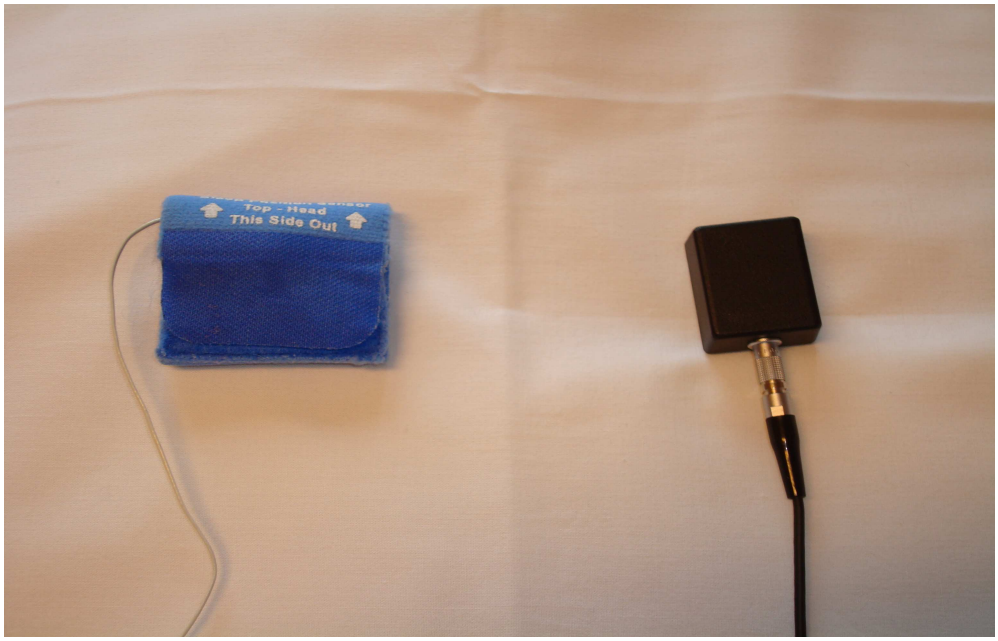

Figure 10. Body position sensors

SLEEP SCORING

Sleep is manually scored in 30-second epochs according to Rechtschaffen and Kales [5] using recordings of EEG, EOG and EMG. Sleep recordings are scored in five different stages; stage wake, stages 1, 2, 3-4 and REM. The stages are visualized in a hypnogram, shown in Figure 11, with REM marked in red.

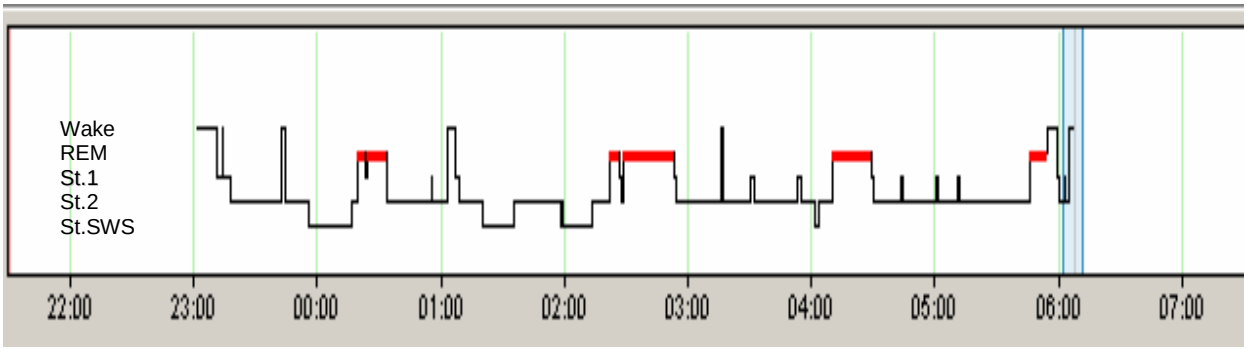

Figure 11. Hypnogram

Time in bed: Time from lights out till final wake up.
Sleep period: Time from sleep onset to final wake up.
Wake time after sleep onset (WASO): Wake time during the sleep period.
Total sleep time (TST): Time from sleep onset to final wake up minus WASO.
Sleep efficiency: TST divided by time in bed
Sleep latency: Time from lights off to first continuous three epochs of sleep.

Scoring rules for sleep stages according to Rechtshaffen and Kales and American Academy of Sleep Medicine [5].

Stage Wake (W) is characterized by alpha activity (8-14 Hz) and/or low voltage, mixed EEG frequency often with rapid eye movements and eye blinks. Score stage W, when more than 50% of the epoch has alpha rhythm (Figure 12).

Stage 1 is characterized by a mixed frequency of 4-7 Hz with slow eye movements and vertex sharp waves with duration of < 0.5 seconds. Score stage 1 when alpha rhythm is attenuated and replaced by low amplitude mixed frequency activity 4-7 Hz for more than 50% of the epoch (Figure 13).

Stage 2 is characterized by low amplitude, mixed frequency with presence of K-complex as a negative sharp wave immediately followed by a positive component standing out from the background with duration of ≥ 0.5 seconds. Another common sign is sleep spindles as a train of distinct waves with a frequency of 11-16 Hz with duration of ≥ 0.5 seconds.

Score stage 2 if the first half of the epoch or the last half of the pervious epoch consists of one or more K-complex with duration of ≥ 0.5 seconds or sleep spindles (Figure 14).

Stages 3-4 are characterized by waves of frequency of 0.5Hz-2 Hz and with peak- to- peak amplitude of > 75 μV. Eye movements typically do not occur during slow wave sleep. Score stages 3-4 when 20% or more of an epoch consists of slow wave activity (Figure 15).

Stage REM is characterized by relatively low voltage EEG and there are sharply peaked rapid eye movements. The EEG pattern looks like stage 1, but in stage REM there are distinctive "saw tooth" waves as trains of sharply contoured or triangular 2-6 Hz waves. The average chin EMG activity is no higher than in any other sleep stage and usually at the lowest of the entire recording, but there are also usually short bursts of increased EMG activity in conjunction with rapid eye movements (Figure16).

New scoring rules are published in the AASM manual for scoring sleep 2007[47]. Terminology for sleep stages is now recommended as stage N1, stage N2, stage N3 (old stage 3-4) and stage R.
N stands for NON REM**.** They recommend following three EEG derivations**:** F4-/M1; C4/M1; O2/M1 with backup derivations of F3/M2; C3/M2; O1/M2. Alternative derivations are Fz-Cz; Cz –Oz; C4-M1.

Scoring rules for EEG arousals [48] (Figures 17, 18)
The standard Rechtschaffen and Kales bipolar submental EMG, electro-oculograms (EOG) (LOC/ A1) (ROG/A2) and EEG obtained from C4/A1 or C3/A2 placements is recommended.

An EEG arousal is an abrupt shift in EEG frequency, which may include theta, alpha, and/or frequencies grater than 16 Hz but not spindles, subject to the following rules and conditions [48]:

1. Subjects must be asleep, defined as 10 continuous seconds or more of the indication as any stage of sleep, before an EEG arousal can be scored. Arousal scoring is independent of Rechtschaffen and Kales epoch scoring (i.e. an arousal can be scored in an epoch of recording, which would be classified as wake by Rechtschaffen and Kales Criteria).
2. A minimum of 10 continuous seconds of intervening sleep is necessary to score as an arousal
3. The EEG frequency shift must be 3 seconds or greater in duration to be scored as an arousal

4. Arousals in NREM sleep may occur without concurrent increase in submental EMG amplitude.
5. Arousals are scored in REM only when accompanied by concurrent increase in submental amplitude.
6. Arousals cannot be scored in submental EMG amplitude alone.
7. Artifacts, K complexes or delta waves ate not scored as arousals unless accompanied by an EEG frequency shift (as previous defined) in at least one previous derivation. If such activity precedes an EEG frequency shift, it is not included in reaching the 3 seconds criteria. When occurring within the EEG frequency shift, artifacts, or delta wave activities are included in meeting duration criteria.
8. The occurrence of pen blocking artifact should be considered as an arousal only if an EEG arousal pattern is contiguous. The pen blocking event can be included in reaching duration criteria.
9. Noncurrent, contiguous, EEG and EMG changes, which are individually less than 3 seconds in duration, but together greater than 3 seconds in duration, are not scored as arousals.
10. Intrusion of alpha activity of less than 3 seconds duration into NREM sleep at a rate greater than one burst per 10 seconds is not scored as an arousal. Three seconds of alpha sleep is not scored as an arousal unless a 10-second episode of alpha free sleep precedes.
11. Transitions from one stage of sleep to another are sufficient of themselves to be scored as an EEG arousal unless they meet the criteria indicated above.

New scoring rules for EEG arousals are published in the AASM manual for scoring sleep 2007[47].

1. **Scoring arousal**
   Score arousal during sleep stages N1, N2, N3 or R if there is an abrupt shift of EEG frequency including alpha, theta and/or frequencies greater than 16 Hz (but not spindles) that last at least 3 seconds, with at least 10 seconds of stable sleep preceding the change. Scoring of arousal during REM requires a concurrent increase in submental EMG lasting at least 1 second.

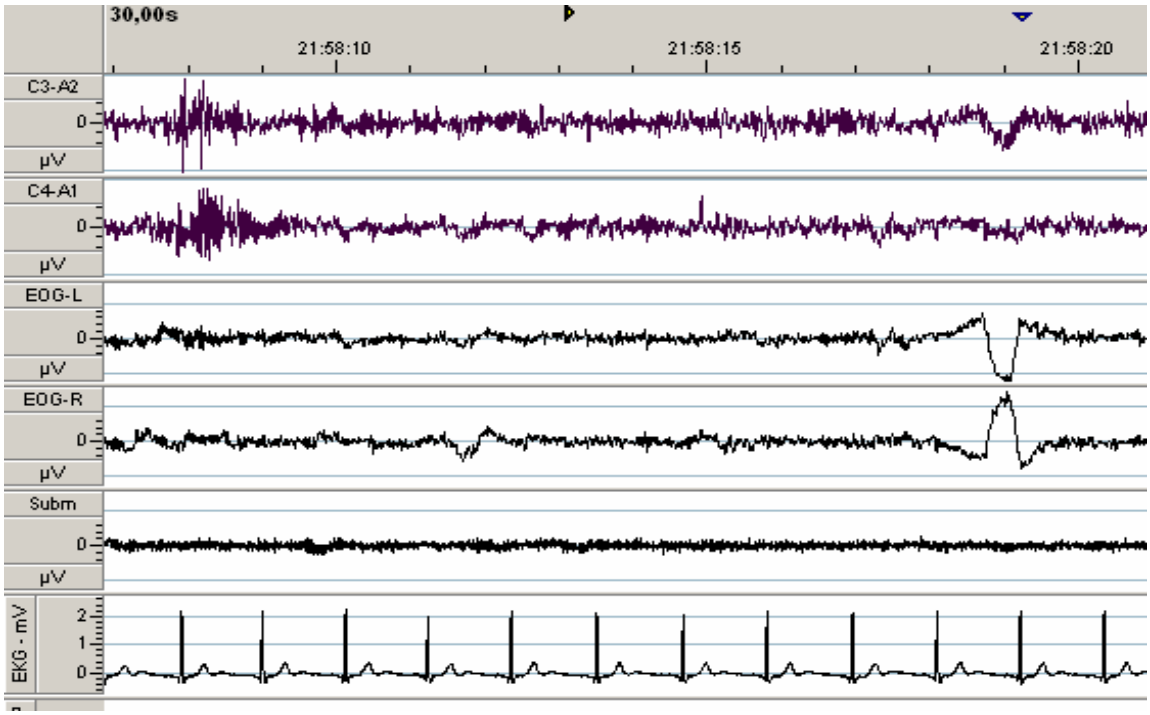

Figure 12. Stage wake. Recordings from above: EEG C3/A2, C4/A1, EOG-left, EOG-right, submental EMG and ECG (V5)

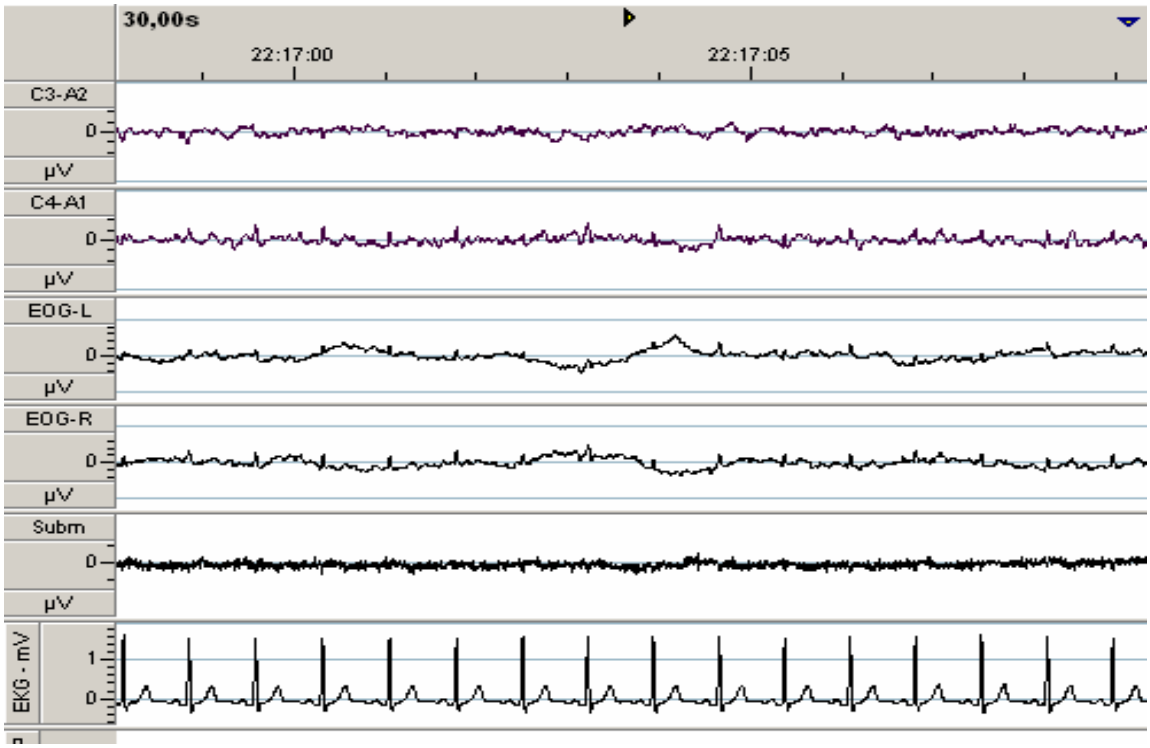

Figure 13. Stage 1. Recordings from above: EEG C3/A2, C4/A1, EOG-left, EOG-right, submental EMG and ECG (V5)

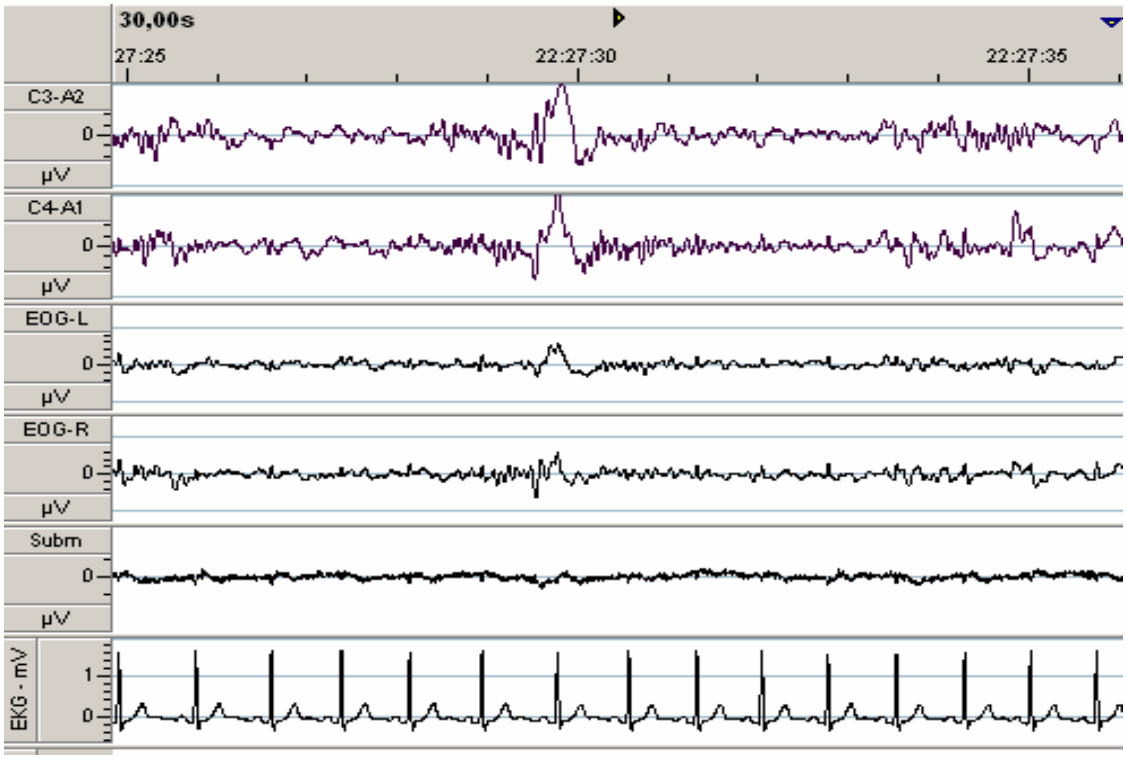

Figure 14. Stage 2. Recordings from above: EEG C3/A2, C4/A1, EOG-left, EOG-right, submental EMG and ECG (V5)

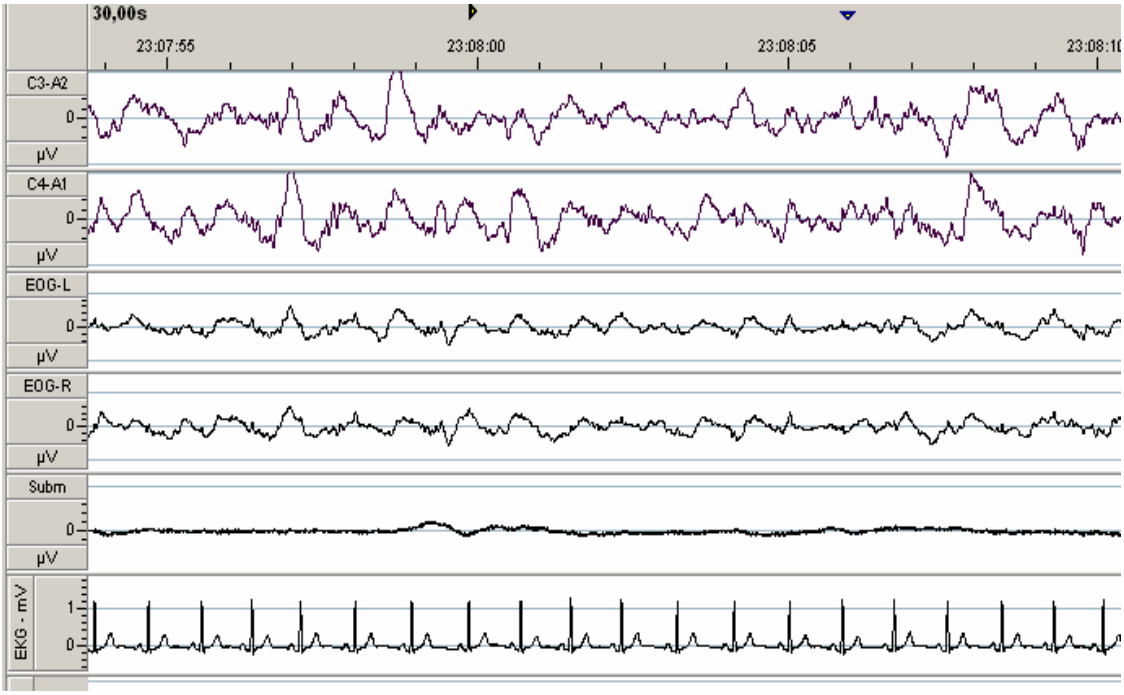

Figure 15. Stages 3-4. Recordings from above: EEG C3/A2, C4/A1, EOG- left, EOG- right, submental EMG and ECG (V5)

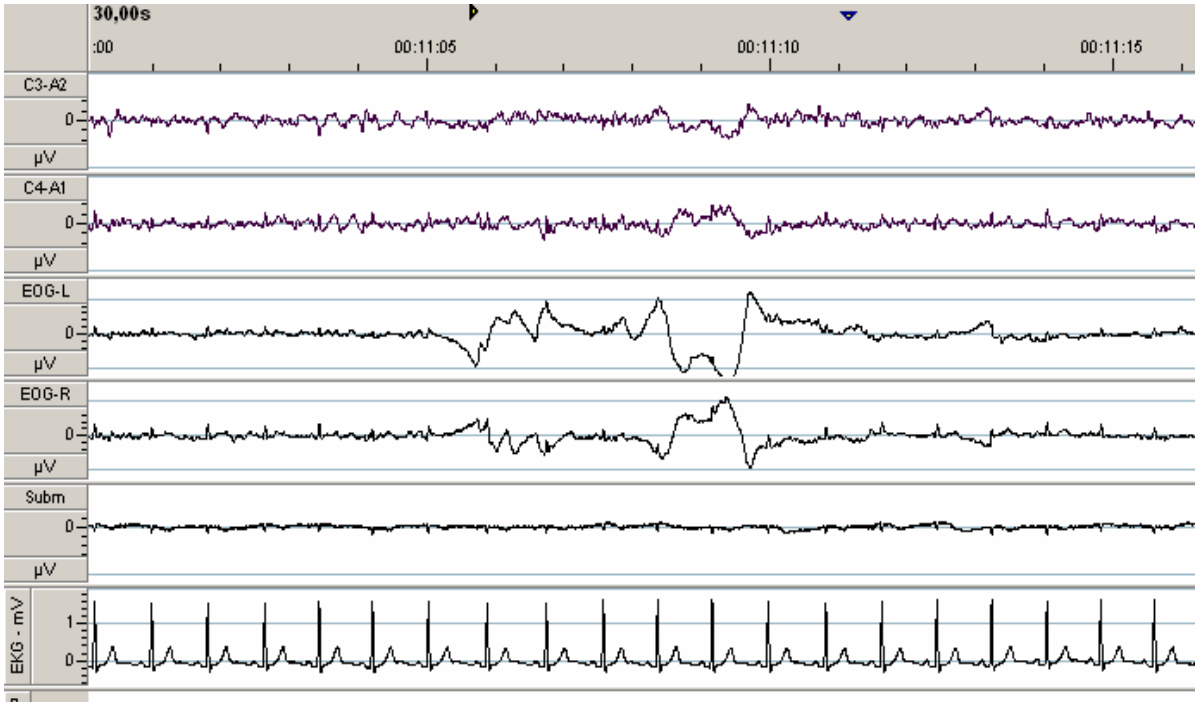

Figure 16. Stage REM. Recordings from above: EEG C3/A2, C4/A1, EOG-left, EOG-right, submental EMG and ECG (V5)

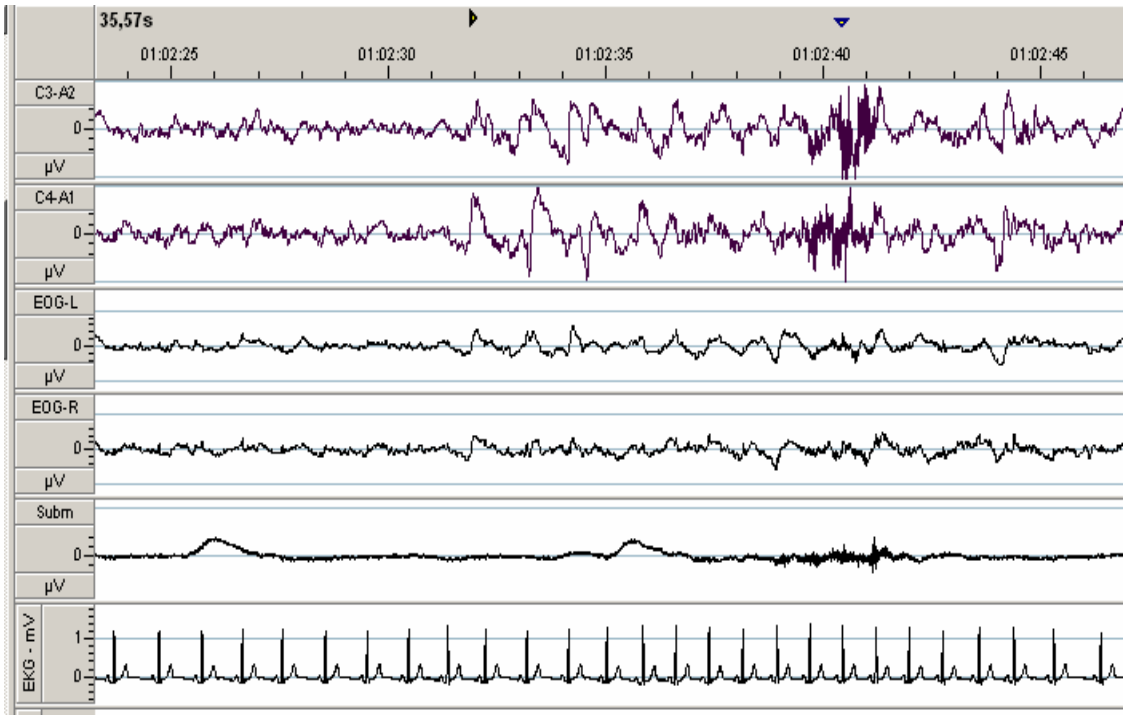

Figure 17. Arousal during sleep stages 3-4**.** Recordings from above: EEG C3/A2, C4/A1, EOG-left, EOG-right, submental EMG and ECG (V5)

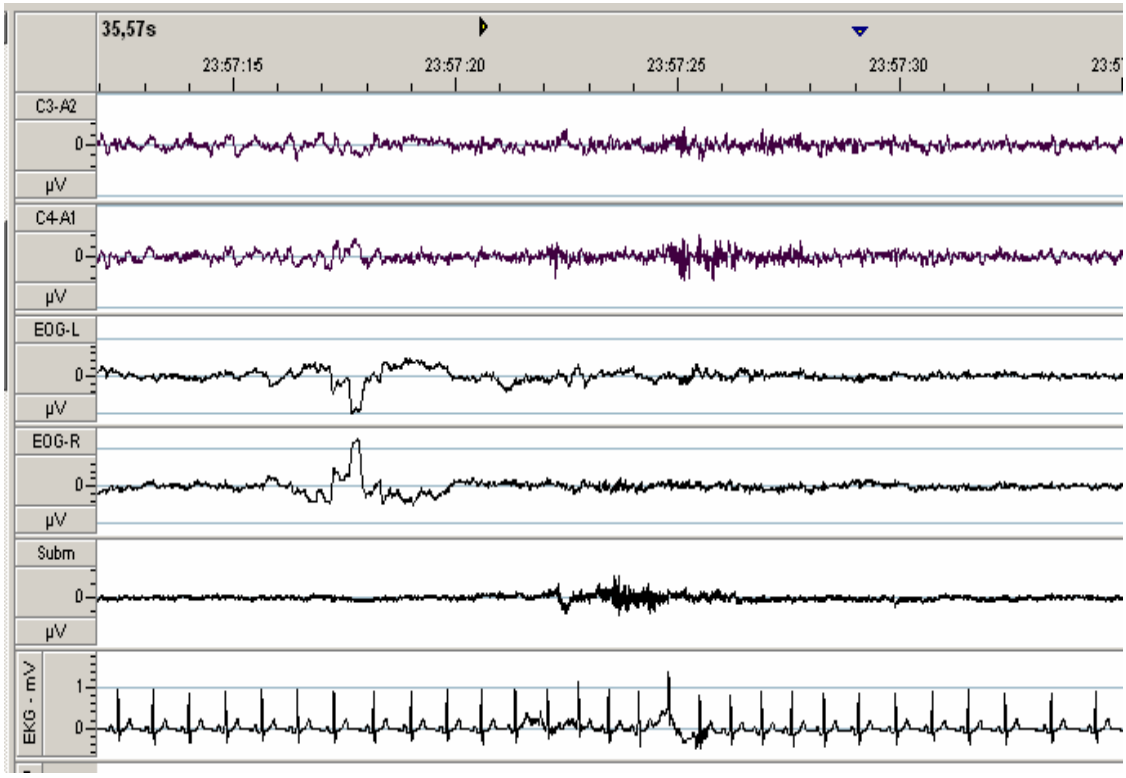

Figure 18. Arousal during REM sleep**.** Recordings from above: EEG C3/A2, C4/A1, EOG-left, EOG-right, submental EMG and ECG (V5)

DEFINITIONS OF AND DIAGNOSTIC CRITERIA FOR SLEEP APNEA

The following definitions and diagnostic criteria are derived from the American Academy of Sleep Medicine [6, 47]

Scoring of apneas [47]

Score an apnea when all of the following criteria are met:

1. There is a drop in the peak thermal sensor excursion by ≥ 90% of baseline.
2. The duration of the event lasts at least 10 seconds or longer.
3. At least 90% of the event´s duration meets the amplitude reduction criteria for apnea.

A. Classify an apnea in an adult based upon inspiratory effort:

1. Score a respiratory event as an obstructive apnea if it meats apnea criteria and is associated with continued or increased inspiratory effort throughout the entire period of absent airflow.
2. Score a respiratory event as a central apnea if it meats apnea criteria and is associated with absent inspiratory effort throughout the entire period of absent airflow.
3. Score a respiratory event as mixed apnea if it meats apnea criteria and is associated with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event.

Hypopnea rules [47]

Score a hypopnea if all of the following criteria are met.

1. The nasal pressure signal excursions (or those of the alternative hypopnea sensor) drop by ≥ 30 % of base line.
2. The duration of this drop occurs for a period lasting at least 10 seconds.
3. There is a > 4 % desaturation from pre-event baseline.
4. At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea.

Obstructive apnea/hypopnea event [6] (Figures 19, 20)

An obstructive event is characterized by a transient reduction, or a complete cessation of breathing. These events must fulfill criteria 1 or 2, plus criterion 3:

1. A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event.

2. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of 3% or an arousal.
3. The event lasts 10 seconds or longer.

Obstructive sleep apnea syndrome [6]

Obstructive sleep apnea syndrome (OSAS) is characterised by recurrent episodes of partial or complete upper airway obstructions during sleep. This manifests as a reduction (hypopnea) in or complete cessation (apnea) of airflow despite ongoing inspiratory efforts resulting in oxygen desaturations and arousals. Daytime symptoms such as excessive sleepiness are thought to be related to sleep disruption (repetitive arousals) and possibly to recurrent hypoxemia.

Diagnostic criteria

A person must fulfil criterion A or B, as well as criterion C:

A. Excessive daytime sleepiness that is not better explained by other factors
B. Two or more of the following that are not better explained by other factors:
   -choking or gasping during sleep,
   -recurrent awakenings from sleep,
   -unrefreshing sleep,
   -daytime fatigue,
   -impaired concentration
C. Overnight monitoring demonstrating five or more obstructive breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort-related arousals.

Severity criteria

Severity of the obstructive sleep apnea hypopnea syndrome has two components: severity of daytime sleepiness and overnight monitoring. A severity level should be specified for both components. The rating of severity for the syndrome should be based on the most severe component.

A. Sleepiness

1. Mild: Unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. Examples include sleepiness that is likely to occur while watching television, reading, or travelling as a passenger. Symptoms produce only minor impairment of social or occupational function.

2. Moderate: Unwanted sleepiness or involuntary sleep episodes during activities that require some attention. Examples include uncontrollable sleepiness that is likely to occur while attending activities such as concerts, meetings, or presentations. Symptoms produce moderate impairment or social or occupational function.
3. Severe: Unwanted sleepiness or involuntary sleep episodes during activities that require more active attention. Examples include uncontrollable sleepiness while eating, during conversation, walking, or driving. Symptoms produce marked impairment in social or occupational function.

B. Sleep related obstructive breathing events
1. Mild: 5 to 15 events per hour
2. Moderate: 15 to 30 events
3. Severe: more than 30 events per hour

Central apnea/hypopnea event [6] (Figures 21-23)
An event characterized by reduced or absent breathing and respiratory effort. These events must meet each of the following criteria:
1. Reduction in airflow
2. A clear reduction in esophageal swings from baseline. There is no relative or absolute reduction in esophageal pressure that can be used to distinguish central hypopneas from obstructive hypopneas. The reduction in esophageal pressure should parallel chronically to the reduction in airflow.
3. The events last 10 seconds or longer.

Cheyne-Stokes breathing rule [47] (Figures 21-23)
At least 3 consecutive cycles of cyclical crescendo and decrescendo change in breathing amplitude and at least one of the following:
1. Five or more central sleep apneas or hypopneas per hour of sleep.
2. The cyclic crescendo and decrescendo change in breathing amplitude has duration of at least 10 consecutive minutes.

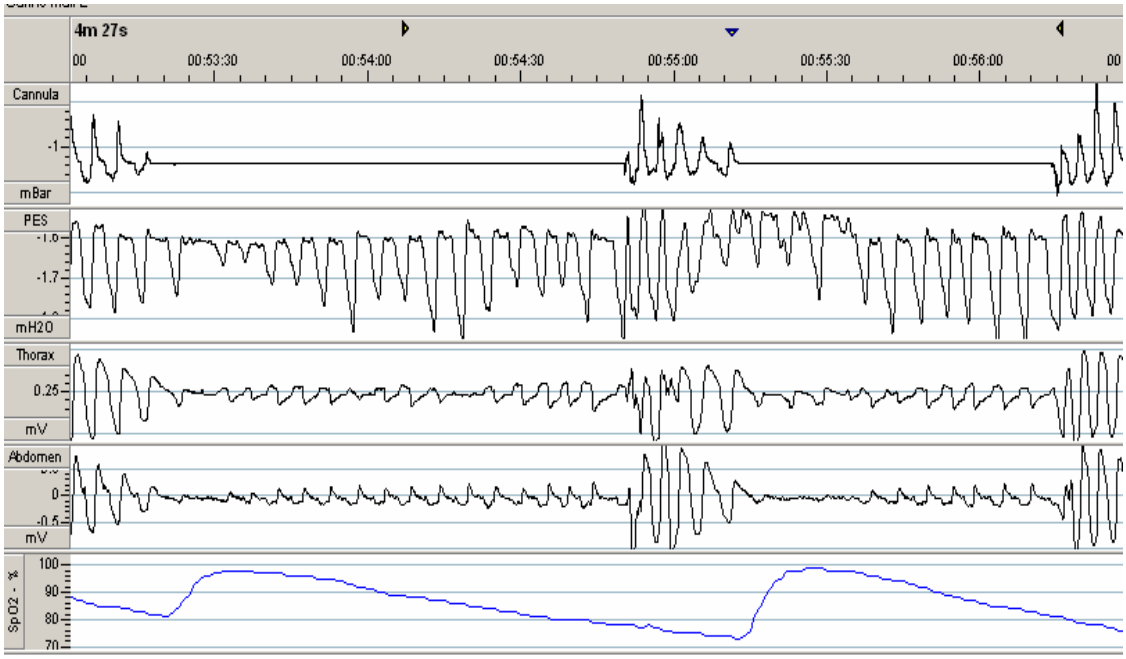

Figure 19. Obstructive apneas**.** Recordings of nasal airflow, esophageal pressure, thoracic movements, abdominal movements and SaO_2.

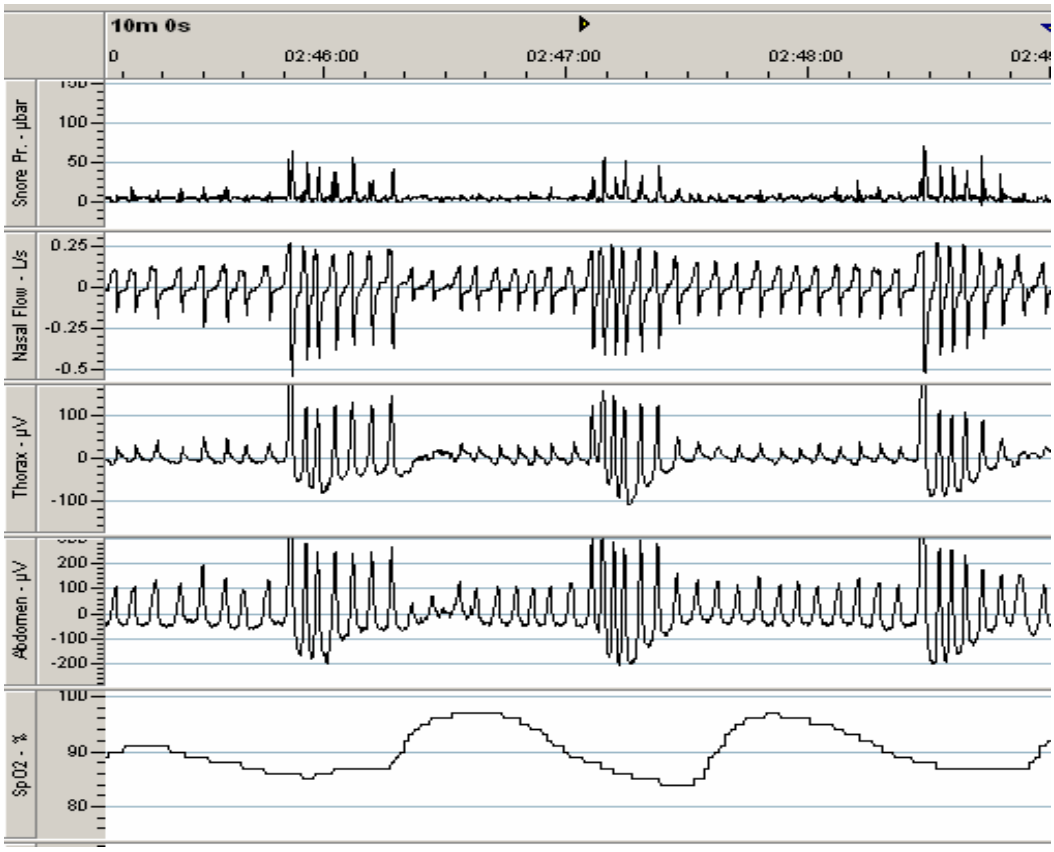

Figure 20. Obstructive hypopneas. Recordings from above: snoring, nasal airflow, thoracic movements, abdominal movements and SaO_2

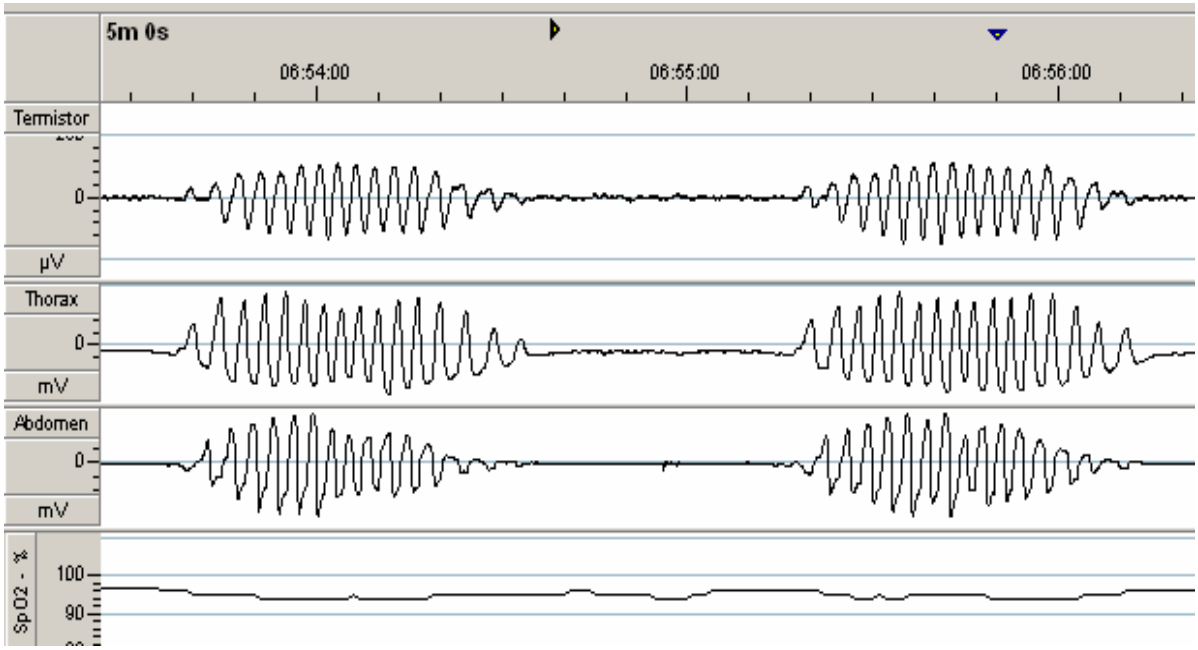

Figure 21. Central apneas during Cheyne-Stokes respiration. Recordings from above: nasal airflow, thoracic movements, abdominal movements and SaO_2

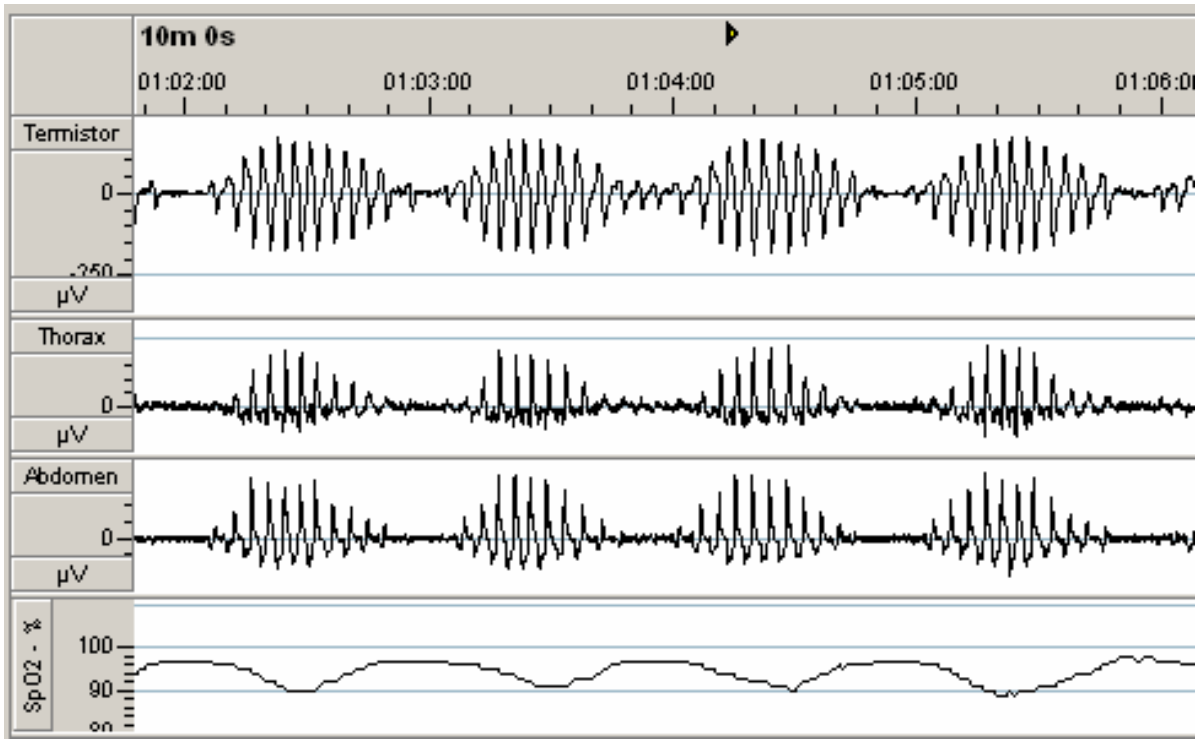

Figure 22. Central apneas during Cheyne-Stokes respiration. Recordings from above: nasal airflow, thoracic movements, abdominal movements and SaO_2

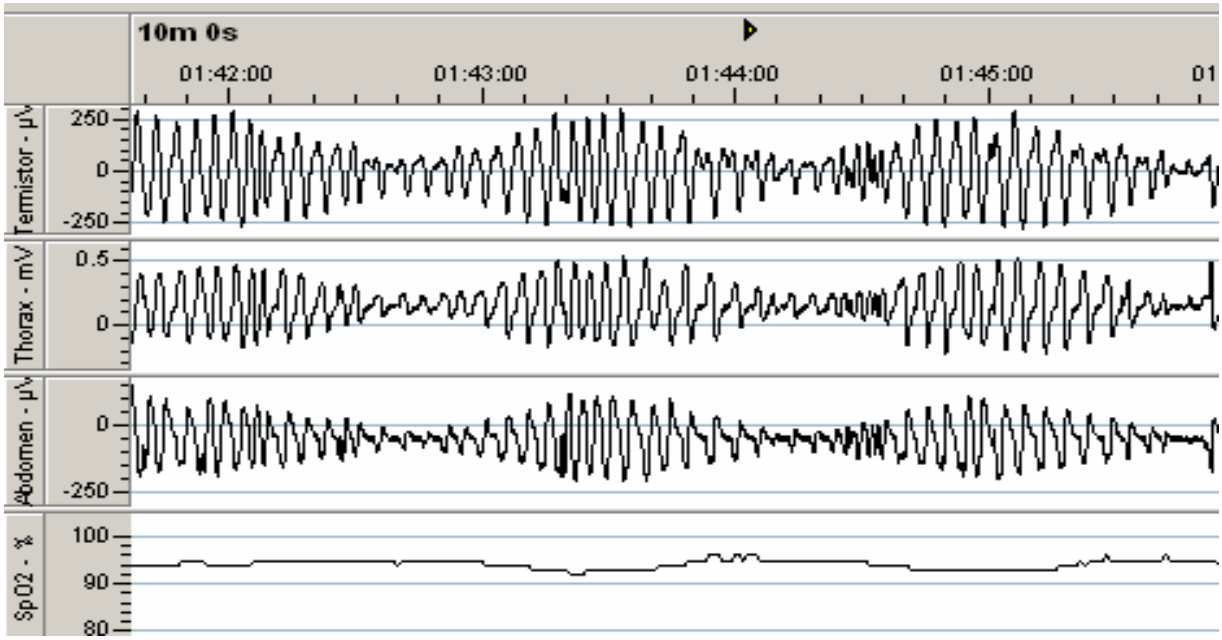

Figure 23. Central hypopneas during Cheyne-Stokes respiration. Recordings from above: nasal airflow, thoracic movements, abdominal movements and SaO_2

INTRODUCTION TO THE PRESENT STUDIES

Study 1 [26]

A mandibular advancement device advances the mandible and widens the upper airway. Previous studies report that the success rate with mandibular advancement devices is higher in people with moderate sleep apnea than in those with severe sleep apnea [49, 50]. There is still a lack of studies in which the effects of mandibular advancement devices on apneas in patients with mild, moderate and severe apneas have been analyzed.

Study II [51]

Many patients presenting with frequent central apneas suffer from congestive heart failure and Cheyne-Stokes respiration, with a typical waxing-and-waning breathing pattern followed by a central apnea [31, 32]. Central apneas and Cheyne-Stokes respiration are most frequent in sleep stages 1 and 2 [52, 53], but the influence of body position on central apneas and Cheyne-Stokes respiration has not previously been studied.

Study III [54]

Stroke is a serious and common disorder and a major cause of death worldwide. Risk factors for stroke include arterial hypertension, atrial fibrillation, diabetes mellitus, smoking and overweight. The secondary prevention of stroke includes smoking cessation, antihypertensive medication, lipid-lowering drugs and antithrombotic medication.

Sleep apnea in the form of obstructive apnea and central apnea occurs frequently among patients with stroke [34, 55-64]. Three previous studies investigated the impact of sleep apnea in patients with stroke and suggested that it was a negative prognostic factor, but none of them reported that a diagnosis of sleep apnea was independently associated with mortality [34, 59, 62]. These studies did not, however, differentiate between obstructive and central apneas.

Study IV [65]

A good night's sleep is dependent on a sufficient amount of deep sleep and sleep efficiency. Sleep efficiency, i.e. total sleep time divided by time in bed, should be more than 85% [66]. Age, overweight, sleep apnea, smoking, alcohol dependency and hypertension are known factors that affect sleep. However, the vast majority of previous studies have been performed on men and there are only a few studies that include a sufficient number of women [67-69]. There is a need for population-based studies presenting normal values for sleep stages in women. There are no studies of the normal values for sleeping positions.

AIMS

To study the effects of a mandibular advancement device on apneas and sleep in patients with mild, moderate and severe obstructive sleep apnea

To study the effect of body position and sleep stages on central apneas during Cheyne-Stokes respiration

To investigate whether obstructive or central sleep apnea is related to reduced long-term survival among patients with stroke

To define normal values for sleep in the form of sleep time, sleep efficiency, sleep stages and positions in women and to investigate how sleep is affected by age, obesity, sleep apnea, smoking, alcohol dependency and hypertension

SUBJECTS AND METHODS

Study design

Study I: Interventional study of patients with a mandibular advancement device
Study II: Cross-sectional study of patients with Cheyne-Stokes respiration
Study III: Cohort study of patients with stroke
Study IV: Cross-sectional, descriptive study in a population-based sample of women

Subjects

Study I. Forty-seven patients treated with a mandibular advancement device because of obstructive sleep apnea were invited to participate. Twenty-six patients were consecutive and only patients with an apnea-hypopnea index of $\geq$ 20 were subsequently included. Three patients refused to participate and 44 patients were evaluated during one night without treatment and one night with the mandibular advancement device.

Study II. This study comprised 20 patients with central sleep apnea (central apnea-hypopnea index >15, obstructive apnea-hypopnea index <5) and Cheyne-Stokes respiration, who slept for at least 20 minutes in the lateral and supine positions respectively during polysomnography.

Study III. The people eligible for this study were 151 consecutive patients admitted to the stroke rehabilitation unit from April 1, 1995 to May 1, 1997. Thirteen patients refused to participate and 138 were investigated a mean (SD) of 23 (8) days after the onset of stroke. Six patients were excluded because of failure in the sleep apnea recordings. A total of 132 patients were included in the analysis and they were followed up prospectively during a mean of 10.0 (0.6) years and no one was lost to follow-up.

Study IV. A postal questionnaire was sent to 10,000 randomly selected women, aged more than 20 years, from the general population in Uppsala, Sweden. The response rate was 70.5%. Full-night polysomnographic recordings were obtained in 400 women aged 20-70 years. They were randomly selected from responders in phase 1, with over-sampling of habitual snorers, and included 230 habitually snoring women and 170 women from the complete sample.

Ethical aspects

Approval for the studies was obtained from the Medical Ethics Committee at Umeå University (Studies I-III) and the Ethics Committee at the Medical Faculty at Uppsala University (Study IV). All patients gave their informed consent.

Gender aspects
Both men and women were included in Studies I-III. Only women were included in Study IV.

Polysomnography (Studies I, II, IV)
Overnight recordings of polysomnography including electroencephalograms (EEG), electromyograms (EMG), electro-oculograms (EOG), electrocardiograms (ECG), oro-nasal thermistors, nasal pressure cannulae (only Study IV), thoracic and abdominal piezo-electrical belts, body position sensors, snoring sensors (except Study 1) and pulse oximetry

Simplified sleep apnea recordings with sleep time estimated from the recordings (Study III)
Overnight recordings using oro-nasal thermistors, thoracic and abdominal piezo-electrical belts, pressure sensitive bed, body position sensors, snoring sensors and pulse oximetry

Definitions of sleep apnea (Studies I-IV)
Obstructive apnea: An apnea was defined as a cessation of airflow for at least 10 seconds with continued respiratory movements.

Obstructive hypopnea: A hypopnea was defined as a 50% reduction in the thermistor tracing compared with baseline, in combination with an arousal, a pulse alteration or an oxygen desaturation of 3% or more.

Central apnea: A central apnea was scored at the cessation of thoracic-abdominal movements for at least 10 seconds.

Central hypopnea: A central hypopnea was scored when thoracic-abdominal movements decreased parallel to airflow, with a 50% reduction in the thermistor tracing compared with baseline, in combination with an oxygen desaturation of 3% or more.

Cheyne-Stokes respiration: A regular waxing-and-waning breathing pattern followed by a central apnea or hypopnea. At least three consecutive cycles of cyclical crescendo and decrescendo change in breathing amplitude should be recorded.

Apnea-hypopnea index (AHI): Mean number of apneas and hypopneas per hour of sleep.

Vital status and dates of death (Study III)
Information on the dates and causes of death was obtained from the Causes of Death Register at the Swedish National Board of Health and Welfare.

Hypertension (Studies III, IV)
Hypertension was defined as a resting systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg or higher or a prior diagnosis of hypertension.

Stroke (Study III)
Stroke was defined according to World Health Organization recommendations as an acute neurological dysfunction of vascular origin with the rapid occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain for more than 24 hours, with no apparent cause of other vascular origin according to a computed tomographic scan of the brain [70].

Body mass index (Studies I-IV)
Body mass index was defined as the weight in kilograms divided by the square of the height in meters.

Alcohol dependency (Study IV)
Alcohol dependency was defined using the cut down, annoyed by criticism, guilt about drinking and eye-opener drinks questionnaire, CAGE: Study IV [71].

Snoring (Studies I, IV)
Study I. The effect of the mandibular advancement device on snoring was estimated by the bedroom partner according to a four-grade questionnaire "satisfactory effect", "slight effect", "no effect" or "worsened effect".
Study IV. A questionnaire with the following question was used: "How often do you snore loudly and disturbingly" with the following five alternative answers: "never", "seldom", "sometimes", "often" and "very often". Participants reporting loud and disturbing snoring "often" or "very often" were characterized as habitual snorers [72].

Smoking (Studies III, IV)
Current smoking was defined as smoking one or more cigarettes a day.

Mini-Mental State Examination (Study III)
The scores range from 0-30 points and a low score indicates cognitive impairment**.**

The Barthel Index of activities of daily living (Study III)
The scores range from 0-20 and a low score corresponds to a dependency on different activities of daily living.

Statistics
Study I
Wilcoxon's signed rank test was used for paired observations. Fisher's exact test was used to test associations in 2 by 2 tables. Spearmen's correlation coefficient was calculated to study the correlation between variables on at least ordinal scale. One-way analysis of variances was used to compare three or more means.

Study II
Wilcoxon's signed rank test was used to compare AHI in the supine and non-supine position. Friedman's test for related samples was used to compare AHI in different sleep stages (more than two).

Study III
Wilcoxon's signed rank test was used to compare AHI in different body positions. Cox's proportional hazards regression was used to analyze the impact of central and obstructive apneas with adjustments of confounders on the time to death from the onset of stroke. Survival curves were calculated using the Kaplan-Meier method and Cox's proportional hazards regression model.

Study IV
Analysis of variance ANOVA was used when comparing 3 or more means. An independent t-test was used when comparing two means. Linear regression was used to analyze the association between outcomes, sleep time, sleep efficiency, sleep stages and various predictors. Weighting was applied because the individuals were sampled with unequal probability due to the oversampling of snoring women.

In all the studies, the null hypothesis was rejected at a level of $p < 0.05$.

RESULTS

Study I [26]

The apnea-hypopnea index and arousal index were significantly reduced, while REM sleep increased with a mandibular advancement device (Figure 24) in patients with mild, moderate and severe sleep apnea. Sleep stages 3-4 were increased in patients with moderate and severe sleep apnea (Table 1).

A successful treatment result defined as a satisfactory reduction in snoring in combination with a decrease in the obstructive apnea-hypopnea index to < 10 during treatment was found in 81% of patients with mild sleep apnea, in 60% of patients with moderate sleep apnea and in 25% of patients with severe sleep apnea. Success defined as a satisfactory reduction in snoring in combination with a reduction in the obstructive apnea-hypopnea index of at least 50% was found in 48% of patients with mild sleep apnea, in 67% of patients with moderate sleep apnea and in 38% of patients with severe sleep apnea.

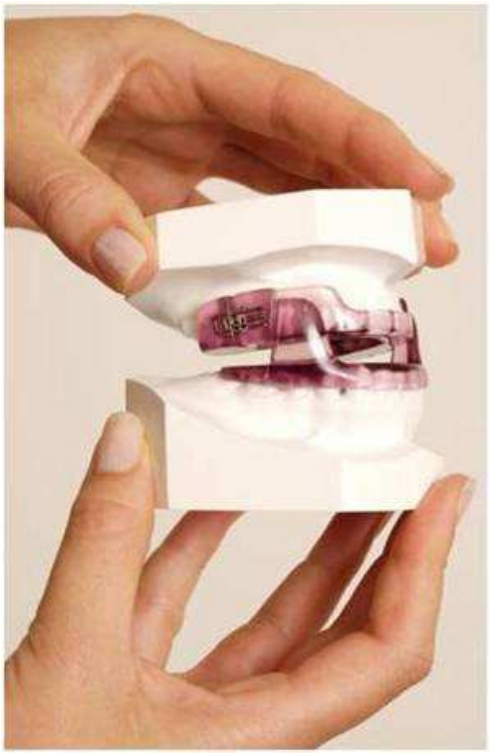

Figure 24. Mandibular advancement device

Table 1. The effect of a mandibular advancement device on sleep, apnea-hypopnea index and arousal index.

	Mild, AHI<20 n=21			**Moderate, AHI 20-40** n=15			**Severe, AHI ≥40** n=8		
	Without device	With device	p-value	Without device	With device	p-value	Without device	With device	p-value
AHI median	11	5.3	<0.001	27	7.2	<0.001	53	14	0.01
TST	426	410	0.79	410	414	<0.001	418	429	0.89
SE %	87	88	0.87	85	88	0.07	88	92	0.26
Supine %	25	41	0.04	28	34	0.12	36	39	0.61
St 1 %	22	19	0.002	29	18	0.001	29	24	0.07
St 2 %	51	50	0.99	46	52	0.14	56	47	0.05
St 3, 4 %	7.3	8.6	0.37	5.8	7.2	0.004	0.2	8.8	0.01
REM %	15	21	0.005	16	21	0.02	14	20	0.01
Arousal index	13	8.5	<0.001	23	10	0.002	34	16	0.01

AHI=obstructive apnea/hypopnea index, TST=total sleep time, SE=sleep efficiency, REM=rapid eye movement, St=stage

Study II [51]

The central AHI was higher in the supine position compared with non-supine positions in 17 of 20 patients. The mean central AHI was 41 ± 13 in the supine position and 26 ± 12 in non-supine positions (p<0.001) (Figure 25). The central AHI was 28 ± 17 while sleeping on the left side and 25 ± 17 on the right side and both were lower than the AHI in the supine position (p<0.001). In every sleep stage, central apneas and hypopneas were more prevalent in the supine position compared with lateral positions (Table 2). Sleep quality was better in the non-supine position, while the amount of stage 1 sleep decreased and the amount of REM sleep and stage 3-4 sleep increased (Table 3).

Central sleep apneas were more frequent in sleep stages 1 and 2 compared with sleep stages 3-4 and REM (p<0.001).

Table 2. Central apnea-hypopnea index at different sleep stages and in different positions.

	REM	**Stage 1**	**Stage 2**	**Stages 3-4**	**p-value**
Supine AHI	28±30	43±15	37±18	23±41	0.007
Non-supine AHI	7±12	32±19	30±17	12±19	<0.001
p-value	0.01	0.04	0.40	1.0	

Data are presented as mean ± SD. REM=rapid eye movement

Table 3. Sleep stages as a percentage of total sleep time, in the supine and non-supine position.

	REM %	**Stage 1 %**	**Stage 2 %**	**Stages 3-4 %**
Supine	8.4±8.6	51±26	38±21	2.0±5.5
Non-supine	15±9.4	33±21	45±17	6.8±5.9
p-value	0.031	0.001	0.150	0.010

Data are presented as mean ± SD. REM=rapid eye movement

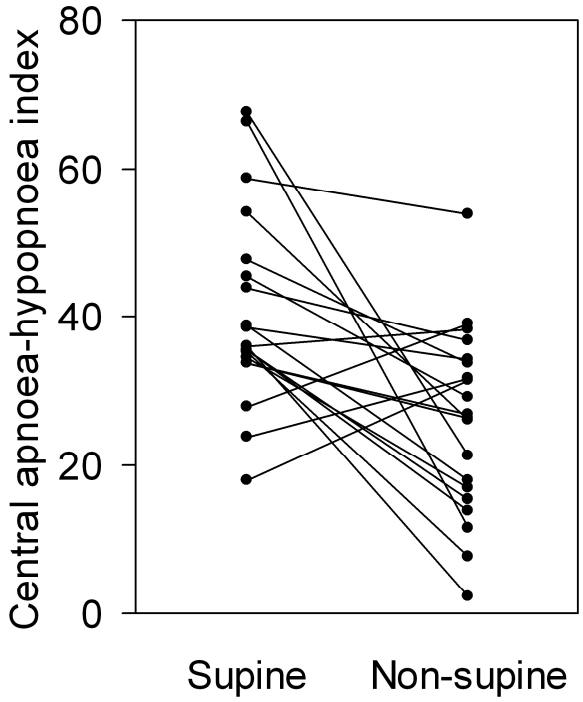

Figure 25. The mean central AHI was 41 ± 13 in the supine position and 26 ± 12 in non-supine positions (p<0.001), from Sahlin et al. [51].

Study III [54]

Twenty-three patients (17%) had predominantly obstructive sleep apnea, while 28 patients (21%) had central sleep apnea during Cheyne-Stokes respiration. Two patients had both central and obstructive sleep apnea in equal amounts and they were excluded from further analysis. Seventy-nine patients had central and obstructive apnea-hypopnea indices of less than 15 and they served as controls. Both obstructive and central apneas were more prevalent in the supine position compared with non-supine positions (p<0.001) Table 4.

At follow-up after 10 (0.6) years, 116 of 132 patients (88%) had died. The causes of death were regarded as cardiovascular in 74%, cancer in 10%, other causes in 14% and unknown in 2%.

Obstructive sleep apnea was related to an increased risk of death in multivariate analysis (adjusted hazard ratio, 1.76; 95% confidence interval, 1.05-2.95; p =0.03), independent of age, gender, body mass index, current smoking, hypertension, diabetes mellitus, atrial fibrillation, Mini-Mental State Examination score and Barthel Index of activities of daily living (Table 5, Figure 26). Moreover, age and a low Mini-Mental State Examination score remained as significant risks of death after adjustment for confounders.

Central sleep apnea was not associated with any increased risk of death (p = 0.80).

Table 4. Mean AHI in patients with central sleep apnea and obstructive sleep apnea.

Patients	**Supine AHI**	**Non-supine AHI**	**p-value**
Central apnea	40±13	18± 20	<0.001
Obstructive apnea	35± 7	9±18	<0.001

Table 5. Unadjusted and adjusted hazard ratios for the risk of death from any cause.

	Unadjusted hazard ratio (95% CI)	**Adjusted hazard ratio (95% CI)**
Controls (O-AHI <15, C-AHI) <15)	1	1
Obstructive sleep apnea (O-AHI ≥15)	1.76 (1.08-2.86)*	1.76 (1.05-2.95)*
Central sleep apnea (C-AHI ≥15)	1.57 (0.99-2.48)	1.07 (0.65-1.76)
Male gender	1	1
Female gender	1.00 (0.69-1.45)	0.84 (0.57-1.24)
Non-smoker	1	1
Current smoker	0.73 (0.32-1.65)	0.74 (0.31-1.74)
No hypertension	1	1
Hypertension	0.89 (0.61-1.30)	1.01 (0.66-1.55)
No diabetes mellitus	1	1
Diabetes mellitus	1.07 (0.73-1.58)	1.16 (0.75-1.80)
No atrial fibrillation	1	1
Atrial fibrillation	2.07 (1.40-3.04)*	1.42 (0.91-2.19)
Age (increase in 8 years)	1.88 (1.51-2.35)*	1.78(1.40-2.25)*
Body mass index (increase in 4 kg/m^2)	0.81 (0.67-0.96)*	0.90 (0.74-1.09)
Mini-Mental State Examination (increase in 8 units)	0.64 (0.53-0.76)*	0.79 (0.63-0.99)*
Barthel activity of daily living (increase in 7 units)	0.78 (0.65-0.95)*	0.79 (0.61-1.00)

CI=confidence interval, O-AHI=obstructive apnea-hypopnea index, C-AHI=central apnea-hypopnea index

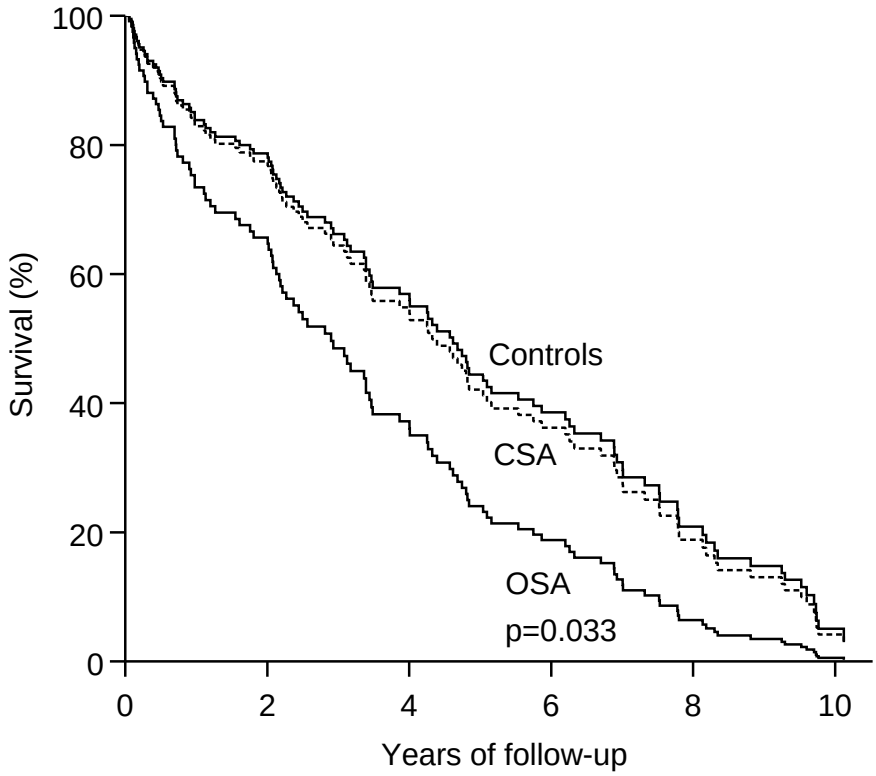

Figure 26. Survival curves calculated from a Cox proportional hazards regression model after adjustments for age, gender, body mass index, current smoking, hypertension, diabetes mellitus, atrial fibrillation, Mini-Mental State Examination score and Barthel Index of activities of daily living, from Sahlin et al. [54].

Study IV [65]

The participating women had a weighted mean age (95% confidence interval) of 48 (46-49) years, a BMI of 25 (25-26) kg/m^2 and an AHI of 8.9 (7.8-10). Hypertension was found in 15% (11-18) of women, current smoking in 16% (13-20) and alcohol dependency in 5.6% (3.0-8.0). Normal values for sleep stages and positions are given in Table 6.

Univariate analyses of sleep in relation to age and AHI are presented in Tables 6 and 7 and Figure 27. Older women spent significantly more time sleeping in the lateral position and less in the supine position. Body position was almost unaffected by the severity of sleep apnea, smoking, alcohol dependency and hypertension.

Multivariate analysis included adjustments for age, BMI, AHI, smoking, alcohol and hypertension.

Age was independently related to a reduced amount of total sleep time, sleep efficiency, stage 3-4 and REM sleep and an increased amount of stage 1 sleep and wake after sleep onset. Body mass index was independently related to a reduced amount of stage 3-4 sleep.

An AHI of more than 30 was independently related to an increased amount of stage 1 sleep and total sleep time and shorter sleep latency.

Smoking women had longer sleep latency, more stage 1 sleep and less wake after sleep onset compared with non-smokers in the multivariate analysis. Alcohol-dependent women had longer sleep latency and a reduced amount of REM sleep. Women with hypertension had long sleep latency, a short total sleep time, low sleep efficiency and a reduced amount of stage 2 sleep compared with non-hypertensive women.

Women on hormone replacement therapy aged 55 and more had less stage 3-4 sleep than women without such therapy ($p<0.001$).

Table 6. Age and sleep in women.

	20-44 years	45-54 years	55-70 years	p-value
TIB (min)	476 (468-485)	473 (465-480)	482 (473-491)	0.333
TST (min)	409 (399-420)	399 (390-408)	364 (350-378)*	<0.001
Sleep latency (min)	22 (18-26)	20 (17-23)	25 (19-31)	0.283
REM latency (min)	112 (97-127)	104 (94-115)	140 (124-157)*	0.002
SE (%)	86 (84-88)	85 (83-86)	76 (73-79)*	<0.001
Stage 1 (min)	27 (25-30)	32 (29-36)	35 (30-39)*	0.004
(% of TST)	6.8 (6.1-7.4)	8.3 (7.4-9.2)*	9.7 (8.5-11)*	<0.001
Stage 2 (min)	251 (244-258)	249 (242-257)	232 (221-243)*	0.003
(% of TST)	62 (61-63)	63 (61-64)	64 (62-65)	0.214
Stage 3-4 (min)	45 (42-49)	40 (36-44)	35 (31-39)*	0.001
(% of TST)	11(10-12)	10 (8.9-11)	9.9 (8.8-11)	0.306
REM (min)	86 (82-91)	77 (73-80)*	63 (58-68)*	<0.001
(% TST)	21 (20-21)	19 (18-20)	17 (16-18)*	0.001
WASO (min)	45 (39-51)	54 (48-60)	92 (81-103)*	<0.001
Supine (%)	48 (44-52)	36 (32-39)*	37 (32-42)*	<0.001
Left (%)	20 (17-23)	26 (23-30)*	26 (22-29)*	0.005
Right (%)	21 (18-23)	31 (27-35)*	30 (26-34)*	<0.001
Prone (%)	11 (7.5-14)	7 (4.9-9.4)	7 (5.6-9.5)	0.118

Values are presented as the weighted mean (95% confidence interval), TIB = time in bed, TST = total sleep time, SE = sleep efficiency, REM = rapid eye movement, WASO = wake after sleep onset, min = minutes. * $p<0.05$ compared with age 20-44 years, using Dunnett's test in post-hoc analysis

Figure 27.

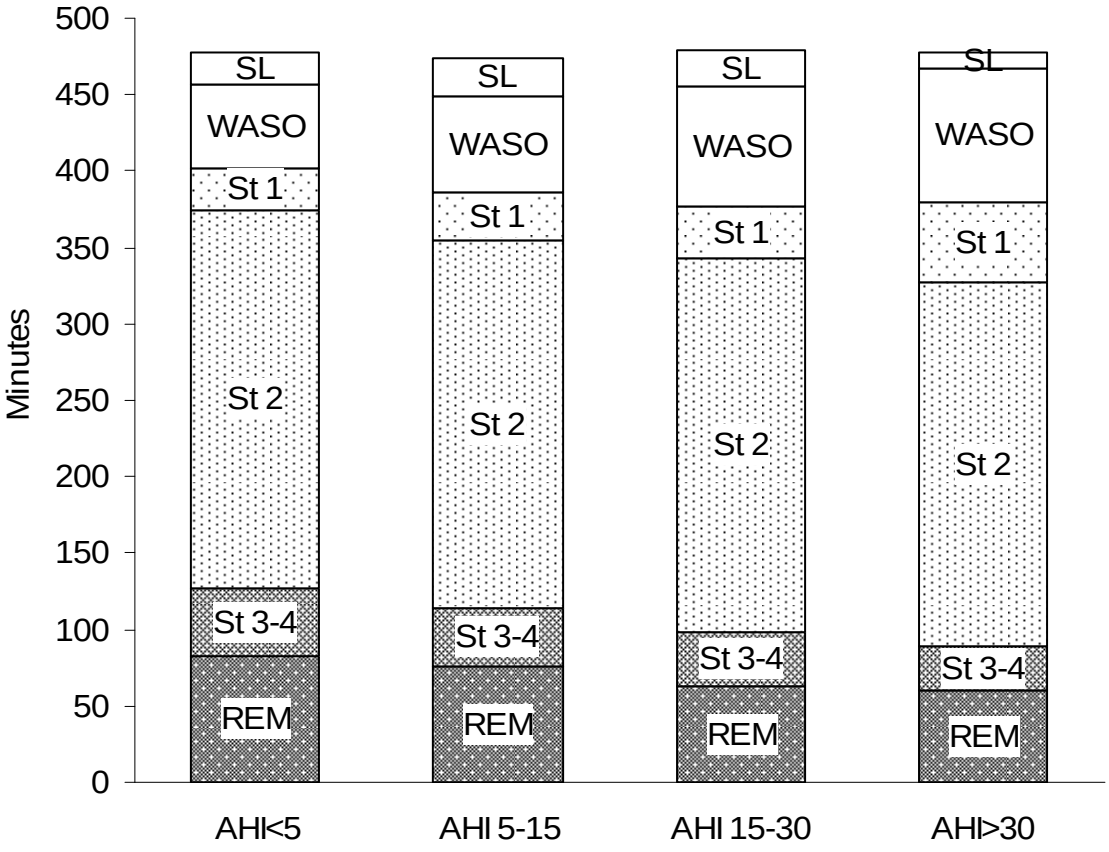

Figure 27. Sleep in relation to the apnea-hypopnea index (AHI). SL = sleep latency, WASO = wake after sleep onset, St = stage, REM = rapid eye movement

Table 7. Severity of the apnea-hypopnea index (AHI) and sleep in women.

	AHI < 5	AHI 5-15	AHI > 15-30	AHI > 30	p-value
TIB (min)	476 (469-483)	473 (463-478)	486 (473-498)	478 (459-498)	0.495
TST (min)	401 (393-411)	387 (373-400)	377 (360-395)	375 (341-409)	0.037
Sleep latency (min)	21 (17-24)	24 (20-28)	29 (18-39)	11 (5.0-17)	0.027
REM latency (min)	105 (94-115)	121 (104-137)	151 (125-177)*	156 (117-194)*	<0.001
SE (%)	84 (83-86)	82 (79-85)	78 (75-82)*	79 (79-85)	0.005
Stage 1 (min)	28 (27-30)	32 (28-35)	34 (29-39)	52 (36-68)*	<0.001
(% of TST)	7.0 (6.5-7.6)	8.7 (7.6-9.8)	9.0 (7.5-11)*	13 (9.6-17)*	<0.001
Stage 2 (min)	247 (240-253)	241 (231-251)	246 (232-259)	238 (207-270)	0.745
(% of TST)	62 (61-63)	62 (61-64)	65 (63-68)*	63 (58-68)	0.020
Stage 3-4 (min)	45 (42-48)	38 (34-43)*	34 (29-39)*	29 (20-38)*	<0.001
(% of TST)	11 (10-12)	9.9 (8.8-11)	9.1 (7.9-10)	8.1 (5.2-11)*	0.013
REM (min)	81 (78-85)	75 (70-80)	63 (56-71)*	60 (46-74)*	<0.001
(% of TST)	20 (19-21)	19 (18-20)	16 (15-18)*	16 (13-19)*	<0.001
WASO (min)	54 (49-60)	63 (52-73)	79 (64-94)*	87 (63-111)*	0.001
Supine (%)	41 (37-44)	38 (34-43)	44 (35-52)	47 (34-60)	0.382
Left (%)	21 (19-24)	29 (25-32)*	23 (17-29)	20 (13-28)	0.014
Right (%)	27 (24-30)	27 (24-30)	25 (20-31)	28 (17-39)	0.956
Prone (%)	10 (7.7-13)	6.5 (4.3-8.9)	8.9 (5.4-13)	4.5 (1.7-7.2)	0.107

Values are presented as the weighted mean (95% confidence interval), TIB = time in bed, TST = total sleep time, SE = sleep efficiency, REM = rapid eye movement, WASO = wake after sleep onset, min = minutes. * $p<0.05$ compared with AHI <5, using Dunnett's test in post-hoc analysis

DISCUSSION

Study I [26]

In the present study, we examined patients with mild, moderate and severe sleep apnea and found that treatment with a mandibular advancement device had an effect on sleep stages and arousals in all three categories. The amount of REM sleep increased after treatment in patients with mild, moderate and severe sleep apnea. Stage 3-4 sleep increased in those with moderate and severe sleep apnea. Polysomnography including EEG, EOG and EMG is necessary in order to record these changes.

Our results confirm those of O'Sullivan et al. who reported that mandibular advancement devices are more effective in the treatment of patients with an apnea-hypopnea index between 20-60 than in those with an apnea-hypopnea index above 60 [50]. Treatment using mandibular advancement devices has become very common in both Sweden and in other countries after this study was published. There have been a number of treatment trials showing evidence of the effect of mandibular advancement on apneas and daytime sleepiness [11]. Tegelberg et al. reported that mandibular advancement devices are successful in patients with mild to moderate obstructive sleep apnea [29, 30]. Walker-Engström et al. made a follow-up of treatment with dental appliances in patients with mild-moderate obstructive sleep apnea both after one year and after 4 years and concluded that dental appliances can be recommended for long-term treatment in these patients [73, 74]. Marklund et al. report that the reduction of the apnea-hypopnea index using a mandibular advancement device is successful in patients with mild sleep apnea but even more successful in patients with supine-dependent sleep apnea [26-28]. It is, however, important to perform sleep apnea recordings during treatment with mandibular advancement devices, as therapy is not successful in all patients [26].

Study II [51]

This is the first study investigating supine dependency in central apneas. It has previously been stated that obstructive apneas/hypopneas are more prevalent in the supine position [75, 76]. We found that central apneas in Cheyne-Stokes respiration were supine dependent. This has since been verified by Szollosi et al. [77].

Central apneas and Cheyne-Stokes respiration occur in patients with congestive heart failure, but the mechanisms are mainly unknown. This is an entirely descriptive study and we cannot explain the mechanisms behind our findings with supine dependency in central apneas. It is important to use body

position sensors in sleep apnea recordings as both obstructive and central apneas are more prevalent in the supine position.

Stroke victims often have both obstructive and central apneas and they are more prevalent in the supine position (Study III). It is of interest to study whether the avoidance of the supine position affects outcome in stroke patients.

Study III [54]

Previous studies have investigated the relationship between sleep apnea and mortality in stroke victims after a mean of 0.5-5 years. Turkington et al. investigated 120 patients within 24 hours after stroke onset and found that 37% of them were dead after 6 months [62]. Parra et al. investigated 161 patients within 2 to 3 days after stroke onset and observed that 14% had died after a mean follow-up of 23 months [59]. The apnea-hypopnea index was lower in survivors but not independently of confounders. The results of these studies confirm our results, but none of them found that a diagnosis of sleep apnea was independently related to mortality and obstructive apneas were not differentiated from central apneas. Our results show that it is important to differentiate central apneas from obstructive apneas when investigating stroke patients.

Confirming the results in Study II, we also found that obstructive and central apneas were more prevalent in the supine position compared with the lateral position. This study thus confirms the importance of using body position sensors in sleep apnea recordings.

Possible mechanisms causing increased mortality among stroke victims who have sleep apnea include nocturnal hypoxemia, nocturnal myocardial ischemia and an increased risk of sudden cardiovascular death during sleep [78, 79]. Cerebral blood flow velocity increases concomitantly with arterial pressure during obstructive apnea, reaching a maximum 5 seconds after apnea termination [80]. The cerebral blood flow velocity and arterial pressure then decrease rapidly to reach a minimum 20 seconds after apnea termination when oxygen saturation is low. The opposite is seen during central apnea, with a decrease in cerebral blood flow during apnea and an increase after apnea termination [81]. These researchers suggest that obstructive apneas are followed by cerebral ischemia, which is not the case after central apneas [80, 81].

Future studies investigating the effect of treating sleep apnea in stroke patients are necessary. We suggest that CPAP, mandibular advancement devices and the avoidance of the supine position should be tested.

Study IV [65]

There are very few population-based studies of sleep quality in women (Table 8). Previous studies have usually investigated sleep in men or compared the results for women with those for men. Most of our data are new, as we investigate sleep in women with regard to normal values and the effect of age, BMI, obstructive sleep apnea, smoking, alcohol dependency and hypertension, independent of each other, on sleep quality. Our data clearly show that the sleep pattern is influenced by all the factors investigated in the present study.

Normal values for sleeping positions in adults have not previously been presented. We found that women normally spend 50% of their time sleeping in the lateral position, 41% in the supine position and 9% in the prone position. With increasing age, women spend less time sleeping in the supine position. Sleep apneas are more prevalent in the supine position than in other sleeping positions [51, 75, 76]. We also observed that the frequency of sleep apneas increased with age in women, as did sleeping in lateral positions. It is possible that increased sleep in lateral positions in middle-aged and older women is a physical adaptation to avoid sleep apneas.

Interest in sleep quality has increased in recent years. This study highlights the opportunity to use polysomnography, including EEG, EOG, EMG and body positions sensors, during unattended investigations at home to detect total sleep time, sleep efficiency and sleep stages.

Few data are available on the effect of age, obesity and sleep apnea on sleep quality in women. In 2004, Redline et al. reported the results of the Sleep Heart Health Study regarding sleep quality in 1,331 women and 1,353 men [82]. They concluded that sleep architecture varies with gender, age, ethnicity and sleep-disordered breathing. Men, but not women, experienced poorer sleep quality with age. In the present women, we found that age, BMI and sleep apnea had similar effects on sleep quality in univariate analysis. However, multivariate analysis revealed that increasing age was related to poorer sleep quality in the form of lower sleep efficiency due to an increased amount of wake after sleep onset, an increase in stage 1 sleep and reduced REM and stage 3-4 sleep. Body mass index was independently related to a decrease in stage 3-4 sleep. Severe sleep apnea with an apnea-hypopnea index of above 30 was related to an increased amount of stage 1 sleep and to short sleep latency, probably due to increased sleepiness during the daytime in these women.

Table 8. Normal mean values for sleep in women in different studies.

	Young [12] 1993	Ehlers [83] 1997	Redline [82] 2004	Walsleben [84] 2004	Roehrs [85] 2006	Sahlin [65] 2009
Design	In laboratory	In laboratory	Unattended home	Unattended home	In laboratory	Unattended home
Number of women	250	28	1331	306	187	399
Age (years)	30-60	20-40	37-92	40-90	31-40	20-70
Total sleep time (min)	358	437		378		392
Sleep latency (min)		12		19	14	22
Sleep efficiency (%)		95	83	86	87	82
Sleep stage 1 (%)	8	4	4	4	11	8
Sleep stage 2 (%)	60	57	53	52	55	62
Sleep stage 3-4 (%)	13	14	23	23	13	10
REM sleep (%)	18	26	21	21	21	19

GENERAL DISCUSSION

It has been recognized that sleep apnea is prevalent in the population. There are large numbers of patients on waiting lists for sleep apnea recordings. This has led to simplified sleep apnea recordings without EEG. The present thesis shows that it is important to use body position sensors in sleep apnea recordings and to measure respiratory effort to distinguish central apneas from obstructive apneas. Polysomnography is still necessary when sleep quality is investigated.

The present studies show that it is important to use body position sensors, as both obstructive and central sleep apneas are more prevalent in the supine position than in the lateral positions. Supine-dependent sleep apnea is also a predictor of treatment success with a mandibular advancement device [27, 28].

Stroke patients run a high risk of both obstructive and central sleep apnea. It is important to register respiratory effort in order to distinguish central apneas from obstructive apneas, as stroke patients with obstructive apnea have a short survival.

Polsyomnography including EEG provides information about sleep quality, including sleep efficiency, total sleep time and the amount of sleep in different sleep stages. Treatment with mandibular advancement devices, age, body mass index, smoking, sleep apnea, hypertension and alcohol dependency affect sleep quality. All this information is lost if simplified sleep apnea recordings are used.

It is suggested that body position sensors, airflow, respiratory effort and oxygen saturation should be mandatory in sleep apnea recordings. Polysomnography including EEG recordings should be used when sleep quality is investigated.

CONCLUSIONS

Obstructive sleep apneas and arousals are reduced and REM sleep is increased using a mandibular advancement device in patients with mild, moderate and severe sleep apnea.

Sleep in the supine body position increases the frequency of apneas and hypopneas in patients with Cheyne-Stokes respiration.

Patients with stroke and obstructive sleep apnea run an increased risk of early death. Central sleep apnea was not related to early death among the present patients.

Normal values for sleep stages and sleeping positions are presented in a population-based sample of women. We conclude that age, body mass index, obstructive sleep apnea, smoking, alcohol and hypertension reduce sleep quality. With age, women spend more time sleeping in the lateral position.

ACKNOWLEDGEMENTS

This thesis could not have been accomplished without the help and support of many other people. I would therefore like to express my sincere gratitude and appreciation to everyone who has contributed. I would especially like to thank the following people.

Karl Franklin, Associate Professor at the Department of Respiratory Medicine and Allergy, my main supervisor. Thank you for friendship and for sharing your wide scientific knowledge in the field of sleep apnea and leading me into research. You have generously supported me with never-ending patience and you have encouraged me to write this thesis.

Eva Lindberg, Associate Professor at the Institution of Medical Sciences, my co-supervisor in Uppsala. I had a great time working in Uppsala and scoring the polysomnograms. Thank you for always being so enthusiastic and positive and for all your constructive comments on the manuscript and thesis.

Eva Svanborg, Professor at the Department of Clinical Neurophysiology, my co-supervisor in Linköping. It has been most valuable to have your help with all your knowledge of the diagnostics of sleep apnea and sleep and your wide experience of research. Thank you for your valuable comments on the manuscript and thesis.

Hans Stenlund, an excellent statistician, who, with pedagogic calm and a simple approach, was able to explain statistics to me and make it interesting.

Thomas Sandström, Professor at the Department of Respiratory Medicine and Allergy, for believing in me and always showing a positive attitude to research on sleep apnea.

Ragnberth Helleday, Head of the Department of Respiratory Medicine and Allergy, for his support and for providing me with excellent laboratory and working facilities.

Ellinor Ädelroth, Professor at the Department of Public Health and Clinical Medicine, for her support.

Marie Marklund, Associate Professor at the Department of Orthodontics. We have had many years of cooperation and friendship and we had a good time in Cairns among the crocodiles.

Rune Lundgren, former Head of the Department of Respiratory Medicine and Allergy, who introduced the diagnosis and treatment of sleep apnea in Umeå. He has supported me in a friendly way during all the years that I have worked here.

Marianne Lidström, my close friend for many years and colleague in research work, who is sadly no longer with us. I miss you so much.

AnnCatrin Edlund, who works with me in the Andningenheten (Respiratory Unit) research group. Every day working with you is a pleasure. Thank you for all your support. You are invaluable.

Anita Renberg and **Monica Kriström**, staff at the Andningsenheten, the most reliable co-workers and my friends for a long time. I have always had your full support. We have had so many nice dinners together tasting wine and there are still many times left.

Other members of the staff at the Andningsenheten and all the staff at Lungavdelning 1 (Pulmonary Dept), plus the staff who work during the night, for taking good care of the sleep apnea patients.

Eva Norrman, Margareta Söderberg, Kennet Nilsson, Anders Blomberg and other doctors at the Department of Respiratory Medicine and Allergy, who supported research in sleep apnea and took care of the patients.

Thomas Bäcklund, Magnus Edlund and other engineers at the Department of Biomedical Engineering and Informatics for excellent support with technical equipment and for instructive co-operation during the years.

Jenny Theorell-Haglöw, Katarina Nisser and the staff at the Institution for Medical Sciences, Department of Respiratory Medicine, Uppsala University, for pleasant meetings during the time I was scoring the polysomnograpic recordings in Uppsala.

Gösta Bucht, Yngve Gustafsson, Olle Sandberg and the staff at the Department of Geriatric Medicine, for recruiting and investigating stroke patients.

Terje Rabben, Department of Clinical Neurophysiology, who initially invited me to score polysomnographic recordings and shared his wide knowledge of this field.

Jeanette Kliger, for excellent linguistic revision.

My mother **Gun** and father **Stig**, for always loving me so much and for supporting me in whatever I wanted to do.

My close friend **Eva Bergmann**, for always believing in me, encouraging me and loving me, I look forward to all the saved-up sauna evenings on the shore of Vindelälven that we are going to have!

Finally, I want to thank my family, **Hans, Anna-Cajsa** and **Björn**, the best supporters I could wish for. They are so proud of me and I am so proud of them and with their support even I believed things were possible. Love you……

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