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Mirja Tenhunen

Detection and Assessment of Sleep-Disordered Breathing with Special Interest of Prolonged Partial Obstruction

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Supervised by

Sari-Leena Himanen, M.D, Ph.D, Associate Professor
Department of Clinical Neurophysiology,
Medical Imaging Centre and Hospital Pharmacy,
Pirkanmaa Hospital District, Tampere, Finland
School of Medicine
University of Tampere, Finland

and

Jari Hyttinen, Dr.Tech, Professor
Department of Electronics and Communication Engineering and BioMediTech,
Tampere University of Technology, Tampere, Finland

Reviewed by

Ulla Anttalainen, M.D., Ph.D
Division of Medicine, Department of Pulmonary Diseases,
Turku University Hospital, Turku, Finland
Sleep Research Center, the Department of Physiology,
University of Turku, Turku, Finland

and

Petro Julkunen, Ph.D, Adjunct Professor
Department of Clinical Neurophysiology
Diagnostic Imaging Centre
Kuopio University Hospital, Kuopio, Finland
Department of Applied Physics
University of Eastern Finland, Kuopio, Finland

Opponent

Tapio Seppänen, Dr.Tech, Professor
Department of Electrical and Information Engineering
University of Oulu, Finland

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Tiivistelmä

Unipolygrafiatutkimus on unihäiriödiagnostiikan referenssimenetelmä. Se on vaativa, työläs ja monikanavainen rekisteröintimenetelmä, jossa uni- ja valveaika voidaan erottaa toisistaan aivosähkökäyrässä, silmänliikekäyrässä ja lihassähkökäyrässä esiintyvien löydösten perusteella. Rekisteröinti suoritetaan useimmiten valvottuna ja etenkin hengityshäiriödiagnostiikkaa tukevien lisälaitteiden kera, joten se vaatii potilaan yöpymisen unilaboratoriossa. Suomessa on pitkät perinteet unipatjojen käytöstä unitutkimuksissa etenkin hengitys- ja liikehäiriödiagnostiikassa. Vanhat, jäykät, sängynkokoiset SCSB-patjat voidaan nykyään korvata pienemmillä, notkeilla Emfit-filmistä valmistetuilla patjasensoreilla. Nämä reaaliaikaiseen liike- ja kohtausseurantaan tarkoitetut patjat soveltuvat myös hyvin hengityksen monitorointiin unenaikana. Emfit-sensoria ei ole kuitenkaan vielä tähän mennessä validoitu kliiniseen käyttöön sopivaksi diagnostiikan apuvälineeksi.
Unenaikaiset hengityshäiriöt ovat yleisiä, nukkumista häiritseviä ja erialaisia väsymysoireita aiheuttavia terveysongelmia aikuisväestön keskuudessa. Niiden diagnosointi ja hoito kuormittavat terveydenhuoltoa enemmän kuin koskaan. Obstruktivinen uniapnea (OSA) ja siihen liittyvät terveyshaitat kuten sydän- ja verisuonisairaudet osataan nykyään tunnistaa varsin hyvin. Yleensä uniapnean hoitoa suositellaan kun hengityskatkoja on keskimäärin yli 15 tapahtumaa nukuttua tuntia kohti. Pitkäkestoinen osittainen ylähengitystieahtauma on jäänyt vähemmälle huomiolle. Siinä unitutkimuksissa ei havaita hengityskatkoja tai periodista hengitystä eikä toistuvia havahtumisia, jotka määrittävät yleisesti hengityshäiriön vaikeusasteen. Se saattaakin jäädä diagnosoimatta ja hoitamatta, vaikka potilasryhmällä on todettu päiväaikaisia oireita, kuten päiväaikaista väsymystä, päänsärkyä ja masennusoireita. Hengityshäiriödiagnostiikassa tulisikin keskittyä ylähengitysteiden toimintahäiriön laadun määritykseen erilaisten indeksien sijaan.

Tässä väitöskirjatyössä Emfit-rekisteröintiä käytettiin periodisten hengityskatkojen ja pitkittyneen osittaisen ylähengitysahtauman havaitsemiseen. Tulosten perusteella Emfit-patjasignaalista luokiteltu hengityskatkojen määrä korreloi hyvin tavanomaisen hengityskatkoanalyysin kanssa. Lisäksi Emfit-patjasignaalista luokiteltuun pitkäkestoiseen osittaiseen ylähengitystieahtaumaan liittyi selkeä rintakehän sisäisen negatiivisen paineen nousu, mikä osoitettiin yhtäaikaisella ruokatorven kautta tapahtuvalla painemittauksella. Sitä pidetään lisääntyneen hengitystyön mittaamisen referenssimenetelmänä. Vaikka siis pitkäkestoinen osittainen ylähengitystieahtauma ei välttämättä näy tavanomaisessa unitutkimuksessa, se aiheuttaa poikkeavia muutoksia unipatjarekisteröinnissä. Pitkäkestoista osittaista ylähengitystieahtaumaa ilman merkittävää uniapneaa todettiin 11%:lla tutkituista, kun selvitettiin retrospektiivisesti vuoden ajalta unilaboratoriossa tutkittavina olleiden potilaiden hengityshäiriön tyyppi. Pitkäkestoista osittaista ylähengitysahtaumaa sairastavat potilaat olivat yhtä väsyneitä kuin uniapneapotilaat, mutta heidän elämänlaatunsa oli huonompi mitattuna GHQ-12 kyselytutkimuksella. Nämä tulokset ja sydämen syke-

vaihtelua mittaavan osatyön löydökset osoittavat että pitkittynyt ylähengitystieahtauma on itsenäinen hengityshäiriö.

Koska helpoille ja halvoille unenaikaisten hengitys- ja liikehäiriöiden seulontamenetelmille on kasvava tarve, niin väitöskirjassa tutkittiin myös trakeaäänen käyttömahdollisuutta hengityshäiriöiden analysoinnissa. Se osoittautui käyttökelpoiseksi periodisen hengityksen ja hengityskatkojen havaitsemisessa, mutta myös pitkittyneen ylähengitysahtauman erotusdiagnostiikassa. Väitöskirjatyön päätavoitteena oli hengityshäiriödiagnostiikan kehittäminen ja parantaminen, ja nimenomaan esitettyjen uusien diagnostiikkamenetelmien osalta niiden luotettavuuden arvioiminen lisääntyneen hengitystyön osoittamisessa. Unirekisteröintien analyysi perustuu vielä pitkälti rekisteröintejä analysoivan lääkärin subjektiiviseen ja visuaaliseen arvioon. Emfit-unipatjalla voidaan erotella unenaikaisia hengityshäiriöitä ja parannetaan myös niiden diagnostista tarkkuutta. Se on toiminnaltaan teknisesti varsin häiriötön, automaattinen, ei-kajoava, eli untahäiritsemätön diagnostiikkamenetelmä, joka sopii mainiosti myös kotona tapahtuviin rekisteröinteihin. Se on kotimainen, edullinen ja soveltuu seulontatutkimusvälineeksi suurille potilasjoukoille. Nykyisin terveysteknologiset biosignaalien mittaussovellukset ovat jokaisen ulottuvilla ja käytettävissä älypuhelimilla tai tietokoneilla. Terveystietämyksen lisääntyminen kannustaa meitä kaikkia seuraamaan ja ottamaan vastuun omista terveyteen vaikuttavista tottumuksistamme jo paljon varhemmin ennen ongelmien esiintymistä. Hyvän unen tarve on tunnustettu tosiasia hyvälle ja terveelle elämälle.

Abstract

Sleep-disordered breathing (SDB) has become more common and puts more strain on public health services than ever before. Obstructive sleep apnea (OSA) and its health consequences such as different cardiovascular diseases are nowadays well recognized. In addition to OSA, attention has recently been paid to another SDB; prolonged partial obstruction. However, it is often undiagnosed and easily left untreated because of the low number of respiratory events during polysomnography recording. This patient group has found to present with more atypical subjective symptoms than OSA patients.

Polysomnography (PSG) is considered to be the gold standard in reference methods in SDB diagnostics. PSG is a demanding and laborious multichannel recording method and often requires subjects to spend one night in a sleep laboratory. There is long tradition in Finland to use mattress sensors in SDB diagnostics. Recently, smaller electromechanical film transducer (Emfit) mattresses have replaced the old Static Charge-Sensitive Bed (SCSB) mattresses. However, a proper clinical validation of Emfit mattresses in SDB diagnostics has not been carried out.

In this work, the use of Emfit recording in the detection of sleep apneas, hypopneas, and prolonged partial obstruction with increased respiratory effort was evaluated. The general aim of the thesis is to develop and improve the diagnostic methods for sleep-related breathing disorders.

Comparisons with both PSG with nasal pressure recording and transesophageal pressure were made. Special attention was paid to the existence of the spiking phenomenon in the Emfit mattress in relation to changes in negative intrathoracic pressure in estimating increased respiratory effort. This entails monitoring the esophageal pressure as a part of nocturnal polysomnography. The recording method is demanding and uncomfortable and is usually not used with ordinary sleep laboratory patients. Thus, reliable and easy indirect quantification methods for respiratory effort are needed in clinical work. According to the results presented in this work, the Emfit signal reveals increased respiratory effort as well as apneas/hypopneas.

To find out the prevalence and consequences of prolonged partial obstruction among sleep laboratory patients was another aim of this thesis. This was done by retrospective analyses of sleep laboratory patients from one year. The prevalence of patients with prolonged partial obstruction was 11%. They were as sleepy as OSA patients, but their life quality was worse, as assessed by a survey. These results, along with the findings of the heart rate variation evaluation carried out in this thesis, suggest that prolonged partial obstruction and OSA should be considered as different entities of SDB.

With the Emfit mattress sensor, the SDB types can be differentiated, which is expected to enhance the accuracy of diagnostics. However, there is increasing need for easy and cheap screening methods to evaluate nocturnal breathing. In this respect, the usability of compressed tracheal sound signal scoring in SDB screening was estimated. The method reveals apneas and hypopneas but, according to the present findings, it can also be used in the detection of prolonged partial obstruction. The findings encourage the use of compressed tracheal sound analysis in screening different SDB.

The analysis of sleep recordings is still based on a doctor's subjective and visual estimation. To date, no generally accepted and sufficiently reliable automatic analysis method exists. Robust, automatic quantification methods with easier techniques for non-invasive sleep recording would enable the analysis methods to be also used for screening purposes. In this technology-orientated world, people could take much more responsibility and take care of themselves better by following their own biosignals and by changing their health habits earlier. The need for good sleep as a necessity for good life and health is widely recognized.

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I always said that if ever there came the day when I finished my thesis and finally fulfilled my duties and expectations as a medical physicist, I would be the first to let you all know when this important goal in my journey has been achieved. Finally, that day has arrived and I would like to devote this work to my dear departed parents Seija and Arvo Tenhunen who proudly shared my dream.

I owe my deepest gratitude to my principal supervisor, PhD, Associate Professor Sari-Leena Himanen. You have been my mentor and a good friend throughout these working years and without your enthusiasm as a sleep researcher this thesis would never have been completed. Furthermore, the greatest thanks go to Professor Jari Hyttinen who provided me with the opportunity to carry out this thesis under his supervision in the Department of Electronics and Communication Engineering Technology at Tampere University of Technology.

The studies of this thesis were carried out in the Sleep Laboratory of the Medical Imaging Centre at the Department of Clinical Neurophysiology and the Department of Medical Physics, Pirkanmaan Hospital District in Tampere. I would like to thank the head of the department and chief physician, Adjunct Professor Joel Hasan for the opportunity to work in the field of neurophysiology and to share his devotion to sleep research. I also want to express my gratitude to chief physicist, Adjunct Professor Simo Hyödynmaa for his support during my dissertation process.

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I believe that the brightest and most innovative days of sleep research are still ahead, and I look forward to watching and contributing to its further success with my wise and skilled colleagues PhD Jussi Virkkala, Dr.Tech Antti Saastamoinen, Dr.Tech Eero Huupponen and PhLic Herkko Mattila. Without your valuable guidance and inspiring discussions, this work would never have been finished.

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Tampere, May 2015

Mirja Tenhunen

Table of Contents

List of Symbols and Abbreviations

AHI	apnea-hypopnea index
AI	apnea index
ANS	autonomic nervous system
ARI	arousal index
ASDA	American Sleep Disorders Association
BCG	ballistocardiography
BMI	body mass index
CPAP	continuous positive airway pressure
CPB	central periodic breathing pattern
COPD	chronic obstructive pulmonary disease
DFT	discrete Fourier transform
ECG	electrocardiography
EEG	electroencephalography
Emfit	electromechanical film transducer
EMG	electromyography
EOG	electrooculography
ESS	Epworth sleepiness scale
GHQ-12	general health questionnaire
HF	high frequency
HRV	heart rate variability
ICSD	international classification of sleep disorders
IRR	increased respiratory resistance
LF	low frequency
M	movement pattern
NB	normal breathing pattern
NREM sleep	non-rapid eye movement sleep

ODI4	oxygen desaturation events of 4%-unit or more
OP1-3	obstructive periodic breathing patterns, types 1-3
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
pESO	esophageal pressure
P1	periodic breathing pattern, type 1
PLM	periodic leg movements
PLMI	periodic limb movement index
PM	periodic movement pattern
POB	periodic obstructive breathing
POB%	percentage of time with periodic obstructive breathing patterns (OP1%+OP2%+OP3%)
PSG	polysomnography
PVDF	polyvinylidene fluoride film-type sensor material
REM sleep	rapid eye movement sleep
REMlat	latency to REM sleep
RERA	respiratory effort-related arousal
ROC	receiver operating characteristic
SaO_2	arterial oxyhemoglobin saturation
SCSB	static charge-sensitive bed
SDB	sleep-disordered breathing
SEI	sleep efficiency index
SL	sleep latency
$TcCO_2$	transcutaneous carbon dioxide
TIB	time in bed
TST	total sleep time
UARS	upper airway resistance syndrome
VLF	very low frequency

List of Publications

This thesis is based on five original manuscripts, referred to in the text by their Roman numerals I-V. In addition, some unpublished data are presented. The original manuscripts are reprinted with the permission of the copyright holders.

I. Tenhunen M., Rauhala E., Huupponen E., Saastamoinen A., Kulkas A. & Himanen S-L., High frequency components of tracheal sound are emphasized during prolonged flow limitation. Physiological Measurement. 30 (2009) 5, pp. 467-478

II. Tenhunen M., Rauhala E., Virkkala J., Polo O., Saastamoinen A. & Himanen S-L., Increased respiratory effort during sleep is non-invasively detected with movement sensor. Sleep and Breathing. 15 (2011) 4, pp. 737-746.

III. Tenhunen M., Elomaa E., Sistonen H., Rauhala E. & Himanen S-L., Emfit movement sensor in evaluating nocturnal breathing. Respiratory Physiology & Neurobiology. 187 (2013) 2, pp. 183-189.

IV. Tenhunen M., Hyttinen J., Lipponen JA., Virkkala J., Kuusimäki S., Tarvainen MP., Karjalainen PA. & Himanen S-L., Heart Rate Variability Evaluation of Sleep Mattress Breathing Categories in NREM sleep. Clinical Neurophysiology, 126 (2015) 5, pp. 967-974.

V. Tenhunen M., Huupponen E., Hasan J., Heino O. & Himanen S-L., Evaluation of the different sleep disordered-breathing patterns of the compressed tracheal sound. Clinical Neurophysiology, accepted in November 2014, in press.

Author´s contribution

The author of this thesis contributed to all publications as the main author, as detailed below. The publications were written in close collaboration with the co-authors, who have given their expertise and knowledge one-way or another. None of these papers have been used as a part of any other person's academic dissertation.

Publication I

The author designed the study protocol, selected the different sleep-disordered breathing patterns, made the analyses and conclusions, and wrote the manuscript. Professor Sari-Leena Himanen and Adjunct professor Esa Rauhala performed the visual scoring of sleep and conventional sleep parameters. The external tracheal sound signal was synchronized to the polysomnography recordings by PhD Jussi Virkkala and Dr.Tech Antti Kulkas and was spectral analysed by Dr.Tech Eero Huupponen.

Publication II

The author designed the study protocol, participated in data acquisition, analyzed the measured data and produced a statistical analysis. External manometer device signal, which was used as the validation reference, was synchronized to the polysomnography recordings with the help of Ph.D Jussi Virkkala. Professor Sari-Leena Himanen visually scored the conventional sleep parameters. The visual scoring of the Emfit signal and the analysis of the results, making conclusions, and writing the manuscript were done in collaboration with Professor Sari-Leena Himanen, Adjunct Professor Esa Rauhala and Professor Olli Polo.

Publication III

The author designed the study protocol. The author carried out consensus scoring of the Emfit signal, analyzed the results, produced statistical analyses, and wrote the manuscript. Professor Sari-Leena Himanen classified the conventional sleep parameters. Medical student Heli Sistonen collected retrospective patient data. The Emfit signal was scored by medical student Ella Elomaa and Professor Sari-Leena Himanen. This paper was written in collaboration with Professor Sari-Leena Himanen and Adjunct Professor Esa Rauhala.

Publication IV

The author designed the study protocol. The Emfit signal was scored by the author and Professor Sari-Leena Himanen. Professor Sari-Leena Himanen classified the conventional sleep parameters. The author made the data selection for heart rate variation analyses with medical student Sonja Kuusimäki and PhD Jussi Virkkala. PhD Jukka Lipponen, Professor Mika Tarvainen, and Professor Pasi Karjalainen performed the heart rate variation analyses in the De-

partment of Applied Physics at the University of Eastern Finland. The author analyzed the results and the statistics and prepared the manuscript with Professor Sari-Leena Himanen and Professor Jari Hyttinen.

Publication V

The author designed the study protocol. The visual scoring of the compressed tracheal sound signal was performed with medical student Otto Heino and Professor Sari-Leena Himanen. The selection of the analyzed epochs was performed by the author in collaboration with Professor Sari-Leena Himanen. Dr.Tech Eero Huupponen made the automatic analyses. The analyses, conclusions, and the writing of the manuscript were done by the author in collaboration with Professor Sari-Leena Himanen and Adjunct Professor Joel Hasan.

1 Introduction

Sleep disorders have become more common, and puts more strain on public health services than ever before. One major sleep disorder consists of repetitive respiratory events, apneas and hypopneas, which are caused by obstruction of upper airways. These sleep-disordered breathing abnormalities can lead to daytime symptoms, and is called the obstructive sleep apnea syndrome (OSAS). In clinical work the severity of OSAS is estimated by the number of apneas or hypopneas per hour of sleep, the apnea hypopnea index (AHI). The health consequences of OSAS, including various cardiovascular disorders such as hypertension, arrhythmias, coronary artery disease even heart failure and stroke, are nowadays well-recognized. Sleepiness, the main complaint of sleep-disordered breathing (SDB) patients, is thought to be explained mainly by the respiratory effort-related arousals, which fragment the sleep process and often prohibits the patient to enter deep sleep. However, the mechanisms of OSAS related daytime symptoms are not yet fully understood.

In addition to patients with a high AHI index and marked clinical symptoms, there are subjects with prolonged partial upper airway obstruction. The low AHI value group (AHI <5/h and mild OSAS AHI 5-15/h) may include patients with prolonged partial obstruction. Such patients are often left undiagnosed and untreated. Upper airway obstruction is associated with increased respiratory effort, which is considered to be its primary marker. The clinical significance of prolonged partial obstruction is, however, still unclear. Nevertheless, according to clinical practice, some of these patients clearly have similar symptoms to OSAS patients and many of them would benefit from treatment. There are also findings that sustained partial obstruction is associated with pathophysiological changes, for instance, elevated transcutaneously measured carbon dioxide (Aittokallio et al., 2009, Rauhala et al., 2007, Rimpilä et al., 2014). Part of the health consequences of SDB might be mediated by changes in the function of the autonomic nervous system. This can be studied by the measurement and analysis of heart rate variability (HRV). It has been shown that OSAS is associated with increased sympathetic activity that is considered to reflect increased strain on the cardiovascular system and increased risk of vascular co-morbidity. To date, knowledge of changes in HRV during prolonged partial obstruction is lacking. It is therefore possible that all SDB disorders are important health problems, that decrease quality of life, and are associated with increased co-morbidity and mortality (Anttalainen & Kalleinen, 2014, Anttalainen et al., 2010a, Marin et al., 2005, Young et al., 2002).

Clinical polysomnography (PSG) is considered to be the gold standard and the reference method of choice for sleep disorder diagnostics. It is, however, a laborious and rather expensive multi-channel recording method and usually requires the patient to stay at least one night in the sleep laboratory. Validated, reliable, and non-invasive clinical tools to detect prolonged partial obstruction with increased respiratory effort without arousals are few. In PSG, indirect effort quan-

tification methods such as nasal pressure profile measurement are used. In the signal, the obstructed nasal airflow shapes are flattened instead of being the normal round shapes, indicating flow limitation.

Partial upper airways obstruction with increased respiratory effort is associated with increased negative pressure inside the chest. The reference method to estimate this increased intrathoracic negative pressure is the measurement of transesophageal pressure with a pressure sensitive catheter. Transesophageal pressure reflects pleural pressure. The measurement of prolonged partial obstruction with a thick, water-filled catheter is a demanding procedure, but the use of new thin catheters has made the measurements easier and more comfortable for the patient. The modern measurement systems with thinner and smoother catheters are well-tolerated and do not disturb the patient's sleep in the same way as the older ones did (Oeverland et al., 2005a). However, the recording of increased respiratory effort during sleep is still somewhat uncomfortable and laborious when applied to every sleep laboratory patient.

In Finland, there is long tradition of diagnosing SDB and sleep-related movement disorders using sleep mattress sensors (Alihanka et al., 1981). The original Static Charge-Sensitive Bed (SCSB) mattress was first used for gross body movement detection during sleep. The workload of the heart can be estimated by ballistocardiography (BCG). BCG is caused by the movement of the heart and the flow of blood from the left ventricle to the aortic artery. By filtering and amplifying the mattress signal, respiration can also be measured and periodic apnea/hypopnea breathing can be detected (Alihanka et al., 1981, Polo, 1992). Increased respiratory workload causes a so-called spiking phenomenon in the mattress signal (Kirjavainen et al., 1996).

In recent years, the large, the ElectroMechanical Film transducer (Emfit) has replaced the stiff and expensive SCSB transducer. The Emfit was invented in Finland in the late 1980s, and it is the first truly cellular polymer electret film available for commercial applications (Paajanen et al., 2000). Sensors made from this film-type material were found to be useful especially in the measurements of physiological pulsatile signals. Sensors constructed from commercial film materials were soon recognized to be potentially suitable for non-invasive sleep research. Although polyvinylidene fluoride (PVDF) belts and Emfit mattresses are used in sleep recordings, there is a lack of clinical validation of these methods compared with PSG and other methods used to detect SDB. Evidence is needed especially to find out, how reliable the Emfit sensor is in measuring prolonged partial obstruction with increased respiratory effort, which is considered to be the primary marker of upper airway obstruction.

In this work, the use of Emfit recording for the detection of sleep apneas, hypopneas, and prolonged partial obstruction with increased respiratory effort was evaluated. Comparisons both to PSG with nasal pressure recording and transesophageal pressure were made. Special attention was paid to the existence of the spiking phenomenon in the Emfit mattress in relation to changes

in negative intrathoracic pressure recorded by transesophageal catheter in estimating increased respiratory effort.

In some of the subjects, the tracheal sound was also measured to find out its usefulness for sleep-disordered breathing diagnostics. In this part of the study, the spectral content of tracheal sound in different sleep-disordered breathing patterns was analyzed in order to see whether different compressed tracheal sound signal patterns could be distinguished in different breathing entities. These patterns were also compared to intrathoracic pressure measurement findings.

In order to study the effects of prolonged partial obstruction on the function of the autonomic nervous system, HRV in relation to different breathing patterns was analyzed. The idea was to evaluate whether prolonged partial obstruction would cause corresponding changes to autonomic nervous system function as seen in obstructive sleep apnea (OSA). This would encourage more studies on the possible health consequences of prolonged partial obstruction.

The analysis of sleep recordings is still based on somewhat subjective visual estimation. So far, no generally accepted and sufficiently reliable automatic analysis method exists. Robust automatic quantification methods with easier techniques for non-invasive sleep recording would enable such methods to be also used for screening purposes. In this technology-orientated world, people could take much more responsibility and take better care of themselves by following their own biosignals and by changing their health habits earlier. Application of current and the development of new easy-to-use and low-cost diagnostic methods could increase public health and quality of life. As a result, SDB-associated co-morbidities could be avoided or at least diminished. The need for good sleep as a necessity for good life and health has been widely recognized.

2 Sleep-disordered breathing

Sleep-disordered breathing (SDB) comprises a broad spectrum of different respiratory symptoms. The mildest symptom in the spectrum is considered to be primary snoring without marked upper airway obstruction. In the middle, is upper airway resistance syndrome (UARS) with increased respiratory effort. At the most severe end of the spectrum is obstructive sleep apnea syndrome (OSAS) with hypoxemia, hypercapnia, and sleep fragmentation (Guilleminault et al., 1993).

2.1 Snoring

The snoring sound is an inspiratory noise and results from vibrations of the soft tissues of the pharynx, soft palate, and uvula. Increased snoring is often the first symptom that prompts patients to seek sleep examination. The prevalence of habitual, frequent snoring has been found to be 10-60% (Lindberg et al., 1998b, Sporndly-Nees et al., 2014, Svensson et al., 2008). The prevalence is higher among men than women and it is shown to increase along with age (Lindberg et al., 1998b, Sporndly-Nees et al., 2014).

Snoring can be considered to be a marker of increased respiratory effort (Bäck et al., 2002, Ylikoski & Bäck, 2006). Snoring has been related to sleepiness (Gottlieb et al., 2000) and different morbidities such as hypertension, angina pectoris, and cerebral stroke (Koskenvuo et al., 1985, Lindberg et al., 2007, Nieto et al., 2000). However, it is possible that these associations are at least partly explained by the fact that snoring is usually connected to OSAS (Gottlieb et al., 2000). The harmful effects of simple snoring without upper airway obstruction have remained less clear. In fact, in one study no cardiovascular consequences related to simple snoring were found (Marin et al., 2005). However, there is evidence that the vibration of snoring may cause local nervous lesions to the muscles of the upper airway, which enables the airway to collapse at inspiration (Friberg et al., 1998). Mechanical vibration can also induce injury to the carotid arteries (Cho et al., 2011). In addition, snoring is related to sleepiness, work performance problems, and traffic accidents, even in the absence of sleep apnea (Jackson et al., 2011, Svensson et al., 2008, Ulfberg et al., 1996, Young et al., 1997a).

Obesity, smoking, nasal congestion, and physical inactivity have been found to be associated with snoring as well as structural characteristics such as narrowness of the upper airway caused by hypertrophy of the soft palate, palatal arch, and uvula (Koskenvuo et al., 1994, Lindberg et al., 1998a, Sporndly-Nees et al., 2014, Young et al., 2002). Additionally, enlarged adenotonsillar or a large tongue base may obstruct the upper airway (Pevernagie et al., 2010, Svensson et

al., 2006). The use of alcohol or sedative medication decreases the tonus of upper airway muscles, and thus increases snoring (Bloom et al., 1988, Nagayoshi et al., 2011).

Occasional snoring is common. However, there is still uncertainty about how to define pathological snoring. This causes difficulties in clinical practice because no clear guidelines exist about the level of snoring that needs intervention. As a result, several different methods have been developed in order to evaluate and quantify snoring. For example, the intensity of snoring has been shown to increase with the severity of OSA (Maimon & Hanly, 2010), and the higher acoustic intensity has been found to reflect more severe respiratory obstruction (Itasaka et al., 1999, Lugaresi et al., 1983, Wilson et al., 1999). The spectral analysis of the snoring signal taken from simple snorers has been used in differentiating sleep apnea patients (Agrawal et al., 2002, Hill et al., 1999, Osborne et al., 1999, Perez-Padilla et al., 1993, Saunders et al., 2004). In addition, different features of snoring epochs have been extracted in order to differentiate between normal and pathological snoring. It has been reported that when compared with simple snorers, the snoring epochs of sleep apnea patients consist of more signal variability (Cavusoglu et al., 2008, Sola-Soler et al., 2005). The treatment for snoring is often individualized, and includes conservative measures such as weight loss, alcohol and sedative avoidance, smoking cessation, and sleep-position training. Active treatment methods for habitual snoring include mandibular advancement appliances and nasal continuous positive airway pressure (CPAP) treatment. Even the surgical intervention of the soft palate has been used if sleep apnea and other SDBs have first been excluded (Tien & Kominsky, 2014).

2.2 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by repetitive, total, or partial closures of the upper airway during sleep. The prevalence of OSA has been found to increase with age (Ancoli-Israel et al., 1991) and it is higher among men than women. Among the adult population the prevalence of sleep apnea has been reported to be 4% in men and 2% in women, but a higher prevalence of up to 24% and 9% in men and women, respectively, has been reported (Gislason et al., 1988, Punjabi, 2008, Young et al., 1993, Young et al., 1997b). According to a Finnish questionnaire study, 8% of the general adult population may suffer from sleep apnea (Kronholm et al., 2009), and a Norwegian study reports that 25% of the middle-aged population has an increased risk of developing OSA (Hrubos-Ström et al., 2011).

The diagnosis of OSA is based on the rules established by the American Academy of Sleep Medicine (Berry et al., 2012). The apnea is considered obstructive when polysomnography reveals episodes of no airflow with continuing inspiratory effort. According to the latest rules, the respiratory event is classified as hypopnea when the reduction of airflow is 30% or greater and

lasts for at least 10 seconds, and it is associated with an arousal or at least a 3% reduction in oxygen saturation. Usually, the quantization of OSA is based on the apnea-hypopnea index (AHI, number of respiratory events per hour of sleep) calculated from a sleep recording. The severity limits of AHI for adults are as follows: AHI < 5 (normal), 5 ≤ AHI < 15 (mild OSA), 15 ≤ AHI < 30 (moderate OSA), and AHI ≥ 30 (severe OSA), (American Sleep Disorders Association, ASDA 1999).

Typical symptoms that OSA patients complain of are snoring, daytime sleepiness, memory and mood problems, fragmented sleep, nocturia, decreased libido, and morning headaches (Epstein et al., 2009, Krakow et al., 2001, Lavie, 2007, Park et al., 2011). In addition, OSA is known to increase the number of traffic accidents (Young et al., 1997a). Women may report more atypical symptoms related to OSA than men. These symptoms include insomnia, depression, (Shepertycky et al., 2005), and morning fatigue (Ambrogetti et al., 1991).

Obesity is one major risk factor for sleep apnea (Peppard et al., 2000). In addition, male sex, snoring, smoking, increasing age, and increasing neck circumference are all known to increase the risk of sleep apnea (Fogelholm et al., 2007, Leger et al., 2012, Schwab, 1999, Wetter et al., 1994, Young et al., 2002). Alcohol and muscle relaxants increase the risk by relaxing the muscles in the upper airway (Al Lawati et al., 2009). It is known that female hormones may have an impact on the neurologic control of the upper airway muscles. Indeed, the risk of OSA increases in females after the menopause (Bixler et al., 2001).

Obstructive sleep apnea has been proven to be an independent risk factor for stroke and cardiac disease (Canessa & Ferini-Strambi, 2011, McNicholas & Bonsigore, 2007). This may be explained by the repetitive oxygen desaturations and arousals, that are known to increase sympathetic tone (Palma et al., 2013, Ringler et al., 1990), and, in addition to systematic inflammation and oxidative stress, sympathetic tone might be one of the main predisposing factors for the cardiovascular morbidity associated with OSA (McNicholas & Bonsigore, 2007).

The most effective treatment for OSA is CPAP. Overweight patients are encouraged to change lifestyle and join weight-management programs. Bariatric surgery can be applied with very obese patients. Other surgical procedures, like bipolar radiofrequency thermal ablation of the soft palate and mandibular corrections can be used in selective groups of patients (Kryger et al., 2011).

2.3 Upper airway resistance syndrome

Guilleminault et al. first reported upper airway resistance syndrome (UARS) in 1993. Conventionally, UARS represents a form of sleep-disordered breathing without apneas/hypopneas but

with repetitive increases in resistance to airflow leading to flow limitation and esophageal pressure swings followed by brief respiratory effort-related arousals (RERAs) (Guilleminault et al., 1993). The prevalence of UARS was found to be 8.4% among academic military personnel at a sleep disorder center (Kristo et al., 2005). The prevalence of UARS in the general population is unknown, but it has been thought to be as common as sleep apnea (Pepin et al., 2012).

In the diagnosis of UARS, the quantification of arousals is essential, and therefore full polysomnography with electroencephalography (EEG) is needed. The progressive increase in respiratory effort related to RERAs can be estimated by measuring the esophageal pressure or another respiratory effort parameter, for example, the changes in pulse transit time (Pepin et al., 2012). UARS is defined by the occurrence of excessive daytime sleepiness unexplained by other causes (Pepin et al., 2012). In UARS, hypopneas and apneas are rare. UARS is found to be more common in young and less overweight patients than OSA (Stoohs et al., 2008). Subjective symptoms such as mood disorders, decreased libido, and cognitive impairment, with changes in attention, concentration, executive function, and fine-motor coordination are often present and they may resemble the symptoms of OSA (Pepin et al., 2012). Insomnia and sleep quality complaints are more frequent with UARS patients than with OSA patients (Stoohs et al., 2008).

Patients with UARS may suffer from anatomical nasal abnormalities or increased collapsibility of the upper airway (Chen & Kushida, 2003, Gold et al., 2002). In addition, they may present with long face, cross-bite, high-arched hard palate, and small mandible in back position (Guilleminault et al., 2001b). An interesting finding is that patients with UARS often present with hypotonia (Guilleminault et al., 2001b).

Even if OSAS and UARS events have been found to result in differences in HRV parameters (Guilleminault et al., 2005), there has been and there still is a debate about the true existence of UARS as a specific disorder (Douglas, 2000). The International Classification of Sleep Disorders, ICSD3 (American Academy of Sleep Medicine, 2014) includes UARS as a part of OSA, and it is not considered as a separate entity. Treatment of UARS comprises similar approaches to those in OSA.

2.4 Prolonged partial upper airway obstruction

Increasing attention has been paid to prolonged partial upper airway obstruction during sleep. In particular, Finnish sleep research has a long tradition of SCSB studies (Anttalainen et al., 2010b, Anttalainen et al., 2006, Anttalainen et al., 2007a, Anttalainen et al., 2007b, Polo, 1992, Polo-Kantola et al., 2003, Saaresranta et al., 2001). This phenomenon is assessed by sustained negative increase in esophageal pressure or by a prolonged flow limitation pattern in the nasal pres-

sure transducer signal (Bao & Guilleminault, 2004, Hernandez et al., 2001). Prolonged flow limitation periods of up to several minutes have been found to be common findings in sleep studies (Hernandez et al., 2001). During CPAP treatment, the prolonged partial obstruction appears if the treatment pressure is insufficient (Calero et al., 2006). Often, prolonged partial upper airway obstruction is considered to be a mild form of SDB, with no need for active treatment as discussed previously (Anttalainen et al., 2013).

Prolonged partial obstruction is the most common type of SDB found in women, and in a clinical setting it is found to be more frequent in women than in men (Anttalainen et al., 2007a, Anttalainen et al., 2007b). Women with prolonged partial obstruction suffer from the same excessive daytime sleepiness as OSA patients (Anttalainen et al., 2013).

It is thought that the pathophysiology behind the prolonged partial obstruction is caused by anatomical structural differences. Patients with prolonged partial obstruction have been found to have narrower airways at tongue base level and hyoid bone level and more micrognathia than OSA-patients (Anttalainen et al., 2013, Polo et al., 1991).

In SCSB-studies, prolonged partial obstruction and OSA-findings are often combined and the symptoms, risk factors, and the consequences of pure prolonged partial obstruction have been studied less. It has been reported that transcutaneous carbon dioxide tension ($tcCO_2$) increases cumulatively during prolonged partial obstruction, whereas during periodic breathing with apneas and hypopneas no cumulative increase was obtained (Rauhala et al., 2007). The consequences of the prolonged partial upper airway obstruction have been evaluated in one study, where an association between asthma and chronic obstructive pulmonary disease (COPD) with prolonged partial obstruction was found. In addition, that study pointed out that the prevalence of hypertension was lower in women with prolonged partial obstruction compared with women with OSA (Anttalainen et al., 2010b).

The symptoms and consequences as well as the risk factors of pure prolonged partial obstruction have been investigated only slightly. Although prolonged partial obstruction presents with a similar non-apneic increase in negative esophageal pressure as seen in UARS, a recent review considered prolonged partial obstruction and UARS to be different entities (Guilleminault et al., 2001a, Pepin et al., 2012). However, it might also be that there is a lack of clarity in terms.

CPAP treatment is used in prolonged partial obstruction, and some surgical procedures can be useful. In addition, medications might be needed to relieve mood problems (Anttalainen et al., 2013).

3 Recommended sensors for detecting sleep-disordered breathing

3.1 Scoring of sleep and associated events

Polysomnography (PSG), which includes the simultaneous recording of various physiologic parameters, is the gold standard for diagnosing SDB. The differentiation between sleep and wakefulness is performed by sleep staging electroencephalogram (EEG), along with eye movements (electrooculogram, EOG), and submental muscle tension electrodes (electromyogram, EMG). The recommended derivations for EEG are F4-A1, F3-A1, C4-A1, C3-A2, O2-A1, and O1-A2, where the primary electrode is placed above the brain area according international 10-20 system, and the reference electrode is the contralateral mastoid. The EOGdx is placed 1 cm above the right outer canthus and the EOGsin electrode 1 cm below the left outer canthus and the reference electrode is the left mastoid for both (Iber et al., 2007). Using these signals, the recording is categorized as Rapid Eye Movement (REM) and Non-REM (NREM) sleep. The NREM category generally includes three stages of sleep: light sleep N1, N2, and deep sleep N3. Usually, the quality of sleep is assessed by the amount of deep sleep. The number of arousals is found to increase and the amount of deep sleep decreases in sleep apnea (Saunamäki et al., 2009). In UARS, arousals are frequent (Guilleminault et al., 1993).

Diagnosing sleep-disordered breathing requires the synchronized recording of respiration, cardiac function, and body movements. For this, airflow, respiratory effort, snoring, electrocardiogram (ECG), oxygen saturation, leg movements, and body position are measured. Simultaneous video monitoring is used to distinguish SDB from other sleep disorders.

3.2 Airflow sensors

During breathing, airflow is reduced during hypopneas and absent during apneas. The recommended reference device for measuring respiratory airflow is the pneumotachograph. The measurement principle is direct and the tidal volume can be quantitatively measured. However, measuring the pneumotachograph signal requires a sealed facemask, that many find cumbersome, and it is not routinely used in clinical sleep studies (Farre et al., 2004).

Thermistors and thermocouples are sensors whose electrical characteristics (resistance and voltage) depend on their temperature. They sense differences in the temperature of the cooler in-

spiratory and warmer expiratory airflow when placed close to the airway, i.e. the nose or mouth. These sensors do not have a linear relationship with the true airflow, and thus they are inaccurate flow measuring devices. Their use for quantifying hypopneas may lead to considerable under detection of the respiratory events (Ballester et al., 1998). The main limitations of these thermal devices are that their dynamic response is poor because of slow response, which largely depends on their exact position at the airway opening. Accordingly, thermistors and thermocouples are not suitable to accurately quantify the magnitude of flow, but they are simple to use, small in size, and well tolerated.

A nasal cannula placed in the nostrils and connected to a pressure transducer detects the pressure fluctuations caused by inspiration and expiration, and thus indirectly measures airflow. A airflow turbulences at the nostrils induce a pressure change that is directly related to airflow magnitude. As compared to pneumotachograph, the nasal cannula has been shown to be a valid tool for identifying apneas/hypopneas in clinical practice (Heitman et al., 2002, Thurnheer et al., 2001). Because the nasal cannula slightly overestimates the number of hypopneas, square-root linearization of the signal is recommended (Farre et al., 2001).

The nasal cannula has a rapid time-response that allows for a detailed analysis of the inspiratory flow. If the sampling rate is high enough (at least 200 Hz), nasal prongs also provide information on snoring and on the shape of the inspiratory flow waveform (Hernandez et al., 2001). The flow waveform is modulated by the collapsibility of the upper airway wall (Series & Marc, 1999). A round flow shape is observed during a regular, normal inspiratory phase of the breathing cycle. A flattened, non-round flow shape (flow limitation) is present during partial obstruction. Signal loss can happen due to the obstruction of the cannula by secretion, displacement of the cannula, narrowness of the nostrils, or a deviated septum (Lorino et al., 1998). The potential drawback of the nasal cannula is that it does not detect mouth breathing.

Although a pressure transducer has been found to be more sensitive than thermocouples in detecting AHI (Hernandez et al., 2001), the thermal airflow sensor is recommend in the identification of an apnea using the AASM 2.0 (Berry et al., 2012). For hypopnea detection, the nasal pressure transducer with or without linearization is recommended.

3.3 Measuring respiratory effort

As a consequence of an obstruction of the upper airway, a patient with obstructive SDB exerts increased inspiratory efforts in an attempt to maintain ventilation. The gold standard signal to quantitatively assess the inspiratory effort is esophageal pressure measurement (pESO). It detects changes in pleural pressure produced by the work of the inspiratory muscles and requires

the use of an invasive esophageal balloon or catheter (Mead & Gaensler, 1959, Milic-Emili.J et al., 1964). The trans-nasal insertion of the pressure catheter is often considered uncomfortable. Therefore, the technique is mostly used for research purposes only and in clinical work indirect, noninvasive methods have replaced esophageal measurement. During inspiration the pleural pressure normally varies from -5 cmH_2O to -7.5 cmH_2O (Guyton & Hall, 2006). There is no absolute esophageal pressure level that is known to be abnormal (AASM, (Berry et al., 2012). During periodic apnea/hypopnea breathing, a crescendo- type pattern of negative inspiratory pressure can vary between -13 and -35 cmH_2O. The pressure values are found to be lowest just after the relief of occlusion. In severe OSA, pressure values under - 40 cmH_2O have been measured. In UARS, deep pESO increases can also be obtained (Guilleminault et al., 1993).

Belt sensors can be used to measure inspiratory effort non-invasively. The method that is based on the use of two bands, one placed around the thorax and another placed around the abdomen, is called inductive plethysmography. Each band includes an inductive coil whose electromagnetic properties depend on the thoracic and abdominal cross-sectional areas. The changes in the cross-sectional areas provide an indirect method to measure respiratory effort. This technique is simple to use, and it does not interfere with the patient's sleep. However, the volume changes do not reflect muscle activity when upper airway impedance changes. The disadvantage of the belts is that the method requires calibration (pneumotachograph or spirometer), which has to be repeated if there is displacement of the bands or posture changes during the registration period (Chokroverty, 1994, Farre et al., 2004).

Another non-invasive method to assess respiratory effort is to measure the surface electromyography (EMG) of respiratory muscles. Diaphragmatic EMG has been shown to reflect relative changes in respiratory effort during sleep and it is used instead of esophageal manometry (Knaack et al., 2005). However, the use of diaphragm or parasternal EMG is limited because reliable recordings are often difficult to obtain (Chokroverty, 1994). In clinical work the respiratory muscle EMG recordings are often used in children's PSGs only.

3.4 Snoring

The AASM recommendation for monitoring snoring is to use an acoustic sensor (e.g. microphone), piezo-electric sensor or nasal pressure transducer. The sampling rate should be high enough, 500 Hz desirable and 200 Hz minimal, (AASM, Berry et al., 2012) for accurate detection of the amplitude variation of snoring. If the preprocessing of snoring results in a continuous sound level or in a sound intensity level, AASM recommendations allow lower sampling rates. Many commercial programs analyze snoring using an envelope technique with a certain preset threshold value, and give a snoring index as a time percentage for total sleep time. However, no

reference values for a snoring index exist. The acoustic analysis of the snoring sound spectrum has been developed in order to find a more accurate and objective way to evaluate the snoring site and source and its treatment (Dalmasso & Prota, 1996, Fiz et al., 1996, Moerman et al., 2002). In OSA and UARS, snoring is frequent but intermittent (Pepin et al., 2012). In prolonged partial obstruction, snoring is often continuous, but valid studies are lacking.

3.5 ECG and HRV analysis

The electrocardiogram (ECG) is recorded to detect respiratory-related heart rate changes during sleep. According to AASM recommendations (Berry et al., 2012), bipolar electrodes should be placed with slight modification of electrocardiograph Lead II (leads between the lower left rib cage and the right clavicula notch). Additional leads may be used if clinically indicated, but often the current nocturnal evaluation is limited to rough estimations of arrhythmias from one channel. The beat-to-beat heart rate recording and simple statistics of heart rate variability (HRV) is a generally recognized approach for assessing autonomous nervous system activity. The spectrum of heart rate variability is usually analyzed in different frequency bands: the low frequency band (LF), 0.04-0.15 Hz, which corresponds to 10-s variation and refers to a cumulative variation of sympathetic and parasympathetic components, and the high frequency band (HF), 0.15-0.4 Hz, which corresponding to fast variations almost exclusively containing the parasympathetic component of heart rate. Thus, the ratio between LF/HF allows us to obtain the sympathetic index correlated to heart rate changes. The very low frequency band (VLF), 0.003-0.04 Hz, is thought to reflect slow regulatory mechanisms such as the renin-angiotensin system and thermoregulatory processes and is possibly mediated by the sympathetic system (American Heart Association, 1996).

A lot of basic research has been done that, for example, has studied the effects of sleep cycles, sleep stages, and OSA on the autonomous nervous system (Penzel et al., 2003, Penzel et al., 2002, Stein & Pu, 2012). In OSA, an increase in sympathetic activity is well documented (Somers et al., 1995). HRV studies of UARS are, however, sparse and HRV during increased respiratory resistance has not been evaluated.

3.6 Pulse oximetry

Finger oximetry is the most common method for monitoring arterial oxygen saturation (SaO_2). The measurement principle of pulse oximetry is based on the different red and infrared light absorption of oxyhemoglobin and deoxyhemoglobin (Yoshiya et al., 1980). Light absorption in

blood is usually measured with transmission technique. The arterial oxyhemoglobin saturation reflects the percentage of oxygenated hemoglobin. The sensor should be fixed carefully on a translucent site with good blood flow. The method is especially sensitive to a patient's movements, which may lead to severe motion artifact. Light absorption due to arterial pulsation can be used to calculate heart rate. The heart rate value is averaged and does not exactly represent the beat-to-beat rate. The maximum acceptable signal averaging time is three seconds according to AASM recommendations (Berry et al., 2012). According to the current guidelines, oxygen desaturation is used to define the hypopnea events. This strengthens the need for the continuous, good quality monitoring of SaO_2 in sleep studies.

Non-conventional sensors in SDB diagnostics

3.7 Tracheal sound

Tracheal breathing sounds are usually collected using a microphone placed on the suprasternal notch. The use of other recording sites such as lateral neck and more than one site has been investigated (Kaniusas et al., 2005, Krumpe & Cummiskey, 1980). Higher sampling rates are more commonly used than in snoring detection because obstruction of the upper airway has been found to increase the number of high signal frequencies over 200 Hz (Fiz et al., 1999, Herzog et al., 2008, Kaniusas et al., 2005, Michael et al., 2008, Pasterkamp & Sanchez, 1992, Rao et al., 1990, Yonemaru et al., 1993). Usually respiratory sounds are divided into different frequency bands. The low frequency band (under 100 Hz), where heart and thoracic muscle sounds overlap, is usually filtered and omitted in analyses. The middle frequency band (200–600 Hz) and the high frequency band (600–1200 Hz) comprise the major frequency components of tracheal breathing sounds (Gavriely et al., 1981, Pasterkamp et al., 1997).

A snoring sound is considered as part of the respiratory sounds (Pasterkamp et al., 1997, Sovijärvi et al., 2000). Indeed, many studies concentrate on the analysis of snoring using tracheal sound (Cummiskey et al., 1982, Peirick & Shepard, Jr., 1983). In addition, tracheal sound measuring methods have been developed to detect OSA in both adults and children (Beckerman et al., 1982, Cummiskey et al., 1982, Krumpe & Cummiskey, 1980, Kulkas et al., 2009, Nakano et al., 2004, Sanna et al., 1991). In one preliminary work, the data compression of tracheal sound was used in the screening of SDB. The data compression revealed three distinct sound patterns: plain, thick, and thin. The plain sound pattern would indicate normal breathing, the thick sound pattern was found to be associated with periodic apneas and hypopneas, and the thin sound pattern might be associated with prolonged flow limitation (Rauhala et al., 2008). Also, the development of portable respiratory sound screening devices has been carried out because

the need for a simple and reliable means of diagnosing OSA and other SDB has increased (East & East, 1985, Hida et al., 1988, Lugaresi et al., 1983).

3.8 Mattress sensors

Static charge-sensitive bed, (SCSB)

Many researches, especially in Scandinavia, have utilized the static charge-sensitive bed (SCSB) in diagnostics of SDB (Anttalainen et al., 2010b, Anttalainen et al., 2006, Anttalainen et al., 2007a, Anttalainen et al., 2007b, Erkinjuntti et al., 1984, Lojander et al., 1998, Saaresranta et al., 2001, Salmi & Leinonen, 1986, Salmi et al., 1986, Svanborg et al., 1990). Jukka Alihanka and Kaarlo Vaahtoranta from the Department of Physiology at Turku University developed the SCSB (Figure 1) in the late 1970s for the long-term monitoring of sleep movements. The SCSB is a non-invasive sensor that is placed under a normal foam mattress to detect a sleeper's gross body movements, breathing, and heart beats without any electrodes being attached to the subject (Alihanka et al., 1981, Polo, 1992, Polo et al., 1989, Polo et al., 1988, Polo et al., 1993, Polo et al., 1992). The charge of the sensor is modified when static charge layers of the mattress move in conjunction with the sleeper's body movements. The movements induce potential differences, which can be measured with a differential AC amplifier.

Nocturnal breathing induces alternations in the SCSB signal. In the diagnostics of SDB, three different SCSB signal channels are usually used. In the early years, the 0.2 - 40 Hz band was utilized in the detection of gross body movements. Respiratory movements were achieved from the low frequency band (0.2 - 1 Hz), and the ballistocardiography (BCG) signal (4 - 40 Hz) was used to monitor the workload of the heart and reveal high frequency spiking. Using the three channels mentioned above, the signal was visually scored into normal breathing (NB), four different types of periodic breathing (P1, OP1, OP2, OP3), and increased respiratory resistance (IRR) pattern in three-minute epochs.

The suitability of SCSB in OSA diagnostics has been evaluated and it has been shown to identify obstructive apneas with high sensitivity (Polo et al., 1988). The OP3 pattern was suggested to consist of obstructive apneas, whereas the other periodic breathing categories comprised more hypopneas (Polo et al., 1989, Polo et al., 1988). IRR was reported to be a constant phenomenon without periodic breathing variation. Instead, prominent continuous high frequency spikes emerged during IRR. The high frequency spikes were considered to be episodes of prolonged partial obstruction and were often associated with constant heavy snoring.

The origin of the high frequency spikes were a matter of debate until Kirjavainen with his co-workers (Kirjavainen et al., 1996) reported that during experimental respiratory challenging,

healthy, awake adults produced spiking when respiratory efforts became stronger. These spikes have a close time-link to respiratory movements (onset of either inspiration or expiration) rather than heart movements. In this way, the emergence of spikes would reflect increased respiratory effort and, can be detected non-invasively instead of using the esophageal catheter.

Electromechanical film transducer, Emfit

The electromechanical film transducer (Emfit) is commonly used as an access control system in old people's homes, in seizure monitoring, and in vital signs monitoring (Van et al., 2013). In sleep studies, the Emfit mattress has been in use since 1997. As compared to SCSB, the Emfit mattress is small, easy to handle and quite inexpensive. In sleep studies, the Emfit mattress is placed under the normal foam mattress and under the thoracic area of the patient (Figure 1). Usually, the Emfit mattress is connected to a PSG device as an external sensor through a signal monitor box. Alametsä with co-workers have evaluated the Emfit sensor and found it to be suitable and reliable for BCG and pulsewave measurements (Alametsä et al., 2009). The Emfit sheet is very sensitive, and even periodic leg movements can be detected with the mattress placed under the thoracic area of the sleeper (Alametsä et al., 2006, Rauhala et al., 2009).

Emfit sheet is an elastic, permanently charged polypropylene ferro-electret film that responds to mechanical stress. It is composed of thin polymer layers that are separated by air voids. When an external force is applied on the film, orthogonal mechanical pressure changes the thickness of these air voids more than the stiff permanently charged layers. As a result, the Emfit signal mainly arises from the movement of the permanently charged polymer layers with respect to the internal layers, and are called "quasi-piezoelectric" as the charge is not produced by direct pressure changes but is proportional to the change in force (Paajanen et al., 2000, Rajala & Lekkala, 2010). The sensor operation has a capacitive nature and it is mainly based on thickness variations caused by an external force in the middle of the film.

Generated change of output voltage can be calculated as

$$\Delta V = (1/C) \times S_q \times \Delta F,$$

where ΔF = change of impact force acting on the film, C = total capacitance [pF] and S_q = sensitivity coefficient [25-250 pC/N] of the Emfit sensor.

The sensitivity of the Emfit material is very high vertical to mattress surface, but very small (1 % of vertical) in horizontal directions. So the impact of stretching of the film is very small (Rajala & Lekkala, 2012). The voltage signal can also be monitored and linked to different digital signal acquisition systems.

In SDB diagnostics, according to the established practice, the raw Emfit signal is filtered into two different frequency bands. The low-frequency band (0.3–10 Hz) shows breathing movements, and the high frequency band (6–16 Hz) reveals movements related to heart activity as well as high frequency spikes (Alametsä et al., 2006, Polo et al., 1988). The gross body movements are seen on the raw data channel. The Emfit breathing categories are visually scored by these three channels, as in SCSB scoring. However, the detailed evaluation of the different breathing categories as well as the comparison of the breathing categories to the conventional sleep parameter is lacking.

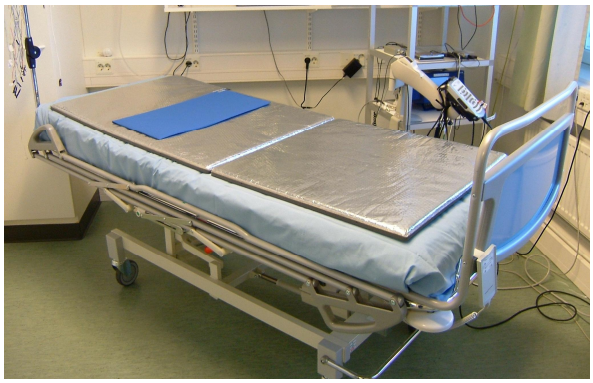


Figure 1. The blue Emfit- mattress on top of the traditional SCSB-mattress (coated silver foil). In clinical use, they both are placed under a normal foam mattress.

A polyvinylidene fluoride (PVDF) piezoelectric transducer can also be used as a sleep mattress. PVDF is a semicrystalline polymer, which has a solid and homogenous structure compared with cellular Emfit. The PVDF generates measurable voltage when deformed and it also reacts for lateral stretching. The capability of PVDF to measure heart and respiration rate has been compared with Emfit film with good correlation (Kärki et al., 2007, Kärki & Lekkala, 2008, Kärki & Lekkala, 2009). Quite recently, the PVDF-based device Sonomat (Sonomedical Pty Ltd, Balmain, NSW Australia) for SDB diagnostics has been introduced (Norman et al., 2014). The Sonomat is able to detect breathing movements and airflow in the form of breath sounds. The correlation of the AHI detected by Sonomat when compared with conventional PSG has been found to be good.

4 Aims of the thesis

The main aim of the present study was to develop and improve the analysis methods of different SDB by

1. Evaluating the capability of the Emfit mattress to detect increased respiratory effort during sleep.

2. Validating the Emfit mattress in OSA diagnostics.

3. Evaluating the prevalence and consequences of prolonged partial obstruction.

4. Evaluating prolonged partial obstruction with tracheal sound.

5 Materials and Methods

The polysomnographies of Studies I-V were performed in the Sleep Laboratory of the Department of Clinical Neurophysiology at Tampere University Hospital. The Ethical Committee of the Pirkanmaa Hospital District approved Studies I, II, IV and V. The medical director of Tampere University Hospital approved the protocol of Study III, as in retrospective analyses in general. In every study, the subjects gave their written informed consent to participate. Specific methods for each study are presented in their respective sections.

5.1 Subjects

Study I – Tracheal sound

Thirty-six consecutive patients (30 male, 6 female) referred to the Sleep Laboratory volunteered to participate in this study. Two patients were examined because of suspected narcolepsy, one because of the suspicion of restless leg syndrome, and the others were suspected to have SDB. The demographic data and sleep parameters of the patients are presented in Table 1.

Sleep is quantified using numerous parameters. The scored time for each sleep stage as a percentage of total score time (%S1-S4, %SREM) is reported to provide an estimation of the distribution of the sleep stages through the night. Sleep is entered through the non-REM sleep stage that normally constitutes around 75-80% of sleep. Each sleep cycle ends to REM sleep stage, constituting 20-25% of sleep. SWS (slow wave sleep stages S3+S4, nowadays combined to the N3 stage) predominates in the first third of the night and is linked to sleep onset and the length of the time spent awake. REM sleep predominates in the last third of the night and is linked to the circadian rhythm of body temperature. Good sleep is very individual but often comprises 4-6 sleep cycles and around 10-15% of stage 4 sleep. Most young adults report sleeping around 7.5-8.5 hours (total sleep time TST). People who sleep for less than 5 hours are short sleepers and people who sleep for more than 10 hours are long sleepers. The other sleep quality parameters are the sleep efficiency index (SEI normal if > 85%), which is calculated as the ratio of TST to time in bed (TIB), sleep latency (SL normal if < 15 min), which means bedtime, duration of time from lights off to the onset of sleep, and REM sleep latency, which is the interval from sleep onset to the first appearance of the REM sleep stage (REMlat varied around 90 min). The level of breathing problem is estimated with indices calculated from the occurrences of respiratory events such as hypopneas, apneas, arousals, and desaturations (AHI, ARI, and ODI4), which are calculated per hour of total sleep time. The periodicity of limb or leg movements are estimated with the PLMI index, which is the calculated number of PLMs per hour of sleep. PLMI > 15 determines clinical significance, but the finding should be adjusted to other findings in PSG.

Table 1. Sleep parameters and demographic data of the 36 subjects in Study I.

	Median	**Min**	**Max**
Age (years)	45	16	68
BMI[1] (kg/m^2)	27.3	21.8	44.6
TST[2] (h)	6.7	3.7	8.8
SEI[3] (%)	84.0	65.5	99.0
SL[4] (min)	9.0	0.0	53.5
REMlat[5] (min)	119.0	1.5	223.5
%S1[6]	9.4	1.9	39.6
%S2[7]	66.3	49.5	86.8
%S3[8]	6.1	0.0	17.7
%S4[9]	0.2	0.0	21.3
%SREM[10]	15.4	0.4	25.5
ARI[11] (n/h)	41.9	10.9	108.1
AHI[12] (n/h)	19.3	0.4	91.2
ODI4[13] (n/h)	6.8	0.3	95.3

[1]Body mass index
[2]Total sleep time
[3]Sleep efficiency index
[4]Sleep latency
[5]Latency to REM (rapid eye movement) sleep
[6-10] Percentage of sleep stage (S1-SREM) referred to TST
[11]Arousal index = number of cortical arousals per hour of TST
[12]Apnea-hypopnea index = apneas and hypopneas per hour of TST
[13]Oxygen desaturation index = number of desaturations $\geq$ 4% per hour of TST

Study II – Emfit and esophageal pressure (pESO)

A total of 32 patients (27 males, 5 females) with suspected SDB volunteered to participate in Study II. The sleep parameters and the demographic data of the patients are presented in Table 2.

Table 2. Sleep parameters of the 32 patients.

	Median	Min	Max
Age (years)	43	25	60
BMI[1] (kg/m^2)	30.5	22.2	53.9
TIB[2] (h)	8.0	5.3	10.4
TST[3] (h)	6.7	3.9	9.0
SEI[4] (%)	81.4	65.3	95.1
SL[5] (min)	16.8	1.0	67.0
REMlat[6] (min)	160.5	44.0	372.0
%N1[7]	8.7	2.5	35.1
%N2[8]	65.5	41.3	80.5
%N3[9]	9.2	0.6	39.9
%REM[10]	14.9	0.0	24.1
ARI[11] (n/h)	24.4	6.5	82.6
AHI[12] (n/h)	16.0	1.5	105.7
ODI4[13] (n/h)	6.0	0.7	86.7
SaO_2min[14] (%)	87.0	75.0	94.0
PLMI[15] (n/h)	1.0	0.0	43.0

[1]Body mass index
[2]Time in bed
[3]Total sleep time
[4]Sleep efficiency index
[5]Sleep latency
[6]Latency to REM (rapid eye movement) sleep
[7-10] Percentage of sleep stage referred to TST
[11]Arousal index=number of cortical arousals per hour of TST
[12]Apnea-hypopnea index=apneas and hypopneas per hour of TST
[13]Oxygen desaturation index=number of desaturations $\geq$ 4% per hour of TST
[14]Minimum of oxygen saturation
[15]Periodic limb movement index

Study III – retrospective Emfit

The polysomnographies of adult patients (>18 years) that were recorded between 03/2005–03/2006 in the Sleep Laboratory of Tampere University Hospital were evaluated retrospectively. The total number of PSGs was 189. Due to technical problems with some sensors, 32 recordings were excluded. Therefore 157 patients (97 male and 60 female) were included in the further studies. The reasons for referral were hypersomnia (66/157), SDB (40/157), insomnia (28/157), CPAP control (9/157), parasomnia (6/157), and others (8/157). The demographic data and the PSG parameters of the patients are presented in Table 3.

Table 3. Demographic and PSG data of the 157 subjects in Study III.

	Median	**Min**	**Max**
Age (years)	47	18	71
BMI[1](kg/m^2)	27	16	45
ESS[2]	10	0	22
GHQ-12[3]	3	0	12
SST[4] (h)	6.3	0.0	10.0
TST[5] (h)	6.8	3.1	10.0
TIB[6] (min)	8.3	5.9	10.7
SEI[7] (%)	84.0	39.0	98.0
SL[8] (min)	16.0	0.0	151.5
REMlat[9] (min)	124.0	1.5	543.0
%N1[10]	7.2	0.1	54.4
%N2[11]	66.1	39.8	88.7
%N3[12]	7.3	0.0	45
%REM[13]	14.4	0.3	31.2
ARI[14] (n/h)	18.3	5.8	97.7
AHI[15] (n/h)	9.7	0.1	93.8
AI[16] (n/h)	1.1	0.0	85.3
ODI4[17] (n/h)	2.0	0.0	81.0
SaO_2min[18] (%)	88.0	53.0	96.0
Pulse (bpm)	60.4	40.1	96.0
PLMI [19] (n/h)	4.5	0.0	145.9

[1]Body mass index, [2]Epworth sleepiness scale, [3]12-item General Health Questionnaire, [4]Subjective sleep time, [5]Total sleep time, [6]Time in bed, [7]Sleep efficiency index, [8]Sleep latency,[9]Latency to REM (rapid eye movement) sleep, [10-13]Amount of sleep stage referred to TST, [14]Arousal index, [15]Apnea-hypopnea index; [16]Apnea index, [17]Oxygen desaturation index, number of desaturations $\geq$ 4% per hour of TST, [18]Minimum percentage of oxygen saturation, [19]Periodic limb movement index

Study IV – Emfit and HRV

Fifty-three subjects (37 male, 16 female), referred to the Sleep Laboratory because of suspected SDB. The exclusion criteria were as follows: cardiac arrhythmias, pacemaker or ischemia, cardiomyopathy, history of neurological or pulmonological diseases, diabetes, and drugs known to impair the function of the autonomic nervous system. Forty-four out of the 53 patients had OSA (AHI > 5/h). Fifty-one patients had at least one 3-minute periodic obstructive breathing (POB)-epoch, 47 patients had at least one IRR-epoch, and 51 had one or more NB-epochs. The sleep parameters of the patients are presented in Table 4.

Table 4. Sleep parameters of the 53 patients in Study IV.

	Median	**Min**	**Max**
Age (years)	45	25	68
BMI[1] (kg/m^2)	29.7	20.1	53.9
TIB[2] (h)	8.2	5.8	10.7
TST[3] (h)	6.8	3.7	9.8
SEI[4] (%)	85.9	47.8	97.1
SL[5] (min)	15.5	1.0	74.5
REMlat[6] (min)	138.0	44.0	466.5
%N1[7]	7.2	0.1	40.6
%N2[8]	65.5	41.3	86.8
%N3[9]	9.7	0.0	45.0
%REM[10]	15.0	0.0	24.1
ARI[11] (n/h)	20.7	0.5	59.2
AHI[12] (n/h)	11.0	1.5	88.0
ODI4[13] (n/h)	4.0	0.1	63.0
SaO_2min[14](%)	87.0	66.0	93.0
PLMI[15] (n/h)	3.7	0.5	42.0

[1]Body mass index, [2]Time in bed, [3]Total sleep time, [4]Sleep efficiency index = TST/TIB, [5]Sleep latency, [6]Latency to REM (rapid eye movement) sleep,
[7-10]Percentage of sleep stage (N1-REM) referred to TST, [11]Arousal index, number of cortical arousals per hour of TST, [12]Apnea-hypopnea index, apneas and hypopneas per hour of TST, [13]Oxygen desaturation index, number of desaturations $\geq$ 4% per hour of TST, [14]Minimum of oxygen saturation, [15]Periodic limb movement index

Study V – Compressed tracheal sound

Twenty-seven consecutive patients (22 male, 5 female) referred to the Sleep Laboratory due to the suspicion of SDB volunteered to participate in this study. The sleep data derived from the sleep recordings of the 27 subjects are shown in Table 5.

Table 5. Demographic data and sleep parameters of the 27 subjects in Study V.

	Median	**Min**	**Max**
Age (years)	42	28	58
BMI[1] (kg/m^2)	30.0	22.2	53.9
TST[2] (h)	6.7	3.9	9.4
SEI[3] (%)	81.7	65.3	95.1
SL[4] (min)	15.5	1.0	67.0
REMlat[5] (min)	171.0	44.0	372.0
%N1[6]	9.8	2.5	35.1
%N2[7]	64.6	41.3	80.5
%N3[8]	11.1	0.8	39.9
%REM[9]	14.6	0.0	24.1
ARI[10] (n/h)	22.8	6.5	59.2
AHI[11] (n/h)	13.9	1.5	88.0
ODI4[12] (n/h)	6.0	0.7	63.0
%SaO_2min[13]	86.5	77.0	94.0
%SaO_2mean[14]	94.0	90.9	96.5

[1]Body mass index
[2]Total sleep time
[3]Sleep efficiency index, [4]Sleep latency
[5]Latency to REM (rapid eye movement) sleep
[6-9]Percentage of sleep stage (N1-REM) referred to TST
[10]Arousal index, number of cortical arousals per hour of TST
[11]Apnea-hypopnea index, apneas and hypopneas per hour of TST,
[12]Oxygen desaturation index, number of desaturations $\geq$ 4% per hour of TST
[13]Minimum oxygen desaturation
[14]Mean oxygen desaturation

5.2 Instrumentation and analysis

5.2.1 Recording montages

The Embla N7000 device (Embla®, Natus Medical inc., USA) and Somnologica Studio software (Medcare®, Flaga, Reykjavik, Iceland) were utilized in all studies. The PSG recordings consisted of six or eight EEG derivations (Fp1-M2, Fp2-M1, C3-M2, C4-M1, O1-M2, O2-M1 or Fp1-M2, Fp2-M1, F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), two EOG channels (EOGdx and EOGsin), three electromyogram channels (chin and both legs), airflow with a thermistor and a nasal pressure transducer, thoracic and abdominal respiratory movements with inductive belts, pulse and oxygen saturation by an integrated pulseoximeter (Nonin Medical Inc, USA), position sensor, and electrocardiogram (ECG) electrodes. Also, video signal was recorded in every study. A sampling rate of 2 Hz was used for the pulse oximetry (SpO2 and pulse rate), 10 Hz for respiratory movements, 500 Hz for ECG, and 200 Hz for the other signals.

5.2.2 Emfit recordings

In all studies, the Emfit mattress (32 cm x 62 x 0.4 cm, Emfit Ltd, Finland) was placed under a normal foam mattress below the thoracic area of the sleeping subject. The Emfit mattress was connected to a PSG device with touch proof connectors through an electronic monitor. The unfiltered Emfit signal was acquired directly as a separate trace in the Somnologica software with a sampling rate of 200 Hz. When the patient lies on the mattress, the sensor produces a small voltage signal that ranges from a few microvolts to a few volts depending on the force of movement.

5.2.3 Tracheal sound measurement

The tracheal sound recordings in studies I and V were performed with an electret microphone (Panasonic WM-60A, Matsushita Electric Industrial Co, Ltd, Kadoma Osaka, Japan). The sensitivity of the microphone was 10 mV/Pa and the frequency range in the free field was 20 Hz - 20 kHz, $\pm$ 2 dB (Sovijärvi et al., 1998). The microphone was attached to the skin in the suprasternal notch as presented in previous studies (Kulkas et al., 2010, Rauhala et al., 2008). The tracheal sound signal was amplified and high-pass filtered with a cut-off frequency of 50 Hz and fed into a Sound Blaster Audigy 2 NX sound card (Creative Labs, Singapore) for a 24-bit A/D conversion. The galvanic isolation between the patient and the recording device was handled with an USI-01 isolator (MESO, Mittweida, Germany). The raw sound signal from the sound card was converted into Embla data format and synchronized with PSG signals at a sampling rate of 11025 Hz. Somnologica Studio software (Medcare®, Flaga, Reykjavik, Iceland) was used for the visual analysis of the signal.

5.2.4 Esophageal pressure measurement

The esophageal pressure measurements in studies II, IV and V were performed with the Reggie (Camtech AS, Norway) commercial pressure-monitoring device presented in Figure 2. The pressure catheter is made of soft silicon and is 1.9 mm in diameter. The pressure transducer consists of a diaphragm covering a Wheatstone bridge, which is part of the electrical circuit able to change the electrical resistance according to the tension of the bridge. The tension changes result in changes in the signal voltage. The signal was calibrated, giving a numerical pressure value in cmH_2O units. The catheter contained five pressure sensors; the upmost sensor is situated in the nasal cavity and the others at the epipharynx, oropharynx, and hypopharynx. The proximal sensor in the esophagus was situated 15 cm distally from the hypopharynx-sensor. Special software was developed in order to import the pESO signal to the Somnologica software. The sampling rate for the Reggie signal was 10 Hz. A patient with extended full PSG equipment is shown in Figure 2.

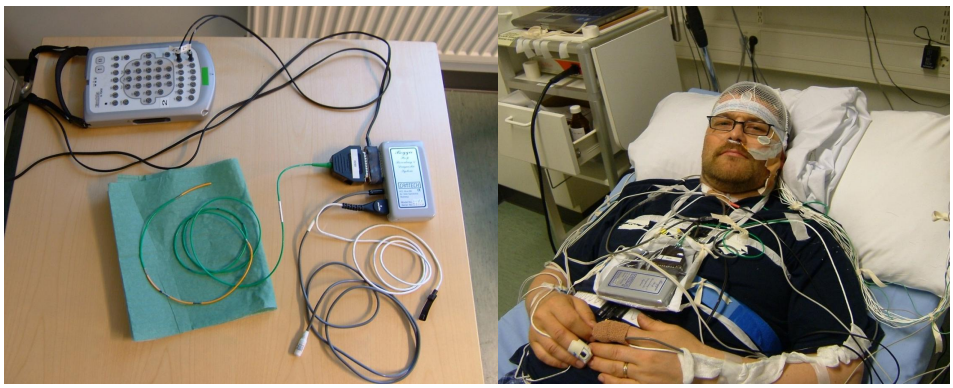


Figure 2. On the left the Reggie esophageal manometry device with the esophageal catheter (green one), oximeter probe (white wire) and actimeter (grey wire). On the right a picture of a patient with full PSG equipment. The figure is published with permission of the patient.

In the Reggie device, the esophageal pressure value -8 cmH2O is considered to be the cut-off value between obstructive and non-obstructive breathing (Oeverland et al., 2005b). This threshold is commonly used both in clinical practice and in scientific work, and therefore it was employed in the present studies.

5.3 Analysis of polysomnographies

5.3.1 Conventional sleep parameters

The recordings in studies I and II were scored into sleep stages according to the criteria of Rechtschaffen and Kales (Rechtschaffen & Kales, 1968). In studies III-V the rules by AASM were utilized (Iber et al., 2007). The same rules were applied in the classification of the respiratory events. For hypopneas rule 4b was used, which means amplitude diminutions ≥ 50% of airflow with additional criterion of concomitant arousal or desaturation of ≥ 3% (Iber et al., 2007). An AHI index was calculated as the number of apneas and hypopneas per hour, and arousals were scored according to the criteria of the American Sleep Disorders Association (ASDA, 1992).

5.3.2 Scoring of the Emfit signal (Studies II, III, IV)

The raw Emfit signal, which shows gross body movements, was filtered into two additional channels with band-pass of 0.3-10 Hz (low frequency channel, LF) and 6-16 Hz (high frequency channel, HF). The LF channel visualizes respiratory movements and the HF channel discloses heart-related movements and respiratory related spikes (Kirjavainen et al., 1996). These three channels were used in the visual scoring of the Emfit signal into different Emfit breathing categories. Two independent scores performed the scoring in 3-minute epochs from a lights off-event to the final awakening, and their consensus scoring was used in the analyses. The scoring principles are slightly modified from the former SCSB rules (Polo et al., 1992). The breathing categories used were normal breathing (NB), periodic breathing (P1), obstructive periodic breathing, types 1, 2, and 3 (OP1, OP2, OP3), increased respiratory resistance (IRR), and central periodic breathing (CPB). Epochs with large movements that lasted for more than 40 seconds were classified as movement epochs (M), and epochs with several short periodic movements without respiratory variation were scored as periodic movement (PM) epochs. In studies III and IV, the periodic obstructive breathing categories (OP1, OP2, and OP3) were combined to form one periodic obstructive breathing category (POB). The scoring rules are presented in Table 6 and examples of the stages are given in Figure 3a, b, c, and d.

Table 6. Characteristics of mattress breathing categories (scoring rules).

	Breathing movements in LF channel (0.3-10 Hz)	High frequency spikes in HF (6-16 Hz) channel	Gross body movements in the raw Emfit signal
NB	Regular	No	No
P1	Periodic amplitude variation	No	No
OP1	Periodic amplitude variation	Periodic/ intermittent	No
OP2	Periodic amplitude variation	Periodic/intermittent	Present between apneas/hypopneas
OP3	Periodic amplitude variation	Periodic/intermittent	Present between apneas/hypopneas
CPB	No movements during apnea, periodic movements between apneas	May be present between apneas	May be present between apneas
IRR	Regular	Continuous	No
M	May vary	Artifact	Prolonged (duration > 40s)
PM	Regular	No	Periodic; more than 3 short (< 10s) movements per epoch

LF=Low frequency Emfit-signal power band 0.3-10 Hz, HF=High frequency Emfit-signal power band 6-16 Hz, NB=normal breathing, P1=periodic breathing type1,OP1=obstructive periodic breathing type1, OP2 =obstructive periodic breathing type 2, OP3 =obstructive periodic breathing type 3,CPB =central periodic breathing, IRR = increased respiratory resistance, M = movement,PM = periodic movement

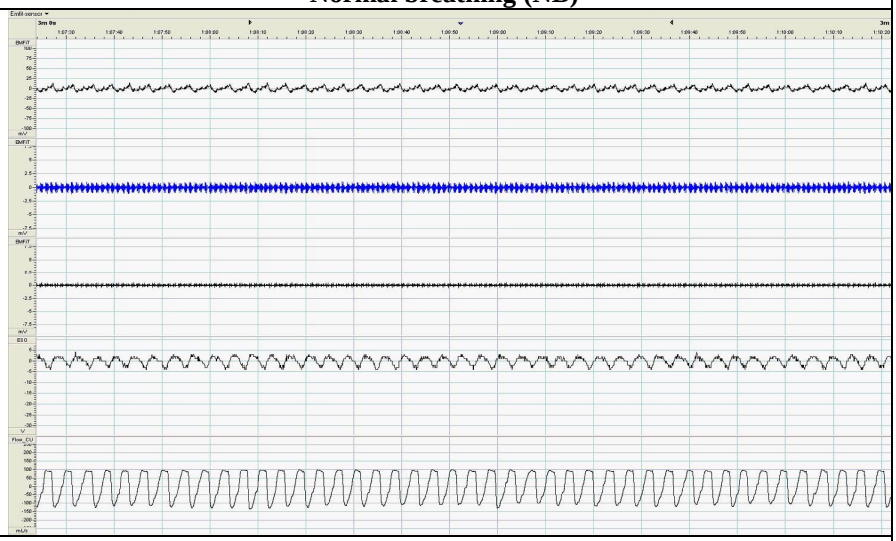
	Normal breathing (NB)
Emfit LF HF RAW **pESO** **Flow**	
	NB: regular respiratory movements in LF and HF signal bands, no body movements (Raw Emfit signal). pESO above –5 cmH_2O. Round flow shapes in linearized nasal pressure channel (Flow).

Figure 3a. Example of normal breathing category with pESO and flow signal (3-min interval).

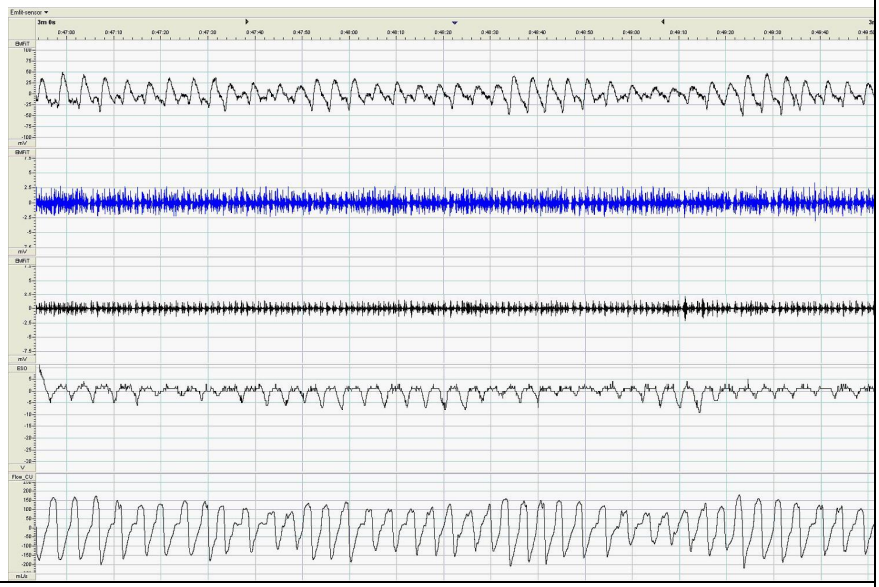
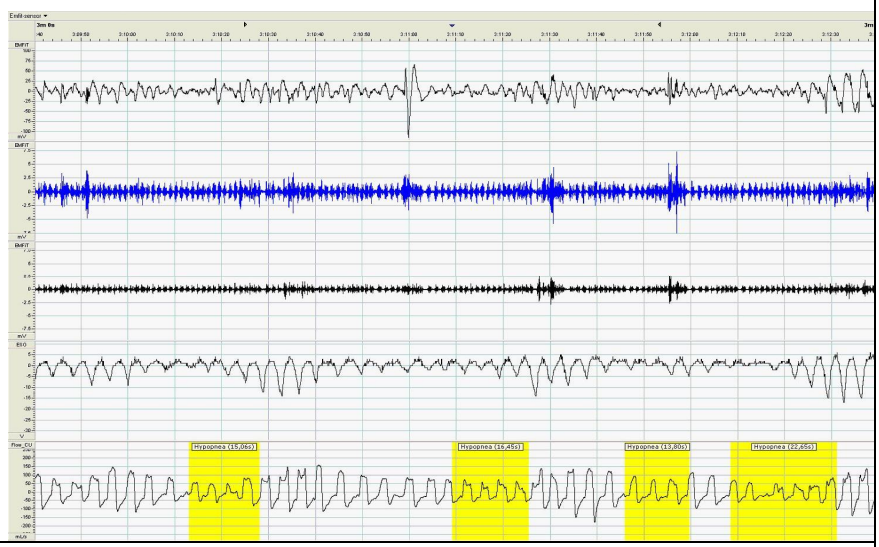
	Periodic Type 1, P1
Emfit LF HF RAW **pESO** **Flow**	
	P1: Periodic amplitude variation in LF band. No spikes in HF band. No body movements. pESO above -8 cmH_2O, slight variation. Non-round and round flow shapes in flow channel.
	Obstructive Periodic Type 1, OP1
Emfit LF HF RAW **pESO** **Flow**	
	OP1: Periodic amplitude variation in LF band. Intermittent spikes in HF band. No body movements. pESO decrease up to -15 cmH_2O between events. Hypopneas with non-round flow shape in flow channel.

Figure 3b. Examples of P1 and OP1 Emfit breathing categories. Hypopneas events are marked with yellow background in flow channel.

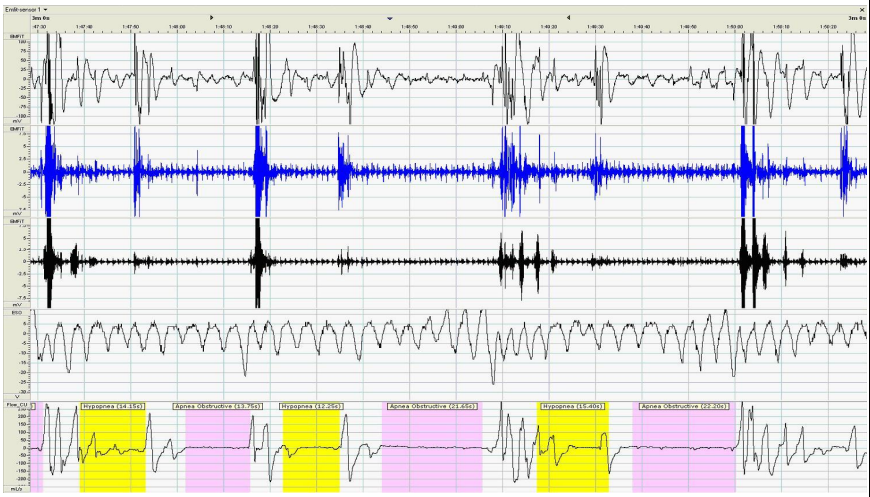
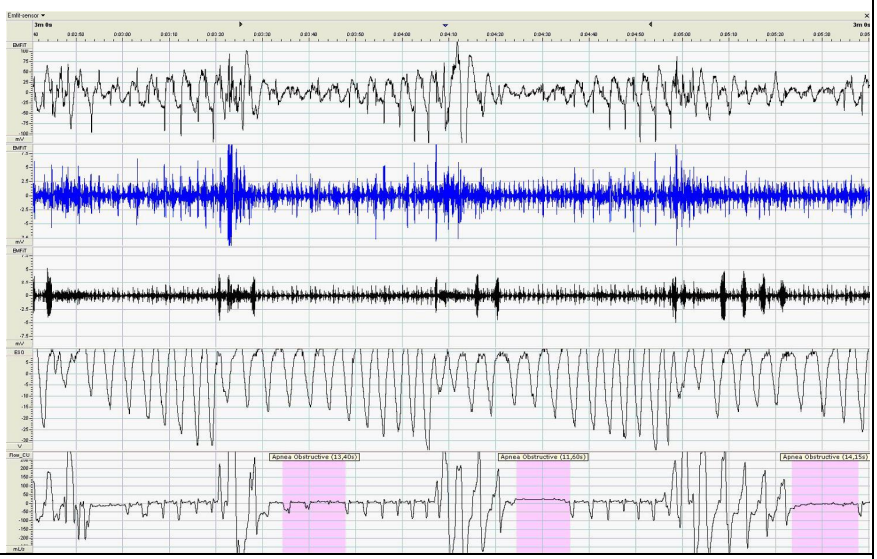
	Obstructive Periodic Type 2, OP2
Emfit LF HF RAW **pESO** **Flow**	
	OP2: Periodic amplitude variation in LF band. Large respiratory related spikes in HF band. Body movements in raw trace. pESO decrease up to -20 cmH_2O between breathing events. Hypopneas and apneas with non-round shape in flow channel.
	Obstructive Periodic Type 3, OP3
Emfit LF HF RAW **pESO** **Flow**	
	OP3: Large periodic amplitude variation in LF band. Crescendo-type spikes in HF band. Body movements in raw signal trace. pESO swinging from -10 cmH_2O to -30 cmH_2O. Hypopneas and apneas with non-round flow shapes in flow channel.

Figure 3c. Examples of obstructive OP2 and OP3 Emfit breathing categories. Obstructive apnea events are marked with red and hypopneas with yellow background in flow channel.

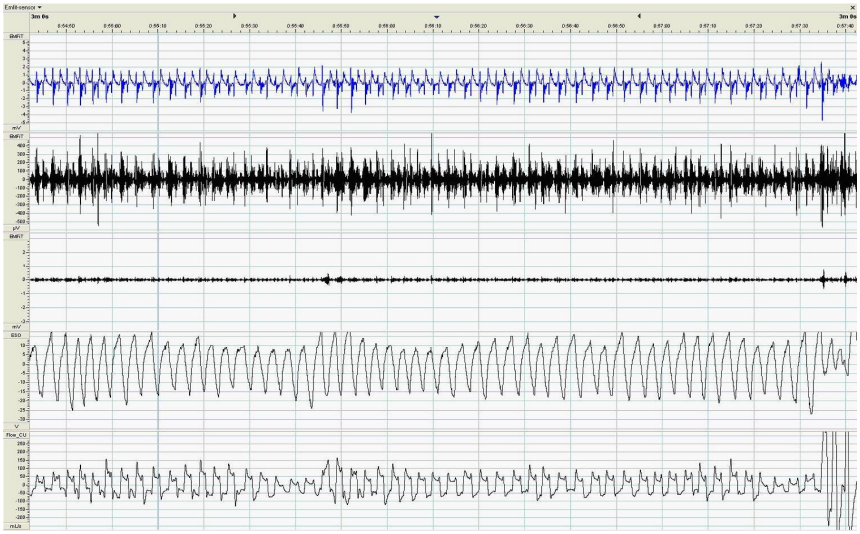
	Increased Respiratory Resistance, IRR
Emfit LF HF RAW **pESO** **Flow**	
	IRR: Regular respiratory in LF band, some amplitude increase. Continuous spiking in HF band. No body movements. Sustained pESO decrease from -15cmH_2O to -25cmH_2O. Non-round flow shape in flow channel.

Figure 3d. Example of IRR Emfit breathing category. The Emfit signal is presented as raw channel with low frequency band pass (LF 0.3-10 Hz) and high frequency range (HF 6-16 Hz). Esophageal pressure (pESO) values range from +10 to -30 cmH_2O. Airflow is calculated from the nasal pressure transducer (Flow).

5.3.3 Scoring of the tracheal sound in the Study V

The tracheal sound data was overviewed by compressing the signal data, as presented previously (Rauhala et al., 2008). In the reduction procedure only the maximum and minimum sound signal values of each consecutive 15-s epoch were taken. This compressed sound information (four maximum and minimum samples per minute) was used in the visual analyses in study V. The compressed tracheal sound signal was scored into four different categories: a plain signal curve close to zero, a thin signal curve deviating clearly from zero and a thick, highly varying signal curve. The fourth category comprised signal periods of low quality, which were omitted from the analyses.Examples of the compressed tracheal sound patterns are presented in Figure 4.

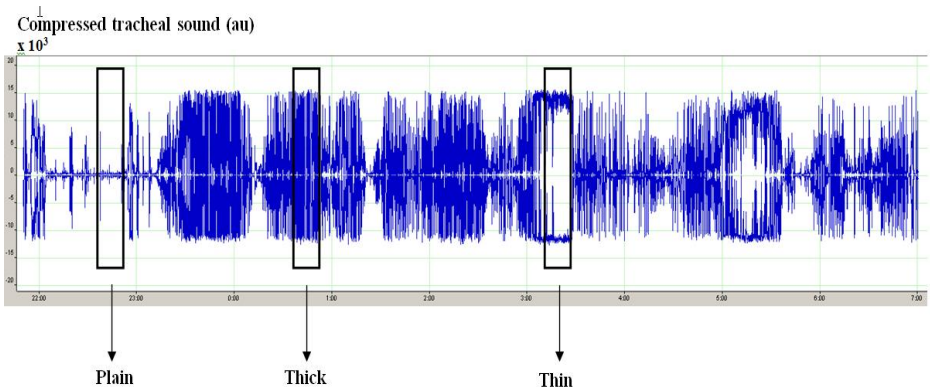


Figure 4. Compressed tracheal sound curve of an OSA patient (AHI 75/h). The 10-minute long plain, thick and thin patterns are indicated with black rectangles. The arbitrary unit of amplitude is denoted as 'au'.

5.4 Detailed methods of the Studies

Study I

Three different 10-minute long breathing epochs were selected from the nasal flow channel of each patient. The periodic breathing pattern was selected if repetitive apneas or hypopneas were present during the epoch. The other breathing epochs were selected based on the shape of the inspiratory flow curve, and therefore the inspirations with a round flow shape were visually distinguished from the non-round, flow-limited inspirations. During normal breathing, 80% or more of the inspirations had to be round shaped. During the prolonged flow limitation epochs, 80% or more of the inspirations had to be non-round. Only epochs during NREM-sleep were taken into account.

To explore the tracheal sound spectrum of the different breathing epochs, the raw sound signal was spectral analyzed with one-second segmenting. After the mean removal, each signal segment was weighted with a Hanning window function of respective length. No zero padding was used, and hence the frequency resolution of the spectrum was 1 Hz. The discrete Fourier transform (DFT) was performed to provide the complex-valued spectrum, which was scaled to the corresponding amplitude spectrum as presented previously (Huupponen et al., 2008).

The overall spectral content during the selected epochs was calculated by The Welch estimate of the amplitude spectrum using 50% overlapping. From the Welch spectrum the average amplitude in the total frequency range of 50-5512 Hz, as well as in narrower frequency bands were

determined. In addition, the percentage-proportions of the sound amplitudes in the low, middle, and high frequency bands (50-100 Hz, 101-600 Hz, 601-5512 Hz) were extracted for each epoch.

Study II

In study II, the number of different polysomnographic events as well as the esophageal pressure variations in different Emfit breathing categories during NREM sleep were studied. To achieve this, one 3-minute epoch of every Emfit breathing category (whenever present) was selected from each patient. The number of respiratory events, arousals, and desaturations during the 3-minute breathing epochs were calculated visually.

The proportion of time (referred to TST) with pESO values ≤ -8 cmH20 in both 3-minute Emfit epochs and in the different Emfit categories of the whole night was calculated automatically. In addition, the most negative pESO values within the 3-minute epochs were extracted automatically.

Study III

Demographic data of the 157 patients were collected from the questionnaires routinely in use in the Sleep Laboratory. The data comprised age, sex, BMI, reason for referral, end-diagnosis, score of the Epworth Sleepiness Scale (Goldberg et al., 1997, Johns, 1991), subjective time in sleep, and medications.

The Emfit respiratory scoring results were correlated to AHI, and the Emfit category with the best correlation with AHI was used in further analyses. The simple linear regression was used to fit a straight line to estimate the time percentage of impaired breathing by the Emfit sensor that corresponds to the AHI-values of 5/h, 15/h, and 30/h. The obtained percentage values were used in computing the sensitivities, specificities and accuracies of the Emfit stages in detecting the patients with AHI 5/h, 15/h, and 30/h.

Based on the obtained percentage values, the receiver operating characteristics curve (ROC) was extracted and the area under curve (AUC) was defined.

To compare the OSA patients with the patients with prolonged partial obstruction, the patients were first divided into four groups based on AHI and the time percentage of IRR. The cut off values AHI 15/h and IRR 15% were utilized. In the further analyses, only the results of the OSA-group (AHI $\geq$ 15/h, IRR < 15%) and the IRR-group (AHI < 15/h, IRR $\geq$ 15%) were compared.

Study IV

The parameters of heart rate variability (HRV) were calculated from the three different Emfit breathing categories (NB, POB, IRR) in study IV. The esophageal pressure signal was used to confirm increased respiratory effort during the POB and IRR epochs.

The mean HRV values of all at least 6-minute periods of NB, POB, and IRR were first calculated and then averaged over categories. The RR-intervals were extracted from the ECG signal by using an adaptive QRS detection algorithm to recognize R-peaks. The HRV calculations were carried out using Kubios HRV analysis software (Tarvainen et al., 2014). The standard deviation (SDNN), mean (mean RR) as well as minimum and maximum of normal- to-normal RR intervals (RRmin, RRmax) were calculated for each breathing category. The frequency domain parameters of heart rate variability were analyzed in three frequency bands: the very low frequency band (VLF, 0.003-0.04 Hz), the low frequency band (LF, 0.04-0.15 Hz), and the high frequency band (HF, 0.15-0.4 Hz). In addition, the LF/HF –ratio was calculated.

Study V

One 10-minute representative episode of plain, thin and thick compressed tracheal sound pattern from each subject (see Figure 4), whenever present, was selected for further analyses. Two researchers confirmed this selection.

The percentage of the time (referred to total sleep time) when the pESO values were below -8 cmH_2O was calculated automatically for each selected 10-minute compressed sound pattern and for each patient if existing. The spectral analyses were performed as in study I with frequency bands of 50-1000 Hz, 1001-2000 Hz, 2001-3000 Hz, 3001-4000 Hz, and 4001-5512 Hz for each 10-minute episode.

5.5 Statistics

Statistical analyses were performed with SPSS® for Windows versions 16.0 and 17.0 (SPSS Inc.) in studies I-II and IBM® SPSS® Statistics versions 20.0 and 21.0 (IBM corp.) in studies (III-V). Non-parametric tests were used because all variables were not normally distributed. The Friedman test was used to estimate if multiple dependent variables varied by tested category. The Wilcoxon signed-rank test with appropriate Bonferroni corrections was used in post hoc analyses (studies I, II, IV, V). The p-values < 0.05 were considered as significant in the statistical tests.

In Study III, the Spearman's correlation coefficient was computed to assess the relationship between Emfit scoring and the AHI. Based on AHI level 15/h, a receiver operating characteristic (ROC) curve was derived and an area under the curve (AUC) was calculated. The sensitivities and specificities were computed using standard formulae. The two patient groups were compared with the Mann-Whitney test.

6 Results

6.1 Capability of the Emfit mattress to detect respiratory effort during sleep (Study II)

Intrathoracic pressure variations during the Emfit breathing categories were evaluated in study II. Normal breathing pattern (NB) was identified in 29/32 patients, P1 pattern was present in 30 patients, OP1 pattern in 31 patients, OP2 pattern in 26, OP3 pattern in 14, and IRR pattern in 24 patients. NB with periodic movements (PM) covered 18.6% (median, range 0.0-72.3%) of TST. The number of other breathing categories as median percentage of TST were consecutively: P1 14.2% (0.0-39.4%), OP1 34.5% (0.6-72.4%), OP2 2.9% (0.0-30.9%), OP3 0.0% (0.0-16.7%), and IRR 3.8% (0.0-19.7%). Gross body movements (M) covered 4.9% of TST (0.0-36.7%).

The proportion of time (referred to TST) with increased respiratory effort (pESO values ≤ -8 cmH20) during the different Emfit breathing categories were calculated within 3-minute epochs and from the overnight sleep period (Table 7). In the 3-minute epochs, respiratory effort remained low in NB-epochs when compared with OP1, OP2, OP3, and IRR ($p = 0.006$, 0.009, 0.033 and 0.002, respectively). Respiratory effort was increased in IRR-epochs when compared with P1, OP1, and OP2 ($p = 0.002$, 0.001, and 0.023, respectively). Respiratory effort was also lower in P1-epochs when compared with OP3 ($p = 0.033$).

The most negative esophageal pressure values (pESOmin) in 3-minute epochs are presented in Table 7. The pESOmin value of NB was higher than the values of P1, OP1, OP2, OP3, and IRR ($p = 0.011$, 0.001, 0.004, 0.043, and 0.003, respectively). In addition, pESOmin in P1 was higher than pESOmin values of OP2, OP3, and IRR ($p = 0.043$, 0.033, 0.005, respectively).

Table 7. The proportion of time with increased respiratory effort (pESO ≤ -8 cmH_20, median value with range) and the minimum value of pESO in different breathing categories.

Emfit category	3-minute representative epochs		Overnight Emfit recording
	pESO values ≤ -8 cmH_20 (%)	pESOmin (cmH_2O)	pESO values ≤ -8 cmH_20 (%)
NB	0.0 (0.0-4.0)	-8 (-4 to -16)	1.9 (0.0-26.3)
P1	0.7 (0.0-22.5)	-12 (-5 to -23)	2.6 (0.0-25.9)
OP1	3.7 (0.0-28.3)	-16 (-4 to -35)	6.4 (0.0-24.4)
OP2	7.7 (0.0-26.1)	-16 (-7 to -41)	8.0 (0.2-25.3)
OP3	15.3 (0.7-30.9)	-26 (-13 to -42)	13.1(1.1-27.5)
IRR	23.5(0.1-36.1)	-21 (-9 to -41)	18.7 (0.0-44.2)

NB normal breathing, P1, OP1, OP2, OP3 different forms of periodic breathing, and IRR increased respiratory resistance. Median values with ranges are presented.

Figure 5 presents the overnight proportion results when pESO ≤ -8 cmH_20 with p-values in Emfit breathing categories. Respiratory effort increased during OP1, OP3, and IRR when compared with NB. In addition, effort was high during IRR when compared with P1, OP1, and OP2. Effort remained low during P1 when compared with OP1 and OP3. The rest of the comparisons did not reach statistical significance.

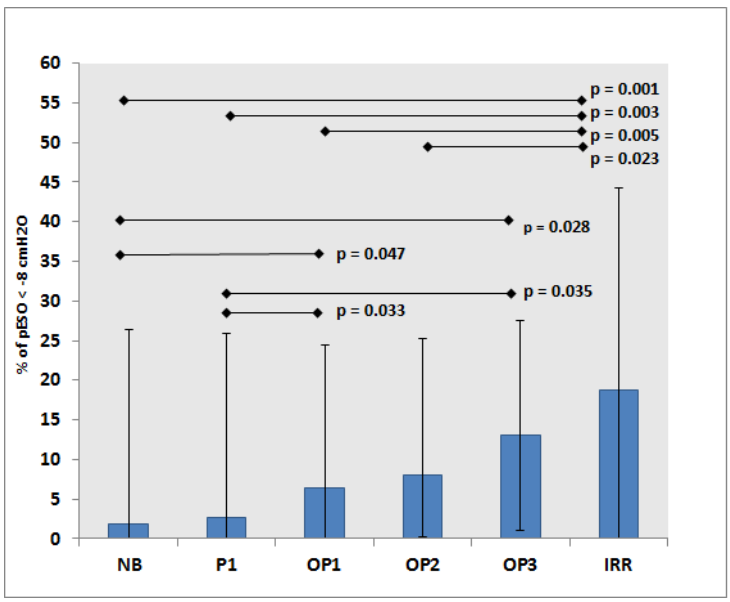


Figure 5. Percentage proportion with increased respiratory effort (pESO values ≤ -8 cmH2O) in Emfit scoring categories during the overnight sleep.

6.2 Validation of the Emfit mattress in OSA diagnostics

6.2.1 Respiratory events, arousals and desaturations in 3-minute epochs of the different Emfit breathing categories, Study II

The number of respiratory events (apneas + hypopneas), arousals, and desaturations (≥ 4%) in the representative 3-minute Emfit breathing epochs of Study II are presented in Figure 6. Apneas or hypopneas were present in P1 and OP-epochs but not found in NB or IRR-epochs. The statistically significant differences between breathing categories are presented in Figure 6, and all p-values are $p < 0.049$.

The smallest number of arousals occurred during NB and IRR, with no statistical difference. Arousals were abundant during OP1- and OP2- epochs when compared with NB- epochs (p-values 0.002 and 0.001, respectively). More arousals were found in P1 ($p = 0.003$), OP1 ($p = 0.0003$), OP2 ($p = 0.001$), and OP3 ($p = 0.047$) when compared with IRR-epochs. P1 consisted of a lower number of arousals than OP2 ($p = 0.007$).

No desaturations were present in NB or IRR epochs. In other breathing categories, desaturations were found, but the only significant differences were obtained between IRR vs. OP1 ($p = 0.014$), IRR vs. OP2 ($p = 0.014$), NB vs. OP2 ($p = 0.014$), and P1 vs. OP2 ($p = 0.006$).

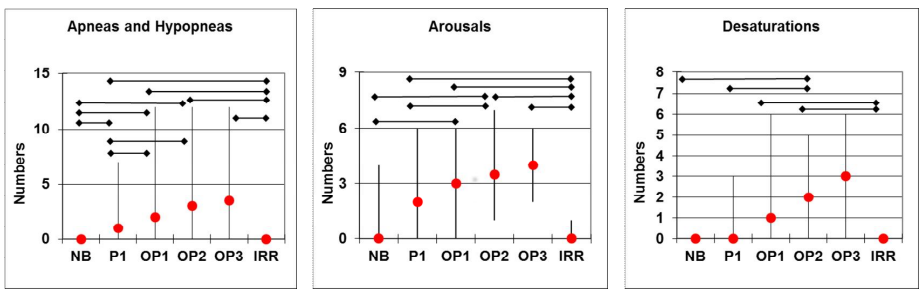


Figure 6. Different events in representative 3-minutes epochs during the Emfit breathing categories. The statistically significant differences are marked with lines.

6.2.2 Correlation between AHI and Emfit breathing categories, Study III

The Emfit respiratory scoring results were correlated to AHI in Study III. The correlation coefficients are presented in Table 8. NB-pattern presented marked negative correlation with AHI (-0.806). The highest positive correlation (0.891) was found between AHI and the combined OP patterns (= OP1 + OP2 + OP3). Therefore, a POB-category (POB = OP1% + OP2% + OP3%) was used in further analyses.

Table 8. Spearman´s correlation coefficients between AHI index and different Emfit breathing combinations. Correlations with statistical significance are marked with an asterisk. The highest Emfit correlation with AHI is marked in bold.

Emfit breathing category	Correlation with AHI
NB%	-.806*
P1%	-.105
OP1%	.865*
OP2%	.558*
OP3%	.499*
IRR%	.248*
OP1+OP2%	.888*
OP2+OP3%	.596*
OP1+OP3%	.872*
P1+OP1%	.777*
P1+OP2%	.270*
P1+OP3%	.113
P1+OP1+OP2%	.828*
P1+OP2+OP3%	.790*
P1+OP1+OP2+OP3%	.790*
OP1+OP2+OP3%	**.891***
OP1+OP2+OP3+IRR%	.849*
P1+ OP1+OP2+OP3%	.835*
P1+ OP1+OP2+OP3+IRR%	.824*

AHI = apnea-hypopnea index,
NB = normal breathing,
P1 = periodic breathing type 1,
OP = obstructive periodic breathing type 1-3,
IRR = increased respiratory resistance

The POB percentages corresponding to the selected AHI cut-off values were extracted from the regression analysis between the AHI and POB% (Figure 7). The selected AHI cut-off values were 5/h, 15/h, and 30/h and corresponding POB percentages turned out to be 9%, 21% and 39%, respectively.

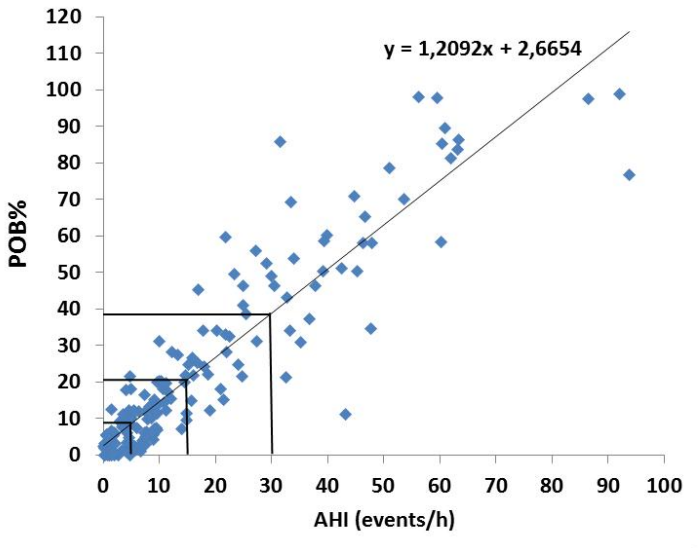


Figure 7. Scatter plot of the correlation between the AHI and the percentage of time spent in POB-patterns (OP1%+OP2%+OP3%). The correlation coefficient R^2 was 0.891. The cut-off values of AHI 5/h, 15/h, and 30/h were used to extract the corresponding POB% values.

The obtained cut-off values were used to calculate the sensitivities, specificities and accuracies of the POB percentage to detect patients with the selected AHI values. The sensitivity (0.948) and specificity (0.918) of the POB percentage to find the patients with AHI ≥ 15/h were both excellent, and accuracy was a little lower (0.879). These numbers, with other sensitivities, specificities, and accuracies are presented in Table 9.

Table 9. The sensitivities, specificities and accuracies for the POB-parameter in different AHI cut-off levels

	AHI 5/h POB 9%	**AHI 15/h POB 21%**	**AHI 30/h POB 39%**
Sensitivity	0.766	0.948	0.935
Specificity	0.809	0.918	0.824
Accuracy	0.803	0.879	0.892

AHI = apnea-hypopnea index
POB% = percentage of combined obstructive periodic breathing categories referred to total sleep time

Based on the threshold definition (AHI ≥ 15/h), receiver operating characteristic (ROC) curve was derived and an area under the curve (AUC) was calculated. In Figure 8, the ROC is presented to reflect the diagnostic capability of the POB percentage when the AHI threshold is set at AHI ≥ 15/h (means moderate disordered breathing). With this limit, the area under the curve was 0.978. This means good accuracy, with 97.8% probability randomly chosen patient with moderate sleep-disordered patients would be correctly identified as such and differentiate from randomly chosen healthy ones (AHI < 15/h). Chosen cut-off 21 for POB% gives sensitivity of 91.8% and specificity of 94.8%.

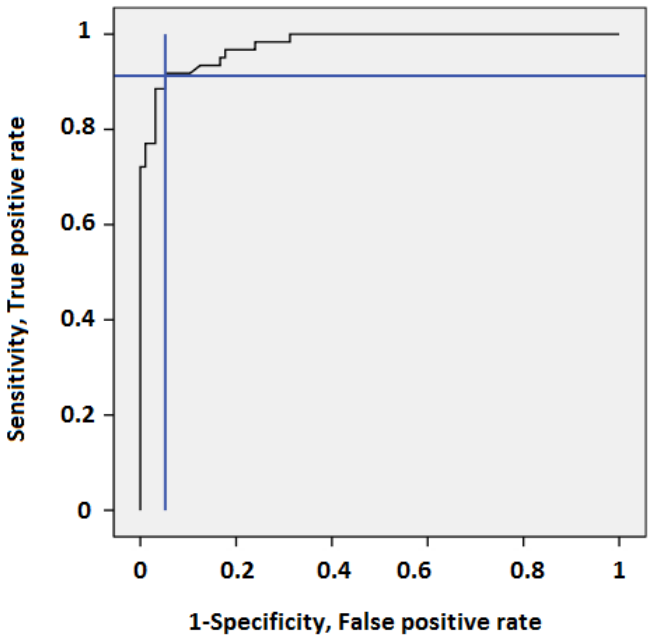


Figure 8. Receiver operating characteristic (ROC) curve reflecting the Emfit scoring limit (POB%) for threshold AHI ≥ 15/h. Blue lines point sensitivity (91.8%) and specificity (94.8%) to the chosen POB% cut-off 21%.

6.3 Clinical evaluation of prolonged partial obstruction (Study III and IV)

6.3.1 Prolonged partial obstruction among sleep laboratory patients (Study III)

In study III, the impact of prolonged partial obstruction on sleep quality and subjective sleepiness was evaluated among 157 sleep laboratory patients. The results of Emfit scoring of the patients are presented in Table 10.

Table 10. Percentages of time (referred to TST) spent in different Emfit categories (n=157 patients).

	Median	**Min**	**Max**
NB%	51.6	0.0	89.4
P1%	5.0	0.0	33.2
OP1%	11.3	0.0	95.9
OP2%	0.7	0.0	43.3
OP3%	0.0	0.0	36.3
CPB%	0.0	0.0	0.0
IRR%	3.5	0.0	55.3
M%	3.0	0.0	19.7
PM%	4.1	0.0	59.0

NB = normal breathing
P1 = periodic breathing type 1,
OP1 = obstructive periodic breathing type 1,
OP2 = obstructive periodic breathing type 2,
OP3 = obstructive periodic breathing type 3,
CPB = central periodic breathing,
IRR = increased respiratory resistance,
M = movement,
PM = periodic Movement

The cut-off value of AHI = 15/h and the IRR-percentage of 15% were utilized when the subjects were divided into four groups. Forty-seven subjects (=29.9%) had OSA (AHI ≥ 15/h, IRR < 15%, OSA+ -group). The IRR+ -group had 17 subjects (10.8%, AHI < 15/h, IRR ≥ 15%). The OSA+IRR+ -group had 13 subjects (8.3%, AHI ≥ 15/h, IRR ≥ 15%). The OSA-IRR- -group comprised 80 subjects (51.0%, AHI < 15/h, IRR < 15%). The sleep disorder end-diagnoses based on polysomnography of the patients in the OSA-IRR- -group differed markedly. As in the other groups, the first end-diagnose was always sleep disordered breathing. Therefore, the OSA-IRR- -group was replaced with the group of 20 patients with mild OSA with no other sleep dis-

orders, (AHI 5-14.9/h, MildOSA-group). The demographic parameters and survey results of the subjects in these groups are presented in Table 11.

Table 11. Demographic parameters and medication of the subjects in different groups.

	OSA+ (n=47)	**IRR+ (n=17)**	**OSA+IRR+ (n=13)**	**MildOSA (n=20)**
Age (years)	52	47	51	49
BMI[1] (kg/m^2)	28.1	30.0	31.0	26.0
ESS[2] (score)	9	8	12	9
GHQ-12[3] (score)	2	8	2	3
SST (h)[4]	7.0	7.8	6.0	5.8
Short-acting sleeping pill (%)	6.4	17.6	23.1	35.0
Benzodiazepine (%)	8.5	5.9	7.7	10.0
Antihypertensives (%)	36.2	23.5	38.5	20.0
Cholesterol drug (%)	12.8	11.8	23.1	10.0
Antidepressant (%)	19.1	17.6	15.4	25.0

[1]Body mass index
[2]Epworth sleepiness scale,
[3]12-item General Health Questionnaire,
[4]Subjective sleep time

Further comparisons were performed between the OSA+ -group and the IRR+ -group (Table 12). The scores of the ESS (Johns, 1991) questionnaire revealed that IRR-patients are as sleepy as the OSA patients, but they had higher scores in the GHQ-12 questionnaire (Goldberg et al., 1997). In addition, their objective sleep quality was better as indicated by a higher SWS percentage, a lower arousal index, and a lower PLM index. The AHI, ODI4, and SaO_2minimum percentage were higher in the OSA+ -group. The use of medications (presented in Table 11) did not differ statistically between the groups.

Table 12. Statistical comparisons of different parameters between the OSA+ and IRR+ groups.

	OSA+ (n=47)	**IRR+ (n=17)**	**OSA+vs IRR+**
ESS[1]	9	8	ns
GHQ-12[2]	2	8	0.009
TST[3] (h)	6.7	7.4	ns
SEI[4] %	83.0	89.3	ns
SL[5] (min)	13	15	ns
REMlat[6] (min)	134.0	125.0	ns
%N1[7]	9.3	5.8	ns
%N2[8]	72.3	65.8	ns
%N3[9]	3.0	9.1	0.005
%REM[10]	12.5	16.8	ns
ARI[11] (n/h)	26.0	11.0	p<0.001
AHI[12] (n/h)	33.2	7.7	p<0.001
ODI4[13] (%)	14.5	1.0	p<0.001
SaO_2min[14] (%)	84.0	87.0	p<0.001
Pulse (bpm)	61.0	60.7	ns
PLMI[15] (n/h)	12.8	1.2	0.002

[1]Epworth sleepiness scale,
[2]12-item General Health Questionnaire
[3]Total sleep time,
[4]Sleep efficiency index,
[5]Sleep latency,
[6]Latency to REM (rapid eye movement) sleep,
[7-10]Percentage of sleep stage (N1-REM) referred to TST,
[11]Arousal index, number of cortical arousals per hour of TST,
[12]Apnea-hypopnea index, apneas and hypopneas per hour of TST,
[13]Oxygen desaturation index, number of desaturations $\geq$ 4% per hour of TST,
[14]Minimum oxygen desaturation,
[15]Mean oxygen desaturation,
[16]Periodic limb movement index

6.4 Evaluation of Emfit stages with HRV (Study IV)

The HRV parameters were calculated for sleep recordings of 53 subjects, and HRV parameters for the Emfit breathing patterns NB, POB, and IRR were extracted. In Figure 9a, b, and c the overnight trends of the HRV parameters from three SDB patients are illustrated. The time domain parameters are presented in Table 13 and Figure 10. The meanRR of the breathing categories did not differ statistically. The standard deviation of normal-to-normal RR (SDNN) that reflects overall HRV was higher during POB than during NB and IRR ($p < 0.001$). The minRR was lower during the POB epochs than during NB and IRR ($p < 0.001$). The maxRR was lower during IRR than during NB and POB ($p < 0.001$). The other comparisons did not show statistically significant differences.

Table 13. Time series measures of HRV (n = 53)

	NB **mean ± SEM**	**POB** **mean ± SEM**	**IRR** **mean ± SEM**
meanRR (ms)	1039.9 ± 22.2	1037.8 ± 22.3	1027.4 ± 22.6
minRR (ms)	783.4 ± 15.7	731.6 ± 15.7	810.7 ± 11.8
maxRR (ms)	1339.3 ± 35.4	1335.0 ± 30.4	1261.9 ± 33.6
SDNN (ms)	43.1 ± 3.1	59.7 ± 4.4	43.2 ± 3.3

HRV heart rate variability,
NB normal breathing,
POB periodic obstructive breathing,
IRR increased respiratory resistance,
meanRR, minRR, maxRR, SDNN = mean, minimum, maximum, and standard deviation of normal-to-normal RR intervals,
SEM = standard error of mean

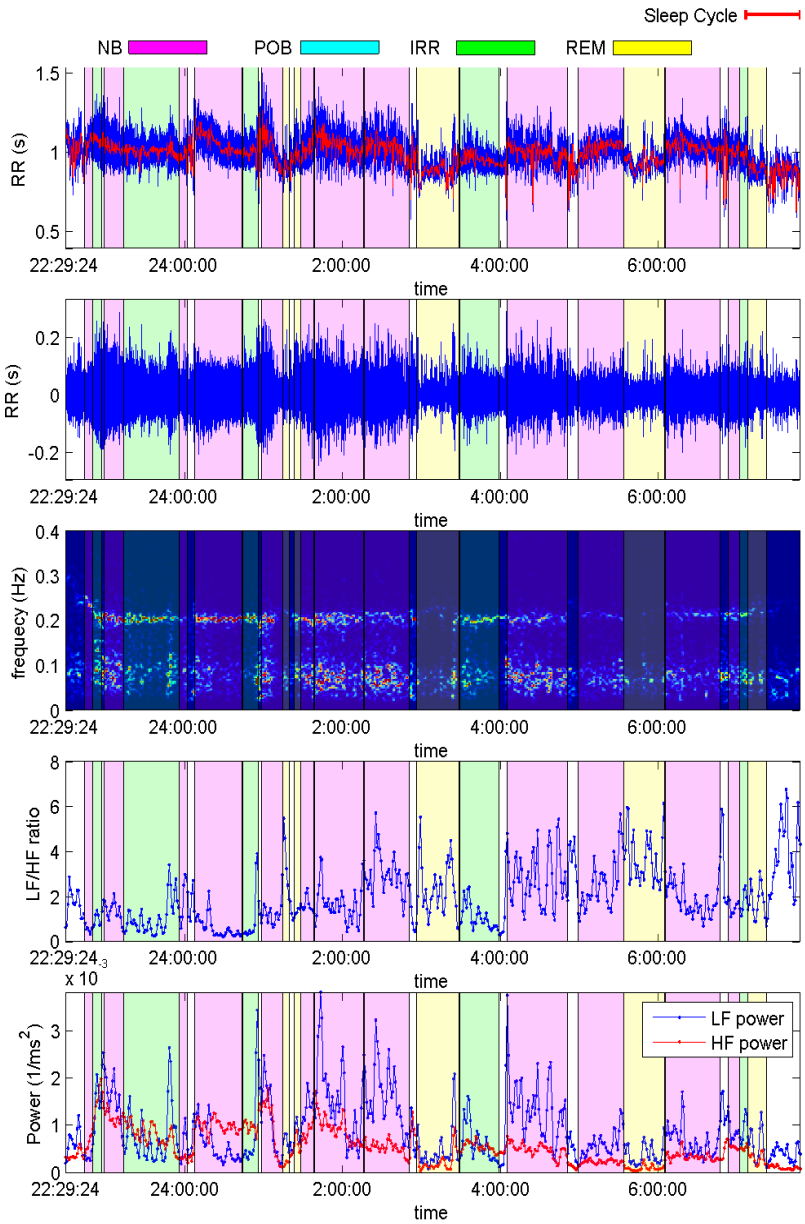


Figure 9a-c. Overnight trends of instantaneous RR-intervals (raw and filtered), and frequency domain measurements (spectrogram, LF/HF ratio, LF and HF power bands). The colored bars represent the different breathing categories (red = NB, blue = POB, green = IRR). Yellow bar = REM-sleep. White areas = wakefulness which was not analyzed.

Figure 9a. Overnight HRV trends of a patient with mainly NB, few IRR periods.

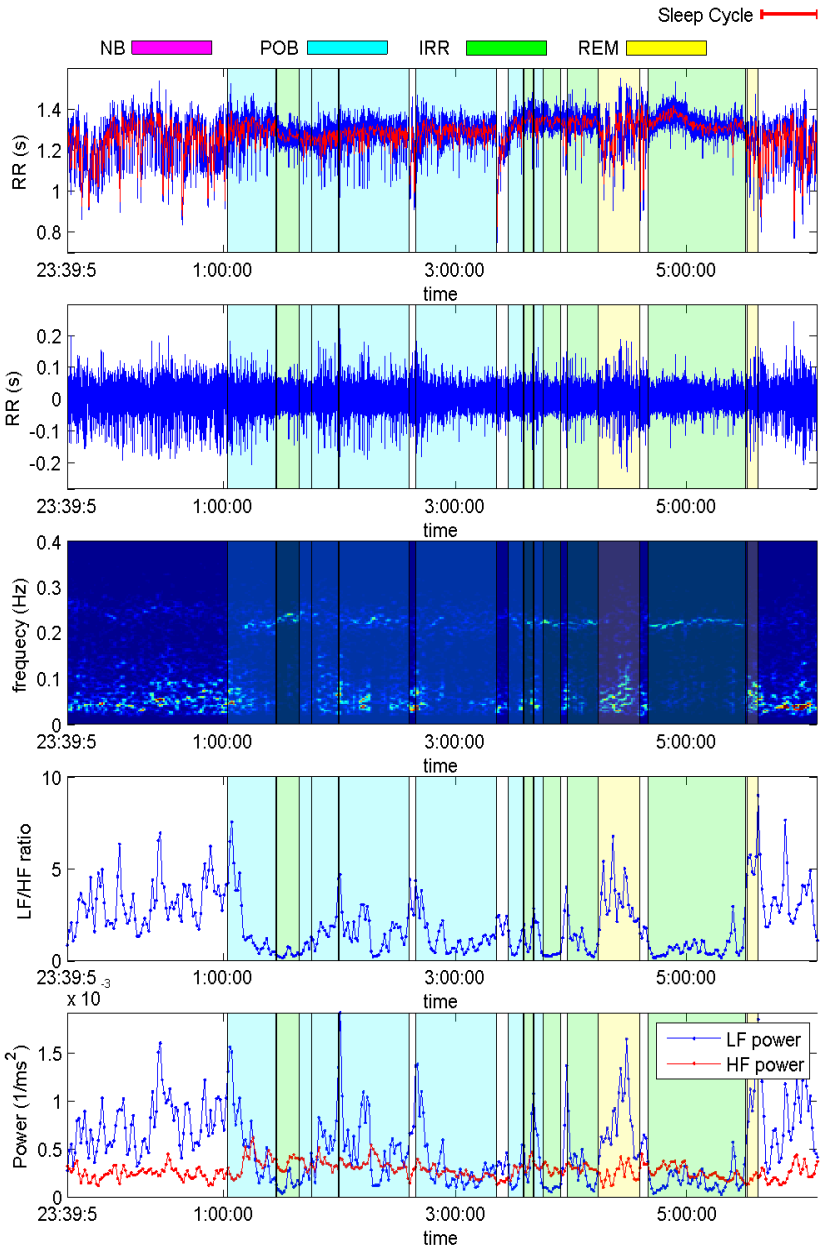


Figure 9b. Overnight HRV trends of a patient with both POB and IRR periods.

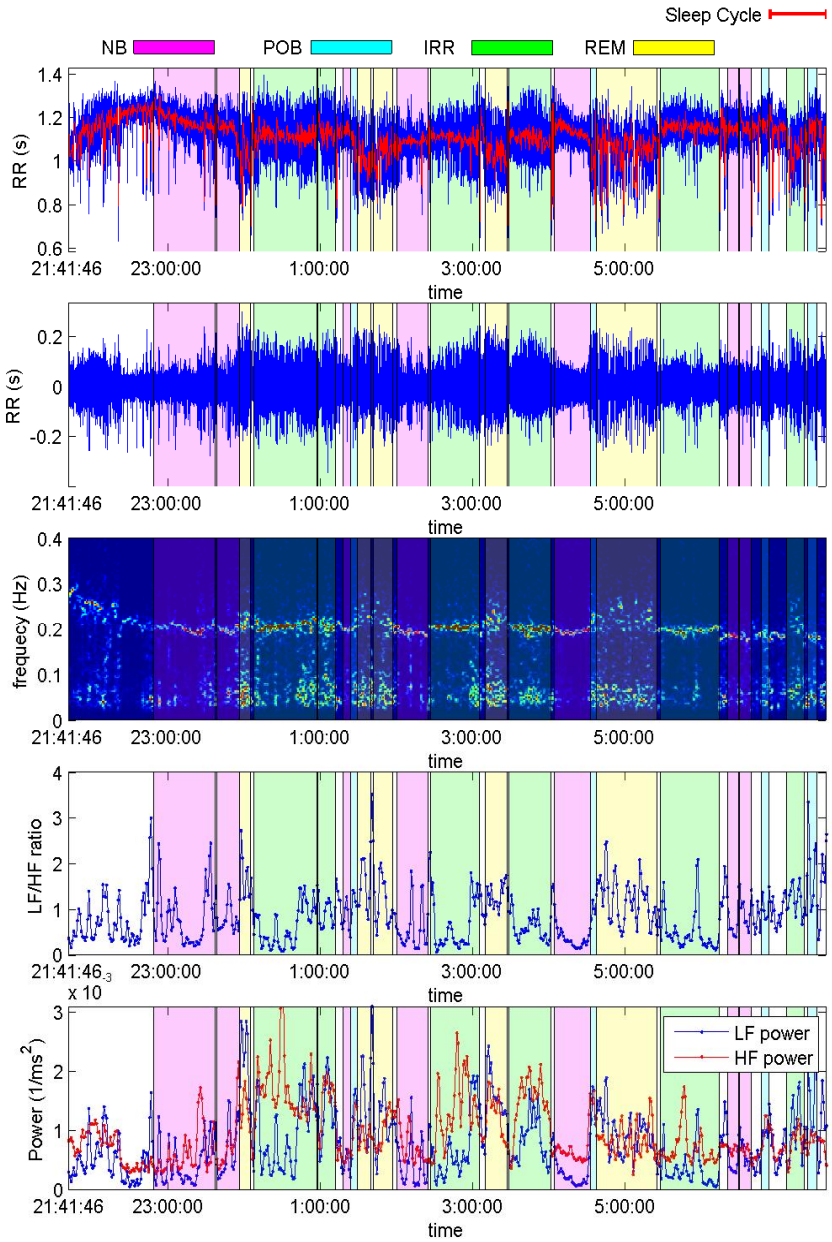


Figure 9c. Overnight HRV trends of a patient with both NB and IRR periods.

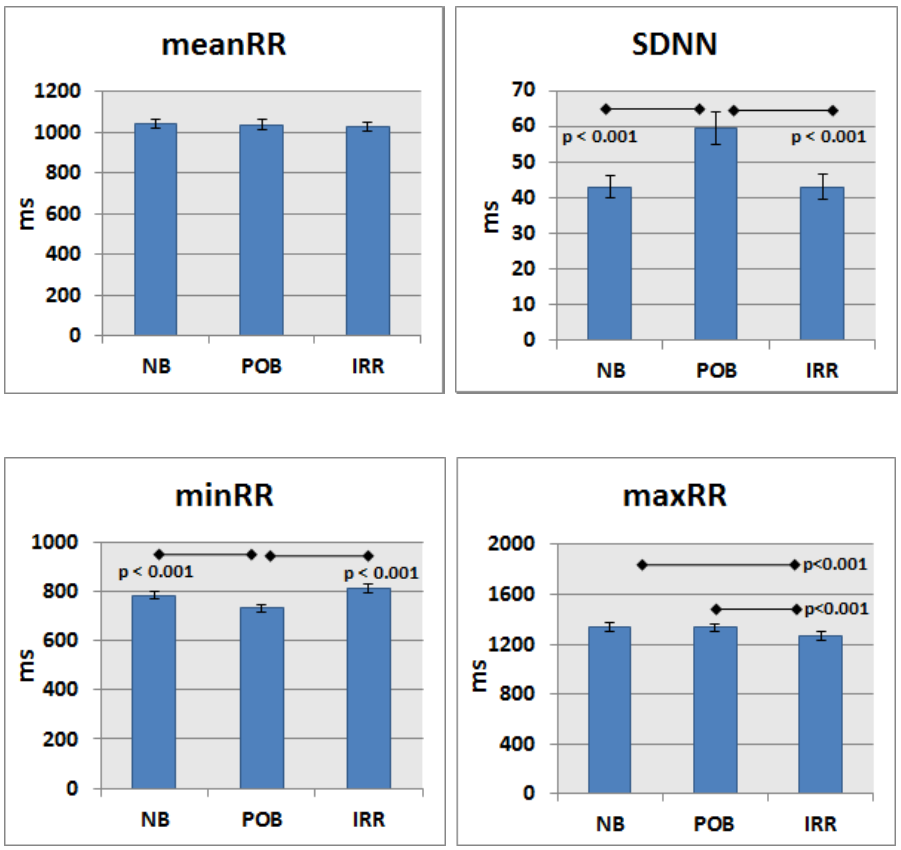


Figure 10. Time series of HRV. Mean, standard deviation, minimum and maximum of normal-to-normal RR intervals (meanRR, SDNN, minRR and maxRR) during normal breathing (NB), periodic obstructive breathing (POB), and increased respiratory resistance (IRR). Mean values in milliseconds (ms) with standard error of mean (SEM) are presented. The statistically significant differences are marked with lines.

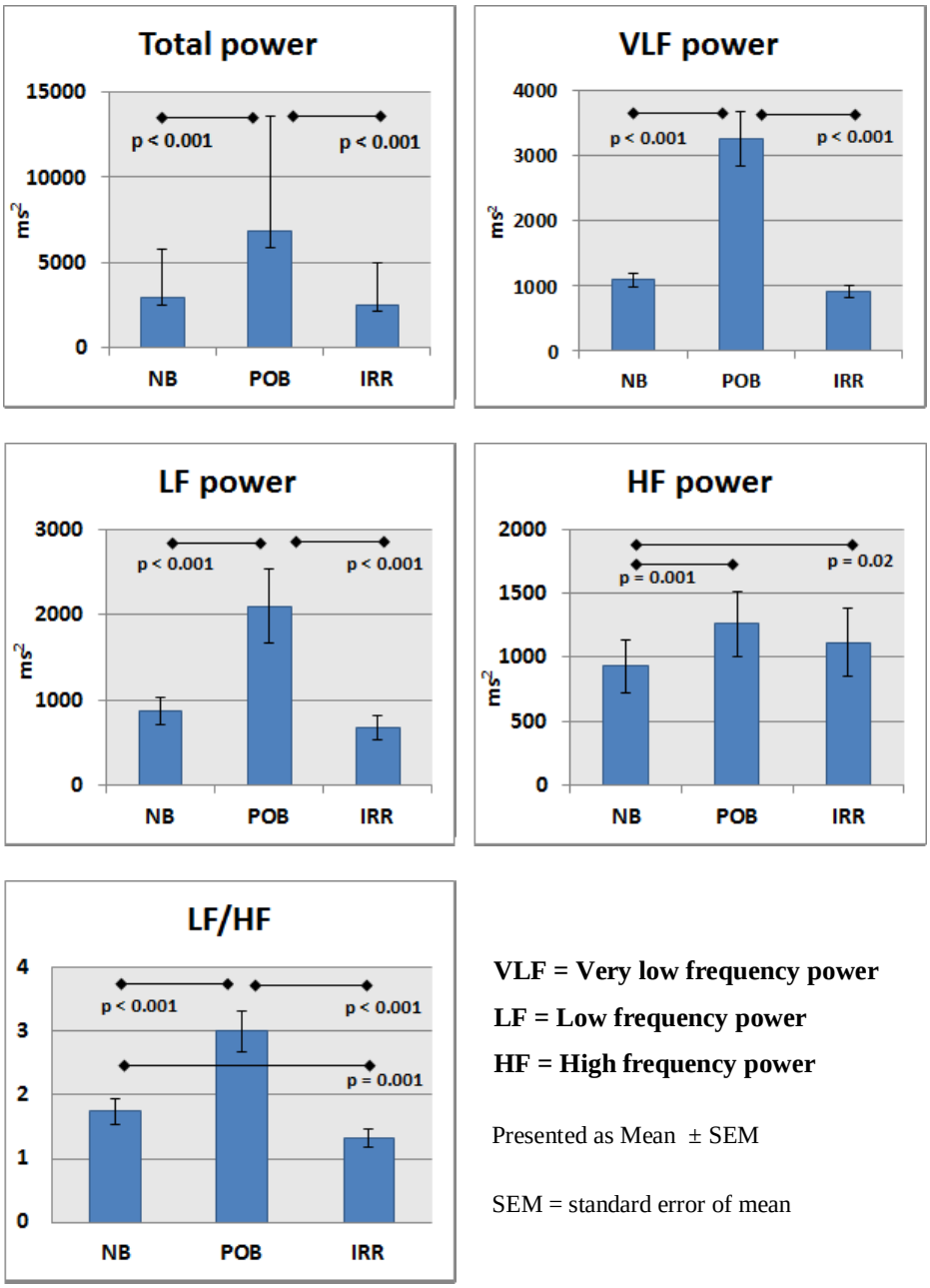


Figure 11. Frequency domain results of HRV during normal breathing (NB), periodic obstructive breathing (POB), and increased respiratory resistance (IRR). The statistically significant differences are marked with lines.

The HRV frequency domain results are presented in Table 14 and Figure 11. The total power, VLF-power, and LF power were highest during POB, but the powers of NB and IRR did not differ from each other. In the HF band, the power was lowest during NB, and the values of POB and IRR did not differ. The LF/HF ratio was highest during POB and lowest during IRR.

Table 14. Frequency domain measures of HRV

	NB **Mean ± SEM**	**POB** **Mean ± SEM**	**IRR** **Mean ± SEM**
TPow(ms^2)	2877.0 ± 389.5	6789.9 ± 974.1	2481.3 ± 371.0
VLF (ms^2)	1097.5 ± 104.4	3259.6 ± 426.8	905.4 ± 96.2
LF (ms^2)	866.6 ± 159.9	2099.5 ± 439.6	679.7 ± 141.4
HF (ms^2)	928.4 ± 206.3	1263.1 ± 252.1	1113.8 ± 265.5
LF/HF	1.7 ± 0.2	3.0 ± 0.3	1.3 ± 0.1

NB normal breathing,
POB periodic obstructive breathing,
IRR increased respiratory resistance,
TPow = Total power,
VLF = Very low frequency power,
LF = Low frequency power,
HF= High frequency power,
SEM = standard error of mean

6.5 Tracheal sound and prolonged partial obstruction (Studies I and V)

6.5.1 Spectral analysis of the tracheal sound in the evaluation of flow limitation pattern, Study I

The tracheal sound amplitudes during the three different breathing patterns derived from the nasal pressure signal (normal breathing, episode with apneas/hypopneas, and flow limitation) were extracted in Study 1. The sound amplitudes in 14 different frequency bands are presented in Figure 12. The sound amplitude of normal breathing was the lowest in the 50-100 Hz band, differing significantly from flow limitation and periodic breathing epochs that did not differ from each other. The sound amplitudes of flow limitation epochs were the highest in all bands above 100 Hz. The lowest amplitudes were found in normal breathing epochs in all bands except the bands 601-700 Hz and 1001-2000 Hz, where the amplitudes of periodic breathing epochs were also low and did not differ significantly from normal breathing (p-values were ≤ 0.032 in all statistically significant comparisons).

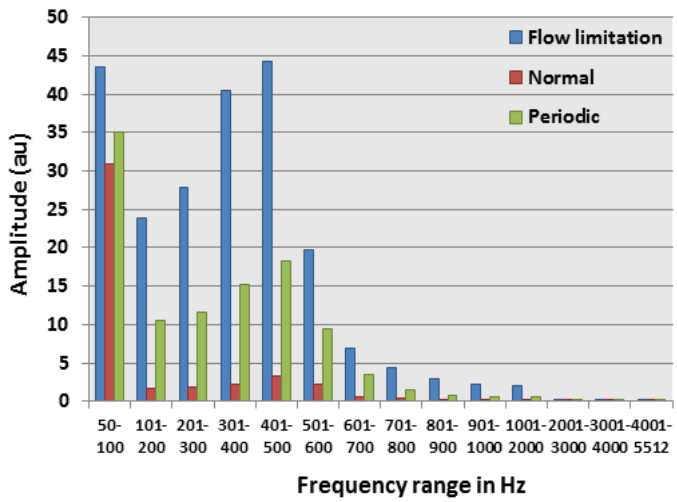


Figure 12. The median tracheal sound amplitudes during 10-minute period of flow limitation, normal breathing, and periodic breathing epochs in 14 frequency bands. The amplitudes are presented in arbitrary units (au).

In the further evaluation, the shares of the spectral components infrequency bands (50-100 Hz, 101-600 Hz, 1001-2000 Hz) were extracted for each breathing pattern. A large amount of normal breathing sound loudness was found in the lowest frequency band (62.4%, Figure 13). The corresponding values of periodic breathing epochs and flow limitation epochs were 29.9% and 18.8%, respectively. All proportional amplitudes in the lowest band differed statistically from each other (all p-values $\leq$ 0.009). The flow limitation epochs presented the highest proportion (64.9%) in the middle frequency band, where normal breathing presented the lowest proportion (31.3%). The value of periodic breathing was 57.8%. In the middle frequency band, all values differed statistically significantly (all p-values $\leq$ 0.011). In the highest frequency band, the flow limitation pattern presented the largest proportion (11.6%), differing significantly from the normal breathing (5.4%) and periodic breathing (10.6%, both p-values $\leq$ 0.047), but there were no other statistically significant differences in the highest band.

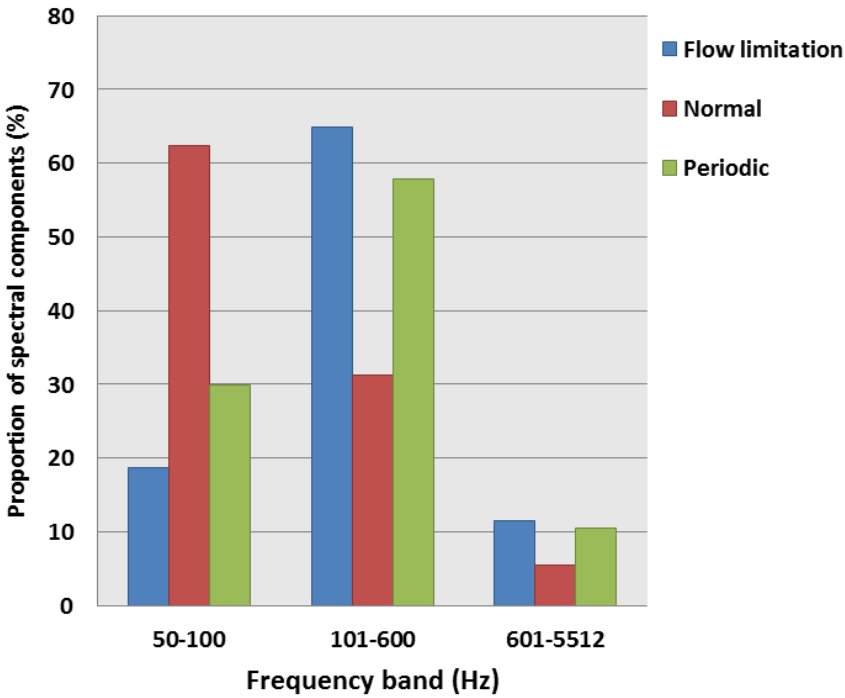


Figure 13. The percentage-proportions of the spectral components during the 10-minute periods of the three breathing categories in the low (50-100 Hz), middle (101-600 Hz) and high (601-5512 Hz) frequency bands. Median values across the patients are presented.

6.5.2 Respiratory effort in the different compressed tracheal sound patterns (Study V)

Ten-minute episodes of the compressed tracheal sound patterns (plain, thick, thin, Figure 4) were selected in this work, where the earlier presented compressed tracheal sound patterns were further studied (Rauhala et al., 2008). Sixteen subjects out of 27 had a 10-minute plain episode. Nineteen subjects had a thick sound episode and another 19 subjects had at least one 10-minute thin episode.

6.5.2.1 Esophageal pressure values in the compressed tracheal sound patterns

The esophageal pressure values were calculated for each compressed sound pattern. The resulting percentage of time with increased respiratory efforts (pESO ≤ -8 cmH_2O) was highest during the thin pattern (median 21.4%, range 3.5-31.9%), differing statistically significantly from the plain sound pattern (0.03%, 0-1.0%, p = 0.01) and the thick pattern (9.6%, 3.9-20.1%, p = 0.002, Figure 14). During the plain sound pattern, the percentage was lowest and differed significantly from the thick pattern (p = 0.02).

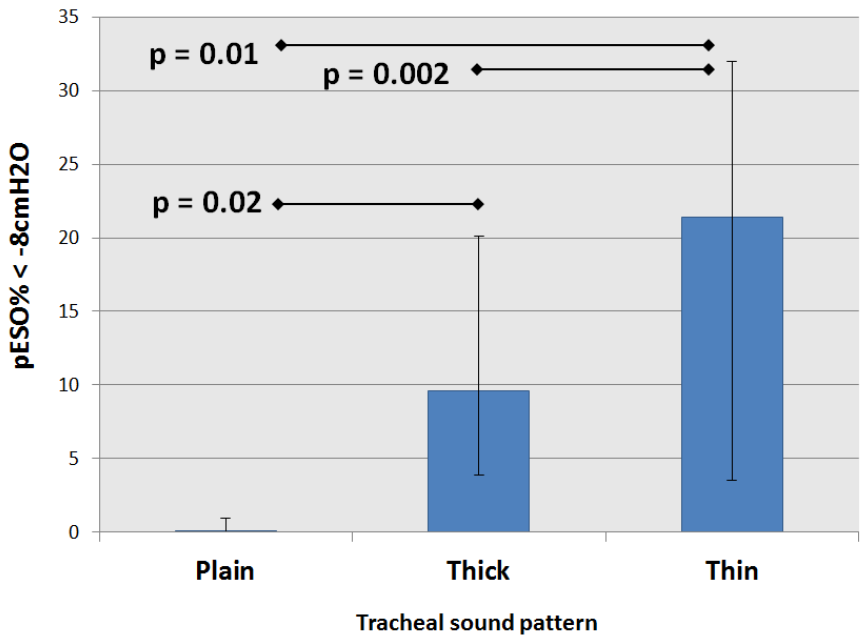


Figure 14. Percentage values of pESO values ≤ -8 cmH_2O during 10-minute episodes of different compressed sound pattern.

6.5.2.2 Spectral analysis of the raw tracheal sound signal during the different compressed tracheal sound patterns

The tracheal sound amplitudes during the 10-minute compressed tracheal sound epochs in the five frequency bands are presented in Figure 15. In all frequency bands, the amplitude was highest during the thin pattern and lowest during the plain pattern (all p-values < 0.05).

The calculated percentage proportions of the spectral amplitudes during the 10-minute compressed tracheal sound epochs in the five bands are presented in Figure 16. The thin pattern had a lower percentage proportion value in the frequency band of 50-1000 Hz (median 81.1%, range 51.6-97.1%) than the thick pattern (90.6%, 53.0-96.5%, p= 0.02). The value of the plain pattern was 93.8% (42.8-96.9%). In the frequency band of 1001-2000 Hz, the thin pattern had the highest percentage proportion value (9.7%, 1.2-17.7%), differing significantly from the plain pattern (2.7%, 1.5-15.9%, p= 0.01) and the thick pattern (5.4%, 2.2-16.2%, p= 0.02). The difference between the thick pattern and the plain pattern was also statistically significant (p= 0.02). The three highest frequency bands showed no statistically significant differences.

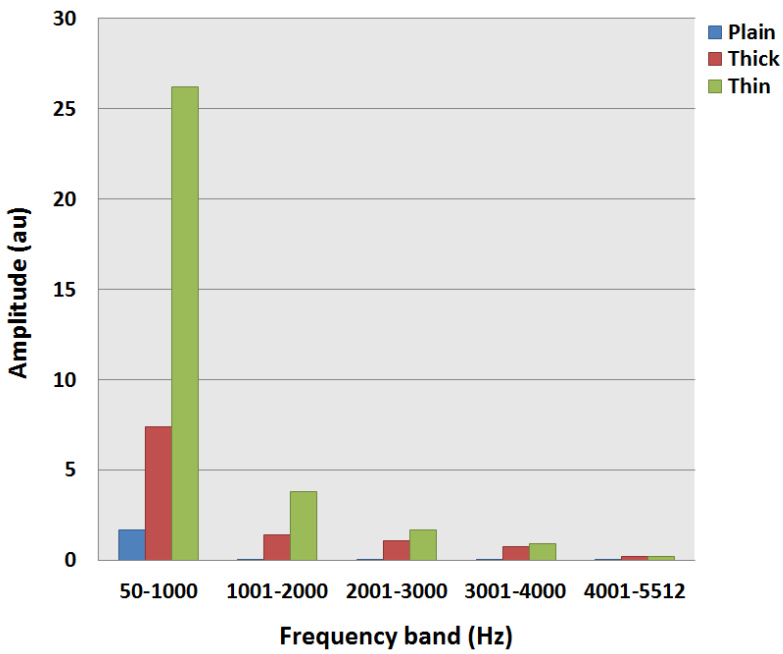


Figure 15. Median tracheal sound amplitudes during the 10-minute compressed sound epochs in the five frequency bands during the plain, thick, and thin sound patterns. The sound amplitude was highest during the thin pattern and lowest during the plain pattern in all frequency bands (all p-values < 0.05).

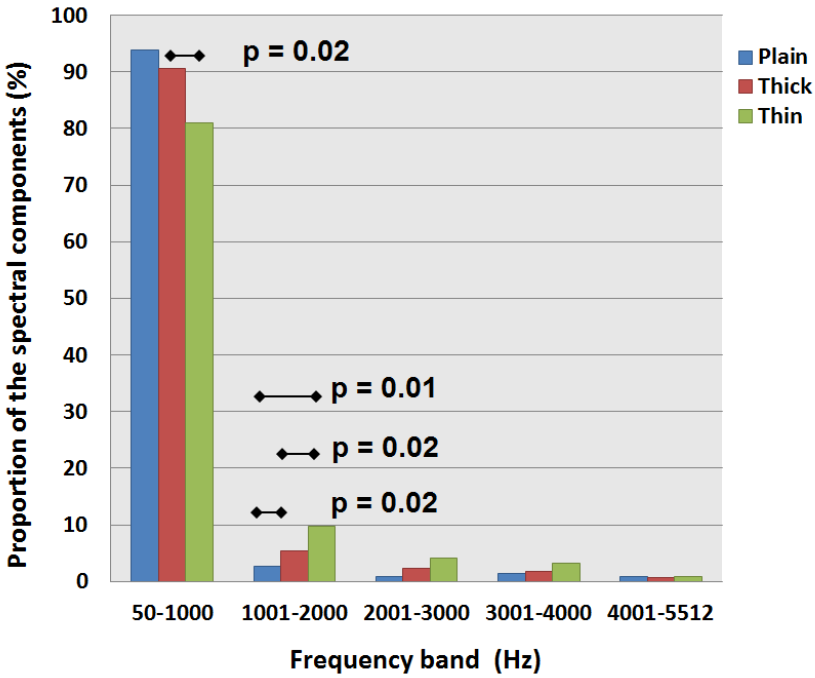


Figure 16. The percentage proportions of the spectral components during the 10-minute compressed tracheal sound epochs in the five frequency bands during the plain, thick, and thin sound patterns. Median values are presented. The statistically significant differences are marked with lines.

7 Discussion

Different sleep problems are common in public health care. As a result, there is an increasing need for quick and easy screening methods. Reliable and non-invasive methods are required to distuinguish which problems need to be treated, because insufficient sleep leads to decreased quality of life, work disability, and health problems such as insomnia, obesity, sleep apnea, and cardivascular diseases.

For many years, the clinical work and quantification of SDB has been based on the calculation of apnea-hypopnea index (AHI). However, the AHI index does not explain all patient symptoms, as it does not take into account the different features of the respiratory events (Muraja-Murro et al., 2014). Some clinical patients suffer from atypical sleep problems, but PSG gives low AHI (Svensson et al., 2008). Often, these patients are left undiagnosed even if this patient group might suffer from prolonged partial airway obstruction that can be treated with CPAP (Anttalainen et al., 2010a, Anttalainen et al., 2013, Anttalainen et al., 2007a).

The SCSB mattress, as a forerunner, has long been used in sleep research to detect movements and SDB, such as apneas and prolonged partial obstruction. Similar patterns can be observed with the Emfit mattress that measures cardiorespiratory functions using ballistocardiography (BCG). In clinical sleep, the Emfit signal can be used to detect periodic movements (Rauhala et al., 2009). However, in the diagnostics of OSA and prolonged partial obstruction it has not been validated. Preliminary reports suggest that prolonged partial obstruction could also be recorded using tracheal sound measurement (Rauhala et al., 2008).

Even if prolonged partial obstruction is frequent in clinical sleep studies (Anttalainen et al., 2007a, Polo et al., 1988, Polo-Kantola et al., 2003), its impact on health and quality of life has been a matter of lesser interest. It has been reported that associations exist between asthma and chronic obstructive pulmonary disease. In addition, women with prolonged partial obstruction suffer less from hypertension than the general population (Anttalainen et al., 2010b).

The capability of the Emfit mattress to detect increased respiratory effort during sleep

That conventional AHI does not reflect the changes in intrathoracic pressure is a drawback in diagnosing different SDB. Measuring intrathoracic pressure variation requires invasive catheterization through the nostrils, which often is too complicated in clinical work and in the worst case causes sleep fragmentation. Thus, other measuring methods are needed to improve the accuracy of diagnostic procedures.

In an experimental study, SCSB high frequency spiking has been shown to evolve with increased inspiratory resistance (Kirjavainen et al., 1996). When scoring is carried out visually

in clinical work, SCSB and the Emfit signal comprise continuous high frequency spikes. To evaluate whether the spikes in the Emfit breathing categories coincide with increased effort, the intrathoracic pressure changes were evaluated in different Emfit breathing categories. Spikes seem to reflect intrathoracic pressure variations because the esophageal pressure values decreased in the Emfit breathing categories where spikes emerged (OP 1-3, IRR). During NB and P1 (without spikes), the pressure values remained more or less normal.

In this way, the Emfit mattress provides a noninvasive and patient-friendly tool to assess intrathoracic pressure variations. There are no restrictions or contraindications on the use of the Emfit mattress. The Emfit film is a patented, Finnish-made commercially available material (Emfit Ltd). Furthermore, it is inexpensive and does not interfere with sleep since there is no need to attach electrodes to the sleeper.

The Emfit mattress in OSA diagnostics

The respiratory scoring principles of the SCSB sensor have been reported by Polo and coworkers (Polo, 1992) and the same principals have been adopted to Emfit scoring. Apneas can be detected with SCSB, but the Emfit sensor has not been evaluated for the detection of apneas before.

In detailed analysis of short Emfit breathing category periods, obstructive apneas, hypopneas, arousals, and desaturations were generally abundant in the OP1, OP2, and OP3 categories. During NB and IRR, no apneas, hypopneas, arousals, or desaturations existed.

The correlation results showed that the longer the time spent with OP-patterns (POB), the greater the AHI values were. Whereas P1 and IRR showed no correlation to AHI, NB had clear negative correlation. In clinical practice, the severity of OSA is expressed by AHI limits; AHI < 5 (normal), $5 \leq$ AHI < 15 (mild OSA), $15 \leq$ AHI < 30 (moderate OSA), and AHI ≥ 30 (severe OSA). Time percentages of POB representing the different AHI limits were extracted to ease the clinical quantification of OSA detected by Emfit. The Emfit pattern scoring was found to perform with excellent accuracy in detecting subjects with AHI 15/h or more. The corresponding POB percentage limit for AHI 5/h was 9%, limits for AHI 15/h and 30/h were 21% and 39%, respectively.

These results revealed the suitability of the Emfit sensor for OSA detection. The easy and rapid manual scoring procedure increases the attraction of using mattress sensors as a diagnostic tool with large patient samples.

Clinical evaluation of prolonged partial obstruction

According to the presented results, OSA prevalence among sleep laboratory patients (mild + severe OSA) was 43% and the prevalence of prolonged partial obstruction by Emfit scoring

(IRR) was 11%. IRR was not found to be a rare phenomenon and it is quite surprising how few of its symptoms and consequences have been examined.

When the IRR patients were compared with OSA patients they had fewer arousals and desaturations, which correspond to the findings of the above mentioned 3-minute detailed Emfit breathing category results. Even if IRR patients had more deep sleep (SWS), they were as tired as OSA patients (ESS survey results). This might stem from the increased inspiratory efforts during obstructive breathing that has been found to contribute to the subjective sleepiness (Pelin et al., 2003).

OSA patients may also have atypical symptoms that include difficulty in falling asleep, frequent awakenings, insomnia, and depression (Valipour et al., 2007). Women have been found to present subjective symptoms with lower AHI than men (Young et al., 1993), and IRR has been recognized more often among women (Anttalainen et al., 2007b). It might be that women suffer both from mild OSA and IRR, and that the atypical symptoms arise because of IRR. This view is supported by the fact that IRR patients had increased GHQ-12 score in the present study, indicating more depressive mood and reduced quality of life.

Physiology of prolonged partial obstruction

OSA is a well recognized risk factor for cardiovascular diseases (McNicholas & Bonsigore, 2007). Yet, IRR has been associated with reduced prevalence of hypertension in females (Anttalainen et al., 2010b). In addition, it has been found that mild stroke patients do not have prolonged partial obstruction, though OSA was found to be common (prevalence 2.4% and 52.4%, respectively, (Väyrynen et al., 2014). The differences may be due to the different effects OSA and IRR have on the autonomous nervous system (ANS). Patients with OSA have increased sympathetic activity even when awake (Somers et al., 1995), but the interactions between prolonged partial obstruction and the ANS have not before been evaluated.

It was shown that periodic obstructive breathing (POB) induced a similar increase in sympathetic activity as presented previously in sleep apnea (Somers et al., 1995). This increase in sympathetic activity was seen from the substantial heart rate variability during POB and the frequency domain results of ECG. The total power, as well as the VLF, LF, and HF powers was high when compared with normal breathing and the LF/HF ratio, which assesses sympathetic activity, had clearly increased. Different physiological mechanisms behind the increase in sympathetic activity in POB are presented in Figure 17. The repetitive increases in negative intrathoracic pressure in POB result in reduced cardiac output, which decreases baroreceptor firing and lead to an increase in sympathetic activity and blood pressure (Bradley et al., 2001, Brinker et al., 1980, Guilleminault et al., 1986, Morgan et al., 1966, Parker et al., 1999, Peters et al., 1988, Shiomi et al., 1991, Tolle et al., 1983). Other mechanisms that are found to increase sympathetic activity are hypoxia, hypercapnia, and arousals (Foster et al., 2009, Morgan et al., 1993, Ringler et al.,

1990, Somers et al., 1989). In addition, hypoxia with arousal can induce an additive increase in sympathetic activity (O'Donnell et al., 1996) and hypoxia may impair local vasodilatation (Foster et al., 2009), thus increasing blood pressure.

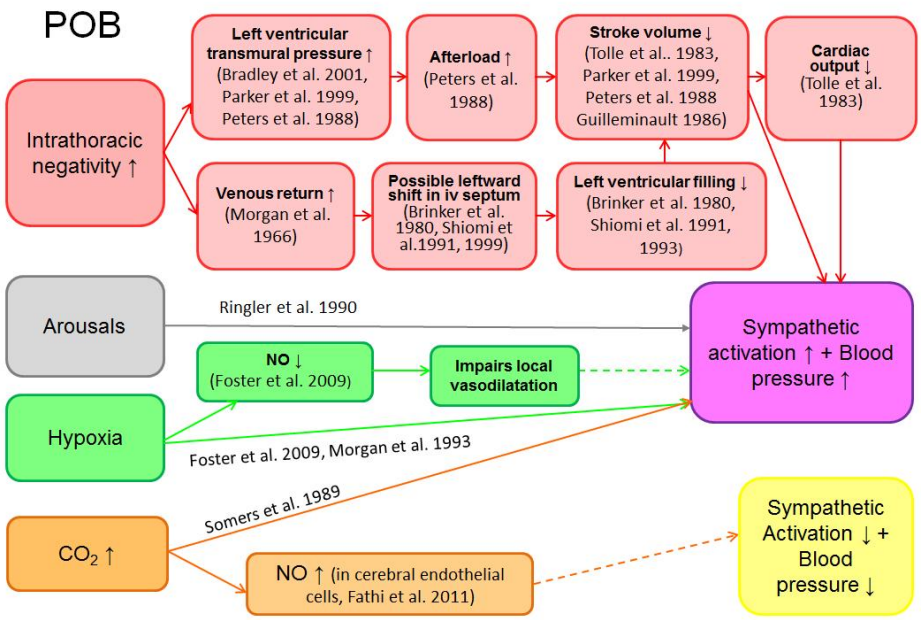


Figure 17. Physiological effects of periodic obstructive breathing

During IRR, sympathetic activity decreased when compared with both NB and POB, and parasympathetic activity increased in IRR when compared with NB. Figure 18 presents the assumed physiological processes in IRR. The intrathoracic pressure variations are supposed to induce a similar increase in sympathetic activity in IRR as seen in POB. However, the effects of transient desaturations and arousals do not emerge because they are not present in IRR. The shift of ANS tone to parasympathetic dominance in IRR might be due to massive activation of the pulmonary stretch receptors caused by the increased inspiratory efforts (Seals et al., 1993). Activation of the stretch receptors is known to inhibit the vasomotor area and sympathetic activity and leads to vasodilatation of the resistance vessels, which decreases blood pressure. In addition, the cumulative increase in $tcCO_2$ during IRR (Rauhala et al., 2007) may have an impact on vasomotor activity by increasing local vasodilatation.

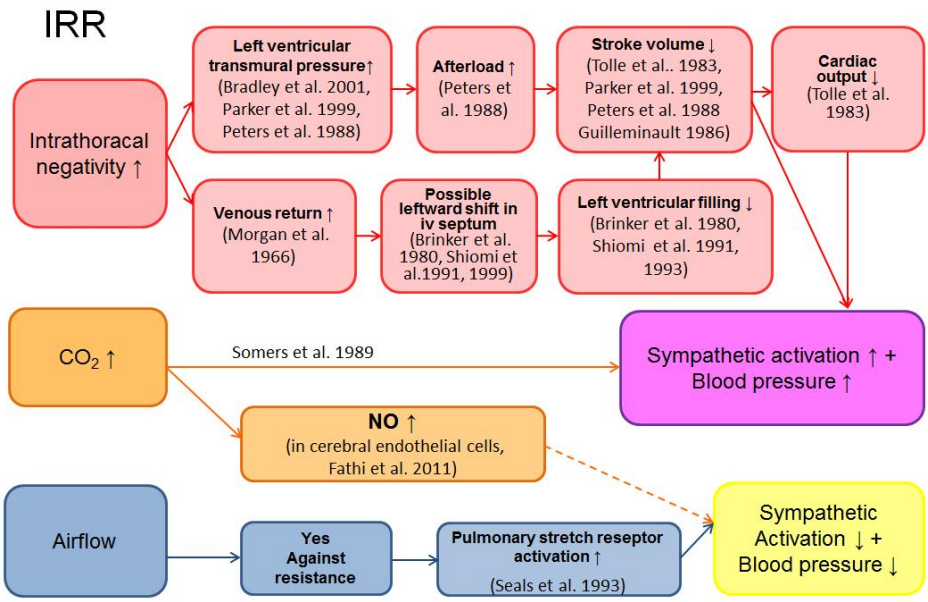


Figure 18. Physiological effects of increased respiratory resistance

Partial obstruction is a common denominator for both IRR and UARS, but in UARS the obstructive episodes are short and repetitive and terminated by arousals (Guilleminault et al., 2005, Poyares et al., 2002). In this respect, the physiological consequences of UARS and IRR can be expected to differ.

There is one study that deals with HRV changes in UARS, but due to the methodological differences the results are not comparable (Guilleminault et al., 2005). The use of HRV analysis in SDB has been criticized because periodic apnea/hypopnea or UARS-like breathing with repetitive arousals do not fulfill the requirements of signal stationarity (Stein & Pu, 2012). However, the increase in sympathetic activity found in the present study is well documented using direct measuring of nerve activity (Somers et al., 1995). Therefore, the findings in POB can be considered reliable. Because IRR presents regular breathing with no arousals and heart rate varies less than during periodic breathing, the IRR epochs that were studied can be considered to fill the stationarity demands.

Is IRR beneficial as it is associated with decreased sympathetic activity and the reduced prevalence in hypertension in females? This seems to be implausible because IRR is found to coincide with heavy snoring that is linked to carotid atherosclerosis (Lee et al., 2008). However, this is possibly explained by the vibration-induced mechanical trauma on endothelium caused by snoring. In addition, increased respiratory resistance has been reported to initiate an inflammatory response with the elevation of plasma cytokines (Vassilakopoulos et al., 2004). The consequences of endothelial dysfunction and inflammatory activation on the general health of IRR patients have not been evaluated in detail. However, it may be that as the influence of IRR on autonomous nervous activity is quite different from the effects of sleep apnea, the comorbidities may differ too. This needs to be further examined.

Tracheal sound and prolonged partial obstruction

In addition to Emfit, prolonged partial obstruction can appear as flow limitation in the nasal pressure signal. It is not uncommon that prolonged flow limitation periods remain unnoticed in clinical sleep recordings. However, the present study showed that prolonged flow limitation episodes contained more high frequency components of the tracheal sound spectrum than periodic breathing in every band over 100 Hz. It might stem from the fact that during flow limitation the upper airway constriction is not as total as the airway closure in periodic apnea-hypopnea breathing. Presumably, airflow then reaches the mouth cavity and teeth, where more high frequency sound components are produced, as in language production (Narayanan & Alwan, 2000)**.**

The analyzed tracheal sound results strengthen the view, that flow limitation represents obstruction because previously higher spectral values have been connected to upper airway obstruction (Herzog et al., 2008, Kaniusas et al., 2005, Michael et al., 2008, Pasterkamp et al., 1997, Rao et al., 1990, Yonemaru et al., 1993). So, it seems that flow limitation should be scored and diagnosed from sleep studies. However, visual detection of flow limitation from nasal prongs is quite laborious and therefore cumbersome to apply to clinical work. More importantly, factors other than intrathoracic pressure can affect the flow contour (Condos et al., 1994). Moreover, the recording sensor itself can induce an increase in respiratory resistance in patients with anatomical variants such as deviated nasal septum or narrow nares (Lorino et al., 1998). In addition, mouth breathing may disturb the contour of the airflow, and the displacement of prongs can produce marked artifacts (Ballester et al., 1998). Therefore, other detection methods that cause fewer disturbances are needed.

Compressed tracheal sound

In the present study, it has been reported that Emfit scoring provides reliable means to detect prolonged partial obstruction. However, there is an increased need for quicker and more unobtrusive methods for SDB diagnostics. One such method is compressed tracheal sound analysis,

as presented in this thesis. Compressed tracheal sound analysis has been shown to detect OSA easily at a quick glance (Rauhala et al., 2008). In tracheal sound analysis three different respiratory patterns dominate: plain pattern, which seems to present normal breathing, thick pattern, which has excellent correlation to AHI, and thin pattern, which is supposed to assess prolonged partial obstruction. In the present study, intrathoracic pressure variations during 10-minute compressed tracheal sound breathing patterns were studied with esophageal pressure monitoring. The intrathoracic pressure increased during the thick and thin patterns suggesting increased respiratory resistance. This is in line with the present spectral analysis result that showed an increased share of higher frequencies of the tracheal sound signal during the thick and thin patterns when compared with the plain pattern.

Many other screening devices can be used to distinguish apneas from normal breathing. This work has succeeded in showing that the use of the compressed tracheal sound signal is an easy and reliable method for screening not only apneas or hypopneas but also prolonged partial obstruction.

Mattress sensors in self-quantifying

Bio-hacking is nowadays a very popular business. The markets are full of health technology products and mobile technology applications for self-quantifying. Memory capacities and data transfer are no longer technical problems. The Finnish companies (Emfit Ltd and Beddit Ltd) have been pioneers in developing these new commercially available health technology products. The quantification packages involved include sleep quality estimation, wellness information, and provide every-day advice by automatically tracking sleeping patterns, heart rate, breathing, snoring, and movements. Challenges appear when breathing, heart-beats or movements are not normal i.e. if subject is suffering, for example, from SDB. Therefore, the proper validation of the sensors that are targeted at the general public is important.

Conclusions

This thesis presents that Emfit mattress scoring can be used with great accuracy in OSA diagnostics. In addition, this non-invasive technique assesses respiratory resistance related to partial obstruction in adult patients. As a result, it is possible to assess intrathoracic pressure without having to use an uncomfortable catheter and to disturb less the patients' sleep. Revealing inspiratory effort improves the accuracy of SDB diagnostics, which helps medical personnel in decision-making and treatment selection.

Whereas Emfit scoring seems to be reliable in SDB diagnostics, the other conclusion of this thesis is that compressed tracheal sound analysis presents a valid tool in SDB screening. Many screening devices reveal OSA, but compressed tracheal sound analysis also indentifies prolonged partial obstruction. The small microphone used in the analysis is easy to wear and is therefore quite suitable for ambulatory assessment of SDB. In addition, the analysis is quick and easy, which enables its use in large patient samples.

Patients with prolonged partial obstruction are left untreated if AHI limits are used as treatment criteria and, as a result, prolonged partial obstruction is left unnoticed. However, the present thesis suggests that OSA and prolonged partial obstruction are quite different phenomena and that prolonged partial obstruction also differs from normal breathing. These differences are summarized in Table 15.

Table 15. Summary of findings in different SDB patterns in this thesis.

	Normal breathing (NB)	**Periodic breathing (apnea /hypopnea)**	**Prolonged partial obstruction**
Apneas/Hypopneas	no	yes	no
Arousals	no	yes	no
Desaturations	no	yes	no
pESO increase	no	yes	yes
High frequency components in tracheal sound	no	yes	yes
SDNN standard deviation of normal-to-normal RR intervals as compared with NB		increase	no change
Sympathetic activity as compared with NB		increase	decrease
Parasympathetic activity as compared with NB		increase	increase

The two methods presented here are easy to implement to sleep recordings. In this thesis, the Emfit signal was used alone to classify breathing. However, the Emfit mattress is easily added as a part of ambulatory sleep recording system. Adding other channels to the mattress signal might further improve the sensitivity and specificity of the mattress scoring. On the other hand, the mattress signal can be used just as an additional sensor to assess increased effort, the quantification of which is still difficult by other means.

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V

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Tampereen teknillinen yliopisto
PL 527
33101 Tampere

Tampere University of Technology
P.O.B. 527
FI-33101 Tampere, Finland

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