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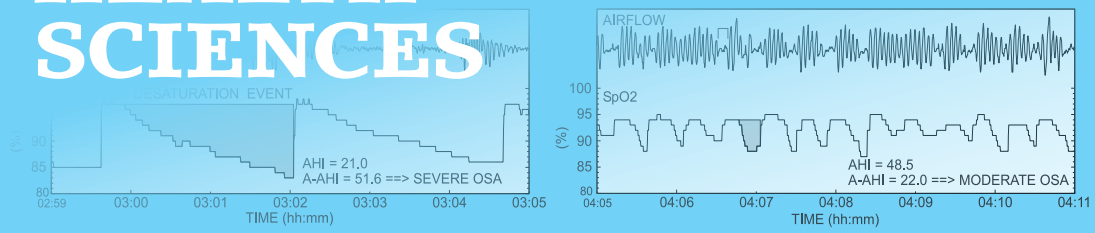
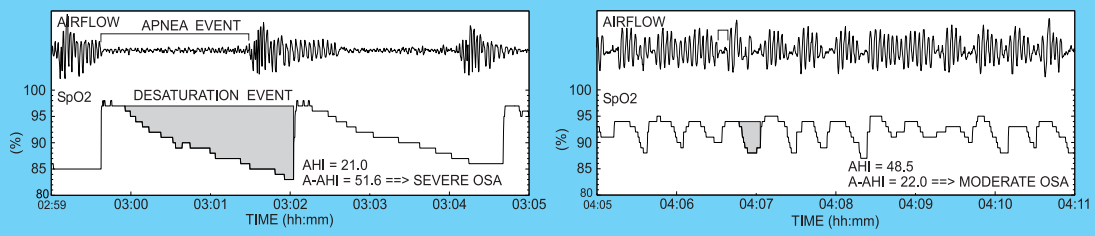


Anu Muraja-Murro

Obstruction Event Severity in Diagnostics of Sleep Apnea



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UNIVERSITY OF
EASTERN FINLAND

ANU MURAJA-MURRO

Obstruction Event Severity in Diagnostics of Sleep Apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is the most common sleep related breathing disorder in adults. Currently, the diagnosis and classification of OSA is based on the number of apnea and hypopnea events or desaturation events per hour, *i.e.* the apnea-hypopnea index (AHI) or the oxygen desaturation index (ODI) detected in polygraphic recordings. Unfortunately, AHI and ODI do not provide detailed information on the severity of individual obstruction events.

The aim of this thesis was to investigate morbidity and mortality related to obstructive sleep apnea and to introduce novel diagnostic parameters incorporating information on morphology and duration of obstruction and desaturation events. The most promising of the new parameters was obstruction severity, which incorporates the duration of obstruction and the area of the related desaturation event. These issues were investigated in retrospective studies with ambulatory polygraphic recordings of men (n = 226-1068) referred to the Department of Clinical Neurophysiology at Kuopio University Hospital due to a suspicion of sleep disordered breathing during the years 1993-2007. In addition to re-analyzing ambulatory polygraphic recordings, information was collected on morbidity and mortality of patients. Finally, an adjusted AHI parameter connecting AHI and obstruction severity was introduced to allow the use of the American Academy of Sleep Medicine (AASM) Guidelines in the diagnostics of the severity of the disease.

The patients with moderate to severe OSA had significantly higher mortality rates as compared to those without OSA. The severity of individual obstruction events showed significant variation between patients having similar AHI. The obstruction severity parameter was found superior to AHI on its own in detecting patients at the highest risk of suffering cardiovascular mortality or morbidity. Adjusted AHI was found to be easily applicable and potentially suitable for clinical use.

The novel parameters introduced in this thesis provide important supplementary information to AHI when assessing the severity of OSA and improve the recognition of those patients who carry the highest risk of suffering severe health consequences of OSA.

National Library of Medicine Classification: WF 143, WF 141
Medical Subject Headings: Sleep Apnea, Obstructive/diagnosis; Sleep Apnea, Obstructive/physiopathology; Sleep Apnea, Obstructive/mortality; Severity of Illness Index

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TIIVISTELMÄ

Obstruktiivinen uniapnea on yleisin aikuisten unen aikainen hengityshäiriö. Nykyinen obstruktiivisen uniapnean diagnostiikka ja luokitus perustuvat poikkeavien hengitys- ja happidesaturaatiotapahtumien lukumäärään tunnissa unen aikana. Käytetyimmät diagnostiset indeksit ovat apnea-hypopnea indeksi (apnea-hypopnea index, AHI) ja happidesaturaatio indeksi (oxygen desaturation index, ODI). Valitettavasti AHI ja ODI eivät sisällä tarkempaa tietoa yksittäisten poikkeavien hengitystapahtumien vakavuudesta.

Tässä väitöskirjassa tutkittiin uniapneaan liittyvää sairastavuutta ja kuolleisuutta sekä kehitettiin uusia diagnostisia parametreja. Uusista parametreista lupaavimmaksi osoittautui obstruction severity -parametri, joka huomioi poikkeavien hengitystapahtumien keston ja niihin liittyvän happidesaturaation pinta-alan. Tutkimuksessa käytiin läpi takautuvasti Kuopion Yliopistollisessa sairaalassa vuosina 1993-2007 tutkittuja potilaita (n = 226-1068), jotka oli lähetetty uniapnea-epäilyn vuoksi ambulatoriseen yöpolygrafiaan. Analyysejä varten potilaista kerättiin sairastavuus- ja kuolleisuustiedot. Väitöskirjassa esiteltiin obstruction severity -parametriin perustuva adjusted AHI-parametri, joka mahdollistaa American Academy of Sleep Medicine:n (AASM) suositusten mukaisen uniapnean vakavuuden luokittelun.

Kohtalaista tai vaikeaa uniapneaa sairastavilla potilailla todettiin merkittävästi korkeampi kuolleisuusriski verrattuna potilaisiin, joilla ei ole uniapneaa. Yksittäisten hengitystapahtumien vakavuudessa havaittiin merkittävää vaihtelua saman AHI:n omaavien potilaiden välillä. Obstruction severity - parametri osoittautui paremmaksi kuin AHI selviteltäessä suurimmassa terveysriskissä olevia uniapneapotilaita. Adjusted AHI todettiin mahdollisesti sopivaksi kliiniseen käyttöön.

Uudet parametrit parantavat korkeimmassa sydän- ja verisuonitaudin riskissä sekä kuolleisuusriskissä olevien potilaiden tunnistamista. Adjusted AHI parametrin käyttö voi parantaa uniapneataudin vakavuuden arviointia kliinisessä työssä.

Luokitus: WF 143, WF 141
Yleinen Suomalainen asiasanasto: obstruktiivinen uniapnea; uniapnea-oireyhtymä; diagnostiikka; indeksit; kuolleisuus

- Faith, Hope and Love make miracles -

To Alpo, Juho, Laura, Juuso and Mette

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I dedicate my dear thanks to my parents, my deceased mother Liisa and my father Paavo for their love and encouragement in my life. I carry the loving memory of my mother in my heart and wish that she would have had opportunity to attend this event. I am grateful to my aunts, Paula for being my spare mother in a time of happiness and sorrow in adulthood, and Asta and Mirja for the memorable discussions about everything in life. I also express my thanks to my parents-in-law Marjatta and Heimo for all practical help we have needed in everyday life. This also in Finnish: Isot Kiitokset Marjatta ja Heimo kaikesta avusta arjessa.

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Kuopio, May 2014

Anu Muraja-Murro

List of the original publications

This dissertation is based on the following original publications referred in the text by their roman numerals:

I Muraja-Murro A, Eskola K, Kolari T, Tiihonen P, Hukkanen T, Tuomilehto H, Peltonen M, Mervaala E, Töyräs J. Mortality in middle-aged men with obstructive sleep apnea in Finland. *Sleep and Breathing, 17(3): 1047-1053, 2013.*

II Muraja-Murro A, Nurkkala J, Tiihonen P, Hukkanen T, Tuomilehto H, Kokkarinen J, Mervaala E, Töyräs J. Total duration of apnea and hypopnea events and average desaturation show significant variation in patients with a similar apnea-hypopnea index. *Journal of Medical Engineering & Technology, 36(8): 393-398, 2012.*

III Muraja-Murro A, Kulkas A, Hiltunen M, Kupari S, Hukkanen T, Tiihonen P, Mervaala E, Töyräs J. The severity of individual obstruction events is related to increased mortality rate in severe obstructive sleep apnea. *Journal of Sleep Research, 22: 663-669, 2013.*

IV Muraja-Murro A, Kulkas A, Hiltunen M, Kupari S, Hukkanen T, Tiihonen P, Mervaala E, Töyräs J. Adjustment of apnea-hypopnea index with severity of obstruction events enhances detection of patients with highest risk of severe health consequences. *Sleep and Breathing, DOI: 10.1007/s11325-013-0927-z, 2014.*

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Abbreviations

A-AHI	Adjusted-apnea-hypopnea index
AASM	American Academy of Sleep Medicine
AF	Atrial fibrillation
AHDI	Apnea-hypopnea-desaturation index
AHI	Apnea-hypopnea index
ApDur	Duration of a single apnea event
ASDA	American Sleep Disorder Association
AV- block	Atrioventricular block
BMI	Body mass index (kg/m^2)
CHD	Coronary heart disease
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
DesArea	Area of a single desaturation event
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
GER	Gastroesophageal reflux
HF	Heart failure
HypDur	Duration of a single hypopnea event
kg	Kilogram
LVEF	Left ventricular ejection fraction
m^2	Square meter
mths	Months
MRA	Mandibular repositioning appliance
n	Number of patients/samples
NIDDM	Noninsulin-dependent diabetes mellitus
NR	Not reported
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
p	Probability of rejecting the null hypothesis
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PSG	Polysomnography
QOL	Quality of life
r	Correlation coefficient
REM	Rapid eye movement
RERA	Respiratory effort-related arousal
RIP	Respiratory inductance plethysmography

SCSB	Static charge sensitive bed
SD	Standard deviation
SpO_2	Saturation of peripheral oxygen
SPSS	Statistical Package for Social Sciences
TAD%	Total apnea duration as a percentage of sleep time
TAHD%	Total combined cumulative apnea and hypopnea duration as a percentage of sleep time
THD%	Total hypopnea duration as a percentage of sleep time
TIA	Transient ischemic attack
UPPP	Uvulopalatopharyngoplasty

1 INTRODUCTION

Obstructive sleep apnea (OSA) is the most common adult sleep disorder and an important factor decreasing quality of life (Young et al., 2002). The disease is characterized by repeated mechanical obstruction of the upper airway during sleep (Krieger et al., 2002). OSA was mentioned in literature for the first time as early as in mid-1800-century in the Pickwick Papers by Charles Dickens. In mid 1960s, the first medical studies on sleep apnea were published (Gastaut et al., 1966, Jung and Kuhlo, 1965). In 1976 Guilleminault together with Dement proposed a measure for the clinical classification of OSA, the apnea-hypopnea index (AHI) (personal communication with Professor Guilleminault). The most effective treatment for the disease *i.e.* continuous positive airway pressure (CPAP) treatment was introduced by Sullivan et al. in Australia (Sullivan et al., 1981).

OSA is estimated to affect 9-24% of all middle-aged individuals (Young et al., 1993). In addition, OSA has been associated with an increased risk of mortality, especially due to cardiovascular morbidity (He et al., 1988, Marin et al., 2005, Won et al., 2013). Since OSA is an important public health issue, the diagnosis should be achieved as early as possible and the patients with the highest risk need to be identified reliably. The gold standard for diagnosis of OSA is full night polysomnography (PSG) including the following parameters: electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), oronasal airflow, chest wall movement efforts, body position, snoring, electrocardiogram (ECG) and saturation of peripheral oxygen (SpO_2). Unfortunately, conducting such elaborate PSG recordings are expensive and not available for all patients. However, ambulatory polysomnography devices with a limited amount of recorded biosignals are generally accepted in the diagnostics of OSA (Collop, 2008). Currently, the diagnosis and classification of the disease is based on OSA-related symptoms and the number of apnea and hypopnea events or desaturation events per hour, *i.e.* the apnea-hypopnea index (AHI) or the oxygen desaturation index (ODI) as assessed in polygraphic recordings (Iber, 2007). Unfortunately, neither AHI nor ODI provide information on the severity of the events. However, it is possible to use more severe ODI-values (*e.g.* ODI10 and ODI20), but even with these values, the combination between apnea/hypopnea events and desaturation will be missed and neither the length nor the depth of the desaturation events is evaluated. In addition, a simultaneous increase in the duration and frequency of apnea and hypopnea events may lead to a paradoxical situation where the AHI can not increase any further. Those patients with especially severe (*i.e.* prolonged and deep) obstruction (apnea and hypopnea) and desaturation events have been thought to suffer more severe health consequences

and to display an elevated mortality rate. Already in 1989, Salmi et al. reported that when conducting automatic analysis, the addition of apnea percentage values (*i.e.* percentage of apneic time of recording) to the polygraphy analysis could provide more information than AHI on its own (Salmi et al., 1989). Thus, the present diagnostic parameters AHI and ODI might not reveal completely the overall severity of the disease and the physiological stress that it evokes (Kulkas et al., 2013a, Otero et al., 2010). Therefore, the overall severity of desaturation is clinically routinely evaluated, for example, as the time below 90% saturation. Otero et al. also reported that sometimes AHI can underestimate the severity of the patient's condition (Otero et al., 2010). They studied recently different parameters of respiratory airflow and desaturation in 274 patients and reported that the combined percentage of the sleep time that the patient had been in apnea, hypopnea or hypoxia, *i.e.* the apnea-hypopnea-desaturation index, could outperform the AHI in the diagnosis of OSA (Otero et al., 2012).

Based on clinical experience, when diagnosing obstructive sleep apnea it would be very valuable to measure multiple parameter values when diagnosing OSA in all patients referred for polysomnography *e.g.* due to daytime somnolence. For example, this would improve the identification of those patients whose individual obstruction events are more severe, and in whom the clinical disease may be more devastating than expected. It is known that the beneficial treatment options are also different in individual patients. In OSA patients with mild disease, effective treatment may ultimately prevent the possible appearance of many subsequent co-morbidities. Otherwise, effective treatment of severe OSA *e.g.*, with CPAP may alleviate or even prevent the most severe health consequences related to OSA.

One could hypothesize that developing novel parameters that would include information on severity of individual obstruction events could provide feasible tools for estimating more effectively the true severity of the disease. In this thesis, this hypothesis has been tested in retrospective studies with ambulatory polygraphic recordings of men who had been referred to the Department of Clinical Neurophysiology at Kuopio University Hospital due to a suspicion of sleep disordered breathing. Basic anthropometric data (height, weight, BMI) and information on age, smoking, the use of continuous positive airway pressure (CPAP) treatment and cardiovascular morbidity were collected from the medical records in Kuopio University Hospital. Furthermore, the primary and secondary causes of death were obtained from Statistics Finland (Helsinki, Finland) for deceased patients.

2 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is defined as repeated episodes of complete or partial blockage of the upper airway during sleep. The muscles in the upper airway temporarily relax and the airway is narrowed or closed and breathing momentarily ceases. An obstructive apnea event is defined as a cessation (over 90% reduction in amplitude) of airflow for ≥ 10 seconds despite breathing efforts. A hypopnea event is defined as a reduction (more than 30%) in thoracoabdominal movement or airflow for more than 10 seconds with related oxygen desaturation of at least 4% (a desaturation event has to occur no later than 20 seconds after the start of the hypopnea) or a 50% reduction in thoracoabdominal movement or airflow amplitude connected with an oxygen desaturation of at least 3%. In both scenarios, at least 90% of the event's duration has to meet the amplitude reduction criteria for hypopnea (Iber, 2007). The apnea-hypopnea index (AHI) is defined as the total sum of the apnea and hypopnea events divided by hours of sleep (AASM, 1999, Iber, 2007).

The prevalence of obstructive sleep apnea (AHI ≥ 5) in adults is estimated to be 17% (Young et al., 2005). Moreover, it has been reported that 93% of women and 82% of men to having moderate to severe OSA have not been clinically diagnosed (Young et al., 1997b). In the Finnish adult population, the prevalence of OSA has been reported to be as high as 8% (*i.e.* 320 000 individuals) (Kronholm et al., 2009). Although OSA is already a severe threat to the wellbeing of the population, it has been predicted to become even more common in the future (Young et al., 2002).

2.1 PATHOPHYSIOLOGY AND ETIOLOGY

The pathophysiology of OSA is complex and still partly unresolved. Pharyngeal anatomy and variable voluntary control in the upper airway dilator muscles are the prevalent causes of pharyngeal collapse in most cases. Other important causes of pharyngeal collapse are a reduction in the competence of muscles of upper airway to respond to the respiratory challenge during sleep, an increase in arousal threshold in response to respiratory neural and/or humoral stimulation, and instability of ventilatory control. The upper airway can be divided into three regions, the nasopharynx, the oropharynx and the hypopharynx (figure 1). In an OSA patient, upper airway closure during sleep occurs most often in the oropharynx (Remmers et al., 1978, Schwab et al., 1995).

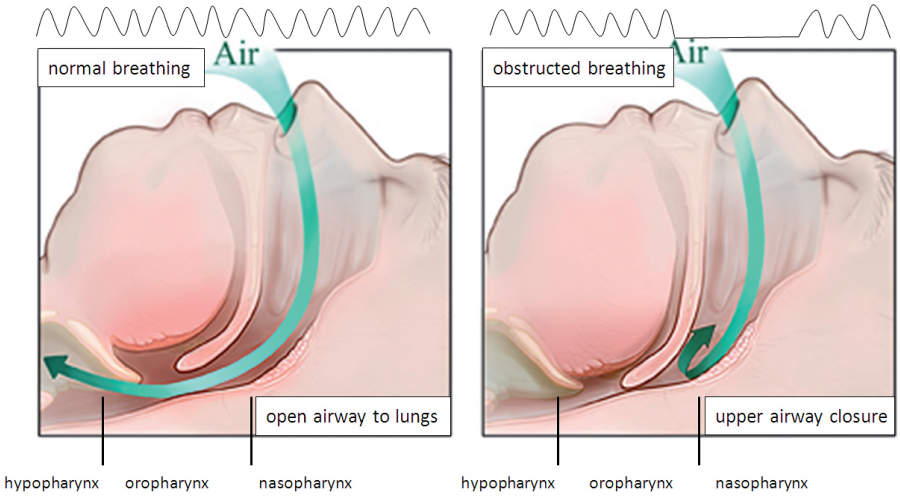

Figure 1. The upper airway may be divided into three regions, the nasopharynx, the oropharynx and the hypopharynx. In OSA, an obstruction of upper airway occurs most often in the oropharynx. (Figure modified from http://www.webmd.com/sleep-disorders/sleep-apnea/obstructive-sleep-apnea-blocked-upper-airway)

The upper airway is composed of numerous muscles and soft tissue but lacks any support from bony structures. A narrow upper airway is generally more prone to collapse than a larger one. OSA patients have been reported (as measured by computed tomography and magnetic resonance imaging) to have a reduced cross-sectional area of the upper airway when compared with subjects without OSA (Burger et al., 1992, Haponik et al., 1983, Schwab et al., 1995). Furthermore, it has been reported that during general anesthesia and related muscle relaxation, OSA patients exhibit a structurally more narrowed and collapsible pharynx when compared to controls (Isono et al., 1997).

Increased negative airway pressure stimulates upper airway muscle activity, dilating the pharyngeal airway and maintaining reasonable levels of airflow resistance during awake. In comparison with normal subjects, OSA patients have higher activity in their genioglossus muscle while awake, but not during sleep leading to pharyngeal collapse (Mezzanotte et al., 1992).

Arousal is an important protective mechanism enabling the airway to reopen (Remmers et al., 1978). It has been reported that OSA patients exhibit more movement arousals than normal subjects (Collard et al., 1996). There is also a correlation between the severity of abnormal respiratory events and arousals, with more severe events resulting in longer arousals (Nigro and Rhodius, 2005). Increasing ventilatory effort (generated by various different stimuli, *e.g.* hypoxia, hypercapnia or respiratory loading) is thought to be the most important stimulus to evoke arousal (Gleeson et al., 1990). OSA patients have been reported to have a

higher threshold for arousal (Berry et al., 1996). The sleep apnea itself may be the reason for the increased threshold (Berry et al., 1996). Sleep apnea increases the arousal threshold related to airway occlusion while nasal-CPAP-treatment decreases the arousal threshold (Berry et al., 1996, Haba-Rubio et al., 2005). Kimoff et al. reported that ending of obstruction was mediated through stimuli related to the level of inspiratory effort at end-apnea, which caused arousal and reopening of the airway (Kimoff et al., 1994).

Ventilatory control is believed to be an important contributor to the pathogenesis of OSA (Eckert and Malhotra, 2008). Patients with OSA have less stable ventilatory control and during wakefulness, the response of OSA patients to hyperoxic CO_2 is higher than in controls (Hudgel et al., 1998).

2.2 RISK FACTORS

Obesity is the most important single risk factor of OSA. However, several other factors such as smoking, alcohol consumption, nasal congestion, male gender and hormonal changes during menopause may also affect the development and progression of OSA (table 1). Furthermore, patients with cardiovascular disease have a high prevalence of OSA. Consequently, patients with congestive heart failure, atrial fibrillation, treatment resistant hypertension, diabetes type 2, stroke, nocturnal arrhythmias and pulmonary hypertension are all high risk patients if they also suffer from OSA (table 1).

A number of studies have reported a significant association between OSA and overweight (Duran et al., 2001, Ferini-Strambi et al., 1994, Young et al., 1993, Young et al., 2002, Vgontzas, 2008). The increased body weight impairs breathing in many ways, including alterations in upper airway structure and function, respiration drive and obesity-induced hypoxemia (Strobel and Rosen, 1996). It has been reported that especially visceral fat is significantly correlated with sleep apnea (Vgontzas, 2008) and that waist circumference is a better predictor for OSA than neck circumference or BMI (Grunstein et al., 1993). Nevertheless, also general obesity (Newman et al., 2001, Young et al., 1993) and neck morphology (Hoffstein and Mateika, 1992, Mortimore et al., 1998, Olson et al., 1995) have been associated with OSA. In severely obese populations, more than every second individual is suffering from moderate to severe OSA (Resta et al., 2001).

Smoking increases sleep instability and causes inflammation of the airway (Wetter et al., 1994). Current smokers are three times more likely to exhibit OSA than non-smokers (Wetter et al., 1994) and smoking has been claimed to be an independent risk factor for OSA (Kashyap et al., 2001). However, in a study with 6440 subjects Newman et al. reported that current smoking and OSA were not

associated (Newman et al., 2001). The authors speculated that severe OSA patients may have been prone to quit smoking, which could explain the findings as current smoking and OSA were not associated.

Alcohol consumption is reported to decrease the size of the pharyngeal airway during wakefulness (Robinson et al., 1985) and to increase the incidence of desaturation and apnea events during sleep in asymptomatic volunteers (Taasan et al., 1981). This was encountered also in the following night, even when no alcohol had been consumed. Furthermore, Scanlan et al. reported that even modest alcohol consumption before sleeping significantly increased both AHI and mean heart rate (Scanlan et al., 2000). However, the association between long-term alcohol use and OSA still needs to be clarified.

Nasal congestion often results from allergic rhinitis and anatomic abnormalities, such as septal deviation, nasal polyps and hypertrophied turbinates. Patients who reported nasal congestion due to allergy were 1.8 times more likely to have moderate to severe OSA as compared to those without nasal congestion (Young et al., 1997c). However, Young et al. also reported that the strongest relationship was found between nasal congestion and habitual snoring and not with AHI (Young et al., 1997c). OSA has been linked to chronic nasal obstruction also in other studies (Liistro et al., 2003, Lofaso et al., 2000). Controversially, in the recent review of Kohler et al. chronic nasal obstruction was postulated to play only a minor role in the pathogenesis of OSA (Kohler et al., 2007). They concluded that a reduction in nasal resistance (by nasal dilators, topically applied steroids or nasal decongestants) would achieve only a minor improvement in OSA or in its severity.

Men have a two to three fold risk of OSA compared to women (Strohl and Redline, 1996, Young et al., 1997d). However, this difference may have been exaggerated by referral and diagnostic biases. Strohl and Redline reported in 1996 that OSA is common in older women, especially in menopausal women (Strohl and Redline, 1996). It has been reported that women with OSA do not complain about apneas, arousals or restless sleep, instead they complain of fatigue, insomnia and morning headaches (Ambrogetti et al., 1991, Alotair, 2008). Menopause is the most important endocrinological risk factor for OSA in women (Bixler et al., 2001, Young et al., 2003) and hormonal substitution therapy can reduce this risk factor. Bixler et al. reported that the prevalence of symptomatic OSA in postmenopausal women with and without hormone replacement therapy was 0.6% and 2.7%, respectively (Bixler et al., 2001). Premenopausal women with polycystic ovary syndrome have an increased prevalence of OSA (Fogel et al., 2001). In the study of Vgontzas et al., women with polycystic ovary syndrome were 30 times more likely to suffer from OSA than the premenopausal controls (Vgontzas et al., 2001). Patients with polycystic ovary syndrome have high levels of androgen secretion, a tendency towards insulin resistance and obesity. In addition, other

endocrinological disorders, such as acromegaly, hypothyroidism and Cushing's syndrome, are risk factors of OSA (Saaresranta and Polo, 2003).

Table 1. Reported risk factors of OSA

Risk factor	Relative risk	References
Obesity	++++	(Peppard et al., 2000a, Strobel and Rosen, 1996)
Male gender	+++	(Schwab, 1999, Young et al., 1993)
Congestive heart failure	+++	(Herrscher et al., Javaheri, 2006, Zhao et al., 2007, Ferreira et al., 2010)
Hypertension	++	(Somers et al., 2008, Fletcher et al., 1985)
Atrial fibrillation	++	(Braga et al., 2009, Gami et al., 2004)
Diabetes type 2	++	(Foster et al., 2009, Resnick et al., 2003, Einhorn et al., 2007)
Stroke	++	(Bassetti and Aldrich, 1999, Dyken et al., 1996, Good et al., 1996, Mohsenin and Valor, 1995, Wessendorf et al., 2000)
Pulmonary hypertension	++	(Dumitrascu et al., 2013, Sajkov and McEvoy, 2009)
Nocturnal arrhythmias	+	(Javaheri et al., 1998, Lattimore et al., 2003)

2.3 CLINICAL FEATURES

The most common symptom in OSA is excessive daytime sleepiness. Bed partner's reports on snoring, gasping or interruptions in breathing during sleep are also commonly related to OSA. Other related clinical features are listed in table 2. In a recent review nocturnal gasping or choking were reported to be the most reliable indicators for OSA (Myers et al., 2013).

Table 2. Symptoms of OSA

Nocturnal	Diurnal
Awakenings with choking	Excessive sleepiness
Snoring	Morning headaches
Nocturnal restlessness	Changes in mood
Insomnia	Lack of concentration
Increased perspiration during sleep	Cognitive deficits, (*e.g.* memory impairment)
Gastroesophageal reflux	Impotence, decreased libido
Nocturia	Cough
Mouth dehydration	Impaired overall quality of life (QOL)

2.3.1 Diurnal symptoms

Excessive daytime sleepiness caused by sleep fragmentation is a central feature of OSA (Bennett et al., 1999, Sullivan and Issa, 1985). CPAP-treatment reduces the number of apnea and hypopnea events thus decreasing the arousal index and relieving the clinical symptoms (Ballester et al., 1999, Guilleminault et al., 1991). However, it has been claimed that differences in the frequency of arousals can not explain the variation in resultant sleepiness as found in the Sleep Heart Health Study (Gottlieb et al., 1999). Despite this result, Gottlieb et al. reported a significant association between the respiratory disturbance index and sleepiness (Gottlieb et al., 1999). Excessive sleepiness is associated with significant morbidity and adverse effects on working performance (Dawson and Reid, 1997, Mitler et al., 1988) family relationship and quality of life (Briones et al., 1996, Roth and Roehrs, 1996, Young et al., 2002). Furthermore, OSA patients have been reported to display an increased risk of motor vehicle and occupational accidents (George et al., 1987, Lyznicki et al., 1998, Ulfberg et al., 2000, Young et al., 1997a, Vorona and Ware, 2002,). It must also be noted that OSA patient's bed partner's sleep may also be disturbed, affecting also his/her quality of life (McArdle et al., 2001).

Snoring and excessive daytime sleepiness have been shown to be mutually associated together (Gottlieb et al., 2000, Guilleminault et al., 1991, Young et al., 1993, Zielinski et al., 1999). Furthermore, almost all patients with severe OSA exhibit snoring-like symptoms (Resta et al., 2001). However, in a recent review, snoring was not reported to be useful for establishing the diagnosis of OSA, although a patient with mild snoring and normal weight was considered unlikely to have moderate or severe OSA (Myers et al., 2013).

OSA and morning headaches are known to be associated. The prevalence of morning headaches has been reported to vary from 11.8% to 74% in OSA patients (Alberti et al., 2005, Boutros, 1989, Guilleminault et al., 1977, Kristiansen et al., 2011, Loh et al., 1999). However, morning headaches have also been linked to other sleep-related disorders (Aldrich and Chauncey, 1990, Poceta and Dalessio, 1995,). In OSA patients, headaches have been linked to the cerebral vasodilation triggered by oxygen desaturation (Loh et al., 1999). In fact, the mechanism responsible for morning headaches is complex and involves also hypercapnia, sleep fragmentation and an increase in intracranial pressure (Jennum and Jensen, 2002). Importantly, the severity of OSA is correlated with the occurrence of morning headaches (Alberti et al., 2005, Loh et al., 1999) and CPAP-treatment has been reported to relieve this symptom (Loh et al., 1999, Neau et al., 2002).

Cognitive dysfunction has been associated with OSA and especially an impairment of executive function and attention has been described by many authors (Bedard et al., 1991b, Berry et al., 1986, Findley et al., 1986, Kim et al., 1997). In a prospective observational study, approximately 25% of OSA patients

was reported to exhibit some degree of neurocognitive dysfunction (Antonelli Incalzi et al., 2004). Adams et al. found that even after excluding comorbid conditions, impairment of working memory, declarative memory and signal discrimination were directly related to the lowered nocturnal oxygen saturation (Adams et al., 2001). The cognitive dysfunction is thought to be caused by hypoxemia during sleep or to excessive daytime sleepiness (Lal et al., 2012, Verstraeten, 2007). Surprisingly, it seems that CPAP-treatment only partially improves the cognitive dysfunction even after complete recovery from daytime sleepiness (Ferini-Strambi et al., 2003).

2.3.2 Nocturnal symptoms

Nocturia is common in patients with OSA (Pressman et al., 1996) with 47.8% of patients suffering from it (Hajduk et al., 2003). Hajduk et al. stated that women suffer nocturia more than men (60.0% vs. 40.9%) and the severity of OSA is linked to the severity of nocturia (Hajduk et al., 2003). In OSA, the increased intrathoracic pressure caused by hypopneas or apneas leads to increased venous return and atrial stretch which induces false signals of fluid volume overload. In the kidneys, this triggers increased secretion of atrial natriuretic peptide and as a consequence, the urine production is increased (Umlauf et al., 2004). There are only a few studies on the effect of CPAP-treatment on nocturia. However, CPAP-treatment has been shown to reduce the nocturia associated with OSA (Margel et al., 2006).

Nocturnal gastroesophageal reflux (GER) has been linked to OSA, and 54-76% of OSA patients suffer from it (Zanation and Senior, 2005). In the general population the occurrence of GER is around 10% (Zanation and Senior, 2005). Nasal CPAP-treatment has been shown to reduce the gastroesophageal reflux (Kerr et al., 1992).

Within the last ten years, numerous studies have reported a high prevalence (39-50% vs. 9-15% in general population) of insomnia symptoms in OSA patients (Chung, 2005, Krakow et al., 2001, Smith et al., 2004). This seems paradoxical as the same patients suffer also from excessive daytime sleepiness.

2.4 DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

The diagnosis of OSA is based on interview and clinical examination of the patient and supporting abnormal results in a polygraphic recording. The severity of the disease is judged based on clinical symptoms, especially daytime sleepiness, and findings in polygraphic recording. More specifically, the clinical diagnostics about the severity is based on the most severe findings of sleepiness, SpO_2 during sleep or AHI (table 3). For example, if a patient has an AHI value of 10 and daily

symptoms of sleepiness at a low activity level, then the severity would be classified as moderate OSA.

Table 3. Criteria for clinical classification of the obstructive sleep apnea*

Severity of disease	Sleepiness	SpO_2 during sleep (%)	AHI
Mild	manifestation only when non-active, not necessarily daily, minimal disadvantages in social and working life	average mean ≥ 90 and minimum ≥ 85	5 ≤ AHI < 15
Moderate	daily symptoms, when low activity level and only little concentration is needed (*e.g.* attending a meeting, watching a movie)	average mean < 90 and minimum ≥ 70	15 ≤ AHI < 30
Severe	daily symptoms in situations which require more attention and concentration (*e.g.* driving, conversation, eating)	average mean < 90 and minimum < 70	30 ≤ AHI

*Modified from The Report of American Academy of Sleep Medicine Task Force (1999) and Obstructive sleep apnea syndrome (online), Current Care Summary, 2010.

The gold standard in diagnosing of OSA is overnight polysomnography (Douglas et al., 1992), which involves recording of *e.g.* sleep stages, respiration and blood oxygen saturation. However, polysomnographic recordings in specialized sleep centers are relatively expensive, require trained technicians and, thus, are not available for all patients. Effective screening of sleep apnea requires systems that are cheaper and simpler than those used for standard polysomnography. For this reason, the introduction of simple portable devices led to a major increase in the diagnostics of sleep apnea in the late 1990's.

Recording for a single night is the normal clinical practice, although it is known that the quality of sleep and results of night polygraphy may vary between nights. The first-night effect is a well-known phenomenon, which is believed to result from sleeping in the unfamiliar environment of a hospital. This phenomenon is characterized with less total sleep time, a lower sleep efficiency index, more awake time after sleep onset, less REM-sleep and longer REM-latency compared to the following nights (Le Bon et al., 2003). Recently, Newell et al. reported, however, that total sleep time did not differ significantly between two consecutive recording nights, and in the OSA-suspected group no statistically significant differences were detected in AHI-values between consecutive nights (Newell et al., 2012). However, when they studied AHI-values of both nights for each patient

individually, 40.9% of patients would have been misdiagnosed in terms of OSA severity if the AHI of one of only the two nights had been used instead of both nights. This is a good example of the impact of night-to-night variability. In addition, Le Bon et al. reported that first night recording showed significantly less severe AHI, while mean O_2 saturation and maximum O_2 were stable across nights (Le Bon et al., 2000). They concluded that it would be worthwhile recording a second polygraphy night if the result of the first one was negative in patients with clinical suspicion and/or symptoms suggesting of OSA. However, Lojander et al. examined data from two polygraphic assessments, the findings were rather similar, there were no significant differences for example in time spent in the supine position or in the classification of OSA and they proposed that in routine clinical work one night polygraphy is adequate (Lojander et al., 1998). In the day-to-day routine in the clinic, almost every patient is subjected to only one-night polygraphy for several reasons (*e.g.*, costs and feasibility). However, the first-night effect should be taken into account by the individuals who analyze the polygraphic data. In practice and in the optimal situation, repeating the sleep recording may be suggested by the analyzer.

In clinical practice, pulse oximetry is often used in measuring oxygen saturation in polygraphic recordings. However, that method suffers from the limitation that the relationship between pulse oximetry values and partial pressure of oxygen is not linear. If a patient's baseline partial pressure of oxygen is low, then an obstructive event (apnea/hypopnea) will evoke deeper desaturation (figure 2). On the other hand, patients whose baseline O_2 levels are more physiological tolerate obstruction events better and suffer only milder desaturations. The literature contains several studies suggesting that pulse oximeters are relatively accurate in the clinically relevant range, but that they experience limitations when the values fall below 80% (Fanconi, 1989, Nickerson et al., 1988).

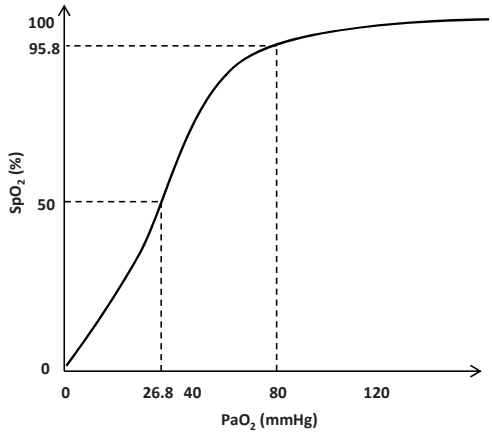

Figure 2. Dissociation curve of oxygen –hemoglobin, the relationship between partial pressure of oxygen in arterial blood (PaO_2) and saturation of peripheral oxygen (SpO_2)

However, CO_2 is a more potent regulator of respiratory drive than oxygen (Dean and Nattie, 2010). During sleep, hypercapnia is more likely to drive breathing than hypoxia. It has been reported that during an obstructive apnea event - and especially with repetitive long apneas – the transcutaneous CO_2 level is slightly increased (Gislason et al., 1989). Rauhala et al. reported that the transcutaneous CO_2 level increased during flow limitation, but during apnea or hypopnea episodes there were no significant elevations (Rauhala et al., 2007). They stated that their patients were eucapnic, only moderately obese and also that their OSA was moderate, and that these reasons may have influenced the results. Rimpilä et al. have very recently reported that a nocturnal target CO_2 level is dependent on both perfusion and ventilation. This level is believed to be determined by several factors, *e.g.* the degree of respiratory drive (Rimpilä et al., 2014). However, the transcutaneous CO_2 measurement is rarely included in polygraphic recordings in clinical practice.

2.4.1 Polysomnographic and ambulatory recordings

Ambulatory sleep recording devices have been used in the diagnostics of OSA since the late 1980's (Penzel et al., 1990). In the early devices only heart rate and breathing *i.e.* snoring were recorded. In Finland, the Static-Charge Sensitive Bed (SCSB) was introduced in 1979 (Alihanka et al., 1981). This method enabled recording of body movements, the ballistocardiogram and breathing efforts (Alihanka et al., 1981). Although interpretation of SCSB recordings was challenging, it was used in Finland in diagnostics of sleep apnea until late 1990s.

Task Force of the Standards of Practice Committee of the American Sleep Disorder Association distinguished four types of sleep monitoring devices (ASDA, 1994) and listed their specifications as summarized in table 4.

The clinical values of ambulatory recording for diagnostics of OSA were systematically evaluated by Flemons et al. (2003). They reported that the ambulatory recordings exhibit variable sensitivities (31-100%) and specificities (48-100%) (Flemons et al., 2003). Flemons et al. (2003) did not find that any given/one device type was superior to the others. However, already in 1997 AASM recommended that ambulatory recording with the type III device would be appropriate for diagnostics of sleep apnea (Chesson et al., 1997, AASM, 1997). The early detection of the patients with severe OSA can achieve major medical and economical benefits (Pelletier-Fleury et al., 2004). In that study, significant improvement in daytime sleepiness, quality of life, and also cost-effectiveness of treatment were reported with an early diagnosis of OSA. Finally, in 2007 AASM concluded that ambulatory recording at home would be suitable for diagnostics of OSA (Collop et al., 2007). Many factors such as lower cost of ambulatory recordings and their better availability support this decision. Patients have also

been reported to sleep better during ambulatory recordings as they can be conducted at home. However, it has to be kept in mind that ambulatory recordings may underestimate AHI, because sleep time cannot be measured accurately without EEG. Furthermore, arousals cannot be identified without EEG data, making thereby detection of arousal related hypopneas virtually impossible.

Table 4. Types of ambulatory devices as specified by the Task Force of the Standards of Practice Committee of the American Sleep Disorder Association and Task Force of the Standards of Practice Committee of the AASM

Device	Number of channels	Biosignals	Body position	Patient recording	Description
Type I	≥ 7	EEG, EOG, EMG, ECG or heart rate, airflow, respiratory movements, oxygen saturation	measured objectively	usually in sleep center (attended)	gold standard polysomnography recorded in a sleep center
Type II	≥ 7	EEG, EOG, EMG, ECG or heart rate, airflow, respiratory movements, oxygen saturation	optional	unattended	complete polysomnography, but ambulatory
Type III	≥ 4	ECG or heart rate, airflow, respiratory movements, oxygen saturation	optional	attended or unattended	ambulatory recording, only to diagnose sleep apnea
Type IV	1-2	oxygen saturation and usually airflow (can be also something else)	not measured	attended or unattended	ambulatory recording with limited channels, not recommended

EEG = electroencephalogram
EOG = electro-oculogram
EMG = electromyogram
ECG = electrocardiogram

The American Academy of Sleep Medicine has been publishing updated detailed recommendations for recordings and analysis of sleep studies. The latest recommendations were published in 2007 and 2012 (tables 5 and 6). The recommendations published in 2007 are more commonly applied than those published in 2012. The most significant difference between the recommendations is the simplification of the criteria defining hypopnea.

Table 5. Diagnostic criteria of respiratory events (AASM 2007)

Event	Sensor	Drop of amplitude (%)	Duration (s)	Associated SpO_2 (%)	Respiratory effort	Arousal based on EEG
Apnea	oronasal thermistor	≥ 90	≥ 10			
obstructive					entire period	
central					absent	
mixed					second portion of event	
Hypopnea	nasal pressure	≥ 30	≥ 10	≥ 4		
Hypopnea	nasal	≥ 50	≥ 10	≥ 3		
	pressure	≥ 50	≥ 10			yes
RERA	nasal pressure	flattening	≥ 10			effort-related
RERA	thoraco-abdominal RIP belts		≥ 10		increasing respiratory effort	effort-related

RERA = respiratory effort-related arousal
RIP = respiratory inductance plethysmography

Table 6. Diagnostic criteria of respiratory events (AASM 2012)

Event	Sensor	Drop of amplitude (%)	Duration (s)	Associated SpO_2 (%)	Respiratory effort	Arousal based on EEG
Apnea	oronasal thermistor	≥ 90	≥ 10			
obstructive					entire period	
central					absent	
mixed					second portion of event	
Hypopnea	nasal pressure	≥ 30	≥ 10	≥ 3		
Hypopnea	nasal pressure	≥ 30	≥ 10			yes
RERA	nasal pressure	flattening	≥ 10			effort-related
RERA	thoraco-abdominal RIP belts		≥ 10		increasing respiratory effort	effort-related

RERA = respiratory effort-related arousal
RIP = respiratory inductance plethysmography

2.5 OSA AND CO-MORBIDITIES

OSA patients often have many co-morbidities, most importantly cardiovascular disease (Peppard et al., 2000b, Shamsuzzaman et al., 2003, Young et al., 2004). In OSA, apneas and hypopneas cause sympathetically mediated vasoconstriction and a consequent increase in systemic and pulmonary pressure, elevated left ventricular afterload and breathing-related changes in cardiac output. All these together with sudden intra-thoracic pressure changes cause hypoxia, reoxygenation, hypercapnia, arousals and sleep deprivation. These situations can induce intermediary mechanisms, which are connected to cardiovascular co-morbidities (figure 3).

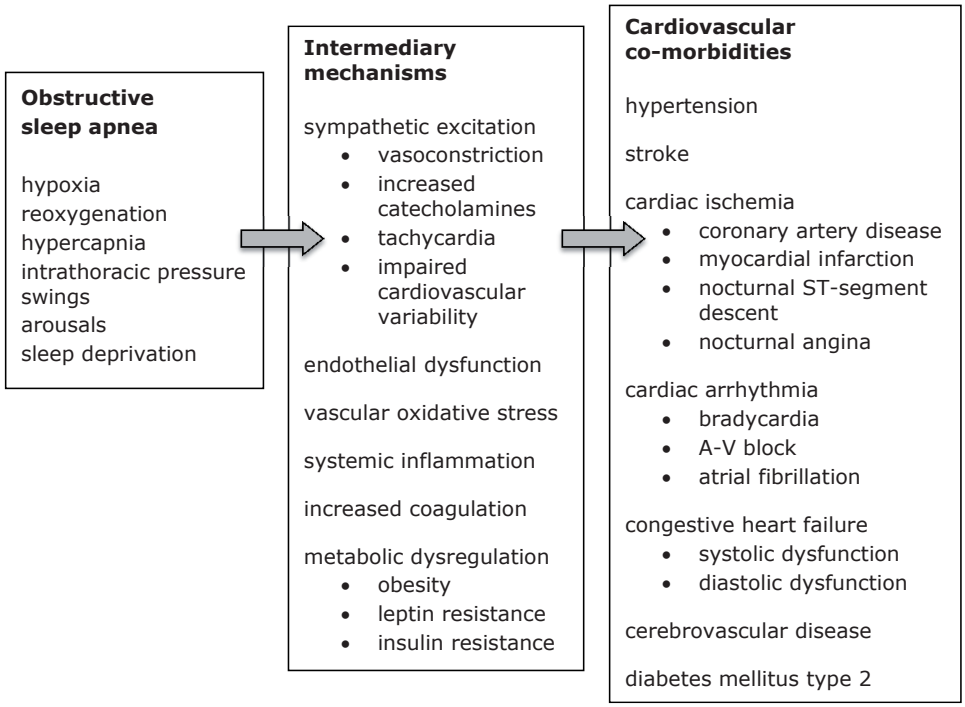

Figure 3. Suggested mechanisms that participate to increase the risk of cardiovascular co-morbidities in patients with obstructive sleep apnea (Modified from Shamsuzzaman et al., 2003)

2.5.1 Cardiovascular co-morbidities

The studies on OSA and related cardiovascular events and all-cause and cardiovascular mortality are summarized in table 7. OSA patients often have coexisting diseases such as obesity, hypertension and diabetes. There are strong indications that there is a causal interaction between OSA and cardiovascular disease (Shamsuzzaman et al., 2003). During sleep, changes in heart rate and blood pressure usually appear 5-7 seconds after the end of an obstructive apnea event. In OSA, negative intrathoracic pressure, hypoxia and arousals are the main pathophysiological features causing cardiovascular consequences.

Negative intrathoracic pressure increases left ventricular transmural pressure, and venous return to the right ventricle causing its dilatation. This can complicate the filling of the left ventricle (Brinker et al., 1980). The combination of an increase in left ventricle afterload and a reduction in preload leads to a reduction in heart stroke volume during obstructive apneas (Shamsuzzaman et al., 2003).

In OSA patients, the increase in sympathetic neural activity triggered by repeated hypoxia and arousal events is thought to be the main mechanism behind the pathogenesis of hypertension. A three-fold increase in risk of de novo hypertension has been found within four years of follow-up of OSA patients having AHI ≥ 15 (Peppard et al., 2000b). Furthermore, the increase in blood pressure has been reported to be linear as a function of AHI (Young et al., 1997d). Lavie et al. found that each apnea event/h increased the risk of hypertension by 1% and a 10% decrease in nocturnal oxygen saturation further elevated the risk by 13% (Lavie et al., 2000). Even when taking account of potential confounders such as age, gender, obesity, alcohol use and smoking, it was claimed that sleep apnea would be associated with hypertension (Nieto et al., 2000). The National High Blood Pressure Education Program included OSA as the first on the list of identifiable primary causes of hypertension (Chobanian et al., 2003). This is in line with the fact that CPAP-treatment reduces blood pressure in OSA patients (Becker et al., 2003, Faccenda et al., 2001, Kaneko et al., 2003a).

Snoring and ischemic stroke have been shown to be associated (Hu et al., 2000, Jennum et al., 1994, Koskenvuo et al., 1987, Palomäki, 1991, Spriggs et al., 1992). Yaggi et al. reported that sleep apnea increased significantly the risk of stroke (Yaggi et al., 2005). Based on a large cohort study, they reported that patients with sleep apnea had an elevated risk (hazard ratio = 1.97) to suffer an initial stroke or death from any cause compared the controls. The risk was reported to be independent of other cardiovascular and cerebrovascular risk factors, such as hypertension (Yaggi et al., 2005). The occurrence of silent stroke is also increased in OSA patients (Minoguchi et al., 2007). The so-called silent stroke is associated with increased platelet activation and systemic inflammation (Minoguchi et al., 2007). Importantly, CPAP treatment has been demonstrated to reduce these

changes (Minoguchi et al., 2007). There are reports that stroke patients have a high prevalence (61-95%) of sleep apnea (Bassetti and Aldrich, 1999, Davis et al., 2013, Dyken et al., 1996, Good et al., 1996, Wessendorf et al., 2000). On the other hand, a stroke may also initiate sleep apnea. Since dysfunction of muscles in the upper airway has been linked to both hemispheric and brain stem strokes (Barer, 1989, Horner et al., 1988, Parra et al., 2000), this functional occlusion of the airway could promote the occurrence of OSA during sleep.

Mohsenin and Valor have also reported that stroke might cause sleep apnea (Mohsenin and Valor, 1995). In their study, none of patients had a previous history of snoring, apnea, obesity, hypersomnolence or neurological impairment, but at the one year follow-up after a stroke, the prevalence of sleep apnea was 80%. Stroke patients with OSA have been reported to have worse outcome and a higher mortality rate than stroke patients without OSA (Good et al., 1996, Sahlin et al., 2008). Dyken et al. also reported that four year mortality for stroke patients was 21% and that the stroke patients who died all had sleep apnea (Dyken et al., 1996). It has also been shown that stroke patients with sleep apnea have a significantly longer admission time in hospital and a significantly worse functional capacity when they return home (Kaneko et al., 2003b). Sleep apnea can be treated with CPAP, but unfortunately stroke patients have a relative low long term compliance for CPAP with values as low as 11-15% being reported (Bassetti et al., 2006, Hui et al., 2002). The reason for this may be that acute stroke patients are typically old and also may experience difficulties in using the CPAP mask due to facial paresis or dysphasia.

Sharar et al. reported that OSA patients (AHI ≥ 11) had a 2.38-fold risk to suffer heart failure (Shahar et al., 2001). It has been speculated that hypertension comes first and then in some patients this eventually leads to heart failure. Those patients, whose blood pressure does not drop normally during sleep (*i.e.* nondippers), have a greater risk for left ventricular hypertrophy and heart failure (Verdecchia et al., 1990). In 1997, Portaluppi et al. reported that male hypertension patients who were nondippers had a higher prevalence of OSA than controls whose blood pressure declined normally during sleep (Portaluppi et al., 1997). Patients with heart failure have a higher prevalence of OSA than the general population, the related studies are summarized in table 8 (Ferrier et al., Javaheri et al., 1998, 2005, Javaheri, 2006, Lofaso et al., 1994, Oldenburg et al., 2007, Sin et al., 1999, Vazir et al., 2007, Wang et al., 2007, Yumino et al., 2009). It is known that CPAP-treatment reduces blood pressure during sleep and diminishes negative intrathoracic pressure changes resulting in decreased left ventricular afterload (Tkacova et al., 1998). In addition, CPAP treatment improves the left ventricular ejection fraction significantly in OSA patients (Egea et al., 2008). However, Smith et al. did not find any improvement in LVEF with the use of autotitrating CPAP-treatment (Smith et al., 2007).

Table 7. Prospective studies on the connection between OSA and cardiovascular events and all-cause mortality (modified from Wang et al. 2013). All recordings were conducted with full polysomnography. AHI = apnea-hypopnea index, Hazard ratio (HR) is the ratio of hazard rates. Hazard rate is the number of events divided by total follow-up time. Odds ratio (OR) is the ratio of the odds *e.g.* of stroke. For example, the odds of stroke is defined as the ratio of the number of individuals with and without stroke in a certain patient group.

Reference	Patients (*n*)	Age (years)	Men (%)	Follow-up (years)	Outcomes (number of events)	Confounders	AHI limit	HR* OR#
Campos-Rodriguez et al., 2012	1116	mean: 56.1	0	6	cardiovascular mortality (*n* = 41)	age, BMI, DM, hypertension and earlier cardiovascular events	> 10	1.60-3.50*
Gottlieb et al., 2010	4422	≥ 40	43.5	median: 8.7	coronary heart disease (CHR) (*n* = 473) and heart failure (HF) (*n* = 308)	age, race, BMI, smoking, DM, blood pressure, cholesterol and antihypertensive medications	> 5	CHR, men ≤ 70 years: 0.91-1.33* HF, men: 0.88-1.58*
Redline et al., 2010	5422	≥ 40	45	median: 8.7	ischemic stroke (*n* = 193)	age, BMI, race, smoking, blood pressure, DM and antihypertensive medications	≥ 4.05	men: 1.86-2.86* women: 1.34-1.21*
Shah et al., 2010	1436	≥ 50	70	mean: 2.9	coronary events or cardiovascular mortality (*n* = 86)	age, race, smoking, alcohol consumption, BMI, AF, DM, hypertension and hyperlipidemia	> 5	2.22-2.82*
Punjabi et al., 2009	6147	≥ 40	46.7	mean: 8.2	all-cause mortality (*n* = 1047)	age, sex, race, BMI, blood pressure, smoking, hypertension, DM and cardiovascular disease	> 5	0.93-1.46*
Martinez-Garcia et al., 2009	166	mean: 73.3	59	5	all-cause mortality (*n* = 81)	age, sex, AHI, CPAP treatment, DM, smoking, BMI, hypercholesterolemia, hypertension, AF and previous stroke or transient ischemic attack (TIA)	≥ 10	AHI ≥ 20: 2.69* AHI 10-19: 0.88*
Young et al., 2008	1522	30-60	55	18	all-cause (*n* = 80) and cardiovascular mortality (*n* = 25)	age, age-squared, sex, BMI and BMI-squared	> 5	all-cause: 1.6-3.0* cardiovascular: 1.8-2.9*
Munoz et al., 2006	394	70-100	57.1	6	stroke (*n* = 20)	age, sex, smoking, alcohol consumption, BMI, blood pressure, DM, AF, hypercholesterolemia, hypertension	≥ 30	2.52*
Arzt et al., 2005	1189	30-60	55	4	stroke (*n* = 21)	age, sex and BMI	≥ 5	AHI ≥ 20: 3.08# AHI 5-20: 0.29#
Marin et al., 2005	1651	≥ 40	100	10.1	fatal cardiovascular events (*n* = 81)	age, diagnostic severity group, cardiovascular disease, DM, hypertension, smoking, alcohol consumption, blood pressure, hypercholesterolemia, use of antihypertensive, lipid-lowering and antidiabetic drugs	≥ 5	1.15-2.87#
Yaggi et al., 2005	1022	≥ 50	71	3.4	stroke or death of any cause (*n* = 88)	age, sex, race, smoking, alcohol consumption, BMI, DM, hypercholesterolemia, AF, hypertension	≥ 5	1.97*

Table 8. Reported prevalence of OSA in patients with heart failure

Reference	Patients (*n*)	All patients, mean BMI (kg/m^2)	Diagnostic entry level AHI (events/h)	OSA patients mean AHI (events/h)	Prevalence of OSA (%)
Yumino et al., 2009	218	29	≥ 10	34	37
Oldenburg et al.,2007	700	27	> 5	25	36
Wang et al., 2007	218	30	≥ 15	34	26
Vazir et al., 2007	55	29	> 15	27	15
Javaheri et al., 2006	100	NR	≥ 15	44	12
Ferrier et al., 2005	53	28	> 10	31	53
Sin et al., 1999	450	29	≥ 10	38	38
Javaheri et al., 1998	81	28	≥ 15	44	11
Lofaso et al., 1994	20	23	≥ 10	30	5

NR= not reported

The most common cardiac arrhythmia is atrial fibrillation (AF) (Calkins et al., 2007, Wolf et al., 1996) and its incidence is reported to have been increasing by 12.6% over 21 years (Miyasaka et al., 2006). AF patients have been reported to have a high prevalence of sleep apnea, which indicates that OSA may be linked to the progression of AF (Braga et al., 2009, Gami et al., 2004, Hoffstein and Mateika, 1994). The Sleep Heart Health Study reported that OSA patients have a four times higher risk of AF than their matched controls (Mehra et al., 2006). Obesity may be the link between OSA and AF. Obesity has a direct association with OSA (Gami et al., 2003) and is also an important risk factor of AF (Frost et al., 2005, Wang et al., 2004). In a large study with over 3000 subjects, both obesity and nocturnal desaturation were found to be independent risk factors for AF (Gami et al., 2007). The multiple pathophysiological mechanisms of OSA, *i.e.* hypoxemia, intrathoracic pressure changes, sympathetic and parasympathetic influences, systemic inflammation and diastolic dysfunction, may participate in the pathogenesis of AF (Ingemansson et al., 1998, Somers et al., 1995).

Bradycardia is another common arrhythmia in OSA patients, and it can proceed even to an asystole. Prolonged apnea and hypoxemia causes vagal activation and simultaneous sympathetic activation of the peripheral blood vessels, this vagal response can elicit bradycardia (Daly et al., 1979, Somers et al., 1992). Asystole usually exists in REM-sleep and is connected with over 4% desaturation (Guilleminault et al., 1983, Koehler et al., 1998). However, all OSA patients do not develop bradycardia. Becker et al. reported that about 7% OSA patients generated bradycardia and all of them had severe OSA (Becker et al., 1995). They also demonstrated that CPAP-treatment could reduce significantly the number of serious bradyarrhythmias.

OSA is an independent risk factor for coronary artery disease (Shahar et al., 2001). There are reports that between 20% to 100% of all OSA patients exhibit nocturnal ST-segment changes with the prevalence being connected with severity of OSA, especially with oxygen desaturation (Franklin et al., 1995, Peled et al., 1999). Patients with severe OSA have a significantly increased risk of suffering fatal cardiovascular events compared to controls matched for age and BMI and the risk decreased with CPAP-treatment (Marin et al., 2005). OSA patients, who do not have cardiovascular diseases, have been claimed to display earlier signs of atherosclerosis than controls without OSA (Drager et al., 2005).

Furthermore, patients with peripheral arterial disease have been reported to experience OSA, and that those OSA patients who/which have AHI > 20 have a strong association with long-term morbidity and mortality (Utriainen et al., 2014). Peripheral arterial disease is an atherosclerotic syndrome being a sign of severe systemic vascular disease (Hirsch et al., 2001).

OSA and type 2 diabetes mellitus share similar risk factors, such as obesity, hypertension and impaired glucose tolerance. Hypoxia causes glucose intolerance (Oltmanns et al., 2004) and connection between OSA, insulin resistance and impaired glucose tolerance has been reported (Ip et al., 2002). OSA is independently associated with insulin resistance, which is a crucial component in the pathogenesis of the metabolic syndrome (Reaven, 1988, Tahrani et al., 2013). This link is supported by the beneficial effect of CPAP-treatment on insulin resistance (Babu et al., 2005, Harsch et al., 2004). Recently, snoring and witnessed apneas were reported to be related to diabetes mellitus in women (Valham et al., 2009). In a Finnish study, men with sleep apnea had an increased prevalence of type 2 diabetes mellitus and abnormal glucose tolerance values (Tuomilehto et al., 2008). This connection between type 2 diabetes mellitus and sleep apnea has also been reported by Cass et al., who indicated that almost half of patients with type 2 diabetes mellitus may be at high risk for OSA (Cass et al., 2013). They also highlighted that most of these patients may remain undiagnosed. Foster et al. also reported a remarkably high prevalence of undiagnosed OSA (86.6%) among obese patients with type 2 diabetes mellitus (Foster et al., 2009).

2.5.2 Non-cardiovascular co-morbidities

Recently OSA has also been associated with non-cardiovascular co-morbidities. An increased cancer mortality has been reported in OSA patients (Campos-Rodriguez et al., 2013, Nieto et al., 2012). The key role in regulating the various stages of tumor formation and progression is hypoxia (chronic and intermittent) (Dewhirst, 2007, Liu et al., 2010, Toffoli and Michiels, 2008). Hypoxia during sleep has been independently associated with an increased risk of cancer (Campos-Rodriguez et al., 2013). Furthermore, when comparing OSA patients with normal subjects, the hazard ratios for cancer mortality were 1.1, 2.0 and 4.8 for patients with mild, moderate and severe OSA, respectively (Nieto et al., 2012).

Furthermore, OSA has been associated with diabetic neuropathy (Tahrani et al., 2012). Tahrani et al. reported that the prevalence of diabetic neuropathy was 60% in OSA patients as compared to 27% in patients without OSA and that OSA was independently associated with diabetic neuropathy even after adjustment for confounders (Tahrani et al., 2012). Furthermore, they reported that the severity of diabetic neuropathy correlated significantly with the severity of OSA and the prevalence of diabetic neuropathy increased with worsening hypoxemia. They postulated that the significant correlation between serum nitrotyrosine and nocturnal hypoxemia could indicate that nitrosative stress was the potential mechanistic link between OSA and diabetic neuropathy.

Patients with OSA have more chronic daily headaches or frequent morning headaches than the general population suffer (Rains et al., 2008). Furthermore, patients with OSA are eight times more likely to suffer from cluster headaches and overweight OSA patients are 24 times more likely to develop cluster headaches (Nobre et al., 2005). In addition, in patients with epilepsy, there is a report of a bidirectional relationship between the seizure frequency and OSA (Malow et al., 2000). A recent review article reported that sleep disturbances are two to three times more prevalent in epilepsy patients than in controls (van Golde et al., 2011). Phillips et al. also reported that 22% of epilepsy patients suffer significant sleep-disordered breathing and it is recommended to include routine polysomnography recordings when these patients are in the epilepsy monitoring unit (Phillips et al., 2013). OSA patients suffer intermittent hypoxia and altered sympathetic activity and these are factors believed to activate epileptogenic regions of the brain, leading to subsequent lowering of the seizure threshold (Malow et al., 2000). This is supported by an earlier study reporting that CPAP-treatment of OSA could reduce the frequency of seizures (Beran et al., 1997).

2.6 TREATMENT

Continuous positive airway pressure (CPAP) is the gold standard of treatment in moderate to severe OSA and also in individuals with mild OSA with prominent symptoms or who are at a high cardiovascular risk. The other treatment options include behavioral guidance, surgical modification of the airway and the use of oral appliances (figure 4). The behavioral guidance includes encouragement to adopt lifestyle modification leading to weight loss and a reduction in alcohol consumption and smoking. Sleeping position therapy (*i.e.* a method that keeps the patient in a non-supine position) should be used if apneas or hypopneas occur only or mostly in supine position.

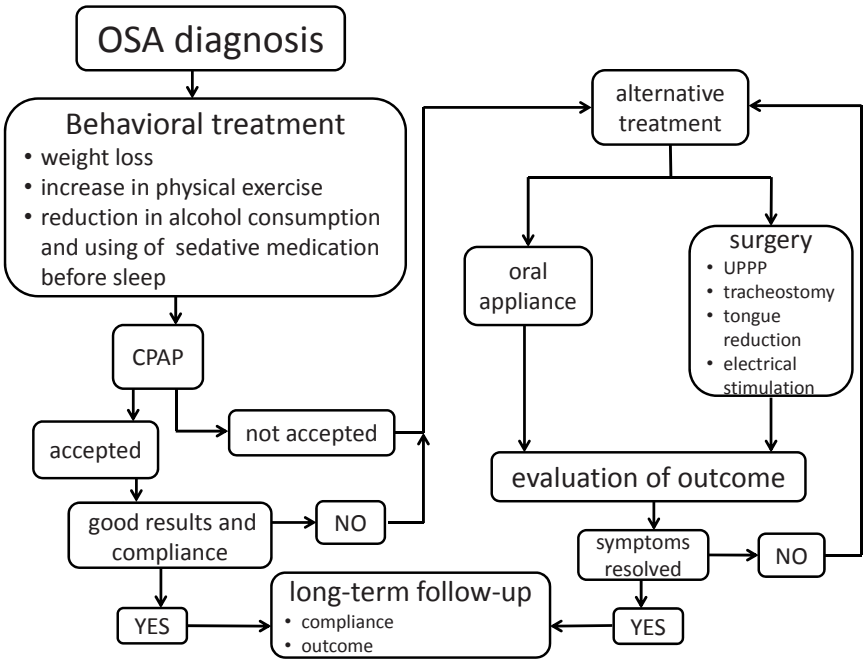

Figure 4. Flow diagram for the treatment of OSA. The treatment of choice is CPAP, even in patients with mild OSA. In addition, every overweight patient should be encouraged to strive for weight reduction. (Modified from Mannarino et al. 2012), UPPP = uvulopalatopharyngoplasty

CPAP is the gold standard for treating OSA in its moderate and severe disease forms and also in mild OSA when there are severe symptoms. CPAP was introduced in 1981 by Sullivan et al., and became quickly widely used in clinical practice (Sullivan et al., 1981). A CPAP device provides appropriate air pressure to the upper airway effectively preventing their obstruction and thus eliminating apneas and hypopneas. Since CPAP reduces intrathoracic pressure, it decreases the afterload in left ventricle, venous return and end-diastolic volumes of both ventricles. However, to be effective treatment CPAP needs to be used for over four hours per night (Barbe et al., 2012). Several studies have indicated that CPAP can reduce blood pressure (Barbe et al., 2010, Becker et al., 2003, Bottini et al., 2012, Kaneko et al., 2003a). Recently, Marin et al. reported that untreated OSA was associated with an increased risk for developing de novo hypertension (Marin et al., 2012). In the same study, long-term CPAP-treatment was shown to reduce the risk of hypertension (Marin et al., 2012). The main problem of CPAP-treatment lies in its limited individual tolerance which is only in the range of 50-85% (Grote et al., 2000, Sin et al., 2002). The CPAP-mask may cause discomfort, even claustrophobia, nasal congestion and difficulties in exhaling (Berry, 2000, Rolfe et al., 1991). The compliance is better in patients with excessive distinct daytime

sleepiness, higher AHI, optimal education about CPAP-treatment, the possibility for prompt consultation should there be problems and also in patients who experienced marked improvements in their daytime symptoms (Kribbs et al., 1993, Sin et al., 2002).

The most important and effective lifestyle intervention is weight loss, because obesity is the most important reversible risk factor for OSA (Malhotra and White, 2002). Apneas and hypopneas, as well as OSA symptoms decrease in conjunction with weight loss (Peppard et al., 2000a, Tuomilehto et al., 2009). Tuomilehto et al. described a 40% reduction in AHI in the weight loss group and two out of three patients were able to move from the mild OSA group into the normal group (AHI < 5) (Tuomilehto et al., 2009). Moderate to severe sleep apnea patients have also been reported to achieve a 67% reduction in the AHI values if they underwent weight loss with a low calorie diet (Johansson et al., 2009). Increased physical exercise is an important way to reduce weight and also to relieve the severity of OSA. A significant reduction in AHI and ODI after 12 week exercise intervention was reported even though patients did not achieve any significant weight loss (Kline et al., 2011). This may have resulted from general strengthening and an increase in fatigue resistance of ventilatory and upper airway dilator muscles (Vincent et al., 2002). Exercise itself has been reported to be significantly connected with good quality of sleep (Flausino et al., 2011, Youngstedt, 2005).

For some patients suffering from moderate or severe OSA and excessive overweight bariatric surgery could represent an option (table 9) (Charuzi et al., 1992, Dixon et al., 2005, Guardiano et al., 2003, Rasheid et al., 2003, Scheuller and Weider, 2001, Sugerman et al., 1992). Recently, they also reported that operated patients not only lost 24-80% of their weight but had a significant fall in AHI, improved sleep architecture and enhanced quality of life with less symptoms of depression (Dixon et al., 2005).

Table 9. Studies of the effects of bariatric surgery in OSA

Reference	**Patients (*n*)**	**Baseline AHI (mean, events/h)**	**Follow-up AHI (mean, events/h)**
Dixon et al., 2005	25	62	13
Guardiano et al., 2003	8	55	14
Rasheid et al., 2002	11	56	23
Scheuller et al., 2001	15	97	11
Charuzi et al., 1992	47	61	8
Sugerman et al., 1992	40	64	26

Other surgical options for treating OSA have focused on the upper airways with attempts to modify dysfunctional pharyngeal anatomy. However, only 2% of adult OSA patients have space-occupying pathological lesion which requires surgical intervention (Sher, 2002). The size and shape of nasal or pharyngeal airway, such as in the nose, soft palate or tongue base may also be surgically modified. The techniques include uvulopalatopharyngoplasty (UPPP), tongue base reduction, radiofrequency tongue base ablation, and anterior mandibular or genioglossal re-positioning, tracheotomy and nasal reconstruction. Unfortunately, surgical treatment has achieved poor long-term efficacy (Sher, 2002). However, in a recent review article Caples et al. reported that maxillomandibular advancement was a promising technique and treated patients reached a substantial reduction in AHI (Caples et al., 2010).

Oral devices are less effective than CPAP, but they may well be treatment options in those patients who do not cope with CPAP. Oral devices are designed to increase the airway space and prevent collapse of upper airway by stabilizing the position of mandibula and to advance the protruding tongue. The mandibular repositioning appliances (MRAs) are the most common type of oral devices (Dieltjens et al., 2012). They are usually well tolerated and inexpensive, but less effective, especially in severe OSA (Johnston et al., 2002). In the two year follow-up study conducted by Doff et al., oral devices were assessed as a feasible treatment in patients with mild to moderate OSA (Doff et al., 2013).

In a recent prospective cohort study, electrical stimulation of the upper-airway was claimed to be an effective treatment of OSA if CPAP treatment is not accepted (Strollo et al., 2014). It was reported that by stimulation of the hypoglossal nerve, the median AHI value decreased by 68% and ODI by 70% compared to the baseline values (Strollo et al., 2014).

3 Objectives of the thesis

The diagnosis and the classification of the obstructive sleep apnea is currently based on the OSA-related clinical symptoms and the number of apnea and hypopnea events or desaturation events per hour, *i.e.* the AHI or oxygen desaturation index (ODI) in polygraphic recordings. AHI and ODI do not contain information about the total time or severity of the obstruction and desaturation events. In this thesis, several novel parameters taking account of the severity of individual events are introduced and are subsequently evaluated. The main objective of this thesis was to devise better tools to early recognition of those OSA patients who are at the highest risk of mortality or cardiovascular morbidity.

The more specific aims were:

I To compare retrospectively the mortality in middle-age men with different severities of OSA and patients without OSA (AHI < 5) in a population living in Eastern Finland.

II To study the relationships of the total duration of the obstruction of upper airway and average oxygen desaturation with the current classification of the severity of the disease based on AHI.

III To investigate whether OSA with especially severe obstruction events would predispose a patient to greater health risks than OSA with a similar apnea-hypopnea index (AHI), but lower severity of individual events.

IV To introduce a novel adjusted AHI parameter comprising information on the number and severity of individual obstruction events, but still allowing use of current AASM criteria for classifying patients to different severity categories.

4 Patients and Methods

This thesis is based on four studies (I-IV). The patient populations, measurement and analysis techniques and determined parameters are summarized in the following chapters and in table 10.

4.1 PATIENTS AND FOLLOW-UP

In all studies the ambulatory recordings were obtained at the baseline of the study and analyzed retrospectively. Basic anthropometric data (height, weight, BMI) and information on age, smoking habits, the use of continuous positive airway pressure (CPAP) treatment, and cardiovascular morbidity were collected from the patients' medical records in Kuopio University Hospital. Furthermore, in studies I, III and IV, the primary and secondary causes of death were obtained from the Statistics Finland (Helsinki, Finland) for deceased patients. The Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland had a favourable opinion on conducting these studies (decision numbers 127/2004 and 24/2013).

Table 10. Summary of patients and methods in studies I-IV

Study	Patients (*n*)	Recordings conducted in	Recorded biosignals	Follow- up (mths, mean±SD)	Endpoint	Main parameters**
I	405*	1993-1997	airflow, respiratory effort, body position and oxygen saturation	187.1±17.6	mortality	AHI
II	267	2006-2007	airflow, abdominal and thoracic movements, oxygen saturation, heart rate, snoring sound and body position	no follow-up	none	AHI, TAD%, THD%, TAHD%, average desaturation and product of TAHD% and average desaturation
III	226*	1993-2001	airflow, respiratory effort, body position and oxygen saturation	198.2±24.7	mortality	AHI and obstruction severity
IV	1068	1993-2001	airflow, respiratory effort, body position and oxygen saturation	198±24.7	mortality and morbidity	AHI and adjusted AHI

* Subgroup of patients investigated in study IV

** The definitions of the parameters are given in chapter 4.3

4.2 EQUIPMENT

In study II, the data was collected with two ambulatory polygraphic devices: Venla (Remote Analysis Ltd, Kuopio, Finland) and Embletta (Embla Co., Broomfield, CO). The signals recorded with these devices, described in detail in the relevant literature (Tiihonen et al., 2009), are summarized in table 10. In studies I, III and IV, a custom-made four-channel polygraphic device was used (Figure 5A). The device enabled recording of airflow, respiratory effort, body position and blood oxygen saturation with synchronous sampling rate of 4 Hz with 8-bit amplitude resolution (Figure 5B). Custom-made Y-shaped triple-head thermistor (2322 636 22103, Philips, Eindhoven, Netherlands) was used for recording of airflow. An in-house-made piezoelectric (PE) sensor was used to measure respiratory effort. The body position was detected with a sensor based on two gravity-sensitive mercury tilt switches fixed at a 90^0 angle to each other and at 45° angles to the plane representing the supine position. In this way, the four main positions (left, right, supine and prone) could be recorded. A Minolta Pulsox-7 finger pulse oximeter (Konica Minolta, Tokyo, Japan) was used to record blood oxygen saturation. The recorded signals are summarized in table 10.

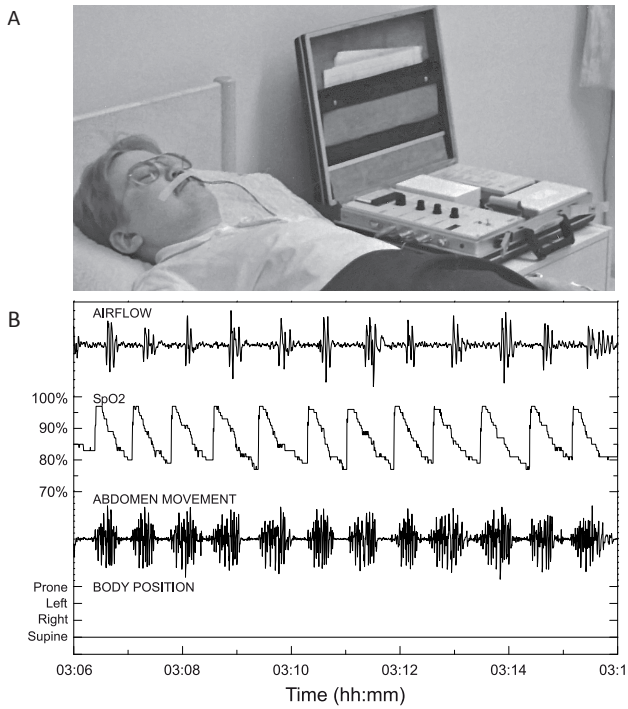

Figure 5. **A)** A custom-made four-channel polygraphic device (subject's permission obtained). **B)** Example of airflow, blood oxygen saturation, respiratory effort (abdomen movement) and body position signals recorded with the device.

4.3 PARAMETERS AND SIGNAL ANALYSIS

All recordings were analyzed based on the standard, internationally used AASM respiratory rules (Iber, 2007). A sleep apnea event was detected when the thermistor signal amplitude fell below 20% of the reference level for at least 10 seconds. Hypopnea events were scored using the rule 4A (Iber, 2007). In order to be scored as hypopnea, the airflow signal had to decrease to 70% and the desaturation event (> 4%) had to occur no later than 20 seconds after the start of the hypopnea. Furthermore, novel parameters, containing exact quantitative information on severity and morphology of individual obstruction and desaturation events, were determined by using a custom-made MATLAB (Mathworks, Natick, MA, USA) script.

In study I, only conventional AHI (equation 1, table 11) was determined. In study II, new parameters were introduced, which contained information on the total duration of respiratory events and average desaturation during the recording. Parameters were total apnea duration as a percentage of sleep time (TAD%, equation 2, table 11), total hypopnea duration as a percentage of sleep time (THD%, equation 3, table 11), total combined cumulative apnea and hypopnea duration as a percentage of sleep time (TAHD%, equation 4, table 11) and also the product of TAHD% and average desaturation (equation 5, table 11).

In study III, a novel parameter called "obstruction severity" was introduced (equation 6, table 11), containing quantitative information on the severity and morphology of individual obstruction and desaturation events. The obstruction severity parameter consisted of the sum of the products of individual apnea and hypopnea events durations and related desaturation areas normalized with the total analysed time. Furthermore, the severities of individual apnea and hypopnea events were determined.

In study IV, the novel "adjusted AHI" parameter was devised (equation 9, table 11). This comprises of information about the number and severity of individual obstruction events. The values of obstruction severity were converted to adjusted AHI through linear fit between square root of obstruction severity parameter and AHI (figure 6).

Table 11. Definitions of the parameters determined in this thesis

study	equation	abbreviation	equation
I	1	AHI	$\frac{\text{apnea + hypopnea events}}{\text{total sleep time}}$
II	2	TAD%	$\frac{\sum_{n=1}^{L} \text{ApDur}_n}{\text{index time}}$
II	3	THD%	$\frac{\sum_{n=1}^{L} \text{HypDur}_n}{\text{index time}}$
II	4	TAHD%	$\frac{\sum_{n=1}^{L} \text{ApDur}_n + \sum_{n=1}^{L} \text{HypDur}_n}{\text{index time}}$
II	5	product of TAHD% and average desaturation	$\frac{\sum_{n=1}^{L} \text{ApDur}_n + \sum_{n=1}^{L} \text{HypDur}_n}{\text{index time}} \times \text{average desaturation}$
III	6	obstruction severity	$\frac{\sum_{n=1}^{L}(\text{HypDur}_n \times \text{DesArea}_n) + \sum_{n=1}^{L}(\text{ApDur}_n \times \text{DesArea}_n)}{\text{index time}}$
III	7	individual apnea-event severity	$\text{ApDur}_n \times \text{DesArea}_n$
III	8	individual hypopnea-event severity	$\text{HypDur}_n \times \text{DesArea}_n$
IV	9	adjusted AHI	$5.328 \times \sqrt{\text{obstruction severity}}$

L denotes the number of the analysed events in the recording, index time denotes the total analysed time (s), ApDur (s) denotes the duration of a single apnea event, HypDur (s) denotes the duration of a single hypopnea event, DesArea (s%) denotes the area of a single desaturation event

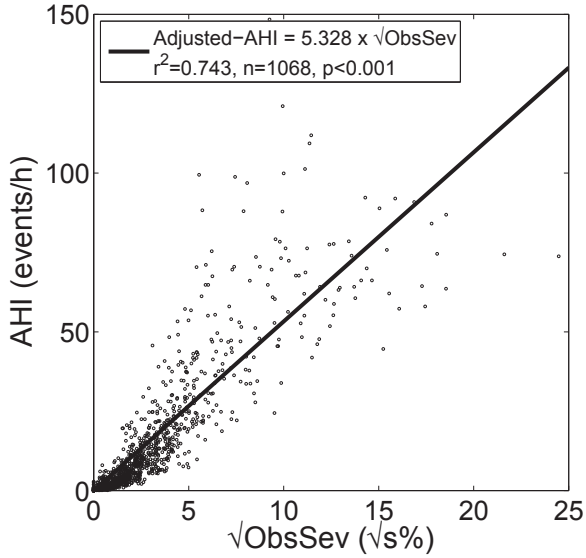

Figure 6. The values of obstruction severity were converted to values of adjusted AHI through linear fit between AHI and square root of obstruction severity.

4.4 STATISTICAL ANALYSES

Statistical analyses were conducted with SPSS software, Stata Statistical Software and R version (table 12). In study I, the Kaplan-Meier estimates of cumulative incidence and the corresponding log-rank tests were used to evaluate the time between ambulatory polygraphic recording and death as a function of the severity of the disease. Furthermore, the uni- and multivariable Cox proportional hazard models were used to determine the statistical significance of differences between a) the normal, b) mild and c) moderate to severe groups. In study II, the statistical significance of the differences between the OSA severity groups were determined with the Kruskal Wallis-test and the correlations between parameters were calculated by determining the Pearson or Spearman correlation coefficients. In study III, multivariable logistic regression analysis was used to assess the differences between living and deceased patients. Furthermore, the mixed-model approach was applied to test the difference between the distributions of the severities of individual obstruction events determined for living and deceased patients. In study IV, the significance of difference between the conventional AHI and adjusted AHI was studied using the Mann-Whitney U test. Linear regression analysis was used to investigate the relationship between the square root of obstruction severity -parameter and AHI. Furthermore, the T-test was used to evaluate the differences in follow-up time normalized risk ratios of mortality and morbidity between the patients with or without OSA. Throughout the thesis the limit of statistical significance was set to $p<0.05$.

Table 12. The statistical tests applied in studies I-IV

Study	Statistical tests	Software
I	Uni- and multivariable Cox proportional Hazard models, Kaplan-Meier estimates, corresponding log-rank tests	Stata Statistical Software 10.1
II	Kruskal Wallis test, Pearson and Spearman's correlation	SPSS versions 14.0 and 17.0
III	Multivariable logistic regression analysis, mixed-model	SPSS version 20.0
IV	Mann-Whitney U test, linear regression analysis, T-test	SPSS version 20.0 and R version 2.15.2, www.r-project.org

5 Results

In summary, OSA was found to be linked to an increased mortality rate and morbidity. The novel parameters incorporating duration and morphology of obstruction and desaturation events were found to provide important supplementary information in addition to that obtained with conventional AHI in the estimation of the severity of OSA.

5.1 ESTIMATION OF SLEEP APNEA SEVERITY WITH AHI

In study I, the patients with moderate and severe OSA had significantly (p<0.05) higher mortality (hazard ratio 3.13) than their counterparts without OSA (table 13). In addition, the cardiovascular mortality was higher in the moderate to severe categories, but after adjustment for age, BMI and smoking, the result was no longer statistically significant.

Table 13. Hazard ratios of mortality of patients in different AHI-groups, (mean and confidence interval are provided)

AHI-group	No disease	Mild	Moderate/ Severe	*p*-value for trend not adjusted	*p*-value for trend, adjusted with age, BMI and smoking
overall mortality	1.0	1.68 (0.74-3.74)	3.13 (1.59-6.15)	<0.001	0.036
cardiovascular mortality	1.0	1.87 (0.44-7.92)	4.04 (1.17-13.9)	0.014	0.142
non-cardiovascular mortality	1.0	1.59 (0.61-4.17)	2.74 (1.23-6.13)	0.008	0.135
mortality related to cancer and tumors (%)	1.0	0.56 (0.05-6.10)	2.16 (0.46-9.97)	0.328	0.148
mortality related to gastrointestinal diseases (%)	1.0	2.21 (0.20-24.5)	5.74 (0.72-45.7)	0.058	0.138
mortality related to miscellaneous causes (%)	1.0	1.95 (0.58-6.64)	2.27 (0.77-6.70)	0.129	0.931

5.2 CONNECTION BETWEEN DURATION AND MORPHOLOGY OF OBSTRUCTION AND DESATURATION EVENTS AND SEVERITY OF OSA

In study II, a significant increase in the durations of total apnea and hypopnea as a percentage of sleep time (TAD% and THD%, respectively) was seen as a function of the severity of disease. The average duration of a single apnea event was found to increase significantly in conjunction with the progression of the disease (figure 7A). Furthermore, the relative time in apnea increased significantly more than that in hypopnea (figure 7B). By multiplying total apnea and hypopnea duration and average desaturation (TAHD%) it was intended to obtain an estimate of the true severity of the disease. The correlation of AHI and product of TAHD% and the average desaturation was r = 0.845 (p<0.001) indicating that AHI may not fully reflect the severity of OSA (figure 7C).

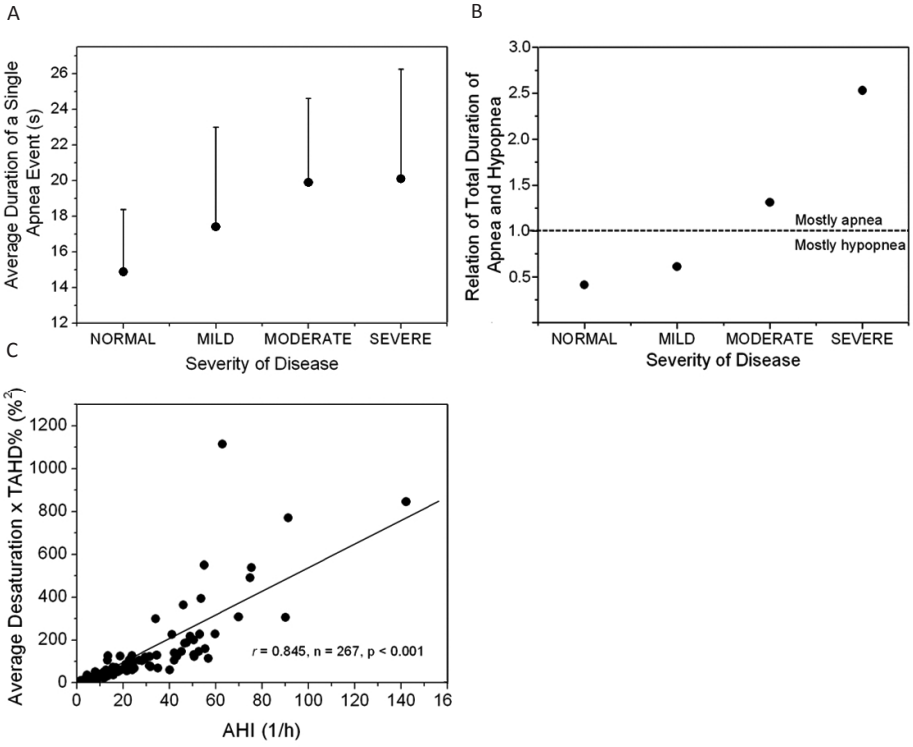

Figure 7. **A)** The average duration (+SD) of individual apnea events was found to increase in conjunction with the progression of OSA. **B)** The relative duration of apnea events increased along with the progression of the disease. **C)** Patients with similar AHI values showed substantial differences in the product of the average desaturation and total duration of apnea and hypopnea events.

In study III, the "obstruction severity" –parameter was introduced, incorporating the severities of individual obstruction events. The potential benefits of this parameter were evaluated by comparing alive and deceased male patients (113 pairs), matched for AHI, BMI, age and follow-up time. The obstruction severity was higher in those patients who died during the follow-up when they were compared with the surviving patients. Furthermore, the obstruction severity was the only parameter statistically significantly related to mortality in patients with severe OSA. In contrast to AHI, the values of obstruction severity for deceased and alive patients correlated only moderately (figure 8).

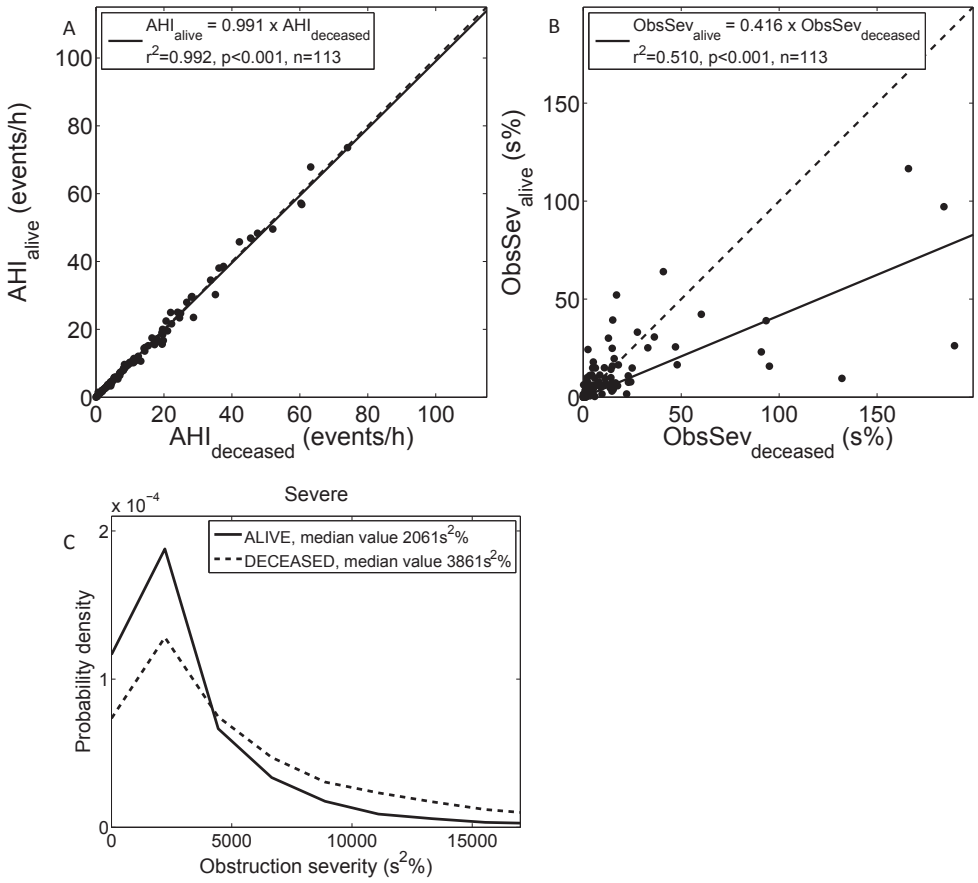

Figure 8. **A)** Spearman's correlation between AHI values of alive and deceased patients. **B)** Spearman's correlation between the obstruction severity-values of alive and deceased patients. The relations between obstruction severity-values of alive and deceased patients deviates from the centre line (dashed) indicating more severe disease in deceased patients. **C)** The probability densities of the individual obstruction events severities in severe OSA for alive and deceased patients. The deceased patients had smaller proportion of less severe events compared to the alive patients and the proportion of more severe events was higher.

In study IV, the obstruction severity parameter was further processed, so that it would be comparable to the values obtained with conventional AHI. To achieve this goal, a method for converting obstruction severity parameter values to values of "adjusted AHI" was devised. This made it possible to use the AASM Guidelines for diagnostics of the severity of the disease. In study IV, it was shown that the risk ratios of all-cause mortality and cardiovascular mortality were higher in moderate/severe OSA-groups formed based on the adjusted AHI parameter in comparison with those based on conventional AHI (figure 9).

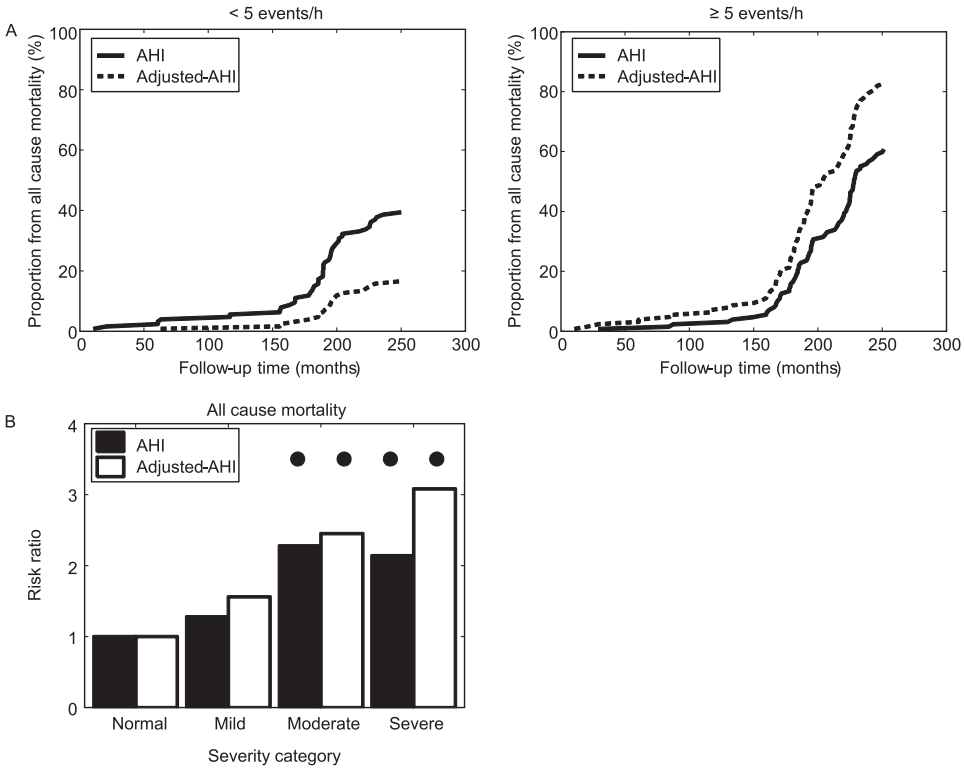

Figure 9. **A)** Proportion of all-cause mortality in patients diagnosed not to have OSA (AHI < 5) or to have OSA (AHI ≥ 5). The group of patients diagnosed as having OSA based on adjusted AHI included a higher proportion of deceased patients than the group estimated from conventional AHI. **B)** Follow-up time adjusted risk ratio of all cause of mortality. Especially in the severe OSA group the risk ratio was elevated when diagnosis was based on the adjusted AHI. The black dot indicates statistically significantly (p<0.05, T-test) elevated risk ratio as compared to the normal group.

Furthermore, it was found that a significant rearrangement of patients between the diagnostic groups took place when the adjusted AHI instead of the conventional AHI was used (figure 10).

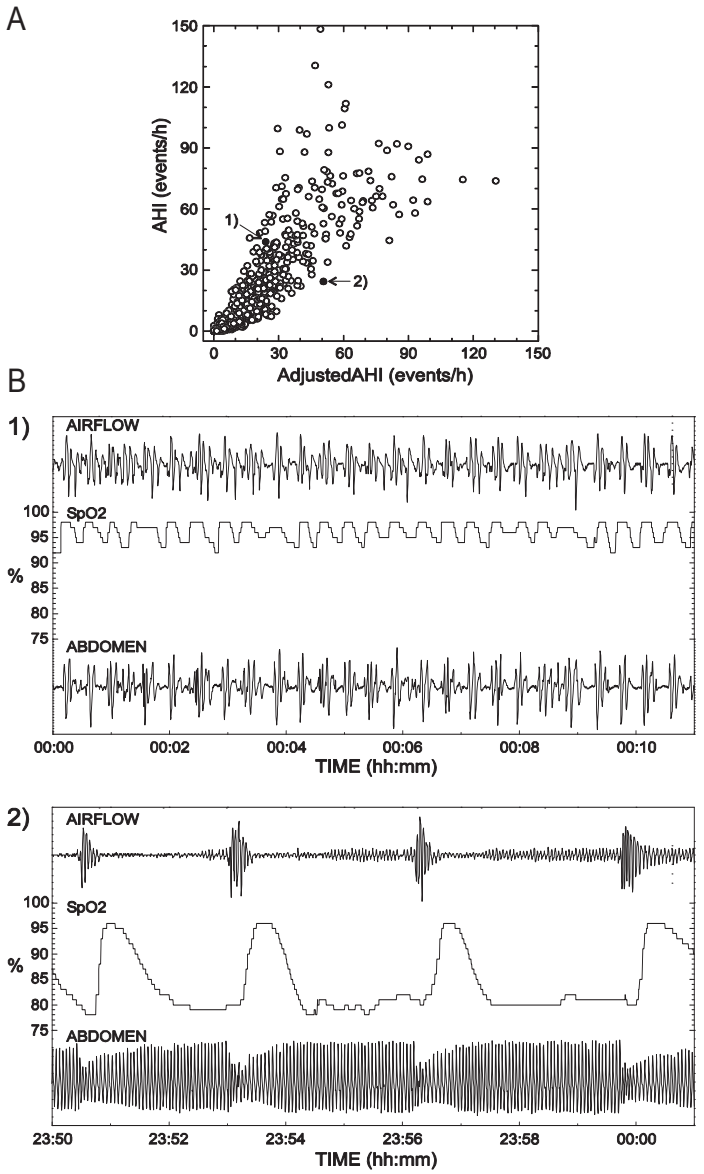

Figure 10. **A)** AHI as a function of adjusted AHI. Patients 1 (AHI = 43.9, adjusted AHI = 23.9) and 2 (AHI = 24.4, adjusted AHI = 50.6) represent typical cases receiving different OSA classifications depending on whether the diagnosis is based on conventional AHI or adjusted AHI. **B)** Polygraphic recordings of the patients. Patient 1 has shorter apneas and less severe desaturation events than patient 2.

6 Discussion

Obstructive sleep apnea (OSA) is a considerable public health burden. A very recent study by Peppard et al. reported that OSA (AHI ≥ 5 and clinical symptoms) occurs in approximately 14% of men and 5% of women aged 30-70 years (Peppard et al., 2013). It has been suggested that the prevalence of OSA will further increase in the future (Young et al., 2002). Becauce of this, an effective screening of OSA and subsequently the identification of those patients who are at the highest risk of suffering severe health consequences are important. The diagnostic and classification of OSA are based on the frequency of apnea and hypopnea events (AHI) including the sleep-related symptoms. The frequency of desaturation events (ODI) is also a commonly used diagnostic index. The relationships between OSA and mortality have been studied thoroughly in a number of countries, though not in Finland (Marin et al., 2005, Won et al., 2013). Furthermore, the severity of individual apnea and hypopnea events has been investigated in only a few studies (Kulkas et al., 2013b, Otero et al., 2010, Otero et al., 2012). Kulkas et al. examined this issue and reported that patients with similar AHI values could suffer from OSA of very different severities (Kulkas et al., 2013a). They also reported that the mortality rate was related with the severity of obstruction events (Kulkas et al., 2013b). The working hypothesis here was that mortality in eastern Finland would be especially high and that the morphology of respiratory and desaturation events would influence prognosis of OSA. The first aim was to study mortality related to sleep apnea in the Finnish population. In Finland, especially in eastern Finland, the proneness to coronary heart disease is significantly elevated in relation to other countries (Jousilahti et al., 1998, WHO, 1993). The second aim was to investigate the connection between the severity of individual obstruction events and mortality and morbidity. Further, it was intended to evaluate novel diagnostic parameters for polygraphy, incorporating the frequency and severity of obstruction events. Finally, it was decided to modify the novel parameters so that they could be applied in conjunction with the AASM Guidelines for determining the true severity of the disease.

Study I analyzed retrospectively ambulatory polygraphic recordings of 405 men and investigated their mortality rates. After adjustment for age, BMI and smoking, the patients with moderate to severe OSA had a significantly (p<0.05) higher mortality over the 12 years follow-up (hazard ratio 3.13) than the patients without OSA. The overall mortality was 26.4% in moderate to severe OSA compared to only 9.7% in the control group (*i.e.*, men with normal findings in PSG). These findings are in line with earlier studies reporting that sleep apnea is an independent risk for all-cause mortality (Marshall et al., 2008, Young et al., 2008). In the present study, the mean age of patients at the baseline was 50.4, which is in

line with the recent study of Martinez-Garcia et al. reporting that also in elderly individuals untreated OSA was associated with the risk of all-cause mortality (hazard ratio 1.99) and cardiovascular mortality (hazard ratio 2.25) (Martinez-Garcia et al., 2012). Here the hazard ratio for cardiovascular mortality (4.04) of patients with moderate to severe OSA was also elevated. This result was not statistically significant, which may be due the limited number of patients. However, this finding is supported by Marin et al. who reported that the odds ratio of suffering fatal cardiovascular events was elevated by 2.87 fold in untreated OSA patients (Marin et al., 2005).

Study II investigated the total duration of apnea and hypopnea events and average desaturation and reported that patients having a similar conventional AHI can display significant differences in the values of these new parameters. Thus either AHI or ODI alone may not reflect the true severity of the disease, because these indices are based on simple counting of events, without incorporating the severity of the events. Furthermore, the durations of apnea and hypopnea can increase such manner that the frequency *per se* paradoxically cannot increase and may even decline. The average of total combined cumulative apnea and hypopnea duration (TAHD%) was over 30% of the recorded time in the severe OSA group. For a patient suffering from the most severe form of the disease the total duration of apnea and hypopnea events was 70% of the recorded time. This is strikingly high and may increase significantly the risk of sudden death or non-fatal cardiovascular events. It was noted that the depth of desaturation increased significantly as a function of the severity of OSA, which indicates that as the disease progresses, the adaptation to higher carbon dioxide levels reduces the central drive to breathe. These results are in line with the views of Otero et al. who reported that AHI may not be the best parameter and that AHDI (apnea-hypopnea-desaturation index) could be a better tool for diagnosing OSA (Otero et al., 2012).

In study III, the potential of obstruction severity parameter introduced along several new parameters by Kulkas et al. (Kulkas et al., 2013b). The novel obstruction severity parameter contains information on the duration of individual apnea and hypopnea events and also the related desaturation areas, normalized to the total time analyzed. It was hypothesized that this new parameter would provide more information than conventional AHI. This hypothesis was evaluated by comparing obstruction severity in deceased and alive patients with similar AHI values. The deceased patients were found to have higher values in terms of obstruction severity than the alive AHI-matched patients. This supports the working hypothesis and indicates that the obstruction severity parameter could provide additional diagnostic and prognostic information than can be obtained from conventional AHI. The present results are supported by reports that patients with excessive daytime sleepiness have longer apnea events and deeper desaturation events (Bedard et al., 1991a, Mediano et al., 2007). Furthermore,

Punjabi et al. reported that only the hypopneas linked to desaturation ≥ 4% were connected with the incidence of cardiovascular disease (Punjabi et al., 2008). The obstruction severity parameter takes into account the total area of the oxygen desaturation event, thus it may characterize the severity of disease even more comprehensively.

Although the obstruction severity parameter was found to be promising, it does not allow for the classification of the disease severity according to the currently used international AASM-Guidelines. Therefore it was decided to convert the obstruction severity parameter into values of AHI. This was achieved by calculating a linear fit between the square root of obstruction severity and AHI. When using adjusted AHI for the classification of patients, a clear rearrangement was evident between the severity categories. After this rearrangement, higher number of deceased patients was found in the OSA-group (AHI ≥ 5). This is line with the view of Otero et al. that conventional AHI underestimates the severity of OSA (Otero et al., 2010). The risk ratios of all-cause mortality and cardiovascular mortality were higher in the moderate and severe OSA groups when the classification was based on the adjusted AHI. Therefore, the adjusted AHI could help in recognizing those OSA patients with the highest risk of suffering severe health consequences. This is in line with the results of Punjabi et al., who reported that the degree of nocturnal hypoxemia was an independent predictor of mortality (Punjabi et al., 2009) and Peker et al. claiming that low oxygen saturation was associated with a risk of coronary artery disease (Peker et al., 2006). Furthermore, longer obstruction and deeper desaturation events have been reported to cause greater physiological stress *e.g.* in the form of increased sympathetic activity and oxidative stress (Narkiewicz et al., 1998, Somers, 1989). It has also been reported that OSA patients have high levels of sympathetic activity even during daytime wakefulness, and that during sleep their blood pressure and sympathetic activity is further elevated (Somers et al., 1995). The increased chemoreflex drive is thought to be one of the reasons for the high level of tonic sympathetic excitation (Narkiewicz et al., 1998).

Despite the very promising results, there are certain limitations to be recognized in the present study. First, all recordings were conducted with ambulatory devices not allowing the recording of EEG. Therefore, it was not possible to conduct an accurate determination of the total time asleep. The total sleep time was estimated by inspecting the raw signals. As all determined parameters involved normalization with the total sleep time, this is a significant source of uncertainty. Furthermore, the lack of EEG data affects the selection of the rule for detecting hypopneas. The arousals could not be detected and the AASM rule 4A had to be used. In studies I, III and IV, a thermistor was used for the detection of airflow. This could have affected the duration of the detected hypopnea events and also influenced the number of detected hypopneas. However, at the time when these patients were examined (1993-2001), nasal

cannulas with sensitive pressure transducers were not widely clinically available. However, all recordings in this thesis were analyzed similarly and in accordance with the AASM Guidelines and thus it is believed that these technical shortcomings have not affected the reliability of the conclusions. One notable factor is the selection of the control group. The patients included into the control group did not meet the criteria for OSA (AHI < 5), but they all were referred to ambulatory polygraphic recordings due to a suspicion of sleep disordered breathing. This is not an optimal control group and in fact random healthy controls from general population would have been more suitable. However, it is a widely used method in related publications to use subjects with the normal findings as "controls". On the other hand, some of our control group patients may have had partial stenosis of the upper respiratory tract or upper airway resistance syndrome. Therefore, if one had access to a true control population completely free from any sleep-related breathing disturbance then it is likely that even higher risk ratios would have been obtained for the patients with OSA.

For practical reasons, the present study was designed to be retrospective. This inevitably led to compromises in the selection of control group and complicated somewhat the collection of patients data from hospital archives. It is also less controlled than could have been with a prospective study.

The very practical clinical benefit of this study may be that it provides a new valuable tool for use in everyday clinical diagnostics. By adopting the new adjusted AHI parameter, the physician (*e.g.*, clinical neurophysiologist responsible for the analysis of polygraphy, or the clinician treating the patients) can estimate better his/her patients´ individual risk for cardiovascular morbidity and mortality. One must be aware of, the physiological fact that the relationship between pulse oximetry values and partial pressure of oxygen is not linear. Therefore, with this new adjusted AHI parameter - which takes into account also desaturation events in terms of their depth and length - these patients whose baseline partial pressures of oxygen are initially low, will probably be judged to have more severe adjusted AHI than otherwise obtained when using the traditional AHI. When applying this new parameter in clinical practice, these patients can also be treated more effectively (*e.g.*, be candidates for early initiation of CPAP-treatment). However, there are a number of polysomnography parameters (*e.g.* ODI10, ODI20 and the lowest SpO_2) that could be compared to the adjusted AHI to assess their predictability on mortality and morbidity in OSA patients. This could also enable development of new improved sensitive and specific polysomnography parameters which would better distinguish those patients that will benefit most from the different treatment options. Furthermore, the inclusion of other factors such as sleeping position in the adjusted AHI could enhance its potential. When estimating the individual risk of several health consequences also other factors should be taken into account *e.g.* patient medical history and lifestyle.

One could recommend that the clinical use of adjusted AHI parameter should be incorporated into commercial polysomnography software packages. We have already realized this in Remlogic® version 3.2, and will release the software modification for public use in the near future.

7 Summary and Conclusions

The most commonly used polygraphy parameter for detecting OSA is the apnea-hypopnea index (AHI). However, AHI does not reveal direct information on the total time or severity of the obstruction. This thesis introduces a novel obstruction severity parameter incorporating this information. In addition, a method was devised for converting the obstruction severity parameter values into units of a parameter called adjusted AHI. This permits one to use the AASM AHI limits for diagnostics of the severity of the disease. The main findings are summarized in respect to the aims of the thesis as follows:

I The OSA-related risk of mortality, especially due to cardiovascular diseases was found to be especially high in the population of Eastern Finland.

II Patients with similar AHI values showed significant variation in the values of the novel parameters incorporating average oxygen desaturation and the total duration of the obstruction of upper airway (TAD%, THD%, TAHD% and the product of average depth of desaturation and TAHD%). This suggests that the novel parameters could reveal supplementary relevant information to conventional AHI when diagnosing the severity of OSA.

III In contrast to AHI, obstruction severity was related in a statistically significant manner to mortality in the severe OSA category. Thus, the obstruction severity parameter provided valuable prognostic information supplementing the AHI data.

IV The adjusted AHI parameter enables efficient recognition of those OSA patients with the highest risk of mortality or cardiovascular morbidity. Since adjusted AHI may be applied together with AASM AHI limits it may be easily adopted into clinical use.

To conclude, in this thesis, novel parameters for diagnostics of OSA were introduced and clinically tested. These parameters were found to provide new information as compared to traditional AHI, particularly in respect to the severity of abnormal breathing and desaturation events.

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ORIGINAL PUBLICATIONS (I-IV)

Anu Muraja-Murro

Obstruction Event Severity in Diagnostics of Sleep Apnea

Obstructive sleep apnea (OSA), the most common sleep disorder, is characterized with repeated episodes of blockage of upper airway during sleep. Currently, diagnosis and classification of OSA is based on the number of apnea and hypopnea events or desaturation events per hour. The purpose of this study was to create a novel diagnostic parameter containing information on severity of individual obstruction and desaturation events. Adjusted AHI parameter was introduced and shown to improve the recognition of the patients with the highest risk of the severe health consequences of OSA.

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