

DISSERTATIONS IN
**HEALTH
SCIENCES**

HENRY BLOMSTER

*Cardiovascular risk
factors in mild obstructive
sleep apnea – the outcome
of lifestyle intervention
with weight reduction*

PUBLICATIONS OF THE UNIVERSITY OF EASTERN FINLAND
Dissertations in Health Sciences No 312



UNIVERSITY OF
EASTERN FINLAND

HENRY BLOMSTER

*Cardiovascular risk factors in mild
obstructive sleep apnea – the outcome of
lifestyle intervention with weight reduction*

To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in Auditorium CA102, Canthia, Kuopio, on Friday, December 4th 2015, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 312

Department of Otorhinolaryngology, Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland
Kuopio
2015

Grano
Jyväskylä, 2015

Series Editors:

Professor Veli-Matti Kosma, M.D., Ph.D.
Institute of Clinical Medicine, Pathology
Faculty of Health Sciences

Professor Hannele Turunen, Ph.D.
Department of Nursing Science
Faculty of Health Sciences

Professor Olli Gröhn, Ph.D.
A.I. Virtanen Institute for Molecular Sciences
Faculty of Health Sciences

Professor Kai Kaarniranta, M.D., Ph.D.
Institute of Clinical Medicine, Ophthalmology
Faculty of Health Sciences

Lecturer Veli-Pekka Ranta, Ph.D. (pharmacy)
School of Pharmacy
Faculty of Health Sciences

Distributor:

University of Eastern Finland
Kuopio Campus Library
P.O.Box 1627
FI-70211 Kuopio, Finland
<http://www.uef.fi/kirjasto>

ISBN (print): 978-952-61-1945-8

ISBN (pdf): 978-952-61-1946-5

ISSN (print): 1798-5706

ISSN (pdf): 1798-5714

ISSN-L: 1798-5706

Author's address: Department Otorhinolaryngology
University of Eastern Finland
P.O. Box 100
FI 70029 KUOPIO
FINLAND
E-mail: henry.blomster@kuh.fi

Supervisors: Docent Henri Tuomilehto, M.D., Ph.D.
Oivauni Sleep Clinic
University of Eastern Finland
KUOPIO
FINLAND

Professor Heikki Löppönen, M.D., Ph.D.
Department of Otorhinolaryngology, Institute of Clinical Medicine
School of Medicine, Faculty of Health Sciences University of Eastern Finland
KUOPIO
FINLAND

Docent Juha Seppä, M.D., Ph.D.
Department of Otorhinolaryngology, Institute of Clinical Medicine
School of Medicine, Faculty of Health Sciences
University of Eastern Finland
KUOPIO
FINLAND

Reviewers: Docent Paula Virkkula, M.D., Ph.D.
Department of Otorhinolaryngology
University of Helsinki
HELSINKI
FINLAND

Docent Antti Loimaala M.D., Ph.D.
Department of Clinical Physiology and Nuclear medicine
University of Helsinki
HELSINKI
FINLAND

Opponent: Docent Leif Bäck, M.D., Ph.D.
Department of Otorhinolaryngology
P.O. BOX 220
FI-00029 HELSINKI
FINLAND

Blomster, Henry

Cardiovascular risk factors in mild obstructive sleep apnea – the outcome of lifestyle intervention with weight reduction

University of Eastern Finland, Faculty of Health Sciences

Publications of the University of Eastern Finland. Dissertations in Health Sciences 312. 2015 p.69

ISBN (print): 978-952-61-1945-8

ISBN (pdf): 978-952-61-1946-5

ISSN (print): 1798-5706

ISSN (pdf): 1798-5714

ISSN-L: 1798-5706

ABSTRACT

Obstructive sleep apnea (OSA) is a chronic, progressive disease. OSA is associated with increased cardiovascular morbidity and mortality, the risk being more frequently encountered with severe degrees of OSA. Endothelial dysfunction, increased sympathetic activation and impaired cardiac autonomic control as reflected by depressed baroreflex sensitivity (BRS) are possible mechanisms involved in the cardiovascular complications of OSA. Obesity is a major risk factor for OSA and therefore weight loss is considered an effective treatment for OSA in overweight patients. Some patients, however, do not benefit from weight loss. It has been postulated that nasal obstruction may act as an independent risk factor for OSA.

The present study includes a prospective randomized study and a cross sectional comparison study. The prospective randomized study explored the effects of a 1-year supervised lifestyle intervention with weight reduction on endothelial function and evaluated whether impaired nasal airflow might explain the missing effect of weight reduction on OSA. The aim of the cross sectional part of the study was to determine whether endothelial dysfunction and depressed BRS existed in mild OSA patients when compared to their age, body mass index and sex matched subjects without OSA. Endothelial function was measured by brachial artery flow-mediated dilatation (FMD), change in nasal resistance was measured by rhinomanometer and the phenylephrine test was used to measure the BRS.

This study showed that cardiovascular risk factors, atleast in terms of FMD and BRS, are not increased in mild OSA patients when compared to their non-OSA countersubjects. 1 year lifestyle intervention with weight reduction resulted in improved AHI and other obesity related risk factors for cardiovascular diseases although no improvement in FMD was detected. Nasal resistance reduced significantly more in patients who had been cured from OSA and smoking had a negative impact on both nasal resistance and improvement of AHI.

Although in mild OSA endothelial function and BRS are still preserved, lifestyle intervention with weight reduction did achieve an improvement in other obesity related risk factors for cardiovascular diseases, thus highlighting the importance of early intervention. In addition impaired nasal breathing and smoking may prevent the beneficial effects of weight reduction in the treatment of OSA.

National Library of Medicine Classification: WF 143, WG 120, QT 235, W 85

Medical Subject Headings: Cardiovascular Diseases; Endothelium; Nasal Obstruction; Overweight; Rhinomanometry; Risk Factors; Sleep Apnea, Obstructive; Smoking; Weight Loss

Blomster Henry

Sydän ja verisuonisairauksien riskitekijät lievässä obstruktiivisessa uniapneassa – painonpudotukseen tähtäävän elämäntapaohjauksen vaikutukset uniapnean hoidossa

Itä-Suomen yliopisto, terveystieteiden tiedekunta

Publications of the University of Eastern Finland. Dissertations in Health Sciences 312. 2015 s.69

ISBN (print): 978-952-61-1945-8

ISBN (pdf): 978-952-61-1946-5

ISSN (print): 1798-5706

ISSN (pdf): 1798-5714

ISSN-L: 1798-5706

TIIVISTELMÄ

Obstruktiivinen uniapnea on krooninen ja etenevä sairaus, joka on yhdistetty suurentuneeseen sydän ja verisuonitautien kuolleisuuteen ja sairastavuuteen. Riski on yleisempi vaikea-asteisessa taudissa. Endoteelin toimintahäiriö, suurentunut sympaattisen hermoston aktiivisuus ja häiriintynyt sydämen autonominen kontrolli, joka määritetään baroheijasteherkkyyden (BRS) avulla, ovat mahdollisia mekanismeja uniapnean liitännäissairauksien, kuten sydän ja verisuonisairauksien synnyssä. Lihavuus on suurin riskitekijä obstruktiiviselle uniapnealle ja siksi painopudotusta onkin pidetty tehokkaana uniapnean hoitomuotona ylipainoisille potilaille. Jotkut potilaat eivät kuitenkaan hyödy painonpudotuksesta. Nenän tukkoisuutta on pidetty yhtenä uniapnean itsenäisenä riskitekijänä.

Tutkimuksemme koostui prospektiivisesta satunnaistetusta seurantatutkimuksesta ja läpileikkaustutkimuksesta. Satunnaistetussa seurantatutkimuksessa pyrimme selvittämään 1-vuoden painonpudotukseen tähtäävän elämäntapaohjauksen vaikutuksia endoteelitoimintaan ja voisiko nenän lisääntynyt virtausvastus estää painonpudotuksen suotuisia vaikutuksia uniapnean hoidossa. Läpileikkaustutkimuksessa selvitettiin eroavatko lievää uniapneaa sairastavien ja ikä, sukupuoli ja painoindeksivakioitujen uniapneaa sairastamattomien verrokkien endoteelitoiminta ja baroheijasteherkkyys toisistaan.

Tutkimustulokset osoittivat, että verrokkeihin verrattuna, lievässä obstruktiivisessa uniapneassa sydän ja verisuonitautien riskitekijät eivät ole ainakaan endoteelitoiminnan ja baroheijasteherkkyyden valossa kohonneet. Yhden vuoden painonpudotukseen johtanut elämäntapaohjaus paransi uniapneaa, apnea hyponea indeksiä, LDL-kolesterolipitoisuutta ja seerumin insuliinipitoisuutta, vaikka varsinaista parantumista ei endoteelitoiminnassa tapahtunut. Nenän virtausvastus väheni merkittävästi enemmän niillä, jotka parantuivat uniapneasta ja tupakointi lisäsi nenän virtausvastusta ja huononsi apnea hyponea indeksin paranemista elämäntapaohjauksen ja painonpudotuksen jälkeen. Vaikka lievässä uniapneassa endoteelitoiminta ja baroheijasteherkkyys eivät olleet vielä häiriintyneet, elämäntapaohjauksella saavutettu painonpudotus paransi muita lihavuuteen liittyviä riskitekijöitä sydän ja verisuonisairauksille. Täten varhaiseen interventioon tulisi pyrkiä. Lisäksi tukkoinen nenä ja tupakointi voivat estää painonpudotuksen parantavia vaikutuksia uniapnean hoidossa. Täten uniapneaa hoidettaessa on painonpudotuksen lisäksi hoidettava myös tukkoista nenää ja tarjota tupakkavieroitusta kaikille tupakoiville potilaille.

Luokitus: WF 143, WG 120, QT 235, W 85

Yleinen Suomalainen asiasanasto: endoteeli; laihdutus; potilasneuvonta; sydän- ja verisuonitaudit; tupakointi; uniapnea-oireyhtymä; varhainen puuttuminen; ylipaino

Acknowledgements

This study was carried out in the Department of Otorhinolaryngology, Kuopio University Hospital and Institute of Clinical Medicine, University of Eastern Finland during the years 2008-2015. Collaboration with the Department of Internal Medicine and Department of Clinical Physiology and Nuclear Medicine in Kuopio University Hospital was essential for this study.

Foremost, I wish to express my sincere gratitude to my supervisor, Docent Henri Tuomilehto, M.D., Ph.D, for the continuous encouragement, support, valuable guidance and expertise with this project. He has been genuinely and actively interested in my work. I am extremely thankful and grateful for his enthusiasm, patience and optimism towards science itself and especially towards this work.

I wish to express my sincere gratitude to my second supervisor, Professor Heikki Löppönen, for his excellent mentoring, advice and support during this work.

I wish to express my warmest gratitude to my third supervisor, Docent Juha Seppä, M.D., Ph.D., for his guidance and help during this thesis.

The official reviewers of this thesis, Paula Virkkula and Antti Loimaala are gratefully acknowledged for their expert advice and critical review.

I want to express my sincere thanks to my co- authors Tomi Laitinen and Juha Hartikainen. Their enthusiastic expertise, advice and dedication were paramount in helping me to gain a comprehension of the complexity of cardiovascular regulatory mechanisms. Without their advice, this work would have lacked the basic scientific fiber. In addition, they always had time for to answer my questions and resolve my problems.

I would like to thank my co-author Tatu Kemppainen for his support during the writing process of the third article. My other co-authors Jouko Kokkarinen, Jukka Randell, Johanna Sahlman, Grigori Smirnov, Esko Vanninen, Tiina Laitinen, Markku Peltonen Tarja Martikainen, Helena Gylling, Pirkko Ruoppi and Jura Numminen are also gratefully acknowledged.

I express my gratitude to our study nurse Taina Poutiainen for her prompt, professional and precise work with this project. I want to thank Ewen MacDonald for reviewing the grammar and spelling.

I'm also grateful of having had the pleasure to work with the most friendly and cheerful group of colleagues in my daily work. I have had tremendous support all throughout this seemingly never-ending scientific work and especially in the clinical field when dealing with difficult and complicated medical issues.

I want to thank my very good friends Jykke and Saku for their superior knowledge of science and for the deep conversations about the philosophy of science and for the multiprofessional ideas that made it possible to avoid a "deus ex machine" in this work. I want to express my sincere gratitude also to my very good friend Nike for his encouragements in my career and my life.

I feel privileged to be blessed with very good friends with whom I have the opportunity to live. I want to express my sincere thanks to my Turku, my Loviisa, my Helsinki, my Sipoo and my Kuopio friends.

I have been fortunate to have two exceptionally brilliant parents who have taught me the most valuable things in life. They have supported me in every decision I have made in my life. I'm grateful to my father that he introduced me to our family barbell and its gravitational properties. This has made it possible for me to discover the concept that multiple repetitions will eventually lead to progress. I'm grateful to my mother that she made me do my homework. I'm lucky also to have the most brilliant sister who has supported me during the writing process.

The most sincere thanks go to our two brilliant boys, Elias and Aaron. They have brought such a great amount of joy and laughter to our lives. I think every scientist should learn something about the true curiosity and creativity of a child when they constantly question, observe and explore the phenomena of the surrounding world.

Last, but certainly not least, I must acknowledge with tremendous gratitude and love, my utterly delightful wife, Niina. You are exceedingly gorgeous and you still delightfully sensitize my baroreceptors. Thank you for being you.

Financial support by the Finnish Otorhinological Society, the Kuopio University hospital research fund, the Organisation for Respiratory Health in Finland (HELI), Kuopio Breathing Association, Antti and Tyyne Soininen Foundation, Väinö and Laina Kivi Foundation, Aarne and Antti Turunen Foundation, the Finnish Medical Foundation, Finnish Anti-Tuberculosis Foundation, and Finnish Research Foundation of Otology are acknowledged with gratitude.

Henry Blomster
November 2015

List of the original publications

This dissertation is based on the following original publications:

- I Blomster H, Laitinen T, Lyyra-Laitinen T, Vanninen E, Gylling H, Peltonen M, Martikainen T, Sahlman J, Kokkarinen J, Randell J, Smirnov G, Seppä J, Tuomilehto H: Endothelial function is well preserved in obese patients with mild obstructive sleep apnea. *Sleep Breath*. 2014 Mar;18(1):177-86.
- II Blomster H, Laitinen T, Hartikainen JE, Laitinen TM, Vanninen E, Gylling H, Sahlman J, Kokkarinen J, Randell J, Seppä J, Tuomilehto H: Mild obstructive sleep apnea does not modulate baroreflex sensitivity in adult patients: *Nat Sci Sleep*. 2015 Jun 25;7:73-80.
- III Blomster H, Kemppainen T, Numminen J, Ruoppi P, Sahlman J, Peltonen M, Seppä J, Tuomilehto H: Impaired nasal breathing may prevent the beneficial effect of weight loss in the treatment of OSA. *Rhinology*. 49(5):587-92, 2011.

The publications were adapted with the permission of the copyright owners.

Contents

1 INTRODUCTION	1
2 REVIEW OF THE LITERATURE	3
2.1 Obstructive sleep apnea	3
2.1.1 Definions and classification	3
2.1.2 Pathogenesis	3
2.1.3 Prevalence and incidence	4
2.1.4 Progression	5
2.1.5 Risk factors.....	5
Obesity	5
Age and sex	5
Nasal resistance	5
Anatomical risk factors	6
Cigarette smoking.....	6
Other risk factors	6
2.1.6 Diagnostic methods.....	6
Symptoms	7
Clinical findings.....	7
Sleep recording	8
2.2 Treatment.....	8
2.2.1 Lifestyle intervention	9
2.2.2 Nasal continous positive airway pressure (CPAP)	9
2.2.3 Oral appliances	9
2.2.4 Emerging therapies	9
2.2.5 Surgical treatment.....	10
Nasal surgery	10
Tonsillectomy and uvulopalatopharyngoplasty	10
Hypopharyngeal procedures.....	10
Maxillomandibular advancement	10
Bariatric surgery.....	10
2.3 Co-morbidities	11
2.3.1 Mortality	11
2.3.2 Cardiovascular co-morbidities	11
Hypertension.....	11
Coronary artery disease.....	12
Stroke.....	12
Heart failure	12
Atrial fibrillation.....	13
Pulmonary hypertension.....	13
2.4 Pathogenesis of cardiovascular co-morbidities in OSA.....	13
2.4.1 Endothelial dysfunction	13
2.4.2 Oxidative stress	14
2.4.3 Inflammation.....	14

2.4.4 Sympathetic activation and baroreflex sensitivity	15
2.4.5 Increased blood coagulation	15
3 AIMS OF THE STUDY	17
4 MATERIALS AND METHODS.....	19
4.1 Subjects	19
4.2 Study design	19
4.2.1 Baseline cross-sectional study on cardiovascular risk factors (Studies I and II).....	19
4.2.2 Follow up study on endothelial dysfunction (Study I).....	19
4.2.3 Follow up study on factors possibly preventing the beneficial effect of weight reduction (Study III).....	20
4.4. Methods.....	20
4.4.1 Anthropometric data	20
4.4.2 Cardiorespiratory monitoring	20
4.4.3 Biochemical measurements.....	21
4.4.4 Ultrasound studies (FMD)	21
4.4.5 Assessment of baroreflex sensitivity	22
4.4.6 Lifestyle intervention	23
4.4.7 Rhinomanometric measurements	24
4.4.8 Symptoms and quality of life measurements.....	24
4.4.9 Clinical examination	25
4.4.10 Statistical analysis.....	25
4.6. Ethical aspects	25
5 RESULTS	27
5.1. Predictors of cardiovascular disease	27
5.1.1. Cross-sectional baseline comparison of patients with mild OSA and weight matched non-OSA snorers	27
5.1.2 Follow up study	30
5.2 Nasal resistance and successful weight reduction	32
5.2.1 Rhinometric measurements	32
5.2.2 Symptom questionnaires	34
5.2.3 Effect of smoking.....	34
6 DISCUSSION	35
6.1 Endothelial dysfunction.....	35
6.2 Baroreflex sensitivity	36
6.3 Lifestyle intervention and endothelial dysfunction	37
6.4 Impaired nasal breathing and lifestyle intervention in mild OSA	37
6.5 Limitations	38
7 CONCLUSIONS	39
8 REFERENCES	41

Abbreviations

AHI	Apnea-hypopnea index
BMI	Body mass index
BRS	Baroreflex Sensitivity
CAD	Coronary artery disease
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
CVD	Cardiovascular disease
FMD	Flow Mediated Dilatation
FMD%	Flow Mediated Dilatation percentage change relative to the resting scan
MAD	Mandibular advancement device
NTG%	Nitroglycerin Induced Dilatation (%)
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
QoL	Quality of Life
REM	Rapid Eye Movement
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SDB	Sleep Disordered Breathing
UARS	Upper Airway Resistance Syndrome
UPPP	Uvulopalatopharyngoplasty
VLCD	Very Low Calorie Diet

1 Introduction

Obstructive sleep apnea (OSA) is a chronic disease which is characterized by frequent episodes of total and/or partial collapse of the upper airway during sleep, leading to recurrent episodes of hypoxia and arousals from sleep (Young et al. 1993). In adults, OSA affects approximately one out of every five men and one out of every ten females (Young et al. 1993, Duran et al. 2001). In recent reports in the literature, moderate to severe OSA has been recognized as an independent risk factor for cardiovascular disease (Floras 2014, Kendzerska et al. 2014, Nieto et al. 2000, Somers et al. 2008, Yaggi et al. 2005). However there are only a few studies which have investigated the association of mild OSA and cardiovascular disease. Since OSA has a natural tendency to worsen over time, particularly if there is an accompanying weight gain (Berger, Berger & Oksenberg 2009), early intervention is essential in order to prevent the serious co-morbidities, mainly in the form of cardiovascular disease. Weight reduction has been reported to be beneficial in most overweight patients with OSA (Tuomilehto et al. 2009, Foster et al. 2009, Johansson et al. 2009). In mild OSA, the disease is at an early stage when it is most likely that the organ systems may still possess the capacity to fully recover from OSA-induced adverse metabolic and cardiovascular effects or at least, the progression of the disease may be prevented (Tuomilehto et al. 2009, Johansson et al. 2009). A deterioration of endothelial function and an impairment of baroreflex sensitivity (BRS) are the early signs of cardiovascular disease (Foster, Poulin & Hanly 2007, Priou et al. 2010, Bayram et al. 2009, Kato et al. 2000, Frattola et al. 1997, La Rovere et al. 1998, Mortara et al. 1997). The present work evaluated endothelial dysfunction and BRS to examine whether risk factors of cardiovascular disease were present in mild OSA when compared to matched snorers without OSA. In some patients, sleep apnea and the apnea hypopnea index (AHI) do not seem to improve even after successful weight loss. The present study also evaluated whether impaired nasal airway function explained a part of the missing effect of weight reduction. Therefore, in prospective randomized controlled trial, we evaluated whether lifestyle intervention with a very low calorie diet would achieve any improvement in the cardiovascular risk factors and furthermore could impaired nasal breathing prevent the positive effects of weight reduction.

2 *Review of literature*

2.1 **OBSTRUCTIVE SLEEP APNEA (OSA)**

2.1.1 **Definitions and classification**

Obstructive sleep apnea has been defined by the American Academy of Sleep Medicine (AASM) as recurrent episodes of upper airway obstruction resulting in cessation (apnea) or reduction (hypopnea) in airflow during sleep (Iber et al. 2007). Obstructive apnea is defined as a cessation of airflow for at least 10 seconds despite the breathing efforts. If one wish to score the apneas there must be a reduction of 90% or more in airflow from baseline but no desaturation of oxyhemoglobin is needed. The AASM 2007 Manual for Scoring Sleep and associated Events recommended that hypopnea should be defined as a 30% or more reduction in nasal pressure signal followed by > 4% desaturation. This manual included also an alternative definition for hypopnea, where hypopnea required that there should be a 50% or more reduction in nasal airflow associated with >3 desaturation or arousal (Iber et al. 2007). In addition, the new 2012 AASM guideline for hypopnea scoring requires that there is a decrease in airflow of >30% lasting >10 s, associated with either >3% desaturation or an arousal (Berry et al. 2012). The apnea-hypopnea index (AHI) is the sum of the hypopnea and apnea episodes in one hour of sleep. Primary snoring is defined according to the International Classification of Sleep Disorders (ICSD) as the presence of characteristic snoring noises during sleep in the absence of episodes of apnea or hypoventilation (AASM 2001).

The severity of OSA has been subdivided into three stages by AHI. Mild OSA is defined by AHI 5-15, moderate OSA as 15-30 events per hour, and severe OSA as 30 or more events per hour (Iber et al. 2007).

The upper airway resistance syndrome (UARS) is closely related to OSA. These patients have typical symptoms of OSA and they have increased upper airway resistance with inspiratory flow limitation, but they do not display any evidence of apneas or hypopneas on polysomnography (Guilleminault et al. 1996)).

2.1.2 **Pathogenesis**

The pathophysiology of OSA is not fully understood but the basic mechanism responsible for the apnea-hypopnea events during sleep is the repetitive collapse of the upper airway due to the possible pathological changes occurring in the upper airway structure and alterations in the neural activation of the upper airway musculature. The pharynx is a very versatile structure which is responsible for multiple, very diverse functions i.e. speech, swallowing and passage of air during breathing. The airway is composed of multiple muscles and soft tissue lacking a rigid, bony, support and therefore it is susceptible to collapse during sleep. There are other mechanisms believed to be important in the pathogenesis of OSA e.g. the synergy of pharyngeal anatomy and diminished ability of the upper airway dilator muscles to maintain a patent airway during sleep (Mezzanotte, Tangel & White 1992). The function of the upper airway has been described as behaving like a Starling resistor where the upper airway is likened to a hollow tube with a partial obstruction at the inlet, corresponding to the nose, and a collapsible section downstream, corresponding to the oropharynx. In this model, if there should be negative pressure during inspiration, then this can cause greater suction forces in the narrow segment and these may contribute in predisposed persons to a collapse of the oropharynx (Smith et al. 1988). During sleep, repetitive collapse and obstruction of the upper airway cause increase the ventilatory effort needed to overcome an occluded airway leading to the triggering of a stress reaction and eventually to arousal from sleep. After the arousal, when the airway and ventilation

are restored, the patient returns to sleep, but the cycle begins again. These recurrent arousals cause sleep fragmentation and therefore sleep becomes lighter and more non-restorative (Kimoff 1996, Berry, Gleeson 1997). Moreover, when the transpharyngeal pressure gradient increases during inspiration and the airflow accelerates in the narrow lumen, the pharyngeal tissues begin to vibrate and may collapse and constant repetitive eccentric muscle contractions against occluded airway can cause mechanical trauma to the upper airway structures. This may lead to adaptive changes in the structure and function of the upper airway musculature, thus promoting further deterioration in the upper airways (Carrera et al. 1999). In addition, lung volume is known to influence the caliber of the upper airway. Decreased lung volume reduces the pharyngeal cross-sectional area, resulting in increased pharyngeal resistance (Bradley et al. 1986, Cormier, Series 1990). However, increased lung volume may act both by dilating and stiffening the pharyngeal wall (Van de Graaff 1988).

2.1.3 Prevalence and incidence

Most of the prevalence studies of OSA are based on the AHI. In the published literature, the prevalence of OSA has been estimate to be 4% in males and 2% in females (Young et al. 1993). On the basis of the average prevalence estimates from studies of cohorts in Wisconsin (Young et al. 1993), Pennsylvania (Bixler et al. 2001, Bixler et al. 1998) and Spain (Duran et al. 2001) consisting predominantly of white men and women with mean BMI of 25 to 28, it has been estimated that 20 % adults exhibit signs of at least mild OSA and 7% have at least moderate OSA (Young, Peppard & Gottlieb 2002). In Finland, it has been estimated that approximately 150,000 patients have OSA, with 57% of them having mild, 33% moderate and 10% of them suffer from severe disease (Laitinen et al. 2003)(Figure 1). Based on the prevalence estimates of previous cohort studies, it is more likely that approximately 250,000 to 300,000 have OSA (Young, Peppard & Gottlieb 2002).

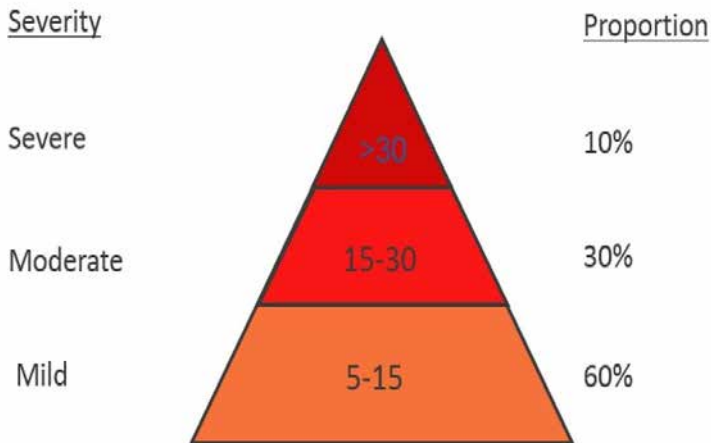


Figure 1. Proportion and severity of obstructive sleep apnea (Laitinen et al. 2003).

Although there are numerous studies on the prevalence of OSA, only a few studies have provided data on the incidence of OSA. In the Cleveland Family study, the 5 year incidence was estimated as 7.5% for moderate OSA and 16% for mild to moderate OSA (Tishler et al. 2003).

2.1.4 Progression

OSA belongs to a group of sleep disordered breathing diseases, it represents a continuum of different levels of nocturnal breathing problems. The available epidemiological data suggests that OSA has a tendency to worsen over time and the progression of OSA can occur in a relatively short time period with the main determinant of progression being weight gain (Berger, Berger & Oksenberg 2009). It seems that there is a linear association in OSA patients between weight gain and worsening of OSA, the greater the weight gain, the larger is the AHI (Peppard et al. 2000).

2.1.5 Risk factors

The main cause of OSA is the upper airway narrowing due to various mechanisms, including obesity, impaired nasal breathing, anatomical factors e.g. large tonsils, prominent uvula, mandibular micrognathia, medication, male sex and aging. Nonetheless, the most important risk factor of OSA is obesity (Young, Skatrud & Peppard 2004) and should the value of BMI exceed 29, this increases the risk for OSA by 10 fold (Pillar, Shehadeh 2008).

Obesity

Obesity is considered to be the most important risk factor for OSA (Young, Skatrud & Peppard 2004). The majority (60 – 90%) of adult OSA patients are overweight, and in patients with BMI>30, the relative risk for OSA is over 10. In addition, in obese patients, the prevalence has been reported to be as high as 30-98%. The development or worsening of OSA with increasing weight has been demonstrated in several studies (Pillar, Shehadeh 2008). The mechanisms underlying the association between OSA and obesity are complex and most likely multifactorial. The possible mechanisms include reduced pharyngeal lumen size due to fatty tissue deposit within the airway or in its lateral walls (Brander, Mortimore & Douglas 1999, Martin et al. 1997, Schwab 2005), decreased upper airway muscle tone and force due to fatty deposits in the muscle (Carrera et al. 2004, Ryan, Love 1996), and reduced upper airway size secondary to a mass effect of the large abdomen on the chest wall and tracheal traction (Pillar, Shehadeh 2008). In addition, central adiposity reduces lung volume (Oppenheimer et al. 2014). Moreover, weight gain has reported to increase upper airway collapsibility (Schwartz et al. 1991). There are recent findings indicating that in patients with OSA, <50% of the overall response to weight loss may be related to reductions in passive mechanical properties and the remaining response to concomitant improvements in neuromuscular control of the upper airway (Kirkness et al. 2008) indicating that there is impaired neuromuscular function in the upper airway musculature.

Age and sex

It is now recognized that male sex and age are risk factors for OSA. Men have a three- to fourfold higher prevalence of OSA than premenopausal women (Young et al. 1993, Duran et al. 2001) although, the prevalence of OSA in postmenopausal women approaches that of men (Bixler et al. 2001, Redline et al. 1994). Age is also a known risk factor for sleep apnea (Oliven et al. 2001, Ware, McBrayer & Scott 2000). The prevalence of OSA increases with age reaching its peak at about 55 years of age (Young et al. 1993, Duran et al. 2001, Bixler et al. 1998).

Nasal resistance

In normal subjects, upper airway resistance is lower during sleep when breathing through the nose as opposed to via the mouth. When the nasal airway is almost completely

obstructed, nose breathing switches to mouth breathing which is associated with up to 2.5 times higher total resistance and increased propensity to OSA (Fitzpatrick et al. 2003). In addition, the nasal ventilator reflex is known to take part in regulation of the nasal resistance during sleep. Activation of nasal receptors during nasal breathing exerts a direct positive influence on spontaneous breathing, leading to a higher resting breathing volume and frequency (Douglas et al. 1983). The nose accounts for more than 50% of the total resistance of the upper airway (FERRIS, MEAD & OPIE 1964). The recent body of literature on the effect of nasal breathing on OSA is somewhat conflicting. A correlation between nasal resistance and OSA has been observed in some studies (Lofaso et al. 2000, Li et al. 2005), whereas in some studies, nasal resistance has not been shown to be related to the severity of OSA (Miljeteig, Hoffstein & Cole 1992) and nasal resistance does not correlate with the AHI (Yagi et al. 2009). Furthermore, in different weight groups, the findings on the correlation between nasal breathing and OSA have been controversial. Significant correlations have been found in obese patients between AHI and nasal resistance (Tagaya et al. 2010), while in another study, this relationship was observed only in non-obese patients (Virkkula et al. 2003). Nasal steroids have been proven to improve the subjective quality of sleep in patients with allergic rhinitis, but are not an effective treatment for adults with OSA (Georgalas 2011).

Anatomical risk factors

Especially in lean patients, anatomical risk factors play a more significant role in predisposing the upper airway to collapse. The possible predisposing factors include large tonsils and uvula (Schellenberg, Maislin & Schwab 2000b), low soft palate, retrognathia, large tongue and low hyoid bone position (Quera-Salva et al. 1988). Due to all of these factors, the airspace of the naso-, and oropharynx decreases and there is a narrowing of the upper airways and this increases the risk of OSA in the supine position and a loss of neuromuscular compensation at the onset of sleep.

Cigarette smoking

A recent review evaluating the interaction between smoking and obstructive sleep apnea reported that smoking may increase the severity of OSA by causing alterations in sleep architecture, upper airway neuromuscular function, arousal mechanisms and upper airway inflammation. On the other hand, there is some evidence to link untreated OSA with nicotine addiction (Krishnan, Dixon-Williams & Thornton 2014). At least in terms of nasal breathing, smoking has been found to exert adverse effects on the nasal airway. It has been associated with increased snoring, nasal obstruction, and pharyngeal soft tissue volume. In summary, the combination of current smoking and altered nasal function seems to compromise the lower airways and thus, predispose to sleep disordered breathing (Virkkula et al. 2007, Virkkula et al. 2005).

Other risk factors

Endocrinological abnormalities have been associated with increased OSA risk. For example, patients with polycystic ovaries have been found to be 30 times more likely to suffer from SDB than controls (Vgontzas et al. 2001). In acromegaly, OSA assessed by polysomnography was found in 69% of patients with active disease (Attal, Chanson 2010). In addition, an increased prevalence of OSA has been found in patients with hypothyroidism (Lin, Tsan & Chen 1992). Alcohol ingestion and sedative medication may also be factors contributing to the increased risk for OSA (Scanlan et al. 2000, Rishi et al. 2010).

2.1.6 Diagnostic Methods

Diagnosis of OSA is based on the day and night-time symptoms of the patient, clinical findings and always confirmed with a sleep recording. In addition, sleep apnea specific questionnaires have been used to quantify the impact on quality of life. Nevertheless, sleep

recordings with a portable polysomnography (PSG) is a golden standard method in diagnosing OSA.

Symptoms

OSA is associated with a huge variety of symptoms in different individuals, which may occasionally also cause problems in identifying the disease. Since the majority of the symptoms, at least in its early state, are only present during sleep, many subjects with OSA may not recognize the symptoms, thus the disease may stay undiagnosed. The most common symptoms can be divided into night-time and daytime and are listed below.

Snoring: Although snoring has a poor diagnostic value in OSA, it is very common among OSA patients (Hoffstein, Szalai 1993). Snoring is usually socially disturbing and due to the noise of intense snoring, patients may be forced to sleep in separate bedrooms from their partners.

Breathing pauses have been viewed as the characteristic symptom for OSA and considered as highly specific for OSA, but many people are unaware of their presence, since their bed partner also sleeps during the night, thus not hearing or recognizing them or alternatively they sleep alone with no-one to act as a witness.

Nocturia is a common symptom of OSA, even though most patients and physicians have little awareness of the pathophysiological link between this symptom and the sleep disorder. A recent study even suggested that nocturia might hold the potential to serve as a screening tool for OSA (Romero et al. 2010).

Daytime sleepiness is the most common feature of OSA. Because of the insidious onset and chronicity of OSA, daytime sleepiness may remain unnoticed or its significance may be underestimated due to the slow progression of the disease. The patient may not recognize the symptom as sleepiness, but may describe the symptoms in other terms, such as fatigue, tiredness, and low energy (Chervin 2000). The patient may complain of consistently falling asleep while reading, watching television, or even more dangerously, while driving a motor vehicle. Even in simple and mild OSA, daytime symptoms may be present. Daytime sleepiness is not a very useful clinical symptom with which to try to diagnose OSA (Ward Flemons, McNicholas 1997). For example, there are patients with low numbers of apneas and hypopneas who complain of significant daytime sleepiness and patients with high numbers of apneas and hypopneas who do not exhibit signs of sleepiness (Vgontzas 2008). In fact, it has been claimed that the prevalence of OSA without symptoms is higher than the prevalence of the disease with symptoms (Young et al. 1993, Duran et al. 2001, Bixler et al. 2001). This might be interpreted to mean that most OSA patients will exhibit only mild, if any, symptoms at all. The severity of OSA and its symptoms usually progress over years and increase with weight gain, aging or at the time of menopause. As the disease progresses, sleepiness becomes present in all daily activities and can become dangerous and disabling. OSA is known to be a possible cause of motor vehicle accidents, resulting in a two-fold, perhaps as much as a seven-fold increased risk of being involved in an accident (Horstmann et al. 2000). Symptoms of depression and cognitive function impairment have also been reported in OSA patients (Engleman, Douglas 2004, Schwartz, Kohler & Karatinos 2005). Although all of these symptoms might affect the quality of life, the clinical relevance of OSA is mainly due to its strong association with cardiovascular comorbidities.

Clinical findings

The most important clinical findings to which particular attention should be paid are the presence of obesity and signs of upper airway narrowing. Other features that might point to the presence of OSA include increased neck circumference, BMI, waist circumference or body fat percentage (Kushida, Efron & Guilleminault 1997), high Mallampati or Friedman tongue position score (Friedman et al. 1999), the presence of retrognathia, tonsillar hypertrophy, macroglossia, elongated or enlarged uvula, high arched or narrow hard palate, nasal abnormalities such as nasal polyps, septum deviation, valve abnormalities or

turbinate hypertrophy (Lofaso et al. 2000, Young, Finn & Kim 1997, Liistro et al. 2003, Zonato et al. 2005, Schellenberg, Maislin & Schwab 2000a).

Sleep recordings

The diagnosis of OSA always has to be confirmed at least by overnight cardio-respiratory monitoring, where the nasal airflow, respiratory efforts by thoracic and abdominal movements, oxygen saturation, heart rate and body position are monitored (Collop et al. 2007). This measurement can be performed with portable devices at home. A more accurate method, which is also the gold standard in OSA diagnostics, is full overnight polysomnography recording which needs to be conducted in sleep laboratory facilities (Epstein et al. 2009). In addition to overnight cardio-respiratory monitoring, polysomnography includes measurements from electroencephalography, eye movements, electromyography, electrocardiography, body movements and behavior (Epstein et al. 2009). Due to the high cost and the need of laboratory facilities, in Finland in patients in whom there is a suspicion of OSA, the diagnosis is often confirmed by un-attended cardio-respiratory or polysomnographic monitoring.

2.2 TREATMENT

Obesity is the most important risk factor for OSA i.e. 60-90% of OSA patients are obese, and therefore weight reduction e.g. via lifestyle intervention, forms the cornerstone for the treatment of OSA and the prevention of its co-morbidities. The principle medical treatment for OSA is CPAP. Other treatment modalities for carefully selected group of patients include surgery and oral appliances.

2.2.1 Lifestyle intervention

The importance and effectiveness of weight reduction in treating OSA were discovered three decades ago (Smith et al. 1985). In the majority of the earlier studies on weight reduction in OSA patients, the weight loss was achieved by low and very low calorie diet programs, the outcomes have ranged extensively i.e. 3-18% loss of weight and 3-62% improvement in AHI (Dixon, Schachter & O'Brien 2005, Kajaste et al. 2004, Kajaste et al. 1994, Suratt et al. 1992, Kansanen et al. 1998). These previous studies have been reviewed; the conclusion was that although weight reduction is important and can facilitate the treatment of OSA, it can rarely cure it without being supplemented with classical techniques, such as CPAP (Barvaux, Aubert & Rodenstein 2000). Thus, one conclusion emerging from these studies has been that while weight loss can reduce the severity of OSA, at least in most patients, it cannot be considered as a curative treatment. Thus, although weight reduction is recommended in all clinical guidelines, until recently there has been a lack of well-executed randomized intervention studies on the effect of weight reduction upon OSA.

In recent randomized controlled studies, it has been demonstrated that lifestyle intervention with weight reduction is a feasible and curative for the vast majority of overweight OSA patients (Tuomilehto et al. 2009, Foster et al. 2009, Johansson et al. 2009). Despite the earlier beliefs that lifestyle intervention with weight reduction could not result in curative outcomes and any beneficial effect would not be long-lasting, data from more recent studies have tended to indicate that these previous assumptions may not be fully justified. In a study conducted in originally severe OSA subjects, it was revealed that almost every second patient no longer required CPAP treatment 12 months after the lifestyle intervention (Johansson et al. 2011). Weight reduction achieved by lifestyle intervention has been demonstrated to exert beneficial, even curative, effects on OSA which have been maintained in longer follow-up studies. In a 2 year follow-up study, favorable effects of weight reduction sustained at least one year after the discontinuation of the intervention

(Tuomilehto et al. 2010). In addition, even though some of the initial weight might have returned, a lifestyle intervention with successful weight reduction sustained beneficial effects for as long as 5 years after the intervention (Tuomilehto et al. 2014). Furthermore, recently it was demonstrated that in the early stages of OSA i.e. mild OSA, a sustained weight loss of as little as 5% from the baseline body weight was sufficient to prevent the disease from worsening and even cure it when this was investigated in a long-term follow-up (Tuomilehto et al. 2014).

2.2.2 Nasal continuous positive airway pressure (CPAP)

Already for decades, nasal CPAP has been the treatment of choice for OSA since it can prevent the upper airway from collapsing during inspiration and expiration, by acting as a pneumatic splint to maintain a positive airway pressure (Sullivan et al. 1981). The treatment not only alleviates the subjective symptoms, but also achieves improvements in objectively measured functions and it can reverse the negative cardiovascular consequences of OSA (Bayram et al. 2009, Craig et al. 2009, Cross et al. 2008, Garcia-Rio et al. 2013, Chung et al. 2011, Ciccone et al. 2011, Alonso-Fernandez et al. 2009). Nasal CPAP therapy is the most effective treatment method to treat OSA but the therapy demands good compliance on the part of the patient, which often is far from optimal. The compliance has been stated to range from 17% to 86%, depending on the method used to measure compliance and the compliance criteria (Weaver, Grunstein 2008, Sin et al. 2002). In clinical work with a careful evaluation of the treatment modality, the compliance rate is usually 70-80%. Possible side effects for CPAP include dry mouth, nasal blockage, increased amount of awakenings, mask pressure and mask leaks (Ulander et al. 2014), which may often be solved by providing careful instructions and if needed, some supplemental treatment for the nose and the addition of humidifier along with the CPAP device.

2.2.3 Oral appliances

Mandibular advancement devices (MAD) protrude the mandible and advance the tongue and therefore increase the pharyngeal airway diameter (Ryan et al. 1999). In the last decade, oral appliances have proven to be an efficient and safe therapeutic approach in treating OSA (Hoffstein 2007). A number of studies have demonstrated the efficacy of MAD use in decreasing the AHI, increasing oxyhemoglobin saturation during sleep, reducing blood pressure, and improving heart rate variability (Coruzzi et al. 2006, Giannasi et al. 2008, Johnston et al. 2002, Otsuka et al. 2006). A recent randomized controlled trial comparing the efficacy on MAD and CPAP demonstrated that health outcomes in patients with moderate to severe OSA were similar after treatment with CPAP and MAD, mainly due to the better compliance with MAD (Phillips et al. 2013).

2.2.4 Emerging therapies

New therapies are emerging for OSA e.g. hypoglossal nerve stimulation and genioglossus muscle stimulation. The hypoglossal nerve stimulator consists of a stimulator electrode, an intrathoracic pressure sensor and a programmable pulse generating system. Delivery of the stimulus is synchronized with the patient's respiratory pattern, allowing the stimulation to be triggered just prior the inspiration. Electrical stimulus is then considered to restore pharyngeal patency by activating the dilator muscles (Schwartz et al. 2001). The device has been demonstrated to increase respiratory flow without arousal from sleep. Two of the recent studies have demonstrated clinically meaningful reductions in AHI and improvements in QoL (Kezirian et al. 2014, Strollo et al. 2014). On other hand, at present, the treatment is expensive and previous studies have also stated that the efficacy of the stimulator device is limited, because residual disease still persists in most patients and since there are some safety concerns about the method, it will require more investigation before it becomes a routine therapy (Eastwood et al. 2011, Mwenge et al. 2013, Van de Heyning et al. 2012).

In transcutaneous genioglossus muscle stimulation, bilateral electrode patches are placed submentally and cables from the patches are connected to the stimulation device. The electrical stimulus to genioglossus muscle evokes a measurable contraction of the tongue and pharyngeal muscles resulting in a reduced ventilatory load. The effectiveness of this novel method for the treatment OSA still needs to be clarified (Steier et al. 2011).

2.2.5 Surgical treatment

The aim of surgical treatment is to achieve an increase in the diameter of the upper airway by removing the obstructed site and therefore decreasing airway resistance. Surgical treatment is seldom used in OSA but in very rare cases where the anatomical site of the obstruction has been identified and other possible causes eliminated, then surgical treatment can be beneficial. Especially in children, OSA is mainly treated with adenotonsillectomy, where hypertrophy of adenotonsillar tissue is present. In these cases, adenotonsillectomy is considered as a curative strategy. The sites of the surgical interest are nose, oropharynx, hypopharynx, maxillofacial structure and trachea. In addition, bariatric surgery has its own distinct place in weight reduction surgery (Kotecha, Hall 2014).

Nasal surgery

Nasal surgery has its benefits not as a curative treatment for OSA but as an adjunctive treatment to improve the efficacy of CPAP (Li et al. 2008). Even though nasal surgery does display some benefits in the improvement of QoL measures, it seldom offers any improvements in terms of AHI (Verse, Maurer & Pirsig 2002).

Tonsillectomy and uvulopalatopharyngoplasty (UPPP)

Tonsillectomy, in two case series, achieved an over 50% reduction in postoperative AHI in patients with mild, moderate and severe OSA and with grade III and IV tonsils (Verse et al. 2000, Tan et al. 2013). Uvulopalatopharyngoplasty is intended to enlarge the retropalatal diameter. The overall success rate in mild to severe OSA is reported to be approximately 40% but it is accompanied by comparatively large morbidity and may interfere with the later CPAP treatment (Browaldh et al. 2013). Thus, nowadays UPPP is very seldom undertaken but uvulopharyngoplasty which includes tonsillectomy, uvuloplasty and minor plasty of posterior palatal arches, is occasionally used to replace UPPP.

Hypopharyngeal procedures

Tongue base surgery with radiofrequency thermoablation has been claimed to exert some beneficial effects which last as long as 24 months after the procedure (Farrar et al. 2008). A case series of midline glossectomy with fifty OSA patients demonstrated an improvement in postoperative AHI values in 56% of the patients. The success rate depended on the tongue position (Suh 2013).

Maxillomandibular advancement

In selected cases, especially in patients with craniofacial deformities, maxillomandibular advancement can achieve an expansion of the upper airway at multiple levels and this is accompanied by positive long term follow up results (Holty, Guilleminault 2010).

Bariatric surgery

In some morbidly obese patients with OSA, bariatric surgery can represent an efficient treatment although it rarely can be considered as curable (Lettieri, Eliasson & Greenburg 2008, Haines et al. 2007) and there is a report that it is not superior to more conventional weight loss therapies (Dixon et al. 2012).

2.3 CO-MORBIDITIES

2.3.1 Mortality

In several studies, the association between moderate to severe OSA and cardiovascular mortality has been demonstrated, although no significant increase has been clearly shown to be associated with mild OSA (Nieto et al. 2000, Somers et al. 2008, Yaggi et al. 2005, Shahar et al. 2001, Gottlieb et al. 2010). In a recent study of Finnish OSA subjects, the overall mortality was 26.4 % in moderate to severe OSA cases while in patients without OSA, it was 9.7 %. It was estimated that the hazard ratio for cardiovascular mortality was 4.04 in the moderate to severe OSA cases and 1.87 in subjects with mild OSA (Muraja-Murro et al. 2013b). On the other hand, in a recent meta-analysis of the studies investigating the relationship of severe OSA and all-cause mortality, the overall pooled RR in relation to severe OSA was 1.92 (Wang et al. 2013) varying from 1.46 (Punjabi et al. 2009) to 3.80 (Young et al. 2008).

2.3.2 Cardiovascular co-morbidities

Several epidemiological studies have highlighted the strong link between OSA and cardiovascular diseases such as hypertension, coronary arterial disease, stroke and heart failure (Nieto et al. 2000, Peppard et al. 2000, Shamsuzzaman, Gersh & Somers 2003). Since OSA is a treatable disease and prevention and treatment of OSA could reduce the incidence of cardiovascular events, a clearer understanding of the relationship between OSA and the risk of cardiovascular co-morbidities could have an important impact on public health and the severity of the possible complications of the disease (Figure 2).

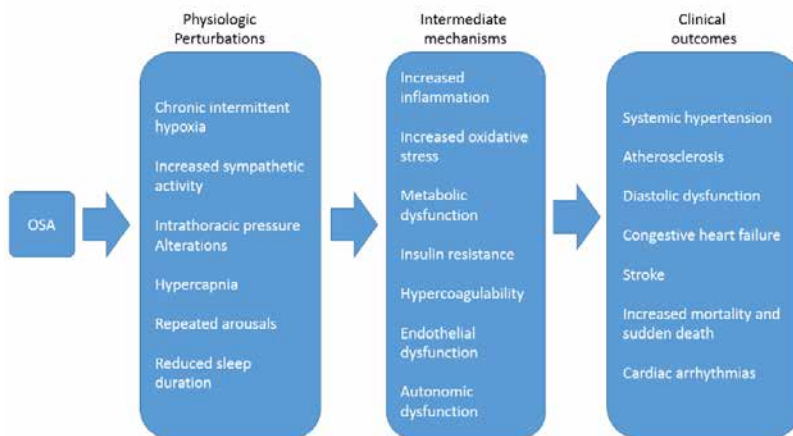


Figure 2. Consequences of OSA and the possible mechanisms of the evolution of cardiovascular co-morbidities. Adapted from (Durgan, Bryan 2012).

Hypertension

There is strong evidence supported by large epidemiological studies that OSA is an independent risk factor for hypertension and furthermore the majority of the OSA population has been reported to suffer from hypertension (Nieto et al. 2000, Bixler et al. 2001, Peppard et al. 2000, Lavie 2003). Patients with mild to moderate OSA had an up to three fold risk of developing new hypertension during a four year follow-up (Peppard et al. 2000). Moreover the association between OSA and the presence of hypertension has been found to be dose related (Nieto et al. 2000, Peppard et al. 2000, Young, Finn & Kim 1997, Lavie 2003, Grote, Hedner & Peter 2001). Importantly, drug resistant hypertension is linked with OSA (Somers et al. 2008). On the other hand, BMI and age are the major risk factors

for both OSA and hypertension (Bixler et al. 1998, Young, Skatrud & Peppard 2004, Hedner et al. 2006) and even mild OSA seems to add to the risk of hypertension (Young et al. 1997). There are several studies suggesting that CPAP, oral appliances and weight loss can achieve a significant reduction in blood pressure (Andren, Sjoquist & Tegelberg 2009, Aucott et al. 2005, Martinez-Garcia et al. 2013) and furthermore, these interventions naturally also improve OSA symptoms and parameters.

Coronary artery disease (CAD)

The underlying mechanisms leading to the formation and progression of atherosclerotic plaques in the arterial wall involve multiple factors such as oxidative stress, endothelial dysfunction, and inflammatory and immunologic factors. In OSA patients, the oxidative stress caused by repeated hypoxia and oxygenation during sleep, can ultimately cause vascular damage. Recent studies have increasingly addressed the role of OSA as an independent risk factor of CAD. In OSA patients without any other risk factors for CAD, signs of atherosclerosis have been found in the large arteries. Because OSA and CAD share the same risk factors, it is difficult to prove that there is causal relationship between OSA and CAD. However OSA has been independently associated with subclinical coronary atherosclerosis, and also OSA patients have a higher prevalence of non-calcified obstructive atherosclerotic plaques. An observation from a study of OSA patients who manifested signs of early atherosclerosis that were responsive to CPAP treatment, supports the theory of OSA being an independent risk factor for atherosclerosis. Multiple longitudinal studies have reported that untreated OSA patients are at risk of developing CAD, when adjusted for other risk factors. In the community-based Sleep Heart Health Study, an association was detected between OSA and incidents of CAD in severe OSA patients. In contrast, recent observational studies have found an association between OSA, acute myocardial infarction, incident coronary events or cardiac death after adjusting for other known risk factors (De Torres-Alba et al 2013).

Stroke

Several studies have recently pointed out that untreated OSA is an independent risk factor for stroke. One observational cohort study stated that OSA was associated with a combined endpoint of stroke and death, with an adjusted hazard ratio of 1.97 and that this risk was independent of other factors such as hypertension (Yaggi et al. 2005). Similarly, elderly patients with severe OSA were found to have an increased risk of stroke. This relationship was independent of other confounders such as blood pressure and hyperlipidemia (Munoz et al. 2006). The Sleep Heart Health study demonstrated that OSA was 30 % more common among those patients who developed ischemic stroke. The study also revealed a strong adjusted association between ischemic stroke and OSA in community-dwelling men with mild to moderate OSA and with moderate to severe OSA in women (Redline et al. 2010). The cross-sectional analysis of the results of the Wisconsin Sleep Cohort Study demonstrated that moderate to severe sleep apnea was associated with an increased risk of stroke after adjustment for confounders (Arzt et al. 2005). In addition, a recent meta-analysis of five studies also concluded that OSA was associated with stroke incident (Loke et al. 2012).

Heart failure

OSA may play a role in the pathogenesis of cardiac failure through mechanical, adrenergic and vascular mechanisms (Bradley, Floras 2003). In a large community study, the presence of OSA increased the likelihood of suffering heart failure with a 2.38 odds ratio, this being independent of other known risk factors (Shahar et al. 2001). In a study investigating male heart failure patients, at least mild OSA was found in 68% of the patients and moderate to

severe OSA in 49% of the patients (Javaheri 2006). Similar results showing a high prevalence of OSA among heart failure patients have been demonstrated in several studies (Bitter et al. 2009, Ferreira et al. 2010, Herrscher et al. 2011, Oldenburg et al. 2007, Zhao et al. 2007). In addition, treatment of OSA has exerted beneficial effects on survival of heart failure patients (Javaheri et al. 2011).

Atrial fibrillation

It has been claimed to be an association between OSA and nocturnal disturbances of cardiac rhythm (Shamsuzzaman, Gersh & Somers 2003). Individuals with OSA experienced a 4-fold increase in their adjusted risk for atrial fibrillation in a cross-sectional component of the Sleep Heart Health Study (Mehra et al. 2006). OSA was found in 49% of the patients who were referred for electrical cardioversion for atrial fibrillation (Gami et al. 2004). In addition, after cardioversion there was a significantly higher recurrence of atrial fibrillation in those individuals with OSA (Kanagala et al. 2003).

Pulmonary hypertension

Due to the variations in methods for defining pulmonary hypertension, it has proved rather difficult to study the association between OSA and pulmonary hypertension. In some recent studies, the estimated prevalence of pulmonary hypertension among OSA patients ranged from 17% up to 53% (Atwood et al. 2004) although there is one study where the prevalence was claimed to be as low as 10% (Javaheri, Javaheri & Javaheri 2013). Treatment of OSA in patients with pulmonary hypertension has resulted in a modest hemodynamic improvement.

2.4 PATHOGENESIS OF CARDIOVASCULAR CO-MORBIDITIES IN OSA

The pathogenesis of cardiovascular complications in OSA is most likely related to sleep fragmentation and hypoxia. Although not completely understood, the exact underlying pathways are considered as being multifactorial. The proposed mechanisms predisposing to cardiovascular disease include sympathetic activation, systemic inflammation, oxidative stress and endothelial dysfunction (Shamsuzzaman, Gersh & Somers 2003, Lavie 2003, Atkeson, Jelic 2008, Jurado-Gamez et al. 2011). Recent epidemiological studies have revealed OSA to be an important risk factor for increased mortality, particularly due to coronary artery disease, and only in those patients with severe OSA (Punjabi et al. 2009).

During nocturnal recurrent episodes of obstructive apnea and hypopnea, the inspiratory effort against an occluded airway leads to negative pressure in the pleural space. Should the apnea or hypopnea persist, hypoxemia and hypercapnia become more profound, leading to pulmonary vasoconstriction and the development of transient pulmonary hypertension (Adegunsoye, Ramachandran 2012). Simultaneously there is a stimulation of the sympathetic nervous system, triggering systemic vasoconstriction and arterial hypertension (Leuenberger et al. 1995). In addition, this phenomenon of hypoxia and hypercapnia followed by subsequent reoxygenation is repeated several times during the same night, causing changes in reperfusion, production of free radicals, endothelial dysfunction and oxidative stress. These changes are considered as major contributors to the cardiovascular consequences in OSA (Somers et al. 2008, Shamsuzzaman, Gersh & Somers 2003, Lavie 2003, Atkeson, Jelic 2008).

2.4.1 Endothelial dysfunction

The endothelium of the vascular wall is responsible for maintaining the balance of vasoconstriction and vasodilatation. Damage in the arterial wall leads to endothelial dysfunction (Shamsuzzaman, Gersh & Somers 2003). In cardiovascular disease, endothelial dysfunction is one of the early markers of atherosclerosis and its presence associates with

increased cardiovascular adverse events (Vita, Keaney 2002). A strong association has been detected between OSA and endothelial dysfunction (Kato et al. 2000, Forgiione, Leopold & Loscalzo 2000, Feng, Zhang & Chen 2011). Vascular endothelial dysfunction represents the loss of normal homeostatic functions in the blood vessels, being characterized by reduced vasodilatation and enhanced vasoconstrictory effects and chronic prothrombotic and inflammatory activity (Davignon, Ganz 2004). Endothelial dysfunction is considered as the first marker of the initiation of atherosclerosis also in OSA subjects (Foster, Poulin & Hanly 2007). Patients with moderate to severe OSA have been found to display impaired endothelial function and thus, to be at an increased risk of suffering cardiovascular diseases (Priou et al. 2010, Bayram et al. 2009, Kato et al. 2000). Several mechanisms have been proposed to explain the association between OSA and endothelial dysfunction. There is evidence also to suggest that OSA may independently impair endothelial function by reducing nitric oxide bioavailability and altering the regulation of endothelial vasomotor tone and cell repair capacity, while promoting vascular inflammation and oxidative stress. The mechanisms thought to be involved in the impaired endothelial function include repetitive hypoxia, sleep fragmentation and deprivation. It seems that there are some controversies related to the association between mild OSA and endothelial dysfunction. In some studies, preserved endothelial function has been observed in mild OSA cases (Yoshihisa et al. 2010, Chung et al. 2007) however, there have also been reports of endothelial dysfunction in patients with mild SDB (Nieto et al. 2000, Vita, Keaney 2002, Duchna et al. 2006, Faulx et al. 2004, Oflaz et al. 2006). In moderate to severe OSA, endothelial dysfunction has been found to be more evident (Bayram et al. 2009, Kato et al. 2000, Oflaz et al. 2006, Nguyen et al. 2010, Patt et al. 2010, Ip et al. 2004, Imadojemu et al. 2002). Impaired FMD has previously been associated with metabolic parameters related to impaired glucose and lipid metabolism, at least in studies conducted in older OSA patients (Nieto et al. 2004), patients with metabolic syndrome (Angelico et al. 2011) and in patients with hyperglycaemia (Caballero et al. 1999). It has been shown that endothelial dysfunction also develops in patients with other cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, obesity, and in smokers even before the signs of atherosclerosis develop. In addition, endothelial function can be restored by treating OSA or other risk factors (Clarkson et al. 1996, Gokce et al. 2001, Tounian et al. 2001).

2.4.2 Oxidative stress

Repetitive hypoxemia and reoxygenation may be one of the main factors in the triggering of oxidative stress mechanisms (Suzuki et al. 2006, Schulz et al. 2000, Prabhakar 2002). Some studies have reported increased levels biomarkers associated with oxidative stress in OSA patients (Lavie 2003) although these changes have not been confirmed in other studies (Svatikova et al. 2005). Microarray measures of gene transcription in OSA subjects before and after sleep have pointed to the activation of several mechanisms that may attempt to modulate or adapt the increase in the levels of reactive oxygen species developing in response to overnight hypoxemia (Hoffmann et al. 2007).

2.4.3 Inflammation

Systemic inflammation is considered to be one of the most important pathophysiological mechanisms explaining the progression of atherosclerosis from the appearance of foam cell to plaque formation and eventually to plaque rupture and thrombosis (Libby 2002). In OSA it is suggested that the oxidative stress caused by intermittent hypoxia will eventually lead to the synthesis of inflammatory cytokines thus promoting the expression of adhesion molecules especially in the vascular endothelium (Lavie, Lavie 2009). The atherosclerotic plaque is a collection of inflammatory cells and their cytokine products which play an essential role in cardiovascular disease (Hansson, Libby 2006).

It has been postulated that OSA activates both the proinflammatory system and inflammatory system (Sahlman et al. 2010). However it still remains uncertain whether OSA

itself modulates the circulating inflammatory biomarkers or do other factors such as the repetitive microarousals, overweight, metabolic syndrome or prediabetes, which are often encountered in OSA patients, alter the inflammatory system (Salmenniemi et al. 2004, Donath 2011).

2.4.4 Sympathetic activation and baroreflex sensitivity

Sympathetic activation appears to be one of the key factors responsible for the hypertension present in patients with OSA (Somers et al. 1995, Noda et al. 1993, Cortelli et al. 1994). Chemoreceptor stimulation induced by intermittent hypoxemia, repeated arousals and impairment of baroreflex control may play a role in the triggering of sympathetic activation in OSA (Carlson et al. 1996, Sforza et al. 1994, Ziegler et al. 1995). The impairment of the baroreceptor reflex sensitivity (BRS) has frequently and independently been observed in OSA patients (Carlson et al. 1996, Parati et al. 1997, Cooper et al. 2005, Grassi et al. 2005). In addition, impaired BRS is a marker of autonomic dysfunction in several major diseases such as diabetes, chronic heart failure and coronary artery disease (Frattola et al. 1997, La Rovere et al. 1998, Mortara et al. 1997). Depressed BRS has been found to be a significant predictor of arrhythmic death in patients recovering from acute myocardial infarction (La Rovere et al. 1998, La Rovere et al. 2001, La Rovere, Schwartz 1997, Farrell et al. 1992). Independent of obesity, BRS is known to be impaired in moderate or severe OSA, but there is no agreement about whether BRS becomes disturbed already in mild OSA (Ryan et al. 2007). Nonetheless, it is generally believed that sympathetic activation is one of the key mechanisms linking sleep apnea to cardiovascular disease (Narkiewicz et al. 1998b, Narkiewicz et al. 1999, Imadojemu et al. 2007).

2.4.5 Increased blood coagulation

Increased platelet aggregation and enhanced coagulability are present in patients with OSA (Bokinsky et al. 1995, von Kanel, Dimsdale 2003). In addition, the levels of coagulation factors are elevated in OSA patients (Wessendorf et al. 2000), along with the levels of plasma fibrinogen and plasminogen activator (Rangemark et al. 1995). Furthermore, it has been reported that treatment with CPAP is associated with a reduction in both fibrinogen levels and the activity of plasminogen activator, suggesting that OSA may be causally associated with increased coagulability (von Kanel et al. 2006, Chin et al. 1996).

3 Aims of the Study

The aims of the present study were

1. To evaluate whether overweight patients with mild OSA displayed endothelial dysfunction, and to assess the effect of a 1-year lifestyle intervention with a very low calorie diet (VLCD) on endothelial function. (Study I).
2. To investigate whether an impairment of BRS could be detected in overweight patients with mild OSA. (Study II).
3. To examine whether impaired nasal airflow might explain the missing effect of weight reduction in OSA (Study III).
4. To determine whether cigarette smoking could exert a negative impact in the improvement of OSA. (Study III)

4 *Material and Methods*

4.1 SUBJECTS

This randomized study was originally conducted to determine the effects of changes in lifestyle with weight reduction program designed to prevent the progression of OSA and cardiovascular risk factors in the most prevalent subgroup of OSA i.e. overweight patients with mild OSA. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland. The recruitment started in October 2004 and ended in December 2006. All patients who were referred to the Department of Otorhinolaryngology of Kuopio University Hospital due to a suspicion of sleep disordered breathing between 2004 and 2006 were assessed. Patients were assigned to undergo diagnostic nocturnal cardiorespiratory monitoring. Weight and height were measured, and the upper airway pathologies of the patients were evaluated. The inclusion criteria for the initial trial were 1) age 18–65 y, 2) body mass index (BMI; in kg/m²) 28–40, and 3) an apnea-hypopnea index (AHI) of 5 to 15 events/h. We also excluded patients due to active treatment of OSA of any kind, as well as pregnant women and those with chronic kidney, thyroid or liver disease. The control group consisted of non-OSA snorers who fulfilled the above mentioned inclusion criteria 1 and 2 as in the OSA group, but had AHI <5.

4.2 STUDY DESIGN

4.2.1 Baseline cross-sectional study on cardiovascular risk factors (Studies I and II)

The baseline cross-sectional study comprised of two analyses; cross-sectional comparison of 1) endothelial function and 2) BRS between patients with mild OSA (AHI 5-15/h) and non-OSA snorers (AHI <5). At baseline, the study population consisted of 83 overweight patients with mild OSA and 46 weight-matched non-OSA subjects.

4.2.2 Follow-up study on endothelial dysfunction (Study I)

The follow-up study represented a 1-year randomized, controlled trial (RCT) on the effect of weight loss on the endothelial function in patients with mild OSA (Fig. 1). At baseline, the study population consisted of 83 overweight patients with mild OSA. The subjects were randomized into two study groups by a study nurse according to a previously generated randomization plan. The study nurse did not participate in the intervention section of the study, nor did the study nutritionist see the patients before the first group session for the intervention group. No stratification was used in the randomization of the participants into the two groups (Tuomilehto et al. 2009). In the RCT, the patients were allocated into either an intensive lifestyle intervention group or a control group. The intervention group received a 1-year lifestyle intervention with an initial weight reduction program with 12 weeks on a very low calorie diet (VLCD). The control group were provided with a single general dietary and an exercise counselling session. The main objective of the study was to assess the endothelial function in patients with mild OSA and the effect of weight loss on endothelial function. The working hypothesis was that already in mild OSA, endothelial function could be impaired and a successful weight reduction with lifestyle intervention would result in an improvement during a 12-month follow-up.

4.2.3 Follow up study on factors possibly preventing the beneficial effect of weight reduction in (Study III)

This study was a 1-year follow-up study. Fifty-two overweight adult patients with mild OSA were recruited and underwent additional rhinometric measurement along with the cardiorespiratory recording. Based on previous studies of lifestyle intervention, it was decided that the lifestyle intervention period of 12 months would be considered successful if the patients achieved a minimum of 5% weight reduction (Lindstrom et al. 2008, Uusitupa et al. 2009). The patients who succeeded in achieving a 5% weight loss were further divided in two groups based on the value of the AHI at the 12-month follow-up. The subjects, who were able to diminish their AHI under the cut point value of 5 events/h, were considered to be objectively cured from OSA (non-OSA group). Patients in the other group had $AHI \geq 5$ events/h (OSA group). For further analysis, the patients were also divided into smokers and non-smokers. The aim of the study was to determine whether impaired nasal breathing and cigarette smoking could prevent the beneficial effects of weight reduction achieved by lifestyle intervention on OSA

4.4 METHODS

4.4.1 Anthropometric data

BMI was determined as weight (kg) divided by the square of height (m^2). Blood pressure was measured on the right arm with the subject in the sitting position, and the measurement was repeated three times, after 10 minutes of rest, using a standard sphygmomanometer. The mean value of the measurements was used as the result. At the study site, a trained nurse measured height, weight, waist circumferences and blood pressure at the baseline and at the 1-year visit. The total body fat percentage was measured with an InBody 3.0 bioimpedance device (Biospace; Seoul, Korea). The multifrequency bioimpedance method provides detailed information on fat mass, and also gives estimates of lean mass, total body water and fat distribution within the whole body and segmental lengths. When compared with the dual energy X-ray absorptiometry method, InBody analysis has been shown to provide a good assessment of fat mass in healthy subjects (Salmi 2003).

4.4.2 Cardiorespiratory monitoring

Nocturnal 6-channel unattended single night cardio-respiratory monitoring by Embletta® (Embla, Broomfield, CO, U.S.A.) at home was conducted in accordance with accepted guidelines for diagnosing OSA (AASM 1999). Nasal flow by nasal flow detector, thoracic and abdominal movements by two piezoelectric belts, oxygen saturation and heart rate by finger pulse oximeter and body position were monitored. A trained physician then evaluated the recordings in a blinded manner. Apnea was defined as a cessation ($\geq 90\%$) of airflow of ≥ 10 seconds. Hypopnea was defined as a reduction ($\geq 30\%$) of airflow of ≥ 10 seconds with oxygen desaturation $\geq 4\%$. The apnea-hypopnea index was defined as the number of apneas and hypopneas per hour, and mild OSA was defined as AHI 5-15 events/h. (Iber et al. 2007, Collop et al. 2007). The following parameters were also assessed; arterial oxygen saturation, time and percentage with arterial oxygen saturation below 90%, and heart rate. The cardiorespiratory recordings were conducted at the baseline and at the 1-year visit. All the biochemical measurements were performed both at baseline and at the 1-year visit after a 12-hour fasting period. In the present study, the results were based on sleep recordings from a single night. In routine practice, repeated recordings are extremely demanding, and the findings of single-night recordings have been found to be reliable in most patients (Fietze et al. 2004).

4.4.3 Biochemical measurements

Biochemical measurements were performed both at baseline and at the 1-year visit in the Laboratory of Clinical Chemistry in Kuopio University Hospital. From fresh serum samples cholesterol, high-density lipoprotein, triglycerides, alanine aminotransferase and glucose were analyzed by using an automated analyzer system (Konelab 60 analyzer; Thermo Fisher Scientific, Waltham, MA), and insulin was measured with a fluoroimmunoassay technique (Wallac; PerkinElmer, Waltham, MA).

4.4.4 Ultrasound studies (FMD)

Ultrasound studies were performed using Sequoia 512 ultrasound mainframes (Acuson, Mountain View, California). To assess brachial flow mediated dilatation (FMD), the left brachial artery diameter was measured both at rest and after reactive hyperaemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mm Hg for 4.5 minutes, followed by release. Three measurements of arterial diameter were performed at end diastole at a fixed distance from an anatomic marker at rest and at 20, 40, 60, 80 and 100 seconds after cuff release. The brachial artery diameter in scans after reactive hyperaemia was expressed both as the change in absolute diameter (FMD) and as the percentage change relative to the resting scan (FMD%). After a 10 min wash-out period, nitrate (glyceryl trinitrate spray 0.4 mg/dose, Nitrolingual-Pocket) was administered per os. Nitrate-related vasodilatation (NTG%) was assessed from the maximally dilated vessel diameter 3–5 min after nitrate administration relative to the vessel diameter at rest before nitrate administration.

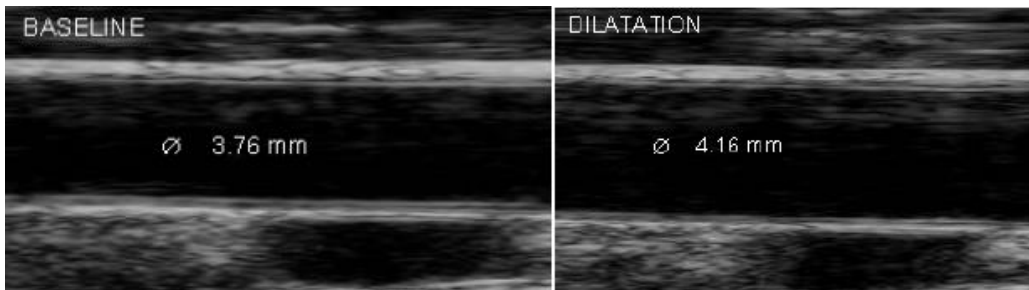


Figure 3. Assessment of brachial artery flow mediated vasodilation (a). Brachial artery at baseline (b). Brachial artery after shear stress (c). $FMD\% = ((4.16 - 3.76)/3.76) \times 100 = 10.6\% \approx 11\%$. Adapted from (Saarelainen 2012).

4.4.5 Assessment of baroreflex sensitivity

Five minutes after the controlled breathing test, BRS was evaluated, following with a modification of the method originally described by Smyth et al. (Smyth, Sleight & Pickering 1969). In brief, a bolus injection of 150 μg phenylephrine was administered into the antecubital vein to produce a rapid increase in blood pressure and a concomitant reduction in heart rate (increase of R-R interval) (Fig 4). Beat-to-beat values of R-R intervals (RRIs) were plotted against the systolic arterial pressure (SAP) values of the preceding cardiac cycle [i.e., $RRI(i)$ vs. $SAP(i - 1)$] during the period in which blood pressure increased after phenylephrine administration. A linear regression analysis between $RRI(i)$ and $SAP(i-1)$ was performed and expressed as follows: $RRI(i)$ (ms (mmHg)), where i is one individual cardiac cycle and $i - 1$ is the cardiac beat preceding the i beat (Fig 4). The slope of the regression line (b) represents BRS, and a and b are a constant and coefficient, respectively, that represent the linear regression (first-order equation). Only tests with correlation coefficients of $r > 0.80$ or that were statistically significant ($P < 0.05$) were accepted. The phenylephrine test was repeated at 10-min intervals up to five times to gather three acceptable measurements. The average of the three measurements was used in the assessment of BRS. In two cases, it was not possible to obtain any acceptable BRS values because of technical problems or ectopic beats. Furthermore, BRS proportional to age and

sex related reference values was calculated as percentage (Laitinen et al. 1998). The coefficient of variation and the correlation coefficient of two measurements that were performed at 3-mo intervals were 7.4% and 0.903, respectively (Hartikainen et al. 1995).

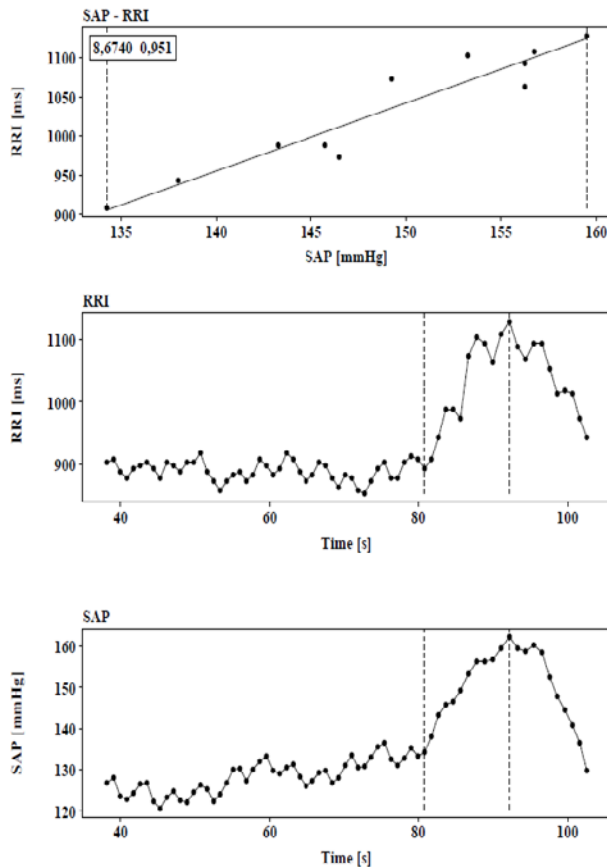


Figure 4. The BRS slope method describes the relationship between the change in the RR interval in response to the change of systolic blood pressure of the preceding cardiac cycle. The slope of regression line corresponds to arterial baroreflex sensitivity of 8.67 ms/mmHg with an acceptable correlation coefficient of 0.95. RRI= RR interval; SAP=systolic arterial pressure.

4.4.6 Lifestyle intervention

On the first visit, the patients were informed about the general health risks associated with OSA and obesity and provided with information about harmful lifestyle habits, such as smoking and alcohol drinking. Both the doctor and the nurse stressed the importance of diet and exercise to the control group, but no specific, individualized programs were offered to the subjects in the control group.

The 12 month intensive lifestyle intervention consisted of 14 visits with the study nutritionist. To estimate their nutrient intake, patients in the intervention group were asked to keep a 3-day food diary at baseline. After screening, participants in the intervention group started to adhere to a group-based very low calorie diet (VLCD) of 600–800 kcal/day (Nutrilett® [Nycomed Pharma, Oslo, Norway], Modifast® [Novartis, Basel, Switzerland], Nutrifast® [Leiras, Helsinki, Finland], or Naturdiet® [Vitamex, Norrköping, Sweden]) for

12 weeks. At the beginning of the intervention, an individual goal was set for weight loss. During the VLCD period, follow-up visits were arranged every second week and the sessions were supervised by the nutritionist. Compliance with the program and supervision for any possible adverse events were monitored by individual interviews at each visit by the nutritionist. Anthropometrics were measured at every visit and the patients were asked about any lifestyle changes he or she had made. In addition to VLCD products, the patients were allowed to consume calorie-free drinks and vegetables in accordance with the outpatient clinic's weight reduction program. The clinical nutritionist provided dietary and lifestyle counseling at each visit, with the emphasis placed on diet, exercise, and modification of lifestyle in general. After the VLCD program, the patients were advised to reduce fat to no more than 30% of total energy by increasing their intake of fruits, vegetables, poultry, fish, and lean meat, and by limiting consumption of dairy fats, fatty meat, sweets, pastries, and desserts. The subjects were recommended to increase their daily physical activity, and endurance exercise (such as walking, skiing, jogging, or swimming) was also recommended. After the VLCD, a physiotherapist supervised two group meetings which focused on circuit-type resistance exercise to improve functional capacity. During the intervention period, the rate of participation in these sessions varied from 70 to 80%.

Any possible adverse events related to the weight reduction program were assessed by the nutritionist at the visits which took place at two week intervals. All the results of the laboratory tests, blood pressure measurements, and electrocardiograms were checked by study physicians. It was decided that if any abnormal test results endangering the health of the study participants were observed, then participants would be informed and referred for appropriate medical care.

4.4.7 Rhinomanometric measurements

Rhinomanometry was performed at baseline, and at 12-month follow-up visit. A NR6-rhinomanometer (GM Instruments Ltd, Glasgow, UK) was used to conduct the rhinomanometric recordings, whereby total inspiratory nasal resistance was recorded at a radius of 200 Pascal. (Broms, Jonson & Lamm 1982) After a 15 minute period for acclimatization, four recordings were made: first in the seated position, next in the supine position after lying down for 5 minutes, the third was conducted at 10 minutes after nasal decongestion in the supine position and the fourth measurement after 5 minutes in the seated position. Nasal decongestion was achieved by swabbing the mucosa of the inferior and middle nasal turbinates with a solution containing 20µg/ml adrenaline and 40mg/ml lidocaine.

4.4.8 Symptoms and quality of life measurements

Epworth Sleepiness Scale (ESS) (Johns 1991), Snore Outcome Survey (SOS) (Gliklich, Wang 2002) and Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini RQLQ) (Juniper et al. 2000) scores were obtained at the baseline and at 12 months. The ESS is an eight item score evaluating daytime somnolence in eight specific situations. Total ESS score can vary from 0 (best) to 24 (worst) and a total score exceeding 10 points is considered to be abnormal. The SOS is a disease specific outcome score that contains eight items evaluating the duration, severity, frequency and consequences associated with SDB, especially snoring. Scores on the SOS are normalized on a scale ranging from 0 (worst) to 100 (best). The MiniRQLQ has 14 items in five domains; activity limitations, practical problems, nasal symptoms, eye symptoms and other symptoms. In the questionnaire, the subjects are asked to consider how they had experienced the previous week and to respond to each question on a seven-point scale (0 = no impairment, 6 = maximum impairment). In the present study, eye symptoms were not assessed leaving the questionnaire with 9 items. Therefore, the range of total miniRQLQ score can vary from 0 (no impairment) to 54 (maximum impairment). Patient's lifestyle habits, such as smoking were also recorded.

4.4.9 Clinical examination

At all the visits, the clinical assessments for all patients were done by an otorhinolaryngologist. A complete otorhinolaryngologic status was obtained, including examination of pharynx and larynx in Müller's maneuver with a fiber-endoscope. Moreover, special attention was paid to possible obstructing sites in the upper airway i.e. enlarged tonsils, retrognathia and Mallampati class, nasal polyps and nasal congestion. Moreover, patients in study III were evaluated more precisely in terms of nasal pathologies. In these patients, nasal polyposis, septal deviation and nasal congestion were evaluated using a three point scale in each variable (0= no polyps/deviation/congestion, 1= minor obstruction caused by polyps/deviation/congestion 2= nasal cavity entirely obstructed by polyps/deviation/congestion). Based on these individually measured nasal factors, the total nasal airway obstruction was evaluated on a seven-point scale (0= no obstruction, 6= total obstruction)

4.4.10 Statistical analysis

To describe the characteristics of two treatment groups, mean values and standard deviations were used. T-test and Fisher's exact test were used to assess equality between the treatment groups at baseline and at 12-month follow-up. The normality of the variables was tested with Kolmogorov-Smirnov test. In variables with a right skewed distribution; a logarithmic transformation was applied before the analysis. Geometric means and confidence intervals (CI) were reported for these variables. The statistical significance of differences in changes between the groups was assessed with t tests, and additionally by analysis of covariance (ANCOVA) with adjustment for age and sex. For non-parametric variables, Wilcoxon test was used. Recovery from OSA was analyzed with a logistic regression model, adjusting for baseline differences in age, sex, BMI, and AHI between the groups. The differences in risk are reported as odds ratios with 95% confidence intervals. All comparisons between the treatment groups were based on the intention-to-treat principle. Power analysis was originally calculated to detect the improvement of AHI where the study sample size was estimated to achieve 90% power at a 5% significance level to detect 25% lower prevalence of mild OSA at follow-up in the intervention group as compared with the control group. This calculation was made under the assumption that there would be no improvement in mild OSA in the control group. In the secondary analysis of continuous variables between the OSA and non-OSA-group, the unequal sample size had a power of 80% and a statistical significance of 0.05 to detect the effect size of 0.54 between the groups in BRS and FMD values and 0.64 between the groups in FMD change. In order to determine predictors of FMD, Spearman's univariate correlations and multiple linear regression models were used. Bonferroni correction was used in table 5 to adjust for multiple comparisons, and two tail P values < 0.003 were considered statistically significant. All characteristics and variables were analyzed with the Statistical Package for Social Sciences program (SPSS software, version 19 for Windows; SPSS Inc, Chicago, IL).

4.6 ETHICAL ASPECTS

The studies were approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (17.8.2004, decision number 127/04. Written consent were signed by the patients after they were given oral and written information about the trial protocol.

5 Results

The cross-sectional data of patients with mild OSA at baseline were analyzed by including predictors of cardiovascular disease in the comparison with the habitual snorers without OSA (study I). In the randomized controlled intervention study, the data of patients with mild OSA were analyzed to assess whether lifestyle intervention would improve cardiovascular risk factors (study II). There were five drop-outs in the intervention group and four in the control group, i.e. 34 and 35 patients completed the 1 year follow up, respectively. Study III explored which factors, particularly those related to nasal resistance, could explain the missing effect of successful weight loss.

5.1 PREDICTORS OF CARDIOVASCULAR DISEASE

5.1.1 Cross-sectional baseline comparison of patients with mild OSA and weight-matched non-OSA snorers

Brachial artery diameter at rest, its flow-mediated vasodilatation as well as the response to glyceryl trinitrate administration were almost identical in these two groups. Furthermore, only in 23 % of subjects in the OSA group and in 38 % of non-OSA snorers was FMD% <50 % of the gender specific reference value (non significance between the groups). (Juonala et al. 2008) Absolute BRS values (9.97 ± 6.70 vs. 10.51 ± 7.16) as well as the BRS values, when estimated proportional to age and sex related reference values, were almost the same in these groups. Furthermore, 6.2 % of subjects in the OSA patients and 2.1 % of non-OSA snorers had BRS% <50 % of the gender specific reference value (NS). Unfortunately, although the baseline cross-sectional control group of non-OSA snorers was weight-matched, patients with OSA were slightly but significantly older than control subjects ($P=0.02$) and there were significantly more males in the OSA group ($P=0.03$). Table 1 shows the characteristics of the study population. The BMI, blood pressure, fasting glucose, insulin, lipid levels and the time interval between the sleep and the ultrasound studies were comparable in the OSA patients and non-OSA snorers.

Table 1. Clinical characteristics of the study population at baseline in OSA and non-OSA groups. The data represent mean values with standard deviations (SD), frequencies or medians with range (min, max).

Parameter	OSA N=81	Non-OSA snorers, N=48	P
Age, years	50 (9)	46 (11)	0.02
Sex (male/female)	60/21	27/21	0.03
BMI, kg/m ²	32.5 (3.0)	31.7 (3.7)	0.17
Systolic blood pressure (mmHg)	130 (11)	132 (12)	0.40

Diastolic blood pressure (mmHg)	81 (8)	83 (10)	0.72
Fasting plasma glucose (mmol/l)	6.2 (1.9)	5.9 (1.1)	0.37
Fasting serum insulin (mU/l)	12.1 (6.0)	11.6 (5.7)	0.68
Fasting serum cholesterol (mmol/l)	4.7 (0.8)	5.0 (0.9)	0.06
Fasting serum HDL-cholesterol (mmol/l)	1.1 (0.3)	1.2(0.4)	0.02
Fasting serum triglycerides (mmol/l)	1.7 (1.1)	1.5 (0.9)	0.32
Hypertension (n)	34	13	0.07
Antihypertensive medication (n)	38	17	0.14
Hypercholesterolemia medication (n)	26	5	0.00
Coronary artery disease (n)	3	0	0.24
Diabetes (n)	7	2	0.28
Current smoker, n	21	11	0.44
Apnea hypopnea Index (AHI)	9.3 (3.3)	1.9 (1.4)	0.00
Average oxygen saturation (%)	94.0 (1.4)	94.8 (1.7)	0.02
Time with oxygen saturation lower than 90% (min)	4.6 (0.4, 304.0)	1.8 (0.1, 337.0)	<0.01
Time with oxygen saturation lower than 90% (%)	1.0 (0.1, 46.06)	0.4 (0.1, 63.4)	0.04

*T-test for continuous variables, Fisher's exact test for continuous variables. *ANCOVA adjusted for age and sex*

In a further analysis, patients who had OSA combined with a decreased FMD% had also elevated fasting insulin levels, higher BMI values, decreased HDL-cholesterol levels as well as lower average oxygen saturation when compared with OSA subjects with well-preserved FMD% .

Table 2. Clinical characteristics in subjects with and without OSA. The data represent mean values with standard deviation (SD), frequencies or medians with range (min, max).

Parameter	Group, (SD)		P
	OSA, N=81	non-OSA snorers, N=48	
Flow-mediated vasodilatation:			
Diameter change (mm)	0.2 (0.1)	0.3 (0.2)	0.71
FMD%	6.6 (0.0, 17.6)	6.5 (0.7, 60.9)	0.67
FMD in relation to the reference value (%)	85 (48)	96 (127)	0.46
Vasodilatation with exogenous nitric oxide:			
Diameter change (mm)	0.6 (0.2)	0.6 (0.2)	0.89
NTG%	16.5 (5.8)	17.2 (5.9)	0.52
Baroreflex sensitivity in phenylephrine test (mmHg/s)	9.97 (6.70)	10.51 (7.16)	0.67
Percentage of the age and sex related reference value	91.4 (22.7)	92.2 (21.8)	0.84

P: P value from logistic regression analysis for dichotomous variables, ANCOVA for continuous variables; adjustment for age and sex. BMI=body mass index, HOMA-IR=the homeostasis model assessment of insulin resistance, HDL= high-density lipoprotein, ALT=alanine aminotransferase, AHI=apnea hypopnea index, SaO2= oxygen saturation. †Adjusted for age. #Adjusted for sex.

In the OSA group, it was found that FMD% was directly correlated with female sex ($r=0.354$, $P<0.01$), fasting plasma HDL-cholesterol ($r= 0.233$, $P<0.05$) and inversely correlated with fasting glucose ($r= -0.284$, $P<0.05$) and insulin levels ($r= -0.311$, $P<0.01$). Furthermore, in

the OSA group, brachial artery diameter was inversely correlated with female sex ($r=-0.435, P<0.01$), and average oxygen saturation ($r=-0.244, P<0.05$), whereas it was directly correlated with percentual time with oxygen saturation lower than 90% ($r=0.242, P<0.05$), BMI ($r=0.239, P<0.05$), fasting glucose ($r=0.349, P<0.01$) and insulin levels ($r=0.254, P<0.05$). In the group of non-OSA snorers, univariate analysis detected an inverse correlation between brachial artery diameter and age ($r=-0.337, P<0.05$) and fasting serum HDL cholesterol ($r=-0.464, P<0.01$).

Linear regression analysis showed that in OSA patients, FMD% was positively associated with mean saturation (standardized beta coefficient =0.26, $P=0.029$), time with oxygen saturation under 90% ($R=0.26, P=0.03$) female sex ($R=0.33, P=0.04$) and insulin level ($R=0.67, P=0.002$). In a further multiple linear regression analysis, age, sex, AHI, BMI, mean systolic arterial pressure, fasting serum glucose level and total serum cholesterol level were added into the model, because of their known clinical importance. In this model, only age ($P=0.03$), female sex ($P<0.01$) and BMI ($P=0.01$) remained significantly associated with FMD.

5.1.2 Follow-up study

In spite of the randomization, the baseline BMI was significantly higher in the intervention group when compared to the control group. In addition, the diameter of the brachial artery was significantly larger and NTG% was significantly smaller in the intervention group than in the control group. There were no significant differences in other relevant baseline variables between the groups. In the lifestyle intervention group, weight decreased by 10.4 kg during the 12 months' study period. In the control group, the change in weight during the 1-year follow-up was -1.9 kg. The change between the groups was statistically significant. In the intervention group, significant improvements were observed in mean AHI, in time with mean saturation below 90% and in mean saturation compared with the control group. Furthermore, BMI, weight, serum triglycerides and plasma fasting insulin improved significantly in the intervention group in comparison with the control group. When correction for multiple comparisons was made, only changes in mean saturation, plasma fasting insulin, BMI and weight remained statistically significant (Table 3).

Table 3. Changes over the 12-month follow-up. The data represent mean changes with 95% confidence interval [CI].

	Control Group (CI) (n=37)	Intervention Group (n=35)	P
AHI (total) events/h	-0.21 (-2.8-2.4)	-3.95 (-5.9-(-2.0))***	0.02
Time with mean SaO ₂ >90% (min)	2.64 (-4.4-9.7)	-15.92 (-38.9-7.1)*	0.04
Mean oxygen saturation (%)	-0.29 (-0.8-0.2)	0.83 (0.4-1.3)***	<0.01##
Brachial artery diameter at rest (mm)	0.40 (-0.2-0.3)	-0.19 (-0.4-(-0.2))*	0.10
Flow mediated vasodilatation FMD % (%)	0.18 (-1.3-1.6)	0.45 (-0.9-1.8)	0.78
Dilatation amplitude in FMD-test (mm)	-0.06 (-0.4-0.7)	-0.11 (-0.4-0.6)	0.34
NTG% (nitric oxide)	-2.09 (-0.2-0.3)*	0.12(-0.3-<0.0)	0.11
Plasma fasting glucose (mmol/l)	-0.36 (-0.9-0.1)	-0.65 (-1.4-0.1)	0.53
Plasma fasting insulin (mmol/l)	-1.11 (-2.4-0.1)	-6.00 (-8.6-(-3.3))***	<0.01##
Serum cholesterol (mmol/l)	0.134(-0.1-0.3)	-0.10 (0.4-0.2)	0.19
Serum HDL cholesterol (mmol/l)	0.06 (<-0.0-0.1)	0.134 (0.6-0.2)**	0.14
Serum triglycerides (mmol/l)	-0.04 (-0.3-0.2)	-0.48 (-4.1-(-2.8))*	0.05
BMI (kg/m ²)	-0.63 (-1.3-0.2)	-3.47 (-4.1-(-2.8))***	<0.01##
Weight (kg)	-1.85 (-3.7-<0.0)	-10.38 (-12.5-(-8.3))***	<0.01##

Asterisks indicate whether the change between follow-up and baseline was statistically significant: *P<0.05, **P<0.01 and ***P<0.001; paired-samples t-test. Independent-samples t-test for changes, Wilcoxon test for nonparametric variables. Bonferroni correction was used to adjust multiple comparisons, and two tail P values < 0.003 were considered significant. ## P<0.003

At the 12-month follow-up, although there were no statistically significant differences between the groups, the brachial artery diameter in the intervention group had improved significantly from baseline. The dilatation response to exogenous nitric oxide (NTG%) decreased significantly in the control group even though no significant differences between the groups were found (Table 3).

5.2 NASAL RESISTANCE AND SUCCESFUL WEIGHT REDUCTION

During the 12 month follow-up, a total of 26/52 patients succeeded in achieving ≥ 5 % weight reduction and of those, 16 improved their AHI to under 5 events/hour, and thus, were considered to be cured from OSA. However, despite the successful weight reduction, the AHI of 10/26 remained at ≥ 5 events/hour. Clinical findings between the OSA and non-OSA groups did not differ significantly e.g. in terms of nasal polyposis, septal deviation or nasal congestion evaluated by clinical examination both at the baseline and at 12-month follow-up visit. At baseline, AHI was significantly higher in the apnoeic group compared to the non-OSA group, whereas the improvement of AHI at the follow-up was significantly greater in the non-OSA group. Furthermore, in the OSA group, 40% (4/10) of the patients were cigarette smokers, whereas in the non-OSA group 19% (3/16) of the patients were smokers. One patient from the non-OSA group managed to quit smoking during the follow-up, but none succeeded from the OSA group.

5.2.1 Rhinometric measurements

At the 12-month visit, non-OSA group displayed significantly less nasal resistance in the supine position (0.14 Pa/cm³/s) than the patients of the OSA group (0.29 Pa/cm³/s, $P=0.006$). The mean changes in nasal resistance during the 12-month follow-up in the non-OSA group and in the OSA group were -0.13 Pa/cm³/s and 0.01 Pa/cm³/s ($P=0.006$) respectively. At 12 months, the effect of nasal decongestion in the supine position was significantly more intense in the OSA group (-0.13 Pa/cm³/s) compared to the non-OSA group (-0.03 Pa/cm³/s, $P = 0.02$). Furthermore, the subjects in the OSA group displayed a greater mean change due to nasal decongestion in the follow-up period compared to those in the non-OSA group ($P = 0.03$) (Table 4).

The correlation between the change in BMI and the change in nasal resistance was borderline statistically significant with the current sample size (Pearson correlation coefficient $r=0.262$, $P=0.07$).

Table 4. Rhinomanometric measurements in supine position. Asterisks indicate whether the change between follow-up and baseline was statistically significant: * $p < 0.05$, ** $p < 0.01$; paired samples t -test. Independent samples t -test, or ANCOVA for changes, adjusted for baseline.

Parameter	OSA (n=10)	non-OSA snorers (n=16)	Significances P
<hr/>			
Mean total nasal inspiratory resistance			
Baseline	0.28 (0.15)	0.27 (0.12)	0.88
12 months	0.29 (0.18)	0.14 (0.08)	0.006
Change	0.01 (0.25)	-0.13* (0.20)	0.006
Mean total nasal inspiratory resistance decongested			
Baseline	0.25 (0.08)	0.22 (0.05)	0.51
12 months	0.17 (0.09)	0.12 (0.06)	0.07
Change	-0.08* (0.11)	-0.11** (0.11)	0.51
Effect of nasal decongestion			
Baseline	-0.03 (0.14)	-0.05 (0.18)	0.52
12 months	-0.13 (0.14)	-0.03 (0.07)	0.02
Change	-0.10(0.20)	0.02 (0.18)	0.03
<hr/>			

5.2.2 Symptom questionnaires

In MiniRQLQ, both groups reported mild impairment in QOL and nose related symptoms. The total miniRQLQ score was 15.0 in the non-OSA group and 19.3 in the OSA group at the 12-month visit. There was no significant change between the baseline and 12 month measurements in miniRQLQ.

5.2.3 Effect of smoking

In a further analysis, when the 26 patients with a significant weight loss were divided into smokers (N=7) and non-smokers (N=19), the mean change in nasal resistance after the weight loss was 0.06 Pa/cm³/s in smokers and 0.12 Pa/cm³/s in non-smokers (P =0.009). Furthermore, the mean change in AHI in cigarette smokers compared with non-smokers was -1.4 and -6.0, respectively (P = 0.035).

6 Discussion

The present study has its origin in observations of patients with mild OSA and the natural tendency of mild OSA to worsen over time. It is well-documented that severe OSA is associated with major macrovascular morbidity and mortality (Punjabi et al. 2009, Muraja-Murro et al. 2013a). However, it is not yet fully understood at what stage of OSA, the microvascular complications start to appear. This is of importance, since recently convincing evidence has appeared that long-term adherence to a healthy lifestyle along with weight reduction can result in marked improvement of OSA and that this can be detected as long as four years after the active intervention, i.e. the intervention was able to prevent the unwanted progression of OSA towards the more severe stages and cardiovascular consequences (Tuomilehto et al. 2013). The present study explored the cardiovascular risk factors in mild OSA. Lifestyle intervention with weight reduction is an efficient treatment modality in the majority of overweight OSA patients. However, for those patients who do not improve their OSA despite the successful weight loss, it was considered necessary to explore the factors related to nasal breathing that might explain why weight reduction did not achieve a curable effect in OSA.

In short, the present study shows that in mild OSA, the risk factors for cardiovascular disease are not yet present at least in terms of endothelial dysfunction and baroreflex sensitivity. In addition, lifestyle intervention with weight reduction is an effective treatment modality in overweight patients with mild OSA. Furthermore, impaired nasal breathing and smoking may explain why patients who despite achieving a successful weight loss, were not cured of OSA.

6.1. ENDOTHELIAL DYSFUNCTION

The present study did not detect evidence of endothelial dysfunction in mild OSA patients, i.e. was no correlation between AHI and FMD. However, the average oxygen desaturation was lower in patients with impaired FMD. It seems that there are some controversies related to the association between mild SDB and endothelial dysfunction. Some studies have observed a preserved endothelial function in mild OSA patients (Chung et al. 2007, Sert Kuniyoshi et al. 2011). However, there have also been reports of endothelial dysfunction in patients with mild SDB (Nieto et al. 2000, Vita, Keaney 2002, Faulx et al. 2004, Oflaz et al. 2006). In cases of moderate to severe OSA, more evident endothelial dysfunction has been found (Bayram et al. 2009, Kato et al. 2000, Oflaz et al. 2006, Patt et al. 2010, Ip et al. 2004, Sert Kuniyoshi et al. 2011, Kohler et al. 2008a, Chung et al. 2009). Based on the current results, in patients with mild OSA, the disease may not be severe enough to evoke marked endothelial dysfunction. This is also supported by the recent epidemiological studies that have revealed OSA to be an important risk factor for increased mortality, particularly due to coronary artery disease, but only in those patients with severe OSA disease (Punjabi et al. 2009).

It has been shown that endothelial dysfunction may also commence in patients with other cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, obesity, and in smokers even before the signs of atherosclerosis develop. In addition, endothelial function can be restored by treating OSA or other risk factors (Clarkson et al. 1996, Gokce et al. 2001, Tounian et al. 2001). These findings support the consensus statement on OSA and metabolism issued by the International Diabetes Federation which emphasized that in both clinical and scientific work, the association between type 2 diabetes, cardiometabolic syndrome and OSA should firmly be kept in mind.

In the present study, the overweight patients with OSA had decreased mean oxygen saturation values and their parameters of metabolic function were impaired, although their endothelial function remained unchanged. This could be interpreted that although some signs of elevated risks for cardiovascular complications were present, the hypoxemia may not have been profound enough to evoke endothelial dysfunction. It is well-documented that OSA can progress from mild SDB to more severe OSA over a varying period of time, but that this may be surprisingly short if it is accompanied by weight gain and the lack of effective treatment (Berger, Berger & Oksenberg 2009, Sahlman et al. 2007). This highlights the importance of lifestyle intervention with weight reduction, since it was observed to lead to significant improvement of both OSA and metabolic parameters.

6.2 BAROREFLEX SENSITIVITY

The main finding of this study was that baroreceptor sensitivity measured by i.v. phenylephrine test during wakefulness is not impaired in mild OSA patients when compared to non-OSA- snorers. Only 6.2% of OSA and 2.6% of non OSA snorers presented evidence of impaired BRS. In our study BRS in mild-OSA and non-OSA snorers averaged 9.97 ± 6.7 and 10.51 ± 7.16 respectively. This is in line with the BRS values of healthy individuals of the same age group (Laitinen et al. 1998). In literature, BRS values in patients with asymptomatic coronary artery disease average 7.8 ± 5.4 (Simula et al. 2013) and the BRS values of type II diabetes patients averaged 6.8 ± 2.9 (Loimaala et al. 2003).

Sympathetic activation is considered to be one of the key mechanisms linking OSA to cardiovascular morbidity and mortality (Narkiewicz et al. 1998b, Narkiewicz et al. 1999, Imadojemu et al. 2007). It has been shown that even mild OSA is associated with increased activation of the inflammatory system, however this can be normalized by achieving a weight loss such as via a successful lifestyle intervention (Tuomilehto et al. 2010, Sahlman et al. 2010). However, at present, there is only limited information available describing at what stage of OSA the impairment of cardiac autonomic regulation appear. Decreased BRS is considered to be one of the early markers of autonomic dysfunction in several diseases such as hypertension (La Rovere et al. 1998), diabetes (Frattola et al. 1997) chronic heart failure (Mortara et al. 1997) and coronary artery disease (La Rovere et al. 2001). BRS measured by the phenylephrine method is known to have clear prognostic value in predicting mortality in many cardiovascular diseases (La Rovere et al. 1998, Farrell et al. 1992, Farrell et al. 1991). Therefore this method was applied in the present study to assess BRS as it has recognized strengths in cardiovascular risk stratification (Goldberger et al. 2008, La Rovere et al. 2011). One of the weaknesses of this method is that, since it entails the intravenous administration of phenylephrine, it cannot be applied during sleep.

The results of earlier studies on BRS in OSA have been somewhat contradictory. The present finding that BRS does not differ between the OSA and non-OSA snorers is in line with the previous study of Ryan et al. (Ryan et al. 2007). BRS assessed by a sequence method during sleep, was not impaired in mild or moderate OSA when compared to severe OSA. Correspondingly, no impairment of BRS was found in severe OSA in the study of Narkiewicz and co-workers who also measured BRS by the phenylephrine test during wakefulness (Narkiewicz et al. 1998a). However, also contradictory findings have been reported. Ward and co-workers found that BRS was impaired during wakefulness in subjects with severe OSA when using the sequence technique, a spectral transfer function technique and an alpha index technique (Ward et al. 2006). Similar results showing decreased BRS in patients with OSA have been observed also in studies in which BRS assessments were performed with the Valsalva technique (Noda et al. 2007) and with the nitroprusside test (Carlson et al. 1996). Studies performed with the sequence method have shown that nocturnal BRS is reduced in severe OSA. (Parati et al. 1997, Ryan et al. 2007, Bonsignore et al. 2006). Some studies have demonstrated reduced BRS even in non-OSA

snorers (Gates et al. 2004, Mateika, Kavey & Mitru 1999). In addition, there are several studies demonstrating that CPAP treatment improves BRS in OSA patients (Bonsignore et al. 2006, Kohler et al. 2008b). However, it is difficult to make direct comparisons between these previous studies and the present study, because in the above trials different methods and/or patients with more severe OSA were employed.

In conclusion, BRS was found to be well preserved in patients with mild OSA. This highlights the importance of an early detection and supports the proposal that in the early stages of OSA, the disease may still be curable before the permanent complications have become established.

6.3 LIFESTYLE INTERVENTION AND ENDOTHELIAL DYSFUNCTION

Weight reduction is an effective treatment for OSA and weight loss is recommended in all clinical guidelines for treating OSA when it is accompanied with obesity (Tuomilehto et al. 2009, Foster et al. 2009, Johansson et al. 2009). In the present study, the intervention did not result in significant improvements of FMD between the study groups. The normal variance of FMD was comparatively high and therefore the sample size was perhaps too small to detect significant changes between the study groups.

In agreement with previous studies, (Wycherley et al. 2010, Clifton et al. 2005) the weight reduction did not result in an improvement of FMD in the 1-year follow up. Possibly, significant improvements in FMD could have been detected if the sample size would have been larger (Corretti et al. 2002). In addition, in studies with shorter follow-up times, some improvements in FMD after the weight reduction have been detected (Ades et al. 2011, Hamdy et al. 2003). Here, impaired FMD was significantly associated with the metabolic parameters related to impaired glucose and lipid metabolism. This correlation was found only in OSA patients. These findings are similar to the previous results described in older OSA patients, (Nieto et al. 2004) patients with metabolic syndrome (Angelico et al. 2011) and in patients with hyperglycaemia (Caballero et al. 1999).

6.4 IMPAIRED NASAL BREATHING AND LIFESTYLE INTERVENTION IN MILD OSA

The present study suggests that impaired nasal breathing might be either one factor preventing the beneficial effect of weight loss in overweight patients with mild OSA or a result of OSA. At the 12-month follow-up, those patients still having OSA despite the successful weight reduction had a significantly higher nasal resistance compared with the patients who were objectively cured from OSA. This suggests that impaired nasal breathing may be one factor preventing the beneficial effect of weight loss in overweight patients with mild OSA. On the other hand, the decrease in nasal resistance in patients who were cured from OSA may be due to the improvement of nasal inflammation which is present in OSA. Recent studies have suggested that higher nasal resistance is rather a result than a cause of OSA, since nasal resistance was reduced after UPPP and tonsillectomy procedures when these procedures lead to the improvement of AHI (Lu et al. 2014, Nakata et al. 2007).

Previously smoking has been found to exert adverse effects on the nasal airway. It has been associated with several symptoms i.e. with increased snoring, blocked nasal breathing, and pharyngeal soft tissue volume. Overall, the combination of cigarette smoking and altered nasal function seem to compromise the lower airways and thus, predispose to sleep disordered breathing (Virkkula et al. 2007, Virkkula et al. 2005). The effects of cigarette smoking on the nasal airway remain mostly an unknown issue, thus they might possibly be secondary to mucosal inflammation (Kjaergaard, Cvancarova & Steinsvaag 2010). In the present study, an adverse effect was also observed of cigarette smoking on nasal breathing.

In non-smokers, nasal resistance improved after the lifestyle intervention, whereas it tended to increase in smokers and in addition, AHI improved more in non-smokers. Since there were more smokers in the OSA-group (40%) compared with the non-OSA group (19%), it is possible that cigarette smoking partly prevented the beneficial effects of weight reduction on OSA.

In the present study, no correlation between AHI and nasal resistance was found in either of the groups. The previous data on the effect of nasal breathing on OSA is conflicting since there is no agreement on whether or not there is any correlation between nasal resistance and OSA (Lofaso et al. 2000, Li et al. 2005, Miljeteig, Hoffstein & Cole 1992, Yagi et al. 2009). Furthermore, the findings on the correlation between nasal breathing and OSA in different weight groups have also been controversial; in one study, significant correlations between AHI and nasal resistance were detected only in obese patients (Tagaya et al. 2010), while in another study the correlation was observed only in non-obese patients (Virkkula et al. 2003).

Only a few studies have explored the relationship between obesity and nasal resistance. A correlation between subjective feeling of nasal blockage and obesity was observed in one population based study (Johansson, Bende 2007). On the other hand, in a study investigating young healthy adults, BMI was found not to exert any effect on nasal resistance (Numminen et al. 2002). In addition, a previous study evaluating the effects of intensive weight reduction on rhinomanometric measures was unable to detect any correlation between changes in BMI and nasal resistance (Kempainen et al. 2008). In the present study, only a borderline correlation was found between BMI and rhinomanometric measurements. However, this is most likely due to the small sample size in this study, as the correlation coefficient was rather high.

6.5 LIMITATIONS

There are some limitations to this study. Endothelial function was measured in the conduit artery level using the non-invasive brachial artery test and ultrasound imaging, but not at the peripheral arterial level. Most of the well-conducted earlier studies evaluating the association between OSA and BRS have included fewer patients, and usually the study groups have been more heterogeneous in terms of the degree of OSA. Therefore, one could argue that the present study, despite some of its weaknesses, does provide new important information about microvascular conditions present in the early stages of OSA. Unfortunately, in baseline cross-sectional analyses, the non-OSA snorers and OSA patients were only weight-matched, not age and sex matched as well. This could possibly been achieved if the group size of OSA and non-OSA snorers had been equal. Unfortunately, it was not executable in a single center setting. Furthermore, in the follow up study, although randomized at baseline, the intervention group was heavier than the control group. This fact among with the comparable small study population, especially when the standard deviation of BRS was comparable high, could degrade the reliability of multivariate analysis in this model. Furthermore, since this intervention was conducted in patients with mild OSA, the findings may not be directly generalizable to all OSA patients. Nonetheless, it does seem that this is the first study with a randomized design to have examined the association between endothelial function and untreated mild OSA. Most of the well-conducted earlier studies on the association between OSA and endothelial function have included fewer patients, and usually the study groups have been more severe or more heterogeneous in terms of the degree of OSA. Therefore, in the search for better clinical guidelines, it is one conclusion of this thesis that despite some of its weaknesses, the new results do provide new important insights into the link between mild OSA and cardiovascular complications.

7 Conclusions

The findings of the present study were

1. In mild OSA, endothelial function was found to be preserved
2. In mild OSA, the baroreflex sensitivity was still preserved.
3. Impaired nasal breathing may prevent the beneficial effect of weight reduction in overweight mild OSA patients and cigarette smoking may exert a negative effect on both nasal resistance and on the improvement in the AHI values.

8 References

American Academy of Sleep Medicine. ICSD - International classification of sleep disorders, revised: Diagnostic and coding manual. American Academy of Sleep Medicine, 2001. ISBN: 0-9657220-1-5

American Academy of Sleep Medicine: International Classification of Sleep Disorders, 2nd ed.: Diagnostic and Coding Manual. Westchester, IL: *American Academy of Sleep Medicine*, 2005, p 204.

"Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force", 1999, *Sleep*, vol. 22, no. 5, pp. 667-689.

Adegunsoye, A. & Ramachandran, S. 2012, "Etiopathogenetic mechanisms of pulmonary hypertension in sleep-related breathing disorders", *Pulmonary medicine*, vol. 2012, pp. 273591.

Ades, P.A., Savage, P.D., Lischke, S., Toth, M.J., Harvey-Berino, J., Bunn, J.Y., Ludlow, M. & Schneider, D.J. 2011, "The effect of weight loss and exercise training on flow-mediated dilatation in coronary heart disease: a randomized trial", *Chest*, vol. 140, no. 6, pp. 1420-1427.

Andren, A., Sjoquist, M. & Tegelberg, A. 2009, "Effects on blood pressure after treatment of obstructive sleep apnoea with a mandibular advancement appliance - a three-year follow-up", *Journal of oral rehabilitation*, vol. 36, no. 10, pp. 719-725.

Angelico, F., Loffredo, L., Pignatelli, P., Augelletti, T., Carnevale, R., Pacella, A., Albanese, F., Mancini, I., Di Santo, S., Del Ben, M. & Violi, F. 2011, "Weight loss is associated with improved endothelial dysfunction via NOX2-generated oxidative stress down-regulation in patients with the metabolic syndrome", *Internal and emergency medicine*, .

Arzt, M., Young, T., Finn, L., Skatrud, J.B. & Bradley, T.D. 2005, "Association of sleep-disordered breathing and the occurrence of stroke", *American journal of respiratory and critical care medicine*, vol. 172, no. 11, pp. 1447-1451.

Atkeson, A. & Jelic, S. 2008, "Mechanisms of endothelial dysfunction in obstructive sleep apnea", *Vascular health and risk management*, vol. 4, no. 6, pp. 1327-1335.

Attal, P. & Chanson, P. 2010, "Endocrine aspects of obstructive sleep apnea", *The Journal of clinical endocrinology and metabolism*, vol. 95, no. 2, pp. 483-495.

Atwood, C.W., Jr, McCrory, D., Garcia, J.G., Abman, S.H., Ahearn, G.S. & American College of Chest Physicians 2004, "Pulmonary artery hypertension and sleep-disordered breathing: ACCP evidence-based clinical practice guidelines", *Chest*, vol. 126, no. 1 Suppl, pp. 72S-77S.

Aucott, L., Poobalan, A., Smith, W.C., Avenell, A., Jung, R. & Broom, J. 2005, "Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review", *Hypertension*, vol. 45, no. 6, pp. 1035-1041.

Barvaux, V.A., Aubert, G. & Rodenstein, D.O. 2000, "Weight loss as a treatment for obstructive sleep apnoea", *Sleep medicine reviews*, vol. 4, no. 5, pp. 435-452.

Bayram, N.A., Ciftci, B., Keles, T., Durmaz, T., Turhan, S., Bozkurt, E. & Peker, Y. 2009, "Endothelial function in normotensive men with obstructive sleep apnea before and 6 months after CPAP treatment", *Sleep*, vol. 32, no. 10, pp. 1257-1263.

Berger, G., Berger, R. & Oksenberg, A. 2009, "Progression of snoring and obstructive sleep apnoea: the role of increasing weight and time", *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*, vol. 33, no. 2, pp. 338-345.

Berry, R.B., Budhiraja, R., Gottlieb, D.J., Gozal, D., Iber, C., Kapur, V.K., Marcus, C.L., Mehra, R., Parthasarathy, S., Quan, S.F., Redline, S., Strohl, K.P., Davidson Ward, S.L., Tangredi, M.M. & American Academy of Sleep Medicine 2012, "Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine", *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, vol. 8, no. 5, pp. 597-619.

Berry, R.B. & Gleeson, K. 1997, "Respiratory arousal from sleep: mechanisms and significance", *Sleep*, vol. 20, no. 8, pp. 654-675.

Bitter, T., Faber, L., Hering, D., Langer, C., Horstkotte, D. & Oldenburg, O. 2009, "Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction", *European journal of heart failure*, vol. 11, no. 6, pp. 602-608.

Bixler, E.O., Vgontzas, A.N., Lin, H.M., Ten Have, T., Rein, J., Vela-Bueno, A. & Kales, A. 2001, "Prevalence of sleep-disordered breathing in women: effects of gender", *American journal of respiratory and critical care medicine*, vol. 163, no. 3 Pt 1, pp. 608-613.

Bixler, E.O., Vgontzas, A.N., Ten Have, T., Tyson, K. & Kales, A. 1998, "Effects of age on sleep apnea in men: I. Prevalence and severity", *American journal of respiratory and critical care medicine*, vol. 157, no. 1, pp. 144-148.

Bokinsky, G., Miller, M., Ault, K., Husband, P. & Mitchell, J. 1995, "Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with

nasal continuous positive airway pressure. A preliminary investigation", *Chest*, vol. 108, no. 3, pp. 625-630.

Bonsignore, M.R., Parati, G., Insalaco, G., Castiglioni, P., Marrone, O., Romano, S., Salvaggio, A., Mancina, G., Bonsignore, G. & Di Rienzo, M. 2006, "Baroreflex control of heart rate during sleep in severe obstructive sleep apnoea: effects of acute CPAP", *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*, vol. 27, no. 1, pp. 128-135.

Bradley, T.D., Brown, I.G., Grossman, R.F., Zamel, N., Martinez, D., Phillipson, E.A. & Hoffstein, V. 1986, "Pharyngeal size in snorers, nonsnorers, and patients with obstructive sleep apnea", *The New England journal of medicine*, vol. 315, no. 21, pp. 1327-1331.

Bradley, T.D. & Floras, J.S. 2003, "Sleep apnea and heart failure: Part I: obstructive sleep apnea", *Circulation*, vol. 107, no. 12, pp. 1671-1678.

Brander, P.E., Mortimore, I.L. & Douglas, N.J. 1999, "Effect of obesity and erect/supine posture on lateral cephalometry: relationship to sleep-disordered breathing", *The European respiratory journal*, vol. 13, no. 2, pp. 398-402.

Broms, P., Jonson, B. & Lamm, C.J. 1982, "Rhinomanometry. II. A system for numerical description of nasal airway resistance", *Acta Oto-Laryngologica*, vol. 94, no. 1-2, pp. 157-168.

Browaldh, N., Nerfeldt, P., Lysdahl, M., Bring, J. & Friberg, D. 2013, "SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea", *Thorax*, vol. 68, no. 9, pp. 846-853.

Caballero, A.E., Arora, S., Saouaf, R., Lim, S.C., Smakowski, P., Park, J.Y., King, G.L., LoGerfo, F.W., Horton, E.S. & Veves, A. 1999, "Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes", *Diabetes*, vol. 48, no. 9, pp. 1856-1862.

Carlson, J.T., Hedner, J.A., Sellgren, J., Elam, M. & Wallin, B.G. 1996, "Depressed baroreflex sensitivity in patients with obstructive sleep apnea", *American journal of respiratory and critical care medicine*, vol. 154, no. 5, pp. 1490-1496.

Carrera, M., Barbe, F., Sauleda, J., Tomas, M., Gomez, C. & Agusti, A.G. 1999, "Patients with obstructive sleep apnea exhibit genioglossus dysfunction that is normalized after treatment with continuous positive airway pressure", *American journal of respiratory and critical care medicine*, vol. 159, no. 6, pp. 1960-1966.

Carrera, M., Barbe, F., Sauleda, J., Tomas, M., Gomez, C., Santos, C. & Agusti, A.G. 2004, "Effects of obesity upon genioglossus structure and function in obstructive sleep apnoea", *The European respiratory journal*, vol. 23, no. 3, pp. 425-429.

Chervin, R.D. 2000, "Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea", *Chest*, vol. 118, no. 2, pp. 372-379.

Chin, K., Ohi, M., Kita, H., Noguchi, T., Otsuka, N., Tsuboi, T., Mishima, M. & Kuno, K. 1996, "Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome", *American journal of respiratory and critical care medicine*, vol. 153, no. 6 Pt 1, pp. 1972-1976.

Chung, S., Yoon, I.Y., Lee, C.H. & Kim, J.W. 2011, "The effects of nasal continuous positive airway pressure on vascular functions and serum cardiovascular risk factors in obstructive sleep apnea syndrome", *Sleep & breathing = Schlaf & Atmung*, vol. 15, no. 1, pp. 71-76.

Chung, S., Yoon, I.Y., Shin, Y.K., Lee, C.H., Kim, J.W. & Ahn, H.J. 2009, "Endothelial dysfunction and inflammatory reactions of elderly and middle-aged men with obstructive sleep apnea syndrome", *Sleep & breathing = Schlaf & Atmung*, vol. 13, no. 1, pp. 11-17.

Chung, S., Yoon, I.Y., Shin, Y.K., Lee, C.H., Kim, J.W., Lee, T., Choi, D.J. & Ahn, H.J. 2007, "Endothelial dysfunction and C-reactive protein in relation with the severity of obstructive sleep apnea syndrome", *Sleep*, vol. 30, no. 8, pp. 997-1001.

Ciccone, M.M., Favale, S., Scicchitano, P., Mangini, F., Mitacchione, G., Gadaleta, F., Longo, D., Iacoviello, M., Forleo, C., Quistelli, G., Taddei, S., Resta, O. & Carratu, P. 2011, "Reversibility of the endothelial dysfunction after CPAP therapy in OSAS patients", *International journal of cardiology*, .

Clarkson, P., Celermajer, D.S., Donald, A.E., Sampson, M., Sorensen, K.E., Adams, M., Yue, D.K., Betteridge, D.J. & Deanfield, J.E. 1996, "Impaired vascular reactivity in insulin-dependent diabetes mellitus is related to disease duration and low density lipoprotein cholesterol levels", *Journal of the American College of Cardiology*, vol. 28, no. 3, pp. 573-579.

Clifton, P.M., Keogh, J.B., Foster, P.R. & Noakes, M. 2005, "Effect of weight loss on inflammatory and endothelial markers and FMD using two low-fat diets", *International journal of obesity (2005)*, vol. 29, no. 12, pp. 1445-1451.

Collop, N.A., Anderson, W.M., Boehlecke, B., Claman, D., Goldberg, R., Gottlieb, D.J., Hudgel, D., Sateia, M., Schwab, R. & Portable Monitoring Task Force of the American Academy of Sleep Medicine 2007, "Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine", *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, vol. 3, no. 7, pp. 737-747.

Cooper, V.L., Pearson, S.B., Bowker, C.M., Elliott, M.W. & Hainsworth, R. 2005, "Interaction of chemoreceptor and baroreceptor reflexes by hypoxia and hypercapnia - a mechanism for promoting hypertension in obstructive sleep apnoea", *The Journal of physiology*, vol. 568, no. Pt 2, pp. 677-687.

- Cormier, Y. & Series, F. 1990, "Effects of lung volume and positive airway pressure on collateral resistance", *Respiration physiology*, vol. 80, no. 1, pp. 103-112.
- Corretti, M.C., Anderson, T.J., Benjamin, E.J., Celermajer, D., Charbonneau, F., Creager, M.A., Deanfield, J., Drexler, H., Gerhard-Herman, M., Herrington, D., Vallance, P., Vita, J., Vogel, R. & International Brachial Artery Reactivity Task Force 2002, "Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force", *Journal of the American College of Cardiology*, vol. 39, no. 2, pp. 257-265.
- Cortelli, P., Parchi, P., Sforza, E., Contin, M., Pierangeli, G., Barletta, G. & Lugaresi, E. 1994, "Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome", *Clinical autonomic research : official journal of the Clinical Autonomic Research Society*, vol. 4, no. 1-2, pp. 57-62.
- Coruzzi, P., Gualerzi, M., Bernkopf, E., Brambilla, L., Brambilla, V., Broia, V., Lombardi, C. & Parati, G. 2006, "Autonomic cardiac modulation in obstructive sleep apnea: effect of an oral jaw-positioning appliance", *Chest*, vol. 130, no. 5, pp. 1362-1368.
- Craig, S., Pepperell, J.C., Kohler, M., Crosthwaite, N., Davies, R.J. & Stradling, J.R. 2009, "Continuous positive airway pressure treatment for obstructive sleep apnoea reduces resting heart rate but does not affect dysrhythmias: a randomised controlled trial", *Journal of sleep research*, vol. 18, no. 3, pp. 329-336.
- Cross, M.D., Mills, N.L., Al-Abri, M., Riha, R., Vennelle, M., Mackay, T.W., Newby, D.E. & Douglas, N.J. 2008, "Continuous positive airway pressure improves vascular function in obstructive sleep apnoea/hypopnoea syndrome: a randomised controlled trial", *Thorax*, vol. 63, no. 7, pp. 578-583.
- Davignon, J. & Ganz, P. 2004, "Role of endothelial dysfunction in atherosclerosis", *Circulation*, vol. 109, no. 23 Suppl 1, pp. III27-32.
- De Torres-Alba F, Gemma D, Armada-Romero E, Rey-Blas JR, López-de-Sá E, López-Sendon JL. Obstructive sleep apnea and coronary artery disease: from pathophysiology to clinical implications. *Pulm Med*. 2013;2013:768064, doi: 10.1155/2013/768064
- Dixon, J.B., Schachter, L.M. & O'Brien, P.E. 2005, "Polysomnography before and after weight loss in obese patients with severe sleep apnea", *International journal of obesity (2005)*, vol. 29, no. 9, pp. 1048-1054.
- Dixon, J.B., Schachter, L.M., O'Brien, P.E., Jones, K., Grima, M., Lambert, G., Brown, W., Bailey, M. & Naughton, M.T. 2012, "Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial", *JAMA : the journal of the American Medical Association*, vol. 308, no. 11, pp. 1142-1149..

- Donath, M.Y. 2011, "Inflammation as a sensor of metabolic stress in obesity and type 2 diabetes", *Endocrinology*, vol. 152, no. 11, pp. 4005-4006.
- Douglas, N.J., White, D.P., Weil, J.V. & Zwillich, C.W. 1983, "Effect of breathing route on ventilation and ventilatory drive", *Respiration physiology*, vol. 51, no. 2, pp. 209-218.
- Drager, L.F., Bortolotto, L.A., Figueiredo, A.C., Krieger, E.M. & Lorenzi, G.F. 2007, "Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea", *American journal of respiratory and critical care medicine*, vol. 176, no. 7, pp. 706-712.
- Drager, L.F., Bortolotto, L.A., Lorenzi, M.C., Figueiredo, A.C., Krieger, E.M. & Lorenzi-Filho, G. 2005, "Early signs of atherosclerosis in obstructive sleep apnea", *American journal of respiratory and critical care medicine*, vol. 172, no. 5, pp. 613-618.
- Duchna, H.W., Stoohs, R., Guilleminault, C., Christine Anspach, M., Schultze-Werninghaus, G. & Orth, M. 2006, "Vascular endothelial dysfunction in patients with mild obstructive sleep apnea syndrome", *Wiener medizinische Wochenschrift (1946)*, vol. 156, no. 21-22, pp. 596-604.
- Duran, J., Esnaola, S., Rubio, R. & Iztueta, A. 2001, "Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr", *American journal of respiratory and critical care medicine*, vol. 163, no. 3 Pt 1, pp. 685-689.
- Durgan, D.J. & Bryan, R.M., Jr 2012, "Cerebrovascular consequences of obstructive sleep apnea", *Journal of the American Heart Association*, vol. 1, no. 4, pp. e000091.
- Eastwood, P.R., Barnes, M., Walsh, J.H., Maddison, K.J., Hee, G., Schwartz, A.R., Smith, P.L., Malhotra, A., McEvoy, R.D., Wheatley, J.R., O'Donoghue, F.J., Rochford, P.D., Churchward, T., Campbell, M.C., Palme, C.E., Robinson, S., Goding, G.S., Eckert, D.J., Jordan, A.S., Catcheside, P.G., Tyler, L., Antic, N.A., Worsnop, C.J., Kezirian, E.J. & Hillman, D.R. 2011, "Treating obstructive sleep apnea with hypoglossal nerve stimulation", *Sleep*, vol. 34, no. 11, pp. 1479-1486.
- Engleman, H.M. & Douglas, N.J. 2004, "Sleep. 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome", *Thorax*, vol. 59, no. 7, pp. 618-622.
- Epstein, L.J., Kristo, D., Strollo, P.J., Jr, Friedman, N., Malhotra, A., Patil, S.P., Ramar, K., Rogers, R., Schwab, R.J., Weaver, E.M., Weinstein, M.D. & Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine 2009, "Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults", *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, vol. 5, no. 3, pp. 263-276.

- Farrar, J., Ryan, J., Oliver, E. & Gillespie, M.B. 2008, "Radiofrequency ablation for the treatment of obstructive sleep apnea: a meta-analysis", *The Laryngoscope*, vol. 118, no. 10, pp. 1878-1883.
- Farrell, T.G., Odemuyiwa, O., Bashir, Y., Cripps, T.R., Malik, M., Ward, D.E. & Camm, A.J. 1992, "Prognostic value of baroreflex sensitivity testing after acute myocardial infarction", *British heart journal*, vol. 67, no. 2, pp. 129-137.
- Farrell, T.G., Paul, V., Cripps, T.R., Malik, M., Bennett, E.D., Ward, D. & Camm, A.J. 1991, "Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction", *Circulation*, vol. 83, no. 3, pp. 945-952.
- Faulx, M.D., Larkin, E.K., Hoit, B.D., Aylor, J.E., Wright, A.T. & Redline, S. 2004, "Sex influences endothelial function in sleep-disordered breathing", *Sleep*, vol. 27, no. 6, pp. 1113-1120.
- Feng, J., Zhang, D. & Chen, B. 2011, "Endothelial mechanisms of endothelial dysfunction in patients with obstructive sleep apnea", *Sleep & breathing = Schlaf & Atmung*.
- Ferreira, S., Marinho, A., Patacho, M., Santa-Clara, E., Carrondo, C., Winck, J. & Bettencourt, P. 2010, "Prevalence and characteristics of sleep apnoea in patients with stable heart failure: Results from a heart failure clinic", *BMC pulmonary medicine*, vol. 10, pp. 9-2466-10-9.
- FERRIS, B.G., Jr, MEAD, J. & OPIE, L.H. 1964, "Partitioning of Respiratory Flow Resistance in Man", *Journal of applied physiology*, vol. 19, pp. 653-658.
- Fietze, I., Dingli, K., Diefenbach, K., Douglas, N.J., Glos, M., Tallafuss, M., Terhalle, W. & Witt, C. 2004, "Night-to-night variation of the oxygen desaturation index in sleep apnoea syndrome", *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*, vol. 24, no. 6, pp. 987-993.
- Fitzpatrick, M.F., McLean, H., Urton, A.M., Tan, A., O'Donnell, D. & Driver, H.S. 2003, "Effect of nasal or oral breathing route on upper airway resistance during sleep", *The European respiratory journal*, vol. 22, no. 5, pp. 827-832.
- Floras, J.S. 2014, "Sleep apnea and cardiovascular risk", *Journal of cardiology*, vol. 63, no. 1, pp. 3-8.
- Forgione, M.A., Leopold, J.A. & Loscalzo, J. 2000, "Roles of endothelial dysfunction in coronary artery disease", *Current opinion in cardiology*, vol. 15, no. 6, pp. 409-415.
- Foster, G.D., Borradaile, K.E., Sanders, M.H., Millman, R., Zammit, G., Newman, A.B., Wadden, T.A., Kelley, D., Wing, R.R., Pi-Sunyer, F.X., Reboussin, D., Kuna, S.T. & Sleep AHEAD Research Group of Look AHEAD Research Group 2009, "A randomized study on

the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study", *Archives of Internal Medicine*, vol. 169, no. 17, pp. 1619-1626.

Foster, G.E., Poulin, M.J. & Hanly, P.J. 2007, "Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea", *Experimental physiology*, vol. 92, no. 1, pp. 51-65.

Frattola, A., Parati, G., Gamba, P., Paleari, F., Mauri, G., Di Rienzo, M., Castiglioni, P. & Mancina, G. 1997, "Time and frequency domain estimates of spontaneous baroreflex sensitivity provide early detection of autonomic dysfunction in diabetes mellitus", *Diabetologia*, vol. 40, no. 12, pp. 1470-1475.

Friedman, M., Tanyeri, H., La Rosa, M., Landsberg, R., Vaidyanathan, K., Pieri, S. & Caldarelli, D. 1999, "Clinical predictors of obstructive sleep apnea", *The Laryngoscope*, vol. 109, no. 12, pp. 1901-1907.

Gami, A.S., Pressman, G., Caples, S.M., Kanagala, R., Gard, J.J., Davison, D.E., Malouf, J.F., Ammash, N.M., Friedman, P.A. & Somers, V.K. 2004, "Association of atrial fibrillation and obstructive sleep apnea", *Circulation*, vol. 110, no. 4, pp. 364-367.

Garcia-Rio, F., Alonso-Fernandez, A., Armada, E., Mediano, O., Lores, V., Rojo, B., Fernandez-Lahera, J., Fernandez-Navarro, I., Carpio, C. & Ramirez, T. 2013, "CPAP effect on recurrent episodes in patients with sleep apnea and myocardial infarction", *International journal of cardiology*, vol. 168, no. 2, pp. 1328-1335.

Gates, G.J., Mateika, S.E., Basner, R.C. & Mateika, J.H. 2004, "Baroreflex sensitivity in nonapneic snorers and control subjects before and after nasal continuous positive airway pressure", *Chest*, vol. 126, no. 3, pp. 801-807.

Georgalas, C. 2011, "The role of the nose in snoring and obstructive sleep apnoea: an update", *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, vol. 268, no. 9, pp. 1365-1373.

Giannasi, L.C., Magini, M., de Oliveira, C.S. & de Oliveira, L.V. 2008, "Treatment of obstructive sleep apnea using an adjustable mandibular repositioning appliance fitted to a total prosthesis in a maxillary edentulous patient", *Sleep & breathing = Schlaf & Atmung*, vol. 12, no. 1, pp. 91-95.

Gliklich, R.E. & Wang, P.C. 2002, "Validation of the snore outcomes survey for patients with sleep-disordered breathing", *Archives of Otolaryngology--Head & Neck Surgery*, vol. 128, no. 7, pp. 819-824.

Gokce, N., Holbrook, M., Duffy, S.J., Demissie, S., Cupples, L.A., Biegelsen, E., Keaney, J.F., Jr, Loscalzo, J. & Vita, J.A. 2001, "Effects of race and hypertension on flow-mediated and

nitroglycerin-mediated dilation of the brachial artery", *Hypertension*, vol. 38, no. 6, pp. 1349-1354.

Goldberger, J.J., Cain, M.E., Hohnloser, S.H., Kadish, A.H., Knight, B.P., Lauer, M.S., Maron, B.J., Page, R.L., Passman, R.S., Siscovick, D., Stevenson, W.G., Zipes, D.P., American Heart Association, American College of Cardiology Foundation & Heart Rhythm Society 2008, "American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention", *Journal of the American College of Cardiology*, vol. 52, no. 14, pp. 1179-1199.

Gottlieb, D.J., Yenokyan, G., Newman, A.B., O'Connor, G.T., Punjabi, N.M., Quan, S.F., Redline, S., Resnick, H.E., Tong, E.K., Diener-West, M. & Shahar, E. 2010, "Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study", *Circulation*, vol. 122, no. 4, pp. 352-360.

Grassi, G., Facchini, A., Trevano, F.Q., Dell'Oro, R., Arenare, F., Tana, F., Bolla, G., Monzani, A., Robuschi, M. & Mancia, G. 2005, "Obstructive sleep apnea-dependent and -independent adrenergic activation in obesity", *Hypertension*, vol. 46, no. 2, pp. 321-325.

Grote, L., Hedner, J. & Peter, J.H. 2001, "Mean blood pressure, pulse pressure and grade of hypertension in untreated hypertensive patients with sleep-related breathing disorder", *Journal of hypertension*, vol. 19, no. 4, pp. 683-690.

Guilleminault, C., Stoohs, R., Shiomi, T., Kushida, C. & Schnittger, I. 1996, "Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension", *Chest*, vol. 109, no. 4, pp. 901-908.

Haines, K.L., Nelson, L.G., Gonzalez, R., Torrella, T., Martin, T., Kandil, A., Dragotti, R., Anderson, W.M., Gallagher, S.F. & Murr, M.M. 2007, "Objective evidence that bariatric surgery improves obesity-related obstructive sleep apnea", *Surgery*, vol. 141, no. 3, pp. 354-358.

Hamdy, O., Ledbury, S., Mullooly, C., Jarema, C., Porter, S., Ovalle, K., Moussa, A., Caselli, A., Caballero, A.E., Economides, P.A., Veves, A. & Horton, E.S. 2003, "Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome", *Diabetes care*, vol. 26, no. 7, pp. 2119-2125.

Hansson, G.K., Libby, P. 2006, "The Immune response in atherosclerosis: a double edged sword", *Nat Rev Immunol*, vol. 6, no 7, pp. 508-19.

- Hartikainen, J., Fyhrquist, F., Tahvanainen, K., Lansimies, E. & Pyorala, K. 1995, "Baroreflex sensitivity and neurohormonal activation in patients with acute myocardial infarction", *British heart journal*, vol. 74, no. 1, pp. 21-26.
- Hedner, J., Bengtsson-Bostrom, K., Peker, Y., Grote, L., Rastam, L. & Lindblad, U. 2006, "Hypertension prevalence in obstructive sleep apnoea and sex: a population-based case-control study", *The European respiratory journal*, vol. 27, no. 3, pp. 564-570.
- Herrscher, T.E., Akre, H., Overland, B., Sandvik, L. & Westheim, A.S. 2011, "High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function", *Journal of cardiac failure*, vol. 17, no. 5, pp. 420-425.
- Hoffmann, M.S., Singh, P., Wolk, R., Romero-Corral, A., Raghavakaimal, S. & Somers, V.K. 2007, "Microarray studies of genomic oxidative stress and cell cycle responses in obstructive sleep apnea", *Antioxidants & redox signaling*, vol. 9, no. 6, pp. 661-669.
- Hoffstein, V. 2007, "Review of oral appliances for treatment of sleep-disordered breathing", *Sleep & breathing = Schlaf & Atmung*, vol. 11, no. 1, pp. 1-22.
- Hoffstein, V. & Szalai, J.P. 1993, "Predictive value of clinical features in diagnosing obstructive sleep apnea", *Sleep*, vol. 16, no. 2, pp. 118-122.
- Holty, J.E. & Guilleminault, C. 2010, "Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis", *Sleep medicine reviews*, vol. 14, no. 5, pp. 287-297.
- Horstmann, S., Hess, C.W., Bassetti, C., Gugger, M. & Mathis, J. 2000, "Sleepiness-related accidents in sleep apnea patients", *Sleep*, vol. 23, no. 3, pp. 383-389.
- Iber, C., Ancoli-Israel, S., Chesson, A. & Quan, S. 2007, "for the American Academy of Sleep Medicine. Westchester, Ill: American Academy of Sleep Medicine; 2007. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.", .
- Imadojemu, V.A., Gleeson, K., Quraishi, S.A., Kunselman, A.R., Sinoway, L.I. & Leuenberger, U.A. 2002, "Impaired vasodilator responses in obstructive sleep apnea are improved with continuous positive airway pressure therapy", *American journal of respiratory and critical care medicine*, vol. 165, no. 7, pp. 950-953.
- Imadojemu, V.A., Mawji, Z., Kunselman, A., Gray, K.S., Hogeman, C.S. & Leuenberger, U.A. 2007, "Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy", *Chest*, vol. 131, no. 5, pp. 1406-1413.

- Ip, M.S., Tse, H.F., Lam, B., Tsang, K.W. & Lam, W.K. 2004, "Endothelial function in obstructive sleep apnea and response to treatment", *American journal of respiratory and critical care medicine*, vol. 169, no. 3, pp. 348-353.
- Javaheri, S. 2006, "Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report", *International journal of cardiology*, vol. 106, no. 1, pp. 21-28.
- Javaheri, S., Caref, E.B., Chen, E., Tong, K.B. & Abraham, W.T. 2011, "Sleep apnea testing and outcomes in a large cohort of Medicare beneficiaries with newly diagnosed heart failure", *American journal of respiratory and critical care medicine*, vol. 183, no. 4, pp. 539-546.
- Javaheri, S., Javaheri, S. & Javaheri, A. 2013, "Sleep apnea, heart failure, and pulmonary hypertension", *Current heart failure reports*, vol. 10, no. 4, pp. 315-320.
- Johansson, K., Hemmingsson, E., Harlid, R., Trolle Lagerros, Y., Granath, F., Rossner, S. & Neovius, M. 2011, "Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study", *BMJ (Clinical research ed.)*, vol. 342, pp. d3017.
- Johansson, K., Neovius, M., Lagerros, Y.T., Harlid, R., Rossner, S., Granath, F. & Hemmingsson, E. 2009, "Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial", *BMJ (Clinical research ed.)*, vol. 339, pp. b4609.
- Johansson, L. & Bende, M. 2007, "Excessive obesity is related to daily symptoms of nasal blockage: the Skovde population-based study", *Rhinology*, vol. 45, no. 3, pp. 205-207.
- Johns, M.W. 1991, "A new method for measuring daytime sleepiness: the Epworth sleepiness scale", *Sleep*, vol. 14, no. 6, pp. 540-545.
- Johnston, C.D., Gleadhill, I.C., Cinnamond, M.J., Gabbey, J. & Burden, D.J. 2002, "Mandibular advancement appliances and obstructive sleep apnoea: a randomized clinical trial", *European journal of orthodontics*, vol. 24, no. 3, pp. 251-262.
- Juniper, E.F., Thompson, A.K., Ferrie, P.J. & Roberts, J.N. 2000, "Development and validation of the mini Rhinoconjunctivitis Quality of Life Questionnaire", *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*, vol. 30, no. 1, pp. 132-140.
- Juonala, M., Kahonen, M., Laitinen, T., Hutri-Kahonen, N., Jokinen, E., Taittonen, L., Pietikainen, M., Helenius, H., Viikari, J.S. & Raitakari, O.T. 2008, "Effect of age and sex on carotid intima-media thickness, elasticity and brachial endothelial function in healthy adults: the cardiovascular risk in Young Finns Study", *European heart journal*, vol. 29, no. 9, pp. 1198-1206.

- Jurado-Gamez, B., Fernandez-Marin, M.C., Gomez-Chaparro, J.L., Munoz-Cabrera, L., Lopez-Barea, J., Perez-Jimenez, F. & Lopez-Miranda, J. 2011, "Relationship of oxidative stress and endothelial dysfunction in sleep apnoea", *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*, vol. 37, no. 4, pp. 873-879.
- Kajaste, S., Brander, P.E., Telakivi, T., Partinen, M. & Mustajoki, P. 2004, "A cognitive-behavioral weight reduction program in the treatment of obstructive sleep apnea syndrome with or without initial nasal CPAP: a randomized study", *Sleep medicine*, vol. 5, no. 2, pp. 125-131.
- Kajaste, S., Telakivi, T., Mustajoki, P., Pihl, S. & Partinen, M. 1994, "Effects of a cognitive-behavioural weight loss programme on overweight obstructive sleep apnoea patients", *Journal of sleep research*, vol. 3, no. 4, pp. 245-249.
- Kanagala, R., Murali, N.S., Friedman, P.A., Ammash, N.M., Gersh, B.J., Ballman, K.V., Shamsuzzaman, A.S. & Somers, V.K. 2003, "Obstructive sleep apnea and the recurrence of atrial fibrillation", *Circulation*, vol. 107, no. 20, pp. 2589-2594.
- Kansanen, M., Vanninen, E., Tuunainen, A., Pesonen, P., Tuononen, V., Hartikainen, J., Mussalo, H. & Uusitupa, M. 1998, "The effect of a very low-calorie diet-induced weight loss on the severity of obstructive sleep apnoea and autonomic nervous function in obese patients with obstructive sleep apnoea syndrome", *Clinical physiology (Oxford, England)*, vol. 18, no. 4, pp. 377-385.
- Kato, M., Roberts-Thomson, P., Phillips, B.G., Haynes, W.G., Winnicki, M., Accurso, V. & Somers, V.K. 2000, "Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea", *Circulation*, vol. 102, no. 21, pp. 2607-2610.
- Kemppainen, T., Ruoppi, P., Seppa, J., Sahlman, J., Peltonen, M., Tukiainen, H., Gylling, H., Vanninen, E. & Tuomilehto, H. 2008, "Effect of weight reduction on rhinometric measurements in overweight patients with obstructive sleep apnea", *American Journal of Rhinology*, vol. 22, no. 4, pp. 410-415.
- Kendzerska, T., Gershon, A.S., Hawker, G., Leung, R.S. & Tomlinson, G. 2014, "Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study", *PLoS medicine*, vol. 11, no. 2, pp. e1001599.
- Kezirian, E.J., Goding, G.S., Jr, Malhotra, A., O'Donoghue, F.J., Zammit, G., Wheatley, J.R., Catcheside, P.G., Smith, P.L., Schwartz, A.R., Walsh, J.H., Maddison, K.J., Claman, D.M., Huntley, T., Park, S.Y., Campbell, M.C., Palme, C.E., Iber, C., Eastwood, P.R., Hillman, D.R. & Barnes, M. 2014, "Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes", *Journal of sleep research*, vol. 23, no. 1, pp. 77-83.

- Kimoff, R.J. 1996, "Sleep fragmentation in obstructive sleep apnea", *Sleep*, vol. 19, no. 9 Suppl, pp. S61-6.
- Kirkness, J.P., Schwartz, A.R., Schneider, H., Punjabi, N.M., Maly, J.J., Laffan, A.M., McGinley, B.M., Magnuson, T., Schweitzer, M., Smith, P.L. & Patil, S.P. 2008, "Contribution of male sex, age, and obesity to mechanical instability of the upper airway during sleep", *Journal of applied physiology (Bethesda, Md.: 1985)*, vol. 104, no. 6, pp. 1618-1624.
- Kjaergaard, T., Cvancarova, M. & Steinsvaag, S.K. 2010, "Smoker's nose: structural and functional characteristics", *The Laryngoscope*, vol. 120, no. 7, pp. 1475-1480.
- Kohler, M., Craig, S., Nicoll, D., Leeson, P., Davies, R.J. & Stradling, J.R. 2008a, "Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea", *American journal of respiratory and critical care medicine*, vol. 178, no. 9, pp. 984-988.
- Kohler, M., Pepperell, J.C., Casadei, B., Craig, S., Crosthwaite, N., Stradling, J.R. & Davies, R.J. 2008b, "CPAP and measures of cardiovascular risk in males with OSAS", *The European respiratory journal*, vol. 32, no. 6, pp. 1488-1496.
- Kotecha, B.T. & Hall, A.C. 2014, "Role of surgery in adult obstructive sleep apnoea", *Sleep medicine reviews*, .
- Krishnan, V., Dixon-Williams, S. & Thornton, J.D. 2014, "Where there is smoke...there is sleep apnea: exploring the relationship between smoking and sleep apnea", *Chest*, vol. 146, no. 6, pp. 1673-1680.
- Kushida, C.A., Efron, B. & Guilleminault, C. 1997, "A predictive morphometric model for the obstructive sleep apnea syndrome", *Annals of Internal Medicine*, vol. 127, no. 8 Pt 1, pp. 581-587.
- La Rovere, M.T., Bigger, J.T., Jr, Marcus, F.I., Mortara, A. & Schwartz, P.J. 1998, "Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators", *Lancet*, vol. 351, no. 9101, pp. 478-484.
- La Rovere, M.T., Maestri, R., Robbi, E., Caporotondi, A., Guazzotti, G., Febo, O. & Pinna, G.D. 2011, "Comparison of the prognostic values of invasive and noninvasive assessments of baroreflex sensitivity in heart failure", *Journal of hypertension*, vol. 29, no. 8, pp. 1546-1552.
- La Rovere, M.T., Pinna, G.D., Hohnloser, S.H., Marcus, F.I., Mortara, A., Nohara, R., Bigger, J.T., Jr, Camm, A.J., Schwartz, P.J. & ATRAMI Investigators. Autonomic Tone and Reflexes After Myocardial Infarction 2001, "Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials", *Circulation*, vol. 103, no. 16, pp. 2072-2077.

La Rovere, M.T. & Schwartz, P.J. 1997, "Baroreflex sensitivity as a cardiac and arrhythmia mortality risk stratifier", *Pacing and clinical electrophysiology : PACE*, vol. 20, no. 10 Pt 2, pp. 2602-2613.

Laitinen, L.A., Anttalainen, U., Pietinalho, A., Hamalainen, P., Koskela, K. & Expert Advisory Group Listed in Foreword 2003, "Sleep apnoea: Finnish National guidelines for prevention and treatment 2002-2012", *Respiratory medicine*, vol. 97, no. 4, pp. 337-365.

Laitinen, T., Hartikainen, J., Vanninen, E., Niskanen, L., Geelen, G. & Lansimies, E. 1998, "Age and gender dependency of baroreflex sensitivity in healthy subjects", *Journal of applied physiology (Bethesda, Md.: 1985)*, vol. 84, no. 2, pp. 576-583.

Lavie, L. 2003, "Obstructive sleep apnoea syndrome--an oxidative stress disorder", *Sleep medicine reviews*, vol. 7, no. 1, pp. 35-51.

Lavie, L. & Lavie, P. 2009, "Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link", *The European respiratory journal*, vol. 33, no. 6, pp. 1467-1484.

Lettieri, C.J., Eliasson, A.H. & Greenburg, D.L. 2008, "Persistence of obstructive sleep apnea after surgical weight loss", *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, vol. 4, no. 4, pp. 333-338.

Leuenberger, U., Jacob, E., Sweer, L., Waravdekar, N., Zwillich, C. & Sinoway, L. 1995, "Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia", *Journal of applied physiology (Bethesda, Md.: 1985)*, vol. 79, no. 2, pp. 581-588.

Li, H.Y., Lee, L.A., Wang, P.C., Chen, N.H., Lin, Y. & Fang, T.J. 2008, "Nasal surgery for snoring in patients with obstructive sleep apnea", *The Laryngoscope*, vol. 118, no. 2, pp. 354-359.

Li, H.Y., Wang, P.C., Hsu, C.Y., Cheng, M.L., Liou, C.C. & Chen, N.H. 2005, "Nasal resistance in patients with obstructive sleep apnea", *ORL; journal for oto-rhino-laryngology and its related specialties*, vol. 67, no. 2, pp. 70-74.

Libby, P. 2002, "Inflammation in atherosclerosis", *Nature*, vol. 420, no. 6917, pp. 868-874.

Liistro, G., Rombaux, P., Belge, C., Dury, M., Aubert, G. & Rodenstein, D.O. 2003, "High Mallampati score and nasal obstruction are associated risk factors for obstructive sleep apnoea", *The European respiratory journal*, vol. 21, no. 2, pp. 248-252.

Lin, C.C., Tsan, K.W. & Chen, P.J. 1992, "The relationship between sleep apnea syndrome and hypothyroidism", *Chest*, vol. 102, no. 6, pp. 1663-1667.

Lindstrom, J., Peltonen, M., Eriksson, J.G., Aunola, S., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Uusitupa, M., Tuomilehto, J. & Finnish Diabetes Prevention

Study (DPS) Group 2008, "Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study", *Diabetes care*, vol. 31, no. 5, pp. 857-862.

Lofaso, F., Coste, A., d'Ortho, M.P., Zerah-Lancner, F., Delclaux, C., Goldenberg, F. & Harf, A. 2000, "Nasal obstruction as a risk factor for sleep apnoea syndrome", *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*, vol. 16, no. 4, pp. 639-643.

Loimaala, A., Huikuri, H.V., Koobi, T., Rinne, M., Nenonen, A. & Vuori, I. 2003, "Exercise training improves baroreflex sensitivity in type 2 diabetes", *Diabetes*, vol. 52, no. 7, pp. 1837-1842.

Loke, Y.K., Brown, J.W., Kwok, C.S., Niruban, A. & Myint, P.K. 2012, "Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis", *Circulation. Cardiovascular quality and outcomes*, vol. 5, no. 5, pp. 720-728.

Lu, Y., Li, S., Jin, H., Song, L., Li, Y., Zhong, N. & Zhang, X. 2014, "High nasal resistance may be a result rather than a cause of obstructive sleep apnea", *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, vol. 271, no. 11, pp. 2999-3003.

Lui, M.M. & Sau-Man, M. 2012, "OSA and atherosclerosis", *Journal of thoracic disease*, vol. 4, no. 2, pp. 164-172.

Marin, J.M., Carrizo, S.J., Vicente, E. & Agusti, A.G. 2005, "Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study", *Lancet*, vol. 365, no. 9464, pp. 1046-1053.

Martin, S.E., Mathur, R., Marshall, I. & Douglas, N.J. 1997, "The effect of age, sex, obesity and posture on upper airway size", *The European respiratory journal*, vol. 10, no. 9, pp. 2087-2090.

Martinez-Garcia, M.A., Capote, F., Campos-Rodriguez, F., Lloberes, P., Diaz de Atauri, M.J., Somoza, M., Masa, J.F., Gonzalez, M., Sacristan, L., Barbe, F., Duran-Cantolla, J., Aizpuru, F., Manas, E., Barreiro, B., Mosteiro, M., Cebrian, J.J., de la Pena, M., Garcia-Rio, F., Maimo, A., Zapater, J., Hernandez, C., Grau SanMarti, N., Montserrat, J.M. & Spanish Sleep Network 2013, "Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial", *JAMA : the journal of the American Medical Association*, vol. 310, no. 22, pp. 2407-2415.

Mateika, J.H., Kavey, N.B. & Mitru, G. 1999, "Spontaneous baroreflex analysis in non-apneic snoring individuals during NREM sleep", *Sleep*, vol. 22, no. 4, pp. 461-468.

Mehra, R., Benjamin, E.J., Shahar, E., Gottlieb, D.J., Nawabit, R., Kirchner, H.L., Sahadevan, J., Redline, S. & Sleep Heart Health Study 2006, "Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study", *American journal of respiratory and critical care medicine*, vol. 173, no. 8, pp. 910-916.

Mezzanotte, W.S., Tangel, D.J. & White, D.P. 1992, "Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism)", *The Journal of clinical investigation*, vol. 89, no. 5, pp. 1571-1579.

Miljeteig, H., Hoffstein, V. & Cole, P. 1992, "The effect of unilateral and bilateral nasal obstruction on snoring and sleep apnea", *The Laryngoscope*, vol. 102, no. 10, pp. 1150-1152.

Mortara, A., La Rovere, M.T., Pinna, G.D., Prpa, A., Maestri, R., Febo, O., Pozzoli, M., Opasich, C. & Tavazzi, L. 1997, "Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications", *Circulation*, vol. 96, no. 10, pp. 3450-3458.

Munoz, R., Duran-Cantolla, J., Martinez-Vila, E., Gallego, J., Rubio, R., Aizpuru, F. & De La Torre, G. 2006, "Severe sleep apnea and risk of ischemic stroke in the elderly", *Stroke; a journal of cerebral circulation*, vol. 37, no. 9, pp. 2317-2321.

Muraja-Murro, A., Eskola, K., Kolari, T., Tiihonen, P., Hukkanen, T., Tuomilehto, H., Peltonen, M., Mervaala, E. & Toyras, J. 2013a, "Mortality in middle-aged men with obstructive sleep apnea in Finland", *Sleep & breathing = Schlaf & Atmung*, vol. 17, no. 3, pp. 1047-1053.

Muraja-Murro, A., Kulkas, A., Hiltunen, M., Kupari, S., Hukkanen, T., Tiihonen, P., Mervaala, E. & Toyras, J. 2013b, "The severity of individual obstruction events is related to increased mortality rate in severe obstructive sleep apnea", *Journal of sleep research*, vol. 22, no. 6, pp. 663-669.

Mwenge, G.B., Rombaux, P., Dury, M., Lengele, B. & Rodenstein, D. 2013, "Targeted hypoglossal neurostimulation for obstructive sleep apnoea: a 1-year pilot study", *The European respiratory journal*, vol. 41, no. 2, pp. 360-367.

Nakata, S., Miyazaki, S., Ohki, M., Morinaga, M., Noda, A., Sugiura, T., Sugiura, M., Teranishi, M., Katayama, N. & Nakashima, T. 2007, "Reduced nasal resistance after simple tonsillectomy in patients with obstructive sleep apnea", *American Journal of Rhinology*, vol. 21, no. 2, pp. 192-195.

Narkiewicz, K., van de Borne, P.J., Cooley, R.L., Dyken, M.E. & Somers, V.K. 1998a, "Sympathetic activity in obese subjects with and without obstructive sleep apnea", *Circulation*, vol. 98, no. 8, pp. 772-776.

- Narkiewicz, K., van de Borne, P.J., Montano, N., Dyken, M.E., Phillips, B.G. & Somers, V.K. 1998b, "Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea", *Circulation*, vol. 97, no. 10, pp. 943-945.
- Narkiewicz, K., van de Borne, P.J., Pesek, C.A., Dyken, M.E., Montano, N. & Somers, V.K. 1999, "Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea", *Circulation*, vol. 99, no. 9, pp. 1183-1189.
- Nguyen, P.K., Katikireddy, C.K., McConnell, M.V., Kushida, C. & Yang, P.C. 2010, "Nasal continuous positive airway pressure improves myocardial perfusion reserve and endothelial-dependent vasodilation in patients with obstructive sleep apnea", *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*, vol. 12, pp. 50.
- Nieto, F.J., Herrington, D.M., Redline, S., Benjamin, E.J. & Robbins, J.A. 2004, "Sleep apnea and markers of vascular endothelial function in a large community sample of older adults", *American journal of respiratory and critical care medicine*, vol. 169, no. 3, pp. 354-360.
- Nieto, F.J., Young, T.B., Lind, B.K., Shahar, E., Samet, J.M., Redline, S., D'Agostino, R.B., Newman, A.B., Lebowitz, M.D. & Pickering, T.G. 2000, "Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study", *JAMA : the journal of the American Medical Association*, vol. 283, no. 14, pp. 1829-1836.
- Noda, A., Nakata, S., Koike, Y., Miyata, S., Kitaichi, K., Nishizawa, T., Nagata, K., Yasuma, F., Murohara, T. & Yokota, M. 2007, "Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome", *Hypertension research : official journal of the Japanese Society of Hypertension*, vol. 30, no. 8, pp. 669-676.
- Noda, A., Okada, T., Hayashi, H., Yasuma, F. & Yokota, M. 1993, "24-Hour Ambulatory Blood Pressure Variability in Obstructive Sleep Apnea Syndrome", *Chest*, vol. 103, no. 5, pp. 1343-1347.
- Numminen, J., Ahtinen, M., 3rd, Huhtala, H., Laranne, J. & Rautiainen, M. 2002, "Correlation between rhinometric measurement methods in healthy young adults", *American Journal of Rhinology*, vol. 16, no. 4, pp. 203-208.
- Oflaz, H., Cuhadaroglu, C., Pamukcu, B., Meric, M., Ece, T., Kasikcioglu, E. & Koylan, N. 2006, "Endothelial function in patients with obstructive sleep apnea syndrome but without hypertension", *Respiration; international review of thoracic diseases*, vol. 73, no. 6, pp. 751-756.

Ohga, E., Tomita, T., Wada, H., Yamamoto, H., Nagase, T. & Ouchi, Y. 2003, "Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1", *Journal of applied physiology (Bethesda, Md.: 1985)*, vol. 94, no. 1, pp. 179-184.

Oldenburg, O., Lamp, B., Topfer, V., Faber, L., Teschler, H. & Horstkotte, D. 2007, "Prevalence of sleep-related breathing disorders in ischemic and non-ischemic heart failure", *Deutsche medizinische Wochenschrift (1946)*, vol. 132, no. 13, pp. 661-666.

Oliven, A., Carmi, N., Coleman, R., Odeh, M. & Silbermann, M. 2001, "Age-related changes in upper airway muscles morphological and oxidative properties", *Experimental gerontology*, vol. 36, no. 10, pp. 1673-1686.

Oppenheimer, B.W., Berger, K.I., Segal, L.N., Stabile, A., Coles, K.D., Parikh, M. & Goldring, R.M. 2014, "Airway dysfunction in obesity: response to voluntary restoration of end expiratory lung volume", *PloS one*, vol. 9, no. 2, pp. e88015.

Otsuka, R., Almeida, F.R., Lowe, A.A. & Ryan, F. 2006, "A comparison of responders and nonresponders to oral appliance therapy for the treatment of obstructive sleep apnea", *American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, its Constituent Societies, and the American Board of Orthodontics*, vol. 129, no. 2, pp. 222-229.

Parati, G., Di Rienzo, M., Bonsignore, M.R., Insalaco, G., Marrone, O., Castiglioni, P., Bonsignore, G. & Mancia, G. 1997, "Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep", *Journal of hypertension*, vol. 15, no. 12 Pt 2, pp. 1621-1626.

Patt, B.T., Jarjoura, D., Haddad, D.N., Sen, C.K., Roy, S., Flavahan, N.A. & Khayat, R.N. 2010, "Endothelial dysfunction in the microcirculation of patients with obstructive sleep apnea", *American journal of respiratory and critical care medicine*, vol. 182, no. 12, pp. 1540-1545.

Peppard, P.E., Young, T., Palta, M. & Skatrud, J. 2000, "Prospective study of the association between sleep-disordered breathing and hypertension", *The New England journal of medicine*, vol. 342, no. 19, pp. 1378-1384.

Phillips, C.L., Grunstein, R.R., Darendeliler, M.A., Mihailidou, A.S., Srinivasan, V.K., Yee, B.J., Marks, G.B. & Cistulli, P.A. 2013, "Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial", *American journal of respiratory and critical care medicine*, vol. 187, no. 8, pp. 879-887.

Pillar, G. & Shehadeh, N. 2008, "Abdominal fat and sleep apnea: the chicken or the egg?", *Diabetes care*, vol. 31 Suppl 2, pp. S303-9.

- Prabhakar, N.R. 2002, "Sleep apneas: an oxidative stress?", *American journal of respiratory and critical care medicine*, vol. 165, no. 7, pp. 859-860.
- Priou, P., Gagnadoux, F., Tesse, A., Mastronardi, M.L., Agouni, A., Meslier, N., Racineux, J.L., Martinez, M.C., Trzepizur, W. & Andriantsitohaina, R. 2010, "Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea", *The American journal of pathology*, vol. 177, no. 2, pp. 974-983.
- Punjabi, N.M., Caffo, B.S., Goodwin, J.L., Gottlieb, D.J., Newman, A.B., O'Connor, G.T., Rapoport, D.M., Redline, S., Resnick, H.E., Robbins, J.A., Shahar, E., Unruh, M.L. & Samet, J.M. 2009, "Sleep-disordered breathing and mortality: a prospective cohort study", *PLoS medicine*, vol. 6, no. 8, pp. e1000132.
- Quera-Salva, M.A., Guilleminault, C., Partinen, M. & Jamieson, A. 1988, "Determinants of respiratory disturbance and oxygen saturation drop indices in obstructive sleep apnoea syndrome", *The European respiratory journal*, vol. 1, no. 7, pp. 626-631.
- Rangemark, C., Hedner, J.A., Carlson, J.T., Glerup, G. & Winther, K. 1995, "Platelet function and fibrinolytic activity in hypertensive and normotensive sleep apnea patients", *Sleep*, vol. 18, no. 3, pp. 188-194.
- Redline, S., Kump, K., Tishler, P.V., Browner, I. & Ferrette, V. 1994, "Gender differences in sleep disordered breathing in a community-based sample", *American journal of respiratory and critical care medicine*, vol. 149, no. 3 Pt 1, pp. 722-726.
- Redline, S., Yenokyan, G., Gottlieb, D.J., Shahar, E., O'Connor, G.T., Resnick, H.E., Diener-West, M., Sanders, M.H., Wolf, P.A., Geraghty, E.M., Ali, T., Lebowitz, M. & Punjabi, N.M. 2010, "Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study", *American journal of respiratory and critical care medicine*, vol. 182, no. 2, pp. 269-277.
- Rishi, M.A., Shetty, M., Wolff, A., Amoateng-Adjepong, Y. & Manthous, C.A. 2010, "Atypical antipsychotic medications are independently associated with severe obstructive sleep apnea", *Clinical neuropharmacology*, vol. 33, no. 3, pp. 109-113.
- Romero, E., Krakow, B., Haynes, P. & Ulibarri, V. 2010, "Nocturia and snoring: predictive symptoms for obstructive sleep apnea", *Sleep & breathing = Schlaf & Atmung*, vol. 14, no. 4, pp. 337-343.
- Ryan, C.F. & Love, L.L. 1996, "Mechanical properties of the velopharynx in obese patients with obstructive sleep apnea", *American journal of respiratory and critical care medicine*, vol. 154, no. 3 Pt 1, pp. 806-812.
- Ryan, C.F., Love, L.L., Peat, D., Fleetham, J.A. & Lowe, A.A. 1999, "Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake calibre of the velopharynx", *Thorax*, vol. 54, no. 11, pp. 972-977.

Ryan, S., Ward, S., Heneghan, C. & McNicholas, W.T. 2007, "Predictors of decreased spontaneous baroreflex sensitivity in obstructive sleep apnea syndrome", *Chest*, vol. 131, no. 4, pp. 1100-1107.

Saarelainen, H. "Endothelial function and regulation of vascular tone in normal and complicated pregnancies", Publications of the University of Eastern Finland. *Dissertations in Health Sciences*, Number 125. 2012. 67 p, pp 27.

Sahlman, J., Miettinen, K., Peuhkurinen, K., Seppa, J., Peltonen, M., Herder, C., Punnonen, K., Vanninen, E., Gylling, H., Partinen, M., Uusitupa, M., Tuomilehto, H. & Kuopio Sleep Apnoea Group 2010, "The activation of the inflammatory cytokines in overweight patients with mild obstructive sleep apnoea", *Journal of sleep research*, vol. 19, no. 2, pp. 341-348.

Sahlman, J., Pukkila, M., Seppa, J. & Tuomilehto, H. 2007, "Evolution of mild obstructive sleep apnea after different treatments", *The Laryngoscope*, vol. 117, no. 6, pp. 1107-1111.

Salmenniemi, U., Ruotsalainen, E., Pihlajamaki, J., Vauhkonen, I., Kainulainen, S., Punnonen, K., Vanninen, E. & Laakso, M. 2004, "Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome", *Circulation*, vol. 110, no. 25, pp. 3842-3848.

Salmi, J. 2003, "Body composition assessment with segmental multifrequency bioimpedance method.", *J. Sports Sci. Med., Journal of Sports Science and Medicine*, vol. 2, no. 3, pp. 1-29.

Scanlan, M.F., Roebuck, T., Little, P.J., Redman, J.R. & Naughton, M.T. 2000, "Effect of moderate alcohol upon obstructive sleep apnoea", *The European respiratory journal*, vol. 16, no. 5, pp. 909-913.

Schafer, H., Koehler, U., Ewig, S., Hasper, E., Tasci, S. & Luderitz, B. 1999, "Obstructive sleep apnea as a risk marker in coronary artery disease", *Cardiology*, vol. 92, no. 2, pp. 79-84.

Schellenberg, J.B., Maislin, G. & Schwab, R.J. 2000a, "Physical findings and the risk for obstructive sleep apnea. The importance of oropharyngeal structures", *American journal of respiratory and critical care medicine*, vol. 162, no. 2 Pt 1, pp. 740-748.

Schellenberg, J.B., Maislin, G. & Schwab, R.J. 2000b, "Physical findings and the risk for obstructive sleep apnea. The importance of oropharyngeal structures", *American journal of respiratory and critical care medicine*, vol. 162, no. 2 Pt 1, pp. 740-748.

Schulz, R., Mahmoudi, S., Hattar, K., Sibelius, U., Olschewski, H., Mayer, K., Seeger, W. & Grimminger, F. 2000, "Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy", *American journal of respiratory and critical care medicine*, vol. 162, no. 2 Pt 1, pp. 566-570.

- Schwab, R.J. 2005, "Genetic determinants of upper airway structures that predispose to obstructive sleep apnea", *Respiratory physiology & neurobiology*, vol. 147, no. 2-3, pp. 289-298.
- Schwartz, A.R., Bennett, M.L., Smith, P.L., De Backer, W., Hedner, J., Boudewyns, A., Van de Heyning, P., Ejnell, H., Hochban, W., Knaack, L., Podszus, T., Penzel, T., Peter, J.H., Goding, G.S., Erickson, D.J., Testerman, R., Ottenhoff, F. & Eisele, D.W. 2001, "Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea", *Archives of Otolaryngology--Head & Neck Surgery*, vol. 127, no. 10, pp. 1216-1223.
- Schwartz, A.R., Gold, A.R., Schubert, N., Stryzak, A., Wise, R.A., Permutt, S. & Smith, P.L. 1991, "Effect of weight loss on upper airway collapsibility in obstructive sleep apnea", *The American Review of Respiratory Disease*, vol. 144, no. 3 Pt 1, pp. 494-498.
- Schwartz, D.J., Kohler, W.C. & Karatinos, G. 2005, "Symptoms of depression in individuals with obstructive sleep apnea may be amenable to treatment with continuous positive airway pressure", *Chest*, vol. 128, no. 3, pp. 1304-1309.
- Sert Kuniyoshi, F.H., Singh, P., Gami, A.S., Garcia-Touchard, A., van der Walt, C., Pusalavidyasagar, S., Wright, R.S., Vasquez, E.C., Lopez-Jimenez, F. & Somers, V.K. 2011, "Patients with obstructive sleep apnea exhibit impaired endothelial function after myocardial infarction", *Chest*, vol. 140, no. 1, pp. 62-67.
- Sforza, E., Parchi, P., Contin, M., Cortelli, P. & Lugaresi, E. 1994, "Do autonomic cardiovascular reflexes predict the nocturnal rise in blood pressure in obstructive sleep apnea syndrome?", *Blood pressure*, vol. 3, no. 5, pp. 295-302.
- Shahar, E., Whitney, C.W., Redline, S., Lee, E.T., Newman, A.B., Javier Nieto, F., O'Connor, G.T., Boland, L.L., Schwartz, J.E. & Samet, J.M. 2001, "Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study", *American journal of respiratory and critical care medicine*, vol. 163, no. 1, pp. 19-25.
- Shamsuzzaman, A.S., Gersh, B.J. & Somers, V.K. 2003, "Obstructive sleep apnea: implications for cardiac and vascular disease", *JAMA : the journal of the American Medical Association*, vol. 290, no. 14, pp. 1906-1914.
- Simula, S., Laitinen, T., Vanninen, E., Pajunen, P., Syvanne, M., Hedman, A. & Hartikainen, J. 2013, "Baroreflex sensitivity in asymptomatic coronary atherosclerosis", *Clinical physiology and functional imaging*, vol. 33, no. 1, pp. 70-74.
- Sin, D.D., Mayers, I., Man, G.C. & Pawluk, L. 2002, "Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea: a population-based study", *Chest*, vol. 121, no. 2, pp. 430-435.

Smith, P.L., Gold, A.R., Meyers, D.A., Haponik, E.F. & Bleecker, E.R. 1985, "Weight loss in mildly to moderately obese patients with obstructive sleep apnea", *Annals of Internal Medicine*, vol. 103, no. 6 (Pt 1), pp. 850-855.

Smith, P.L., Wise, R.A., Gold, A.R., Schwartz, A.R. & Permutt, S. 1988, "Upper airway pressure-flow relationships in obstructive sleep apnea", *Journal of applied physiology (Bethesda, Md.: 1985)*, vol. 64, no. 2, pp. 789-795.

Smyth, H.S., Sleight, P. & Pickering, G.W. 1969, "Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity", *Circulation research*, vol. 24, no. 1, pp. 109-121.

Somers, V.K., Dyken, M.E., Clary, M.P. & Abboud, F.M. 1995, "Sympathetic neural mechanisms in obstructive sleep apnea", *The Journal of clinical investigation*, vol. 96, no. 4, pp. 1897-1904.

Somers, V.K., White, D.P., Amin, R., Abraham, W.T., Costa, F., Culebras, A., Daniels, S., Floras, J.S., Hunt, C.E., Olson, L.J., Pickering, T.G., Russell, R., Woo, M., Young, T., American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, American Heart Association Stroke Council, American Heart Association Council on Cardiovascular Nursing & American College of Cardiology Foundation 2008, "Sleep apnea and cardiovascular disease: an American Heart Association/American College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health)", *Circulation*, vol. 118, no. 10, pp. 1080-1111.

Steier, J., Seymour, J., Rafferty, G.F., Jolley, C.J., Solomon, E., Luo, Y., Man, W.D., Polkey, M.I. & Moxham, J. 2011, "Continuous transcutaneous submental electrical stimulation in obstructive sleep apnea: a feasibility study", *Chest*, vol. 140, no. 4, pp. 998-1007.

Strollo, P.J., Jr, Soose, R.J., Maurer, J.T., de Vries, N., Cornelius, J., Froymovich, O., Hanson, R.D., Padhya, T.A., Steward, D.L., Gillespie, M.B., Woodson, B.T., Van de Heyning, P.H., Goetting, M.G., Vanderveken, O.M., Feldman, N., Knaack, L., Strohl, K.P. & STAR Trial Group 2014, "Upper-airway stimulation for obstructive sleep apnea", *The New England journal of medicine*, vol. 370, no. 2, pp. 139-149.

Suh, G.D. 2013, "Evaluation of open midline glossectomy in the multilevel surgical management of obstructive sleep apnea syndrome", *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, vol. 148, no. 1, pp. 166-171.

Sullivan, C.E., Issa, F.G., Berthon-Jones, M. & Eves, L. 1981, "Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares", *Lancet*, vol. 1, no. 8225, pp. 862-865.

Suratt, P.M., McTier, R.F., Findley, L.J., Pohl, S.L. & Wilhoit, S.C. 1992, "Effect of very-low-calorie diets with weight loss on obstructive sleep apnea", *The American Journal of Clinical Nutrition*, vol. 56, no. 1 Suppl, pp. 182S-184S.

Suzuki, Y.J., Jain, V., Park, A.M. & Day, R.M. 2006, "Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases", *Free radical biology & medicine*, vol. 40, no. 10, pp. 1683-1692.

Svatikova, A., Wolk, R., Lerman, L.O., Juncos, L.A., Greene, E.L., McConnell, J.P. & Somers, V.K. 2005, "Oxidative stress in obstructive sleep apnoea", *European heart journal*, vol. 26, no. 22, pp. 2435-2439.

Tagaya, M., Nakata, S., Yasuma, F., Noda, A., Morinaga, M., Yagi, H., Sugiura, M., Teranishi, M. & Nakashima, T. 2010, "Pathogenetic role of increased nasal resistance in obese patients with obstructive sleep apnea syndrome", *American journal of rhinology & allergy*, vol. 24, no. 1, pp. 51-54.

Tan, L.T., Tan, A.K., Hsu, P.P., Loh, I.C., Yuen, H.W., Chan, Y.H. & Lu, P.K. 2013, "Effects of tonsillectomy on sleep study parameters in adult patients with obstructive sleep apnea-a prospective study", *Sleep & breathing = Schlaf & Atmung*, .

Tishler, P.V., Larkin, E.K., Schluchter, M.D. & Redline, S. 2003, "Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing", *JAMA : the journal of the American Medical Association*, vol. 289, no. 17, pp. 2230-2237.

Tounian, P., Aggoun, Y., Dubern, B., Varille, V., Guy-Grand, B., Sidi, D., Girardet, J.P. & Bonnet, D. 2001, "Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study", *Lancet*, vol. 358, no. 9291, pp. 1400-1404.

Tuomilehto, H., Gylling, H., Peltonen, M., Martikainen, T., Sahlman, J., Kokkarinen, J., Randell, J., Tukiainen, H., Vanninen, E., Partinen, M., Tuomilehto, J., Uusitupa, M., Seppa, J. & Kuopio Sleep Apnea Group 2010, "Sustained improvement in mild obstructive sleep apnea after a diet- and physical activity-based lifestyle intervention: postinterventional follow-up", *The American Journal of Clinical Nutrition*, vol. 92, no. 4, pp. 688-696.

Tuomilehto, H., Seppa, J., Uusitupa, M., Peltonen, M., Martikainen, T., Sahlman, J., Kokkarinen, J., Randell, J., Pukkila, M., Vanninen, E., Tuomilehto, J., Gylling, H. & Kuopio Sleep Apnea Group 2014, "The impact of weight reduction in the prevention of the

progression of obstructive sleep apnea: an explanatory analysis of a 5-year observational follow-up trial", *Sleep medicine*, .

Tuomilehto, H., Seppa, J., Uusitupa, M., Tuomilehto, J., Gylling, H. & Kuopio Sleep Apnea Group 2013, "Weight reduction and increased physical activity to prevent the progression of obstructive sleep apnea: A 4-year observational postintervention follow-up of a randomized clinical trial. [corrected]", *JAMA internal medicine*, vol. 173, no. 10, pp. 929-930.

Tuomilehto, H.P., Seppa, J.M., Partinen, M.M., Peltonen, M., Gylling, H., Tuomilehto, J.O., Vanninen, E.J., Kokkarinen, J., Sahlman, J.K., Martikainen, T., Soini, E.J., Randell, J., Tukiainen, H., Uusitupa, M. & Kuopio Sleep Apnea Group 2009, "Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea", *American journal of respiratory and critical care medicine*, vol. 179, no. 4, pp. 320-327.

Ulander, M., Johansson, M.S., Ewaldh, A.E., Svanborg, E. & Brostrom, A. 2014, "Side effects to continuous positive airway pressure treatment for obstructive sleep apnoea: changes over time and association to adherence", *Sleep & breathing = Schlaf & Atmung*, .

Uusitupa, M., Peltonen, M., Lindstrom, J., Aunola, S., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Valle, T.T., Eriksson, J.G., Tuomilehto, J. & Finnish Diabetes Prevention Study Group 2009, "Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study--secondary analysis of the randomized trial", *PloS one*, vol. 4, no. 5, pp. e5656.

Van de Graaff, W.B. 1988, "Thoracic influence on upper airway patency", *Journal of applied physiology (Bethesda, Md.: 1985)*, vol. 65, no. 5, pp. 2124-2131.

Van de Heyning, P.H., Badr, M.S., Baskin, J.Z., Cramer Bornemann, M.A., De Backer, W.A., Dotan, Y., Hohenhorst, W., Knaack, L., Lin, H.S., Maurer, J.T., Netzer, A., Odland, R.M., Oliven, A., Strohl, K.P., Vanderveken, O.M., Verbraecken, J. & Woodson, B.T. 2012, "Implanted upper airway stimulation device for obstructive sleep apnea", *The Laryngoscope*, vol. 122, no. 7, pp. 1626-1633.

Verse, T., Kroker, B.A., Pirsig, W. & Brosch, S. 2000, "Tonsillectomy as a treatment of obstructive sleep apnea in adults with tonsillar hypertrophy", *The Laryngoscope*, vol. 110, no. 9, pp. 1556-1559.

Verse, T., Maurer, J.T. & Pirsig, W. 2002, "Effect of nasal surgery on sleep-related breathing disorders", *The Laryngoscope*, vol. 112, no. 1, pp. 64-68.

Vgontzas, A.N. 2008, "Excessive daytime sleepiness in sleep apnea: it is not just apnea hypopnea index", *Sleep medicine*, vol. 9, no. 7, pp. 712-714.

Vgontzas, A.N., Legro, R.S., Bixler, E.O., Grayev, A., Kales, A. & Chrousos, G.P. 2001, "Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime

sleepiness: role of insulin resistance", *The Journal of clinical endocrinology and metabolism*, vol. 86, no. 2, pp. 517-520.

Virkkula, P., Bachour, A., Hytonen, M., Malmberg, H., Salmi, T. & Maasilta, P. 2005, "Patient- and bed partner-reported symptoms, smoking, and nasal resistance in sleep-disordered breathing", *Chest*, vol. 128, no. 4, pp. 2176-2182.

Virkkula, P., Hytonen, M., Bachour, A., Malmberg, H., Hurmerinta, K., Salmi, T. & Maasilta, P. 2007, "Smoking and improvement after nasal surgery in snoring men", *American Journal of Rhinology*, vol. 21, no. 2, pp. 169-173.

Virkkula, P., Maasilta, P., Hytonen, M., Salmi, T. & Malmberg, H. 2003, "Nasal obstruction and sleep-disordered breathing: the effect of supine body position on nasal measurements in snorers", *Acta Oto-Laryngologica*, vol. 123, no. 5, pp. 648-654.

Vita, J.A. & Keaney, J.F., Jr 2002, "Endothelial function: a barometer for cardiovascular risk?", *Circulation*, vol. 106, no. 6, pp. 640-642.

von Kanel, R. & Dimsdale, J.E. 2003, "Hemostatic alterations in patients with obstructive sleep apnea and the implications for cardiovascular disease", *Chest*, vol. 124, no. 5, pp. 1956-1967.

von Kanel, R., Loreda, J.S., Ancoli-Israel, S. & Dimsdale, J.E. 2006, "Association between sleep apnea severity and blood coagulability: Treatment effects of nasal continuous positive airway pressure", *Sleep & breathing = Schlaf & Atmung*, vol. 10, no. 3, pp. 139-146.

Wang, X., Ouyang, Y., Wang, Z., Zhao, G., Liu, L. & Bi, Y. 2013, "Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies", *International journal of cardiology*, vol. 169, no. 3, pp. 207-214.

Ward Flemons, W. & McNicholas, W.T. 1997, "Clinical prediction of the sleep apnea syndrome", *Sleep medicine reviews*, vol. 1, no. 1, pp. 19-32.

Ward, S., Ryan, S., Mc Nicholas, W.T. & Heneghan, fucC. 2006, "Comparison of baroreflex sensitivity measures for assessing subjects with obstructive sleep apnea", *Conference proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference*, vol. 1, pp. 3572-3575.

Ware, J.C., McBrayer, R.H. & Scott, J.A. 2000, "Influence of sex and age on duration and frequency of sleep apnea events", *Sleep*, vol. 23, no. 2, pp. 165-170.

Weaver, T.E. & Grunstein, R.R. 2008, "Adherence to continuous positive airway pressure therapy: the challenge to effective treatment", *Proceedings of the American Thoracic Society*, vol. 5, no. 2, pp. 173-178.

- Wessendorf, T.E., Thilman, A.F., Wang, Y.M., Schreiber, A., Konietzko, N. & Teschler, H. 2000, "Fibrinogen levels and obstructive sleep apnea in ischemic stroke", *American journal of respiratory and critical care medicine*, vol. 162, no. 6, pp. 2039-2042.
- Wycherley, T.P., Brinkworth, G.D., Keogh, J.B., Noakes, M., Buckley, J.D. & Clifton, P.M. 2010, "Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients", *Journal of internal medicine*, vol. 267, no. 5, pp. 452-461.
- Yaggi, H.K., Concato, J., Kernan, W.N., Lichtman, J.H., Brass, L.M. & Mohsenin, V. 2005, "Obstructive sleep apnea as a risk factor for stroke and death", *The New England journal of medicine*, vol. 353, no. 19, pp. 2034-2041.
- Yagi, H., Nakata, S., Tsuge, H., Yasuma, F., Noda, A., Morinaga, M., Tagaya, M. & Nakashima, T. 2009, "Morphological examination of upper airway in obstructive sleep apnea", *Auris, Nasus, Larynx*, vol. 36, no. 4, pp. 444-449.
- Yoshihisa, A., Owada, T., Hoshino, Y., Miyata, M., Misaka, T., Sato, T., Suzuki, S., Sakamoto, N., Sugimoto, K., Kunii, H., Nakazato, K., Suzuki, H., Saitoh, S., Ishibashi, T. & Takeishi, Y. 2010, "Flow-mediated dilatation identifies impaired endothelial function in patients with sleep apnea syndrome", *Fukushima journal of medical science*, vol. 56, no. 2, pp. 115-120.
- Young, T., Finn, L. & Kim, H. 1997, "Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group", *The Journal of allergy and clinical immunology*, vol. 99, no. 2, pp. S757-62.
- Young, T., Finn, L., Peppard, P.E., Szklo-Coxe, M., Austin, D., Nieto, F.J., Stubbs, R. & Hla, K.M. 2008, "Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort", *Sleep*, vol. 31, no. 8, pp. 1071-1078.
- Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S. & Badr, S. 1993, "The occurrence of sleep-disordered breathing among middle-aged adults", *The New England journal of medicine*, vol. 328, no. 17, pp. 1230-1235.
- Young, T., Peppard, P., Palta, M., Hla, K.M., Finn, L., Morgan, B. & Skatrud, J. 1997, "Population-based study of sleep-disordered breathing as a risk factor for hypertension", *Archives of Internal Medicine*, vol. 157, no. 15, pp. 1746-1752.
- Young, T., Peppard, P.E. & Gottlieb, D.J. 2002, "Epidemiology of obstructive sleep apnea: a population health perspective", *American journal of respiratory and critical care medicine*, vol. 165, no. 9, pp. 1217-1239.
- Young, T., Skatrud, J. & Peppard, P.E. 2004, "Risk factors for obstructive sleep apnea in adults", *JAMA : the journal of the American Medical Association*, vol. 291, no. 16, pp. 2013-2016.

Zhao, Z.H., Sullivan, C., Liu, Z.H., Luo, Q., Xiong, C.M., Ni, X.H., Zhang, J., Zhang, S. & Yang, Y.J. 2007, "Prevalence and clinical characteristics of sleep apnea in Chinese patients with heart failure", *International journal of cardiology*, vol. 118, no. 1, pp. 122-123.

Ziegler, M.G., Nelesen, R.A., Mills, P.J., Ancoli-Israel, S., Clausen, J.L., Watkins, L. & Dimsdale, J.E. 1995, "The effect of hypoxia on baroreflexes and pressor sensitivity in sleep apnea and hypertension", *Sleep*, vol. 18, no. 10, pp. 859-865.

Zonato, A.I., Martinho, F.L., Bittencourt, L.R., de Oliveira Campones Brasil, O., Gregorio, L.C. & Tufik, S. 2005, "Head and neck physical examination: comparison between nonapneic and obstructive sleep apnea patients", *The Laryngoscope*, vol. 115, no. 6, pp. 1030-1034.

ORIGINAL PUBLICATIONS (I-III)

HENRY BLOMSTER
*Cardiovascular risk
factors in mild obstructive
sleep apnea – the outcome
of lifestyle intervention with
weight reduction*

Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity. Endothelial dysfunction (ED) and depressed baroreflex sensitivity (BRS) are possible mechanisms involved in cardiovascular complications of OSA. ED and BRS in mild OSA patients and the effects of 1 year lifestyle intervention on ED and on nasal resistance were examined. Endothelial function and BRS were both well preserved in mild OSA. Nasal resistance improved more in patients who were cured from OSA.



UNIVERSITY OF
EASTERN FINLAND

PUBLICATIONS OF THE UNIVERSITY OF EASTERN FINLAND
Dissertations in Health Sciences

ISBN 978-952-61-1945-8

ISSN 1798-5706