Obstructive Sleep Apnea in Coronary Artery Disease:

Impact of CPAP treatment

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2016

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ISBN 978-91-628-9473-3 (hard copy)
ISBN 978-91-628-9474-0 (e-pub)
http://hdl.handle.net/2077/38351

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Cover illustration by Kerstin Glantz

Printed by Kompendiet, Gothenburg, Sweden 2016

To my beloved family,
Christer,
Hillevi, Kerstin and Elisabeth

ABSTRACT

Background: Obstructive sleep apnea (OSA) is common in patients with coronary artery disease (CAD). Earlier research has not investigated whether CAD patients should be screened for OSA and subsequently treated with continuous positive airway pressure (CPAP) even if they have no symptoms. This thesis investigated the prevalence and predictors of OSA in a newly revascularized CAD cohort, and further addressed the relationship between OSA and diastolic dysfunction among patients with left ventricular ejection fraction (LVEF) ≥50%. Moreover, the impact of CPAP treatment on diastolic function as well as on long-term cardiovascular outcomes was evaluated in patients with CAD and non-sleepy OSA.

Methods: Patients who underwent a mechanical revascularization in Skaraborg, Sweden, between September 2005 and November 2010 (n=1,291) were invited to participate. Anthropometrics and medical history were obtained, ambulatory sleep recording was performed, and all subjects completed the Epworth Sleepiness Scale (ESS) questionnaire. OSA diagnosis was based on an apnea–hypopnea index (AHI) ≥15/h, and no OSA was defined as an AHI <5/h. Left atrial diameter, myocardial relaxation velocity (é), and the ratio of early diastolic mitral flow to myocardial relaxation velocity (E/é) were evaluated as echocardiographic diastolic function parameters at baseline, three months, and one year. The long-term primary endpoint was the first event of new revascularization, myocardial infarction, stroke or cardiovascular death. Intention-to-treat (ITT) and on-treatment analyses were performed for evaluation of the impact of CPAP in the randomized controlled arm of the CAD patients with non-sleepy OSA (ESS score <10).

Results: OSA was found among 422 of the 662 study participants (64%), of whom 62% were non-sleepy. The prevalence of OSA was higher than the prevalence of obesity, hypertension, diabetes, and current smoking. In the subgroup of patients with preserved LVEF, worse diastolic function was more common in the OSA group (54% vs 41%, p=0.019). OSA was significantly associated with worse diastolic function after adjustment for confounding factors. Regarding the impact of CPAP treatment, there was no significant improvement in any of the diastolic function parameters in non-sleepy OSA patients in the ITT analysis. Neither were long-term adverse outcomes reduced significantly in the ITT population (n=244) during a median follow-up of 57 months. In the on-treatment analysis, CPAP usage of at least four hours per night was associated with an increase in é tissue velocity after adjustment for the confounding factors (odds ratio 2.3, 95% confidence interval (CI) 1.0–4.9; p=0.039). This level of CPAP usage was associated also with a risk reduction (hazard ratio 0.29; 95% CI 0.10–0.86; p=0.026) in long-term adverse outcomes after adjustment for the baseline comorbidities.

Conclusions: The prevalence of unrecognized OSA in this CAD cohort was higher than previously reported, and OSA was associated with worse diastolic function among patients with preserved LVEF. Routine prescription of CPAP to CAD patients with non-sleepy OSA had no beneficial impact on diastolic function and long-term outcomes in the ITT population. However, there was a significant risk reduction after adjustment for baseline comorbidities and CPAP adherence. These findings need to be further explored in larger clinical cohorts with more homogeneous CAD populations.

ISBN 978-91-628-9473-3 (hard copy) http://hdl.handle.net/2077/38351
ISBN 978-91-628-9474-0 (e-pub)

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I Peker Y, Glantz H, Thunström E, Kallryd A, Herlitz J, Ejdebäck J. Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea - RICCADSA trial.
Scand Cardiovasc J 2009; 43:24-31.

II Glantz H, Thunström E, Herlitz J, Cederin B, Nasic S, Ejdebäck J, Peker Y. Occurrence and Predictors of Obstructive Sleep Apnea in a Revascularized Coronary Artery Disease Cohort.
Ann Am Thorac Soc 2013; 10: 350-356.

III Glantz H, Thunström E, Johansson MC, Wallentin Guron C, Uzel H, Ejdebäck J, Nasic S, Peker Y. Obstructive sleep apnea is independently associated with worse diastolic function in coronary artery disease.
Sleep Med 2015; 16:160-167.

IV Glantz H, Johansson MC, Thunström E, Wallentin Guron C, Uzel H, Saygin M, Herlitz J, Peker Y. Effect of Positive Airway Pressure on Diastolic Function in Coronary Artery Disease Patients with Non-Sleepy Obstructive Sleep Apena.
In manuscript

V Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Non-Sleepy Obstructive Sleep Apnea: The RICCADSA Randomized Controlled Trial.
Am J Respir Crit Care Med. 2016 Feb 25. [Epub ahead of print]

CONTENTS

ABBREVIATIONS

ACCF	American college of cardiology foundation
AHA	American heart association
AHI	Apnea–hypopnea index
AMI	Acute myocardial infarction
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CCU	Coronary care units
CAD	Coronary artery disease
CSA	Central sleep apnea
CPAP	Continuous positive airway pressure
CSR	Cheyne stroke respiration
CVD	Cardiovascular disease
DD	Diastolic dysfunction
ECG	Electrocardiogram
EEG	Electroencephalography
EMG	Electromyography
ESC	European society of cardiology
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
ICEC	Independent clinical event committee
ITT	Intention to treat
LVEF	Left ventricular dysfunction
LVFP	Left ventricular filling pressure
MSLT	Multiple sleep latency test
MI	Myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
OR	Odds ratio
PCI	Percutaneous coronary intervention

PG	Polygraphy
PSG	Polysomnography
RICCADSA	Randomized intervention with CPAP in coronary artery disease and sleep apnea
RCT	Randomized controlled trial
REM	Rapid eye movements
SD	Standard deviation
UPPP	Uvulopalatopharyngoplasty
WHO	World health organization

DEFINITIONS IN SHORT

Apnea	Two criteria must be fulfilled: (1) *Amplitude reduction:* There is a drop in the peak thermal sensor excursion by ≥90% of baseline. (2) The *duration* of the event is at least 10 seconds.
Hypopnea (based on the American Academy of Sleep Medicine guidelines from 1999)	Criterion (1) or (2) must be fulfilled in combination with criterion (3): (1) A clear decrease (≥50%) from baseline in the amplitude of a valid measure of breathing during sleep. (2) A clear amplitude reduction on a validated measure of breathing during sleep that does not reach 50% criterion but is associated with either an oxygen desaturation of ≥4% and/or an arousal. (3) The event lasts 10 seconds or longer.
AHI	The apnea–hypopnea index is based on the number of apneas and/or hypopneas per hour of registered sleep.
ODI	The oxygen desaturation index is based on the number of desaturations (≥4%) per hour of sleep time.
OSA	Obstructive sleep apnea is a laboratory diagnosis with three levels: mild (AHI 5-14.9/h), moderate (AHI 15-29.9/h), and severe (AHI ≥30/h).

INTRODUCTION

Coronary artery disease (CAD) is still one of the leading causes of morbidity and mortality in Western countries despite the advances in medical treatment and cardiovascular prevention methods[1]. An increasing number of patients with CAD undergo percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Though, the risk of relapse is in CAD in the years following the intervention is considerable[2,3]. Many of the traditional risk factors contributing to adverse outcomes in these patients are controlled. Both the European Society of Cardiology and the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) guidelines on secondary prevention recommend smoking cessation, blood pressure control, treatment of hyperlipidemia, increasing physical activity, management of obesity and diabetes mellitus, medical treatment (antiplatelet agents, anticoagulants, beta-blockers, renin-angiotensin-aldosterone system blockers), influenza vaccination, management of depression, and cardiovascular rehabilitation[4,5]. Many patients with CAD experience sleep-related problems such as insomnia and disturbed circadian rhythms[6]. Previous research has suggested that patients with CAD have multiple complicating factors such as side effects of drugs and difficulties coping with stress, in addition to their CAD disease, resulting in non-restorative sleep and daytime sleepiness[7].

Obstructive sleep apnea (OSA), which is characterized by intermittent episodes of complete or partial upper airway collapse (apnea/hypopnea) during sleep with large negative oscillations in intrathoracic pressure followed by recurrent hypoxemia[8] is also a common condition in CAD patients[9]. Despite the accumulating research evidence regarding the adverse cardiovascular effects of OSA, this condition has largely been neglected in the treatment of patients with CAD.

Elimination of obstructive apneas and hypopneas via nasal continuous positive airway pressure (CPAP) is the first-line treatment for OSA with daytime sleepiness, reducing these symptoms and improving quality of life. However, the majority of CAD patients with OSA do not experience daytime sleepiness, and there is currently no clearly established rationale for treatment of such patients. Observational studies have demonstrated that CPAP is beneficial in patients with CAD and OSA who are adherent to treatment[10-12]. There are many published short-term randomized controlled trials (RCTs) with CPAP, especially in OSA patients with daytime sleepiness and systemic hypertension, and CPAP has been shown to effectively lower blood pressure (BP) in these patients[13,14]. But trials on those without daytime sleepiness suggest no benefit of CPAP[15-17], with one exception that demonstrated a significant BP reduction in patients with newly diagnosed hypertension[18]. Overall, there is good evidence to suggest that symptomatic OSA patients should be treated with CPAP to reduce daytime sleepiness[19] and the risk of traffic accidents[20] , and also to lower BP in hypertensive OSA patients[13,14,18,21]. Nevertheless, at the initial phase of this work in 2005 and during the time of collection of data and writing this thesis, there was a lack of evidence from long-term prospective RCTs to determine whether patients with CAD and concomitant non-sleepy OSA should be offered CPAP treatment to reduce cardiovascular morbidity and mortality.

Obstructive sleep apnea

Historical remarks

According to a historical review of the western literature by Kryger[22], the first description of obstructive sleep apnea (OSA) was written by Alelinaus in 1666 . Dionysius, who was a tyrant of Heracleia in the era of Alexander the Great, was described as an unusually fat man with a great difficulty in breathing. When he slept, it was impossible to wake him without piercing his flesh with pins. The novelist Charles Dickens wrote the first detailed description of OSA in *The Posthumous Papers of the Pickwick Club*[23] (1837): "Most of the time, Joe is sleeping or eating. He has a voracious appetite. He snores loudly. He clearly has pathological sleepiness and he is difficult to arouse from sleep".

Important knowledge in the 20th century was introduced by Berger[24], 1930, with electroencephalography (EEG) regarding differences between wakefulness and sleep. The introduction of the electrooculogram (EOG) in 1953 by Kleitman and Aserinsky[25] meant a first description of slow eye movements and rapid eye movements (REM) during sleep. Dement and Kleitman[26] were the ones who identified the pattern of REM as well as non-REM (NREM) sleep. In a clinical description Burwell et al.[27] used the term "Pickwickian syndrome", a patient with gross obesity, sleepiness and breathing disturbance. Though, it was then reported that OSA occurred also in individuals without obesity[28].

When OSA was first recognized, the patients with a severe, life-threatening form of the condition were treated by tracheostomy[29]. However, this was neither indicated nor a feasible way to treat all patients with OSA. Uvulopalatopharyngoplasty (UPPP), described by Fujita and coworkers in 1981[30], soon became the main surgical approach. The new non-invasive treatment CPAP, developed by Sullivan in the early 80ths, as well as the development of ambulatory sleep recordings has brought great improvements to the field[31]. The first epidemiological definition of OSA as a risk factor for hypertension was reported from the Wisconsin Sleep Cohort in 2000[32], and as a risk factor for CVD, from the Gothenburg Sleep Cohort in 2002[33].

Definitions

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of airflow cessation (apnea) or airflow reduction (hypopnea) despite persistent thoracic and abdominal respiratory efforts during sleep. These episodes result in hypoventilation as well as hypoxemia, and provoke awakenings (recurrent arousals) that restore pharyngeal dilator muscle tone and airflow. An apnea is defined as a cessation of airflow for at least 10 seconds[28], and hypopnea was originally defined as a reduction in airflow of at least 50% for at least 10 seconds on an overnight polysomnography (PSG)[34]. The definition of hypopnea has been revised many times since then in accordance with technical developments (see below in the section Diagnostic procedures). The severity of sleep apnea is represented by the apnea–hypopnea index (AHI), quantified as the average number of apneas and hypopneas per hour of sleep. Although AHI has gained general acceptance, other measures, such as the oxygen desaturation index (ODI) and

number of arousals, have also been widely used. An AHI of 5 events per hour is the suggested cut-off limit for a diagnosis of OSA, irrespective of clinical symptoms[35].

Pathogenesis

The pathogenesis of OSA is still not completely understood. The airway may collapse when the pharyngeal intraluminal pressure exceeds the forces that dilate the pharynx[36]. Consequently, the activity of the upper airway muscles during inspiration, as well as the upper airway size and the physical properties of the pharyngeal wall, determine the state of the upper airway in sleep. Therefore all factors that can influence airway size and pharyngeal wall strain may contribute to development of OSA. Factors that have this effects, and thus are risk factors for the development of OSA are obesity, alcohol consumption, old age, upper-air-way anomalies and male gender, smoking and genetics.

Arousal

Arousal, which is a physiological state of being awake in EEG terms, is an important protective mechanism for upper airway patency. Usually, arousal has been defined as a 3 s period of alpha rhythm, accompanied by an increase in electromyography (EMG) tone[37]. EEG arousals can occur at the end of an apnea period, and are consistently accompanied by rises in blood pressure; they are described as autonomic or brain stem arousal response[38]. Acoustically induced arousals from normal sleep have been shown to cause a similar but smaller rises in blood pressure, but even these brief events can contribute to excessive daytime sleepiness when induced regularly throughout the night[39]. Arousal can also be induced chemically; especially hypercapnia has been proposed to be a potent arousal stimulus, with most events occurring after a slight increase in arterial carbon dioxide tension[40]. However, the arousal response does not lead to complete awakening, but may rather cause a shift from a deeper sleep stage to a lighter stage.

Risk factors

Upper airway anatomy - A narrow upper airway due to an abnormality of facial structure, or increased volume of the oropharyngeal soft tissue structures[41,42], or nasal septum deviation may reduce airflow and predispose an individual to OSA[43].

Obesity - Several published epidemiological reports have found obesity to be significantly associated with an increased risk of OSA[44]. In the Wisconsin Sleep Cohort Study, a BMI increment of one standard deviation (5.7 kg/m^2) was associated with an odds ratio (OR) of 4.2 for OSA[45]. Neck circumference and waist-hip ratio have also been proposed as predictors of the risk of OSA[46-48].

Age - During childhood, tonsillar hypertrophy or facial malformation, are the main courses of OSA. In the middle age span, 45 to 65 years there is a peak in prevalence. In an early study the prevalence of OSA was found to be 62% in people aged 65 and over, and age has been suggested to increase the risk for OSA based on the PSG criteria regardless of daytime symptoms[49].

Sex - Previous data suggest that the proportion of men to women with OSA in the general population is 2.5:1. The OSA prevalence increases in women after the menopause, suggesting a protective effect of female sex hormones or a promoting effect of male hormones[45].

Smoking - An independent association between smoking and OSA (OR=4.4) was reported by Wetter et al. in the Wisconsin cohort[50].

Alcohol - Early studies have shown that alcohol worsen OSA by impairing both the pharyngeal dilator muscle function and the arousal response to apneas[51].

Genetics - OSA symptoms have been reported more frequently in relatives of OSA patients than in the general population and this has been supported by sleep laboratory evidence[52,53]. A recent study has also shown that the craniofacial structures that have been associated with OSA are heritable[54]. It has been suggested that optimizing phenotyping strategies is critical in the case of OSA, for which intermediate traits such as obesity and craniofacial features may prove to be more tractable for genetic studies[55]. Consequently, studies addressing sleep apnea pheno- and genotypic variations are of great importance for a better understanding of the risk of CVD in OSA patients.

Central sleep apnea-cheyne stokes respiration

A particular breathing pattern that is seen in heart failure is called Cheyne-stokes respiration (CSR), which is a crescendo–decrescendo breathing, separated by periods of central sleep apneas (CSA). This pattern is suggested to be a consequence of cardiac failure[56]. The patients with CSA-CSR are generally described as older and non-obese with at least moderate to severe left ventricular dysfunction (LVEF<30). The risk factors for development of CSR in heart failure patients are recognized as male gender, hypocapnia, atrial fibrillation and advanced age[57]. Hyperventilation is suggested to be the crucial point of the mechanisms that lead to CSA-CSR. Hyperventilation develops as a consequence of unstable breathing, increased chemosensitivity, pulmonary edema, reduced cerebrovascular blood flow, decreased cardiac output, and prolonged circulation time[58].

Diagnostic procedure - polysomnography vs cardiorespiratory polygraphy

Polysomnography (PSG) is the gold standard method for the diagnosis of OSA, and it gives a good assessment of sleep stages due to the inclusion of EEG. This sleep recording means an overnight sleep in hospital, and the evaluation is resource-demanding. Cardiorespiratory polygraphy (PG) does not include EEG, and the estimated sleep time becomes self-reported. The portable equipment can be used at home, and the assessment is less time consuming. Polygraphy is widely used for a much larger group of patients, and there has been a rapid technical development in the diagnostic procedures for this kind of limited recordings improving specificity and sensitivity[59]. However, PG may be insufficient compared to PSG to diagnose OSA in symptomatic patients when the hypopneas are mainly associated with arousals without desaturations. In such cases with excessive daytime sleepiness, when PG is normal, a full-night PSG is recommended[60].

Apnea hypopnea index

The first definition of apnea was based on a complete cessation of airflow for at least 10 seconds by Guilleminault[28], and hypopneas as at least a 50% reduction in airflow for at least 10 seconds[34]. The American Academy of Sleep Medicine (AASM) task force recommendations were published in 1999, providing diagnostic criteria and severity ratings for OSA in order to "facilitate comparability of studies for research purposes and their associated clinical syndromes". At the time of the planning of this thesis, the practical management of OSA patients were based on those criteria, also called "Chicago criteria", as described in Table 1. The first revision of the hypopnea definitions was published in 2007 with two possibilities, one recommended (2007 *recommended*) and one alternative (2007 *alternative*). Comparison of those criteria from 1999 with the new ones from 2007 suggested that many patients with clinical symptoms of OSA would not get the diagnosis if the 2007 recommended guidelines were applied:[61] approximately 40% of those who had OSA according to the Chicago criteria would not get a diagnosis of OSA if 2007 *recommended* was used; and 25% would not get the diagnosis if 2007 *alternative* was used, if apnea hypopnea index (AHI) of at least 5/h was set. This was mainly based on the fact that there was no demand regarding desaturation for a hypopnea, if the nasal airflow has been reduced at least 50%. The AASM Task Force revised the guidelines again in 2012, to score an at least 30% drop in the nasal pressure for 10 seconds or more, associated with at least 3% oxygen desaturation and/or an arousal (Table 1). The clinical changes in the diagnostic definition of OSA which have been made during the course of this study is important to empasize to be able to evaluate the result in comparison under current practice for sleep scoring in the daily management of patients at sleep clinics.

Oxygen desaturation index

The oxygen desaturation index (ODI) was also used as diagnostic criteria in earlier years, especially when using pulse-oximetry as a single screening method. ODI was calculated as the number of significant desaturations (a drop of at least 4% from the immediately preceding baseline) per hour, with a cut-off value of 5 per hour for OSA diagnosis. The changes in the oxygenation secondary to apneas and hypopneas have been suggested to have more importance than the arousals for the cardiovascular endpoints. The cut-off value of a 4% drop has been changed to 3% in the latest recommendations of the AASM from 2012[62].

Clinical symptoms of obstructive sleep apnea

Excessive daytime sleepiness

A case at the hospital in Lidköping:
The patient was a 44 year old man, married, with four children, a truck-driver. He was obese, slept more than ten hours every night, snored loudly, and his family reported long apneas during his sleep. He was extremely sleepy during the daytime, stopped the truck every 50 km to sleep when he was on the road. He had a one-year history of chest pain induced by low physical activity when arriving for the first time at the hospital. He was referred to the cardiology clinic, and was asleep in the waiting room when the nurse called him for the exercise testing. After the test, he fell asleep again

Table 1. Definitions of hypopnea according to different AASM guidelines. (Re-published with the expectance of Erik Thunström)

Hypopnea 1999 guidelines	1 or 2 in combination with 3 1. A clear decrease (more than 50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep), or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern). 2. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of at least 4% or an arousal. 3. The event lasts 10 seconds or longer.
Hypopnea (recommended) 2007 guidelines	A 30% or greater drop in flow for 10 seconds or longer, associated with at least 4% oxygen desaturation
Hypopnea (alternative) 2007 guidelines	At least 50% decreased flow for 10 seconds or longer, associated with at least 3% oxygen desaturation or an arousal.
Hypopnea 2012 guidelines	A 30% drop in the nasal pressure excursion for 10 seconds or longer, associated with at least 3% oxygen desaturation or an arousal.

while he was informed of the results which strongly indicated CAD. This was later confirmed by a coronary angiography and he underwent a CABG. An overnight sleep assessment confirmed severe OSA, and the CPAP treatment was initiated according to the clinical routines with some difficulties in adherence at first. However, there has now been great improvement in his quality of life, working conditions and social life, and he had no signs of relapse of angina pectoris. He is now happy with the CPAP device and is using it regularly.

Epworth sleepiness scale

The Epworth sleepiness scale (ESS) is the most widely used subjective questionnaire for excessive daytime sleepiness[63]. It contains eight questions evaluating the chance of dozing-off under eight different situations (Appendix). The score range is from 0 to 24. Excessive daytime sleepiness is defined as an ESS score of at least 10, even if other cut-off levels were chosen (for instance, ESS>=16) for risk of traffic accidents[64].

Other symptoms

Many individuals with OSA may have other symptoms such as night-sweating, nocturnal diuresis, headache in the morning, dry mouth, memory deficit, personality changes, difficulties in concentration, mood disturbances, and decreased libido[65]. Women usually report fewer symptoms than men. The majority of OSA cases have, minimal symptoms or no symptoms, according to population studies[45,65].

Epidemiology

Population studies in the USA in the early 1990^{ths} suggested that the prevalence of OSA, defined as AHI >5, was estimated to be 9% in women, and 24% in men[45]. A later study from the USA showed an increased prevalence, corresponding to around 17% in women aged 30-70 years, and 34% in men, which was mainly attributed to increasing BMI in the general population over recent decades[66]. Interestingly, a recent study in Europe, the HypnoLaus Study, based on recent hypopnea definitions of the AASM from 2012[62] revealed that 84% of men and 61% of women had OSA based on the polysomnographic AHI cut-off level of 5 in an unselected general cohort of 1525 adults[67]. Thus, the prevalence of OSA is highly dependent on the technical procedures applied, for example using nasal cannulas to record more subtle breathing variations such as hypopneas (instead of the earlier use of thermistors, which are known to have lower sensitivity). The prevalence also changes when applying the latest hypopnea definitions, which are more liberal than the earlier ones.

Prognosis

OSA is most commonly diagnosed among subjects aged 40 to 60. However, OSA patients often report a history of loud snoring and excessive daytime sleepiness, which may precede the diagnosis of OSA by many years[68]. It has also been suggested that OSA is a progressive condition, which was supported by two early studies[69,70], whereas another early study by Sforza[71] indicated that OSA is stable over time.

Treatment

Treatment modalities currently available for clinical OSA management include active weight loss, avoidance of alcohol and sedatives, application of CPAP, oral appliance therapy, and surgical approaches, such as UPPP[72] (see Historical Remarks above). Avoidance of the supine sleeping position may alleviate breathing disturbances in patients with mild, position-dependent apnea[73]. To date, there is no widely accepted pharmacological therapy for the clinical treatment of OSA. CPAP is the most commonly used therapy for patients with OSA[31]. However, based on objective measurements of CPAP usage with a covert timer device installed, it has been estimated that

compliance with CPAP, defined as at least four hours on at least 70% nights[74] was achieved in only half of the patients in the sleep clinic cohorts in the early studies[75,76]. Thus, superior effectiveness in comparison with other treatment modalities was partly depleted by limited compliance.

Coronary artery disease

After Heberden´s description of angina pectoris in 1772[77], it took almost a century for pathologists to focus their attention on the coronary arteries. Coronary artery disease (CAD) is a narrowing or blockage of one or more arteries that provide oxygen and nutrients to the heart. It is mainly caused by atherosclerosis, an accumulation of fatty materials and other deposits on the inner linings of arteries. The resulting blockage restricts blood flow to the heart. The clinical manifestations of CAD include stable and unstable angina pectoris, myocardial infarction, heart failure and sudden cardiac death.

The introduction of coronary care units (CCU) by Desmond Julian in 1961[78] as well as the mobile CCU by Frank Paintridge in 1967[79] were important steps in the development of coronary care. The concept of infarct size limitation was first described by Peter Maroko et al. in 1971, when they showed that early medication in the acute stage of Acute Myocardial Infarction (AMI) in dogs had the potential to limit the infarct size[80]. The treatment of CAD patients was further improved by the introduction of mechanical revascularization of CAD, in the form of coronary artery bypass grafting (CABG) by Favaloro and Effler [81,82] in 1967 and percutaneous coronary intervention (PCI) by Gruntzig et al in 1979[83]. Over the years, CABG became the standard care of symptomatic angina pectoris. More recently, improved technology and experience with PCI has made it possible to treat increasingly complex lesions in the coronary arteries, and thus, its use has rapidly increased, while the use of CABG has reduced. During the last few decades, a number of medications have been introduced in the treatment of CAD. In 1981 it was reported for the first time that giving beta blockers a few days after the onset of AMI improved the outcome[84]. In the latter part of the 80^{ths} and in the beginning of the 90^{ths} aspirin[85], lipid-lowering drugs[86], ACE inhibitors[87], and other platelet-active drugs[88] have been shown to improve the outcomes in various manifestations of CAD.

Clinical manifestations

The first presentation of CAD is usually angina pectoris, as a chest pain or an uncomfortable pressure in the chest in a stable form during exercise or increased effort. Unstable angina pectoris is a condition where chest pain occurs suddenly, maybe at rest, sometimes during the night and becomes worse over time. AMI is defined as a pathological cell death due to prolonged myocardial ischemia. Myocardial ischemia can also cause arrhythmias, sudden death, and heart failure. All these clinical manifestations can also be the first symptoms of CAD.

Epidemiology

Approximately 200 000 individuals in Sweden have been reported to suffer from CAD, and the incidence of AMI is approximately 30 000[89] per year. The incidence

rate of AMI in Sweden is decreasing[90], although there appears to be a variability in different regions[91].

Prognosis

The prognosis for CAD patients often refers to the 30-day or one-year mortality rate. Prognosis for a longer follow-up time has also been described. The 30-day mortality rate among patients with AMI was reported to be 28% when patients who die outside hospital were included, but only 12% among the hospitalized patients in 2013. The mortality rate from myocardial infarction has been decreasing during the two last decades while the mortality rates from heart failure and arrhythmias are increasing[90].

Treatment

Revascularization has been implemented largely in patients with CAD. According to a recent report, CABG constitutes 20% and PCI 80% of all revascularizations in Sweden[92]. For patients with three-vessel disease, or left main CAD, intervention with CABG has been shown to be associated with an improved prognosis compared with PCI[2]. Patients with mild CAD, with minor symptoms which do not limit their ordinary physical activity, are today less often offered a mechanical revascularization. Reports in 2002 showed that the incidence rate for a combination of cardiovascular mortality, AMI, and the need for a new revascularization within the first year of PCI was 27% in Sweden[93]. Another report suggested a repeat revascularization rate of 40% in PCI patients and 10% in CABG patients at five-year follow-up[94]. A recent report also suggests a favorable five-year prognosis for CABG patients compared to patients undergoing PCI with regard to cardiovascular mortality[95].

The use of medication also plays an important role in modern treatment of patients with CAD, and after an AMI. The medications include aspirin, beta blockers, statins, ACE inhibitors, and P2Y12 antagonists. Many patients with angina pectoris are treated with the same drugs with the exception of P2Y12 antagonists.

Traditionally recognized risk indicators and secondary prevention

Secondary prevention among patients with CAD include smoking cessation physical activity blood pressure control, treatment of hyperlipidemia, management of obesity and diabetes mellitus, medical treatment, influenza vaccination, management of depression as well as cardiovascular rehabilitation[4,5]. Thus, many of the traditional risk factors contributing to adverse outcomes in these patients are managed. The paucity of data on the contribution of OSA to adverse outcomes in cardiac patients has been highlighted by the AHA/ACCF 2008[96], and probably contributes to a lack of recognition of OSA in the CAD setting. However, according to the current national guidelines of the Swedish Society of Cardiology, OSA is mentioned among factors to be considered for secondary prevention, and it is recommended to freely refer patients for a diagnostic investigation[97].

Diastolic dysfunction

Traditionally, cardiac function and symptoms of heart failure have mainly been discussed from a “systolic” perspective. During the last two decades, it has also been

shown that many patients with symptoms of heart failure have preserved ejection fraction (HFpEF). In heart failure populations the average prevalence of HFpEF has been reported to be 46-51%[98]. In such cases, a disturbed diastolic function due to a decreased relaxation of the left ventricle, and thereby an increase in the left ventricular filling pressure (LVFP) has been described[98]. The etiology, symptoms, diagnostic criteria, severity, and treatment of diastolic dysfunction (DD) have been intensively debated[99,100]. On the other hand, the clinical significance of DD, based on echocardiographic findings in the absence of the symptoms of heart failure, is yet not clearly understood. Recently a new definition, "pre-clinical DD" has been introduced[101]. It seems that this condition may have clinical significance in individuals with other comorbidities, such as metabolic syndrome, hyperlipidemia, diabetes mellitus, peripheral vascular disease, and CAD. Non-cardiac risk factors, such as renal dysfunction, anemia, and chronic obstructive pulmonary disease may also contribute to the progression from asymptomatic DD to an HFpEF[101].

Myocardial ischemia per se is suggested to be the main mechanism behind the development of DD in patients with CAD but concomitant conditions such as diabetes, obesity, and hypertension have been proposed to be involved[102-104]. The exact definition of DD has varied over time and between different studies[105-107]. Among echocardiographic parameters, the mitral flow pattern and other indices indicating an elevated left ventricular filling pressure (LVFP) have predictive value for worse diastolic function[108,109] and for future hospitalization for the treatment of heart failure[110,111]. The presence of a dilated left atrium has been shown to predict mortality from heart failure in patients with long-standing CAD[112].

Although several studies of patients with OSA have shown significant associations between OSA indices and abnormalities of diastolic filling[113-116], such an association could not be confirmed in a large cross-sectional study that included 500 patients with OSA[117]. A randomized, placebo-controlled study of selected normotensive patients with OSA and without a CVD found that CPAP therapy resulted in improved diastolic function[118]. The impact of CPAP treatment on reversing the functional and structural remodeling of the heart has been confirmed in other smaller studies[119-121].

Prognosis

The literature suggest that the evaluation of DD has both diagnostic and prognostic importance in the management of patients with CAD[108,109,122]. It has previously been shown that patients with DD and preserved LVEF have similar mortality and morbidity rates compared with the heart failure patients with reduced LVEF[123,124].

Treatment

There is a knowledge gap with regard to the treatment of patients with DD. Since DD occurs in association with different cardiovascular comorbidities, it has been suggested that the treatment should focus on the underlying diseases. Treatment is also important for the prevention of progression of the DD[101]. In major randomized controlled trials no positive effect on cardiovascular death of any heart failure medication has been shown[125-127]. However spironolactone has in a post hoc analysis of the TOPCAT trial been shown to have beneficial effect for patients with HFpEF in those that

seemed to take their medication indicating that it might be worth using. Furthermore, in a recently published large observational study it was found that treatment with betablockers resulted in a reduced mortality risk among patients with symptoms of HFpEF[128] further underlining the importance of more research in the field.

Obstructive sleep apnea and coronary artery disease: causality and interactions

Circadian variation in the onset of cardiovascular events

The risk of developing angina pectoris, an acute myocardial infarction or sudden cardiac death increases during the late hours of sleep or in the hours after awakening[129]. A retrospective analysis showed an overrepresentation of sudden death during the sleeping hours in patients with OSA[130]. It has also been shown that the incidence of AMI onset between 06.00 and 12.00 hours was higher in OSA patients (AHI $\geq$5) than in patients without OSA (38% vs 25%, $p<0.05$). Moderate to severe OSA (AHI $\geq$15) has been reported to be associated with a circadian variation (OR 2.0) in cardiovascular events after adjustment for comorbidities[131].

Prevalence of obstructive sleep apnea and coronary artery disease in the general population

The largest study addressing the prevalence of OSA and CAD in the general population is the Sleep Heart Health Study[132]. In this analysis of 6132 subjects undergoing unattended PSG, there was a risk increase (OR 1.27) for self-reported CAD.

Prevalence of coronary artery disease in patients with obstructive sleep apnea

Data are mostly based on uncontrolled studies. In a sleep clinic cohort of 386 subjects[133], CAD was present in about one fourth of subjects with OSA. Simultaneous PSG and electrocardiographic recordings showed that nocturnal ischemia was more common in patients with OSA who also had CAD. These episodes were mainly found during REM sleep, during episodes of high apnea activity, and during sustained hypoxemia[134]. In one study, ST-segment depression was common during sleep in patients with OSA but without a history of CAD, and such changes were eliminated with CPAP[135].

Prevalence of obstructive sleep apnea in coronary artery disease

A case-control study from Australia that investigated middle-aged male survivors of AMI and age-matched controls provided the first evidence of an increased prevalence of OSA in a population of patients with CAD[136]. OSA, defined as an AHI of $\geq$5, was found in one third of these patients compared with 4% of healthy controls. OSA also constituted an independent predictor of AMI after adjustment for traditional risk factors. A larger case-control study showed a similar OSA prevalence (31%), versus 20% in the control group[137]. In the same population, an AHI of >20 was associated with a history of AMI (OR 2.0). In an age-, sex-, and BMI-matched case-control study of 62 patients in Skaraborg, OSA based on an AHI of >10 events/h showed an adjusted OR of 3.1 for CAD adjusted for various cardiovascular risk factors[138]. It has also been

reported that the association between OSA and CAD may be influenced by sex and by age. In patients with CAD verified at coronary angiography, an apnea index of >10 events per hour was twice as common in men under 70 years[139] and three times as common in women under 70 years[140], compared with age-matched controls. An uncontrolled study of 50 randomly selected patients with CAD showed OSA in 50% of cases based on an apnea index of >10 events per hour[141]. Another uncontrolled German study reported an OSA prevalence of 35% (AHI ≥10) in 74 men with CAD but failed to show a significant relationship between the degree of AHI and the number of coronary vessels involved[142]. Overall, there were thus seven available studies accumulating 754 patients with CAD demonstrating an OSA prevalence around 35% at the time when the work of this thesis started (Table 2).

Table 2. Prevalence of obstructive sleep apnea in patients with coronary artery disease

First author (year)	Patients (no.)	Sex	Prevalence (%)	Definition of OSA (events/h)	Control group
Hung (1990)	101	Male	36	AI >5	Yes
Andreas (1996)	50	Both gender	50	AI >10	No
Mooe (1996)	142	Male	37	AHI ≥10	Yes
Mooe (1996)	102	Female	30	AHI ≥10	Yes
Koehler (1996)	74	Male	35	AHI ≥10	No
Peker (1999)	62	Both gender	31	AHI ≥10	Yes
Schafer (1999)	223	Male	31	AHI ≥10	Yes
Total	754	—	—	—	—
Mean	—	—	35,7	—	—

Definition of abbreviations: AI=apnea index; AHI=apnea-hypopnea index

Impact of obstructive sleep apnea on the prognosis of coronary artery disease in observational studies

Patients with CAD who had concomitant OSA have been shown to have an increased cardiovascular mortality risk during the subsequent five years[9,143]. In one study of patients with CAD who had undergone elective PCI, concomitant OSA was significantly related to the development of restenosis after seven months of follow up[144]. In another study, the incidence of cardiac events (cardiac death, reinfarction, and revascularization) was 24% among patients with OSA, compared with 5% among patients without OSA during six months of follow-up[145]. The incidence of stroke was also increased in patients with CAD and OSA[146]. During 10 years of follow-up after a coronary angiography, stroke occurred in 18% of patients with CAD and OSA, as compared with 5% of patients with CAD without OSA. After adjustments for confounders, including hypertension and atrial fibrillation, patients with OSA had a threefold increased risk of stroke[146].

Incidence of coronary artery disease in longitudinal studies

The first report on CAD incidence data in a sleep clinic cohort was a small observational study in Gothenburg, which showed the development of CAD in 25% of patients with OSA who were not treated during seven years of follow up[147]. In comparison, CAD incidence among OSA patients who were treated was 4% and among non-apneic snorers it was 6%. A larger observational study of a sleep clinic cohort, containing about 1300 subjects with OSA who were followed for 10 years, found a three to four times higher incidence of cardiovascular events in patients with severe OSA compared with simple snorers[148]. Multivariate analysis showed that the risk of fatal cardiovascular events was markedly higher in patients with severe OSA (OR 3.2; 95% CI 1.1-7.5) as compared with healthy controls.

Another prospective observational study of a sleep clinic cohort including 1436 consecutive subjects showed that OSA (AHI ≥5) was associated with a twofold increase in risk of CAD events or death from cardiovascular causes during three years of follow up[149]. Moreover, there was a relationship between AHI and composite outcome of CAD events or cardiovascular death (adjusted hazard ratio (HR) 2.8) in patients with severe OSA (AHI ≥30) compared to those without OSA (AHI <5)[149]. Similarly, the 18-year follow-up study of the Wisconsin Sleep Cohort sample reported an adjusted HR of 5.2 (95% CI 1.4-9.2) for cardiovascular mortality in patients with severe OSA (AHI ≥30) who did not use CPAP, versus those without OSA[150].

The longitudinal analysis of the Sleep Heart Health Study, including 4422 men and women who had no CAD and no heart failure at baseline, demonstrated a significant association between severe OSA and incident CAD (adjusted HR of 1.7 for those with AHI ≥30 compared to those with AHI <5) in middle-aged men, but not in women[151]. In contrast, a recent observational follow-up study of 1116 women from two Spanish sleep clinic cohorts reported that untreated severe OSA was associated with increased cardiovascular mortality with an adjusted HR of 3.5 for patients with AHI ≥30 compared to patients with AHI <10[152]. Another report from the same study cohort showed an adjusted HR of 2.8 (95% CI 1.4-5.6) for the incidence of CAD or stroke in women with untreated OSA (AHI ≥10) compared to patients without OSA[153].

Impact of CPAP treatment on coronary artery disease patients with obstructive sleep apnea

The first-line treatment of OSA is CPAP, which has been shown to reduce daytime sleepiness and to improve quality of life in patients with sleepy OSA[154]. A retrospective analysis of 55 patients and comorbid OSA over a follow-up time of 7.3 years showed a significantly lower incidence of either cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for revascularization in patients who were compliant with CPAP therapy[10]. In another follow-up study over 7.5 years, deaths from cardiovascular disease were less frequent in patients with OSA who were treated with CPAP as compared with those who were not[11]. Moreover, a review of 371 revascularized patients with OSA and CAD showed a significantly lower cardiac death rate (3%) among 175 patients treated with CPAP, compared with 10% among 196 patients who were not treated with CPAP during a follow-up period of 5 years[12].

Gaps in knowledge of management of coronary artery disease patients with obstructive sleep apnea in clinical practice

The rationale for considering CPAP for patients with CAD and concomitant OSA regardless of daytime sleepiness is based on the adverse hemodynamic changes observed during the obstructive events[44], which might be reversed by the physiological effects of this device. In general, the event of apnea leads to increased breathing, recurrent episodes with considerable negative intrathoracic pressure, hypoxia/reoxygenation, and fluctuating autonomic activity with fluctuations in heart rate and blood pressure. Increased oxygen demand and reduced oxygen supply during episodes with obstructive events may trigger symptoms of angina pectoris in patients with CAD who already have a reduced coronary flow reserve[44]. OSA is also associated with long-term alterations of cardiac structure, hemodynamic reflex function and vascular structure and function. The disorder leads to immediate and sustained sympathetic activation[155,156]. Baroreceptor and chemoreceptor responsiveness is altered[157]. A series of studies have demonstrated that vascular endothelial function is reduced in OSA[158]. All these changes are specific to OSA and they might be reversed by CPAP[159].

Due to the adverse acute cardiovascular responses during obstructive events, it has been argued not to design long-term randomized controlled trials in OSA patients for ethical reasons. However, since long-term follow-up studies do not always support an acute adverse impact of the disorder, and are not prospectively adjusted for confounding factors such as high age, obesity, insulin resistance, hyperlipidemia, smoking and lifestyle habits, a causal relationship between OSA and CAD has yet not been readily confirmed. Moreover, long-term adherence to CPAP treatment in patients with CAD and concomitant OSA without daytime sleepiness had not been proven in the planning phase of this thesis.

Compared to patients from a sleep clinic cohort, patients from a cardiac clinic population does not actively seeking a referral for their OSA but are rather under consideration for a screening procedure. Thus, OSA is diagnosed as a “laboratory” rather than a “clinical” disorder. For patients with CAD who do not have complaints related to symptoms of OSA, it may therefore be a challenge to convince them to be treated “with a mask on the face” as a kind of “long-term cardiovascular medication”. The issue becomes even more complicated if such an intervention would adversely affect the patient’s quality of life.

Thus, despite a high occurrence of OSA in patients with CAD, these patients were not routinely screened for OSA, and treatment with CPAP was not considered in clinical practice at the start phase of this thesis in 2005.

AIMS

The main aims of the work in this thesis were:

- to survey the research field regarding the association between OSA and CAD, and to explain the rationale of conducting an RCT
- to establish the occurrence and predictors of OSA in a revascularized CAD cohort
- to address the relationship between OSA and diastolic dysfunction in CAD
- to evaluate the impact of CPAP treatment on diastolic function in patients with CAD and non-sleepy OSA
- to evaluate the impact of long-term CPAP treatment on adverse cardiovascular outcomes in patients with CAD and non-sleepy OSA

PATIENTS AND METHODS

Study design

The five papers in this thesis originate from the RICCADSA trial, which is a prospective, open-label, blinded evaluation RCT intervention study.

Paper I
This paper describes the rationale and design of the Randomized Intervention with CPAP in CAD and OSA (RICCADSA) trial.

Paper II
This is a cross-sectional descriptive study of the baseline population of the revascularized CAD patients undergoing sleep screening for inclusion in the main RICCADSA trial. The occurrence and predictors of OSA were investigated in this cohort.

Paper III
This is a cross-sectional analysis of the baseline population of the patients included in the RICCADSA trial. The association between OSA and diastolic dysfunction was addressed in the subgroup of patients with preserved LVEF.

Paper IV
This is a single-center (two-site), prospective, open, randomized 1:1 (CPAP / no CPAP), interventional superiority trial of CPAP treatment. Diastolic function parameters were measured at baseline, as well as after three-month and one-year follow-ups in CAD patients with non-sleepy OSA.

Paper V
This paper reports the primary outcomes of the main RICCADSA trial, namely, the impact of CPAP treatment on long-term cardiovascular adverse outcomes.

The trial was registered with the national researchweb.org, Research and Development in Sweden (FoU i Sverige; nr VGSKAS-4731; 04.29.2005) as well as with ClinicalTrials.gov: NCT (00519597).

The study population

All patients were recruited from two hospitals, Skövde and Lidköping, serving a population of approximately 250,000 living in the Skaraborg County of West Götaland. The PCIs were performed either as an elective or acute/subacute procedure at the hospital in Skövde or at the regional hospital, Sahlgrenska University Hospital in Gothenburg. The CABG intervention was performed in Gothenburg, and all patients were moved to the study hospitals when they were clinically stable after revascularization. Eligible patients who gave informed consent at the coronary outpatient clinics to participate in the interventional study were referred to the Sleep Medicine Unit for sleep studies.

As illustrated in Figure 1, 1291 CAD patients who had newly (within six months) undergone PCI or CABG between September 29, 2005, and November 7, 2010 were asked to participate in the trial. After excluding 32 patients with a known OSA diagnosis and treatment, a total number of 1259 subjects were eligible for the study. Among those, 662 agreed to undergo an ambulatory, PG cardiorespiratory sleep recording at home, and completed the ESS questionnaire.

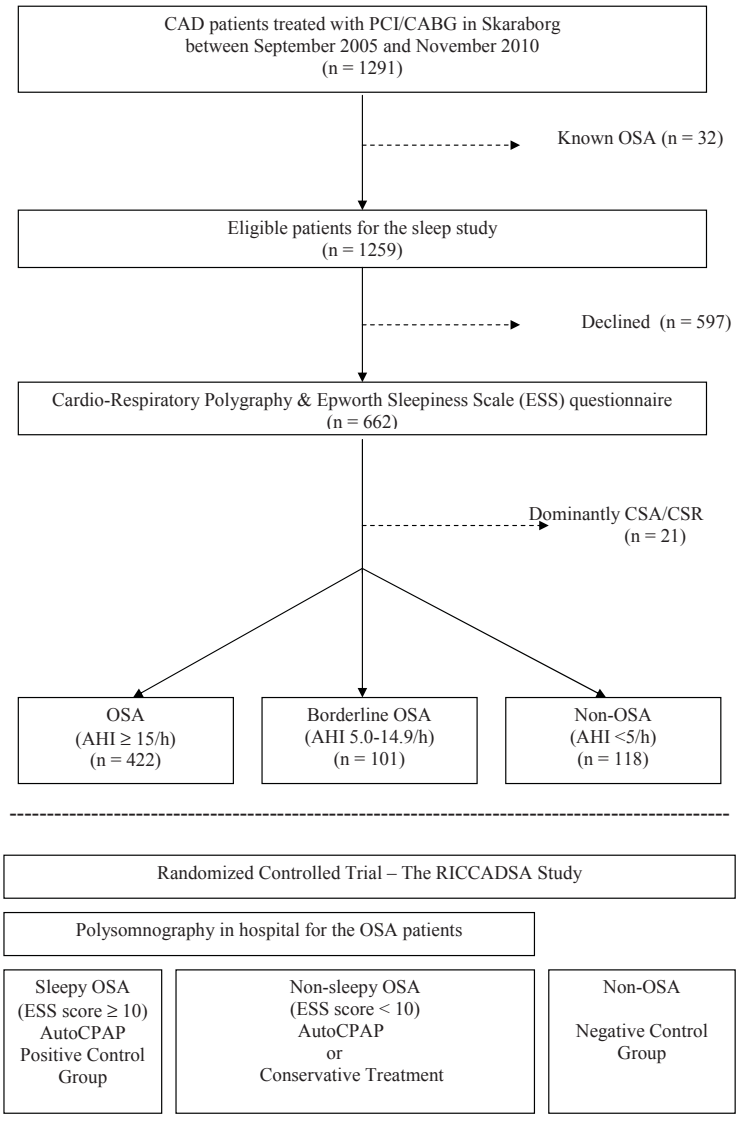

Figure 1. Patient log demonstrating the study cohort and the various subgroups. AHI=apnea–hypopnea index; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CPAP=continuous positive airway pressure; CSA=central sleep apnea; CSR=Cheyne-Stokes respiration; OSA=obstructive sleep apnea; PCI=percutaneous coronary intervention; RICCADSA=Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea.

For the purpose of the study in Paper II, the clinical characteristics of the whole population were obtained. After amendment of the study protocol approved by the local ethics committee inclusion of clinical characteristics data from the patients without sleep recordings as well as the patients with borderline OSA (AHI 5–15) could also be included.

For the main RICCADSA trial, 511 patients were identified: an RCT arm with 244 non-sleepy OSA patients (AHI ≥15 and ESS <10), and an observational arm as additional controls, consisting of 155 sleepy OSA patients (AHI ≥15 and ESS ≥10), and 112 patients without OSA (AHI <5) (Figure 1). Patients were recruited between December 2005 and November 2010, and follow-up for the primary outcomes was completed in May 2013.

For the purpose of Paper III, which addressed the baseline associations of OSA and diastolic function, only patients with adequate baseline echocardiograms and preserved LVEF (at least 50%), and with no atrial fibrillation or severe valve abnormalities were selected. OSA patients (sleepy and non-sleepy) were compared with the patients without OSA (Figure 2).

In Paper IV, 171 non-sleepy OSA patients in the RCT arm with technically adequate echocardiograms at baseline and at follow-ups, and with preserved LVEF and no atrial fibrillation or valve abnormalities constituted the final study population.

For the study population in Paper V, all 244 CAD patients with non-sleepy OSA randomized to CPAP or no CPAP were evaluated in the intention-to-treat (ITT) analysis for the primary research question (Figure 3).

The study oversight

The Ethics Committee of the Medical Faculty of the University of Gothenburg approved the study protocol (approval nr 207-05; 09.13.2005; amendment T744-10; 11.26.2010; amendment T512-11; 06.16.2011), and all patients provided written informed consent. An interim analysis was conducted in February 2010, and the protocol was amended with a new power calculation for the primary endpoints (see below). All data obtained from hospital records and death certificates by the end of May 2013 were reviewed by an independent clinical event committee (ICEC) unaware of patient identities and group allocation. A data and safety monitoring board reviewed the protocol and monitored a random 10% selection of the database for baseline clinical data and follow-up procedures, including CPAP adherence and primary endpoints.

Definition of the baseline characteristics

The anthropometrics, smoking habits, and medical history in the whole population were obtained from the medical records following the mechanical revascularization. BMI was calculated as body weight divided by height squared, and obesity was defined as a BMI of at least 30 kg/m^2 [160]. Information regarding known concomitant diseases at baseline, including hypertension and diabetes, was based on self-reported and physician-diagnosed conditions.

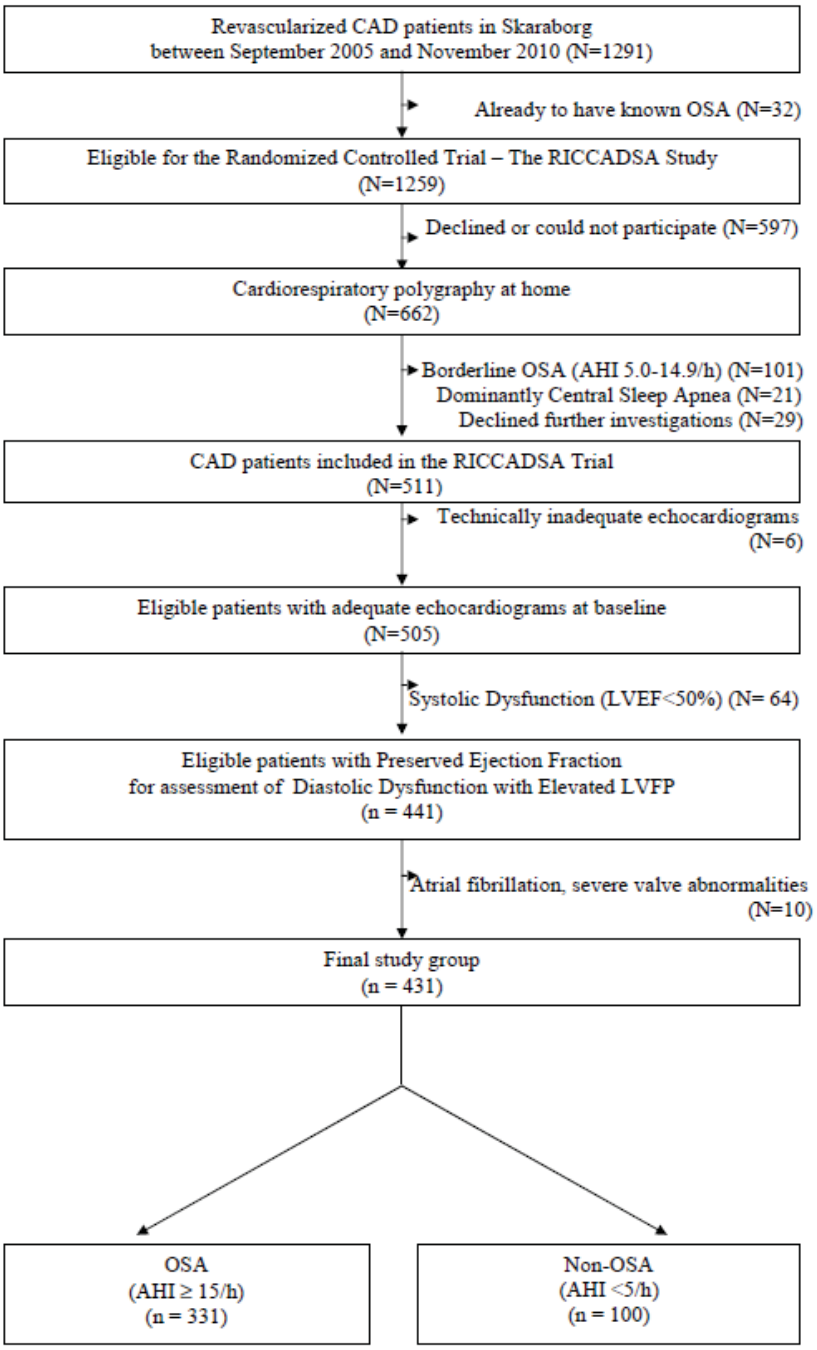

Figure 2. Flowchart demonstrating the study cohort and the two subgroups.

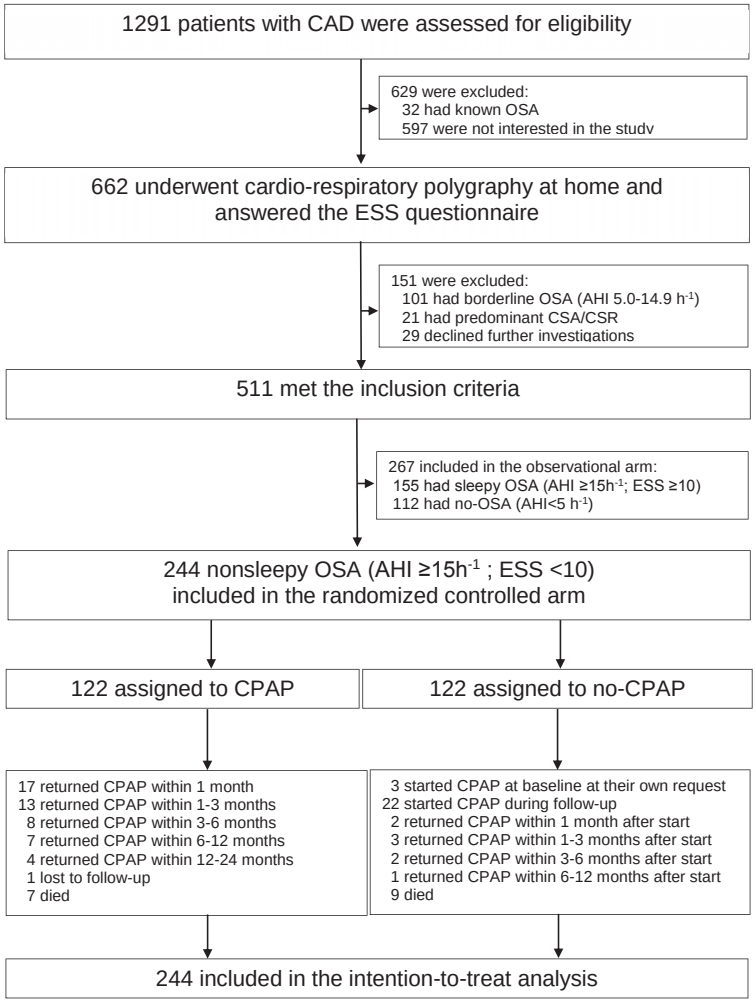

Figure 3. Flow of patients through the study. Definition of abbreviations: AHI, apnea-hypopnea index; CAD; coronary artery disease; CPAP, continuous positive airway pressure; CSA-CSR, central sleep apnea-Cheyne Stokes respiration; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; RICCADSA, Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea.

Cardiorespiratory polygraphy

The portable, limited PG sleep recording performed with the Embletta® PDS (Portable Digital System) device (Embla, Broomfield, CO, USA), consisted of (1) a nasal pressure detection using nasal cannulae or a pressure transducer system, (2) thoraco-abdominal movement detection using two XactTrace™ inductive belts with respiratory inductance plethysmography technology, (3) a finger oximeter detecting heart rate and oxyhemoglobin saturation (SpO_2), and (4) body position and movement detec-

tion. The patient's sleep time was estimated on the basis of self-reporting as well as the pattern of body movement during the sleep recording. Patients with an estimated sleep time of under four hours were offered a new home-based sleep study. Apneas were defined as an almost complete (at least 90%) cessation of airflow. Hypopneas were defined as a reduction of at least 50% in thoracoabdominal movement and/or a decrease of at least 50% in the nasal pressure amplitude for at least 10 seconds, according to the Chicago criteria from 1999[8] as described above. In addition, the total number of significant oxyhemoglobin desaturations (a decrease of at least 4% from the immediately preceding baseline) were scored, and the ODI was calculated as the number of significant desaturations per hour of estimated sleep. Events with a 30% reduction or more in thoracoabdominal movement and/or a minimum 50% decrease in the nasal pressure amplitude for at least 10 seconds were also scored as hypopneas if there was a significant desaturation (at least 4%). Patients with an AHI of 15 or more, independent of symptom occurrence, were defined as having OSA.

Overnight polysomnography in hospital

All patients with CAD and OSA, based on the first PG screening investigation, underwent unattended overnight PSG in hospital using a computerized recording system (Embla A10®, Embla, Broomfield, CO, USA), which included sleep monitoring through three-channel EEG [C4/A1, C3/A2, CZ/A1], two-channel EOG, one-channel submental EMG, bilateral tibial EMG, and two-lead electrocardiogram (ECG), in addition to the cardiorespiratory channels as described for the PG system above. PSG recordings were scored based on 30-second epochs according to the Rechtschaffen and Kales criteria[161] by an observer blinded to clinical data and baseline screening results from the previous PG recordings. Obstructive events on the PSGs were scored according to the same AASM criteria from 1999 applied for the PGs. CAD patients without OSA on PG did not undergo overnight PSG in hospital because AHI values under 5 on the PG system used, have been shown to exclude moderate OSA (AHI $\geq$15) almost as reliably as if a PSG recordings would have been used[59].

Other baseline assessments

Following the PSG night at the Sleep Medicine Unit after a fast of at least 10 hours, all blood samples were collected in EDTA and serum tubes, and fasting blood glucose levels as well as blood lipid levels were determined by standard laboratory methods. P–N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were determined using the commercially available solid-phase two-site chemiluminescent enzyme-labeled immunometric assay on an Elecsys system (Roche Diagnostics; Mannheim, Germany) on samples obtained from 2005–2007; for samples obtained from 2008–2010, an Immulite 2000 XPi (Siemens Healthcare Diagnostics, Cardiff, Wales) was used. Additional blood samples were centrifuged and stored in small portions at –80°C for future analysis of cardiovascular biomarkers (not included in this thesis).

At baseline, a clinical examination was performed, and the coronary angiography data before the revascularization as well as smoking habits, other comorbidity data, and medications were documented in all trial subjects. Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), the Short Form 36 Health

Survey (SF-36), Zung Self-Rating Anxiety Scale and Self-Rating Depression Scale questionnaires were obtained (results not included in this thesis), and a transthoracic echocardiogram (TTE) was performed (see below) before the start of the intervention procedure.

Group assignment, randomization, interventions, and follow-up

Group assignment was based on the cardiorespiratory PG recordings and ESS questionnaires. The in-hospital PSG for OSA patients was conducted the day before start of the RCT, mainly for subsequent studies of further evaluation of sleep architecture in different OSA phenotypes, and for comparison with the baseline PG recordings (not included in this thesis). As the PSGs were scored later during the follow-up period, the group allocation was not changed on the basis of these results. The 1:1 random assignment of patients with CAD and non-sleepy OSA was scheduled by the sealed envelope system with a block size of eight patients (four CPAP, four controls) stratified by gender and revascularization type (PCI or CABG). Thus, four groups of sealed envelopes (a. PCI men, b. PCI women, c. CABG men, and d. CABG women; eight in each group) were prepared in advance by the investigator and the study nurse, and the patients were enrolled in the randomization procedure the morning after the overnight PSG, which was scheduled by the study nurse with no knowledge about the details of the patient characteristics and comorbidity data.

The patients allocated to CPAP treatment in the non-sleepy OSA group and the ones offered CPAP treatment in the sleepy OSA group were informed about the technical procedure the morning after the overnight PSG; the trained staff at the study center provided them with an automatic (self-titrating) CPAP device (S8®, or S9®; ResMed, Sydney, Australia) and a nasal or full-face mask and humidifier.

All participants assigned to CPAP were instructed to use the device at home every night for at least four hours. They were contacted by telephone after one week and given a check-up in the clinic after one month, three months, six months, one year, and then yearly to the end of the main study. Non-sleepy OSA patients who were randomized to the control group and who were obese were given advice about weight reduction, and all OSA patients randomized to no CPAP were informed about the tennis ball technique to avoid the supine position during sleep[162]. All patients were evaluated at three, six, and 12 months and annually thereafter, and were given standard cardiology treatment by their physicians. A new PG sleep recording was performed in all patients at three and 12 months, and annually thereafter (with CPAP in treated OSA patients) as part of a planned future post-hoc analysis comparing reports from the PG device regarding residual AHI and pressures applied during CPAP treatment, and for analysis of the natural course of OSA in patients who were randomized to no CPAP (not included in this thesis).

At the three-month and one-year follow-ups, the questionnaires were completed again, blood samples were drawn in the morning following the new sleep recording, and a new echocardiography was performed. In addition, a maximal exercise testing was performed at three months and one year following the baseline investigations (results

not included in this thesis). For the non-OSA group, blood samples were drawn at one year but not at three months; all other measures were repeated as for the OSA group.

Adherence to CPAP

All OSA patients receiving CPAP treatment brought their device to the clinic at each scheduled follow-up visit; monitoring settings and hours of CPAP use were obtained from the internal clock in the device and recorded. In addition, pressure level, mask leak, and residual AHI measures were noted. All necessary adjustments of the CPAP device and mask fittings were performed according to clinical routines by the sleep medicine unit staff. Patients who were unable to adhere to CPAP treatment were followed as part of the treatment arm, as defined in the ITT analysis.

Echocardiography

All echocardiographic examinations were carried out on the same day that the blood samples were collected: at baseline, three months and one year after inclusion. Comprehensive echocardiographic examinations were performed by experienced echocardiographic technicians according to the site's clinical practice on a commercially available cardiac ultrasound system (Vivid-7 General Electric Healthcare, Fairfield, CT). Images and cine loops were obtained in the left lateral position at rest, from the parasternal and apical position; they were stored and evaluated with a commercially available software program (EchoPAC General Electric Healthcare).

The echocardiographic examinations were all assessed by the same examiner (HG), who was unaware of the patients' clinical and sleep data. Two-dimensional measurements included interventricular septum (IVS) thickness, left ventricular posterior wall (LVPW) thickness, left ventricular diastolic diameter (LVDD) and left ventricular systolic diameter (LVSD). Relative wall thickness (RWT) was calculated as LVPW x2/LVDD. Increased RWT was defined as RWT $\geq$0.42[163]. Left ventricular mass (LVM) was calculated according to the corrected formula of the American Society of Echocardiography and normalized for body size by height to the power 2.7, and expressed as LVM index (LVMI) in g/m$^{2.7}$ [106,163]. Increased LVMI was defined as LVMI $\geq$49 g/m$^{2.7}$ for men and $\geq$45 g/m$^{2.7}$ for women[106,163]. Based on these values, concentric hypertrophy was defined as the combination of an increased RWT and an increased LVMI[106,163]. The left atrial (LA) diameter was measured on parasternal M-mode images as the linear distance between the trailing edge of the posterior aortic wall and the leading edge of the posterior wall.

An overall evaluation of the LVEF was performed by visual estimation and, when appropriate, by Simpson's biplane method. Trans-mitral peak flow velocities in early diastole (E) and peak flow velocity at atrial contraction (A) were recorded at the tips of the mitral valve leaflets. Peak tissue velocities were derived by pulsed tissue Doppler analysis at the septal margin of the mitral annulus for early (é) and late (á) diastolic tissue velocities, and the E/é filling index was calculated. If a detectable tricuspid regurgitation was provided, the maximum velocity in meters per second was measured with the continuous-wave Doppler, and the pressure gradient was calculated.

A standardized value of 5 mmHg was then added to estimate the pulmonary artery systolic pressure (PASP), and a PASP value >35 mmHg was defined as pulmonary hypertension[164].

Definition of the diastolic dysfunction

In Paper III, diastolic function was classified in accordance with recent recommendations with some modifications[106,116,163] as follows: (1) normal diastolic function: LA diameter was <39 mm for women, or < 40 mm for men AND a normal é tissue velocity for age (<40 years: >10 cm/s; 40-59 years: >8 cm/s; ≥60 years: >6 cm/s); (2) mild diastolic dysfunction: LA diameter ≥39 mm for women, or ≥40 mm for men, OR a low é tissue velocity for age, and (3) worse diastolic function with a presumed elevated LVFP: E/é was >13, OR E/é >9 in patients with an enlarged LA diameter (≥39 mm for women and ≥40 mm for men) (Figure 4).

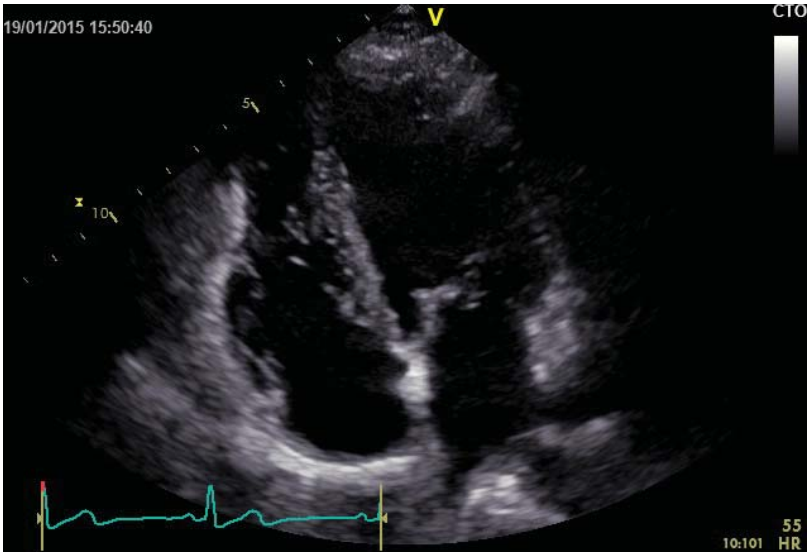

Figure 4. Echocardiography. Four chamber view of the heart.

Primary outcomes in Paper IV

The primary outcome measures in Paper 4 were changes in the above-defined parameters of diastolic dysfunction compared to baseline in absolute values. A further categorization was made as an "improvement" when there was a decrease in E/é, or a reduction in LA diameter, or an increase in é, respectively. All investigations at baseline and follow-ups were all evaluated by the same observer, blinded to the patients' group allocation.

Primary outcomes in Paper V and the thesis

The primary endpoint was a composite of repeat revascularization, AMI, stroke, and cardiovascular mortality. Information was obtained from patients' medical records and, when necessary, from the Swedish Hospital Discharge Register or the Swedish National Cause of Death Registry. Each event was evaluated separately and as part of the combined endpoint. For patients who experienced more than one event during the follow-up period, only the first event was included in the combined endpoint. All-cause mortality and acute hospital admission for cardiovascular reasons were among the secondary endpoints.

Cardiovascular endpoint criteria

An ICEC reviewed all data obtained from hospital records and death certificates by the end of May 2013, blinded to personal identity and group allocation. The ICEC review was based on a previously described definition of the endpoints[165], which was applied in the HOT study[166], and other trials. Overall mortality was based on the death certificate. Cardiovascular mortality was defined as death from any of the following: AMI, stroke (cerebral hemorrhage or cerebral infarction), ruptured aortic aneurysm (thoracic or abdominal), heart failure (as determined by the treating physician), sudden death with presumed exclusively cardiac cause (malignant arrhythmias), and death during or within 28 days of CABG or PCI, and pulmonary embolism.

AMI was defined as at least two of the following signs or symptoms: sudden chest pain or sudden shortness of breath or syncope, new left bundle branch block or new ST elevation or transient ST- or T-wave changes, increase of troponin I levels to >0.10 μg/L in at least two samples, or increases in myocardial necrosis biomarkers (other causes of troponin elevation should be excluded). Evidence of AMI at autopsy could also be used as a single criterion. Stroke was defined as sudden onset of focal neurological signs lasting more than 24 hours (other causes such as brain tumor, subdural or epidural hematoma, subarachnoid hemorrhage, psychosomatic origin, and peripheral nerve lesions should be excluded).

Stroke was defined as cerebral hemorrhage if computed tomography (CT) or magnetic resonance imaging (MRI) of the brain showed intracerebral blood, and defined as cerebral infarction if early CT brain was normal and subsequent follow-up was compatible with stroke, or if later CT brain or MRI showed signs of infarction; or, as a single criterion, evidence of cerebral hemorrhage or infarction at autopsy and determined by the pathologist as the cause of death. CABG was defined as an operation with grafts to coronary arteries, and PCI was defined as dilatation of the coronary arteries with or without stents. Pulmonary embolism was defined as sudden onset of chest pain or shortness of breath or syncope, together with typical CT findings of the pulmonary arteries or pulmonary scintigraphy. Aortic aneurysm (either thoracic or abdominal) was defined as all three of: sudden onset of chest pain or abdominal pain, typical findings on chest or abdominal radiography or ultrasound, and need for intervention (blood pressure treatment, or surgery, or percutaneous transluminal intervention with

or without stent). Acute hospital admissions for cardiovascular events included AMI, stroke, pulmonary embolism, aortic aneurysm (as defined above), as well as acute hospital admissions for heart failure, transient ischemic attacks, chest pain of presumed cardiac origin (e.g. angina pectoris), peripheral emboli, atrial fibrillation and other cardiac arrhythmias, and intermittent claudication.

Data collection and analysis

The primary outcome variables were documented prospectively and were not subject to observer bias. Baseline comorbidity data, results of sleep recordings, and CPAP compliance data were prospectively recorded in separate files on a specific server of the study hospital by research personnel blinded to study group allocation or unaware of the study outcomes, or both.

Statistics

In Papers II, III, IV and V, descriptive statistics were given as mean ± standard deviation (SD) and categorical variables as percentages. The 95% confidence interval (CI) was calculated for prevalence of OSA according to normality approximation. For the baseline cross-sectional variables, differences in means between CAD patients undergoing sleep recording versus no sleep recording were analyzed by Student's t-test, and chi-square test was used to compare categorical variables. For comparison of means between OSA, Borderline OSA and non-OSA groups (Paper II), a one-way ANOVA test was applied with post-hoc Bonferroni analysis. Age, gender, BMI, obesity and comorbid conditions were included in a logistic regression model to test the association with OSA in the cohort. The significant variables that correlated with OSA in the univariate analyses were included in a multivariate logistic regression model, and corrected odds ratios (OR) were calculated from the regression coefficients. All ORs are presented with their 95% confidence intervals (CI). Paired *t* tests were used for comparison of AHI values from PG vs PSG for the OSA group included in the RCT arm (Papers II and V).

In Paper III, inter-observer variability as well as intra-observer variability for IVS, LVPW, LVDD, LA diameter, and E, A and é measurements were evaluated by the intra-class correlation coefficient in 10% of the study population. Bivariate logistic regression was used to determine the relationship between variables associated with diastolic dysfunction with an elevated LVFP. In the multivariate regression analysis, statistically significant variables in the bivariate model, as well as the non-significant variables with supposed clinical relevance, were included.

In Paper IV, a general linear model repeated measures analysis was applied for between-group differences in diastolic function parameters (LA diameter, é tissue velocity, and E/é) at baseline and at follow-ups. A further logistic regression analysis was used to determine the relationship between variables in case of an observed improvement in the above-mentioned diastolic function parameters. In the multivariate model, statistically significant variables in the bivariate analysis as well as age, sex, and BMI were included.

In Paper V, for baseline differences between the groups, the chi-squared test and Fisher's exact test were applied. Total sleep time, time spent in the supine position, and AHI values on the repeated sleep recordings (PG vs PSG) at the individual level were compared with paired *t*-tests. Pearson product-moment correlation coefficient was used to test the linear relationship between the AHI values from PG vs PSG. In order to estimate the impact of CPAP on the primary endpoint, Kaplan-Meier analyses and Cox proportional hazards models were performed in the ITT population. For the on-treatment analysis, a time-dependent Cox model[167,168] was applied. This approach accounts for the time-varying character of the intervention because subject follow-up is split into multiple intervals according to the visit dates of the CPAP usage evaluation. Originally, visits were planned to take place after one, three, six, and 12 months and then annually until the end of the study. One missing sleep recording episode was replaced by the previous observation, if the missing episode was followed by a visit. Two or more subsequent missing visits were replaced by 0. In the case of missing data from the first follow-up visit (after one month), the usage data from the three-month visit was substituted. Multivariate adjustment was made for CPAP nights per period and baseline LVEF, age, gender, AHI, BMI, current smoking, revascularization type, former revascularization, acute AMI, hypertension, diabetes mellitus, and lung disease.

All statistical tests in Papers II to V were two-sided, and a *P*-value <.05 was considered significant. Statistical analysis was performed using SPSS® 22.0 for Windows® (SPSS Inc., Chicago, Illinois, USA) and, in Paper V, Stata version 14 (StataCorp LP, College Station, Texas, USA) was also used.

Sample size estimation

Available literature at the time of the study start in 2005 suggested that the incidence rate for a combination of cardiovascular mortality, AMI and the need for a new revascularization within a year of PCI was 27%[93], and the five-year repeat revascularization rate was reported to be 40.1% in PCI with stents and 9.8% in CABG patients[94]. There were no studies in revascularized patients with CAD and concomitant OSA prior to 2005 to accurately inform estimates of study power for the primary outcome assessments; therefore, a composite endpoint rate of 25% in non-sleepy patients with untreated OSA over a three-year follow-up period was hypothesized. The RCT arm was designed to initially comprise a consecutive sample of 200 patients with (100 non-sleepy OSA randomized to CPAP, 100 to no CPAP). It was assumed that approximately 25% of the OSA subjects would be noncompliant with CPAP during the follow-up period. The trial was expected to have an 80% power to detect a risk reduction in the rate of the composite endpoint from 25% to 10% on an ITT basis ($p<.05$ level, two-sided test). An interim analysis blinded to randomization group performed in February 2010 revealed an incident rate of 21%, and a CPAP adherence rate of 60% at one year, resulting in a protocol amendment. As a result, using an enlarged sample size of 242 patients (121 in each of the randomization arm) and an extended follow-up period of minimum two and maximum seven years, a significant risk reduction for the primary endpoint from 25% to 12% was hypothesized for Paper V. A separate sample size calculation was not carried out for the endpoints in Paper IV.

MAIN RESULTS

Paper II

The occurrence of unrecognized obstructive sleep apnea among revascularized patients with coronary artery disease

As shown in Figure 1, a total of 1259 patients met the inclusion criteria for screening, of whom 662 (52.7%) agreed to do a sleep recording. Diagnostic PG was performed at home after an average of 63 days following mechanical revascularization (median 59 days; interquartile range [IQR] 42–78). In total, 17 home sleep studies were repeated due to short estimated sleep time and/or technical failure. Patients fulfilling the inclusion criteria for the RCT or the observational arm underwent baseline investigations on average 35 days (median 30; IQR 20–45) after home sleep recordings.

As illustrated in Figure 1, OSA, defined as AHI≥15, was found among 422 out of 662 patients (63.7%) who underwent a sleep recording. This was higher than the prevalence of other traditionally recognized risk factors: hypertension, obesity, diabetes mellitus, and current smoking (Figure 5). The CAD patients who did not participate in the study demonstrated a similar anthropometric and clinical profile compared to the studied group except that those who did not participate were slightly older and more often female gender, more of them had undergone CABG and more had pulmonary disease. Patients included in the study who had OSA, had a higher prevalence of obesity, hypertension, and diabetes, as well as a history of atrial fibrillation. Concomi-

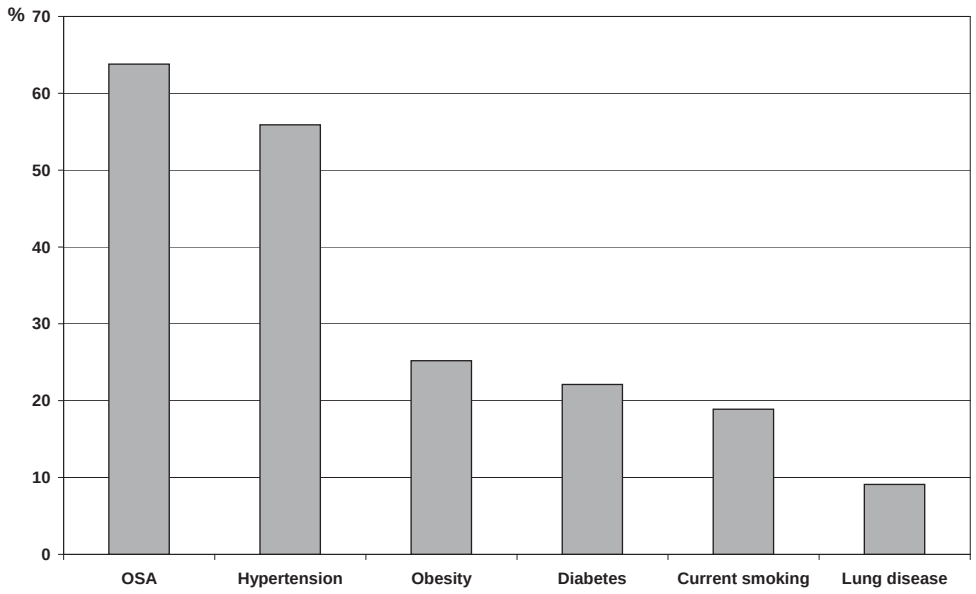

Figure 5. Occurrence of obstructive sleep apnea and the traditionally recognized risk indicators for coronary artery disease. OSA = obstructive sleep apnea.

tant lung disease was more common among the patients without OSA who agreed to participate in the RICCADSA study. Age, male gender, BMI and ESS score, but not comorbidities, were independent predictors of OSA (Table 3).

Table 3. Baseline variables associated with OSA in the study population (n=641)

	OR	95% CI	p Value
Univariate analysis			
Age	1.02	1.00-1.04	0.035
Male gender	1.53	0.99-2.37	0.053
BMI	1.23	1.17-1.30	<0.001
Obesity	4.23	2.63-6.81	<0.001
Current smoking	0.62	0.42-0.93	0.022
ESS	1.12	1.07-1.17	<0.001
Excessive Daytime Sleepiness	3.57	2.34-5.45	<0.001
Hypertension	1.71	1.23-2.39	0.001
Diabetes mellitus	1.89	1.23-2.91	0.004
Multivariate analysis			
Age	1.06	1.03-1.08	0.000
Male gender	1.89	1.12-3.18	0.018
BMI	1.24	1.17-1.32	0.000
Current smoking	0.91	0.56-1.46	0.687
ESS	1.10	1.04-1.16	0.001
Hypertension	1.29	0.88-1.89	0.192
Diabetes mellitus	1.21	0.73-2.00	0.463

Definition of abbreviations OSA=Obstructive Sleep Apnea; OR=Odds ratio; CI=Confidence interval; BMI=Body-Mass-Index; ESS=Epworth Sleepiness Scale

Paper III

Association between obstructive sleep apnea and diastolic dysfunction in revascularized patients with coronary artery disease

More echocardiographic variables showed abnormal findings in the patients with CAD and OSA, compared to the non-OSA patients (Table 4). Diastolic dysfunction with a normal or assumed elevated LVFP based on the given criteria was found among 92.1% of the OSA group and 83.0% of the non-OSA group (p=0.007). CAD patients with OSA had worse diastolic function than non-OSA patients (54.4% vs 41.0%; p=0.019). In a bivariate logistic regression analysis of the categorical variables, OSA, female gender, hypertension, diabetes mellitus, as well as hypertrophic remodeling and pulmonary hypertension were significantly associated with worse diastolic function, while age above 60 years, obesity, abdominal obesity, excessive daytime sleepiness, current smoking, and history of atrial fibrillation did not show an association. As illustrated in Figure 6, in the multivariate logistic regression analysis, OSA, female gender, hypertension and diabetes mellitus remained as significant predictor of worse diastolic function, with ORs between 1.84 and 2.45.

Table 4. Echocardographic findings of the revascularized CAD patients with preserved ejection fraction

Variable*	OSA (n=331)	Non-OSA (n=100)	p Value
IVS thickness (mm)	13.4 ± 2.5	12.2 ± 2.5	<0.001
LVPW thickness (mm)	11.7 ± 2.1	11.0 ± 1.9	0.001
LVDD (mm)	46.9 ± 5.6	47.6 ± 6.8	0.301
LVDS (mm)	29.9 ± 5.8	30.3 ± 5.5	0.504
RWT (mm)	0.51 ± 0.12	0.47 ± 0.10	0.002
LVMI ($g/m^{2.7}$)	51.6 ± 13.0	48.0 ± 15.8	0.022
Hypertrophic remodelling (%)	53.8	44.0	0.086
LA diameter (mm)	43.4 ± 5.5	40.2 ± 4.6	<0.001
é septal (cm/s)	6.8 ± 1.6	7.6 ± 1.8	<0.001
E/A (ratio)	1.0 ± 0.3	1.2 ± 0.4	<0.001
E/é (ratio)	11.0 ± 3.6	10.4 ± 3.7	0.139
LVEF (%)	60.0 ± 5.0	60.2 ± 4.3	0.743
PASP (mmHg)†	30.4 ± 5.5	28.2 ± 5.0	0.007
Pulmonary hypertension (%)†	12.9	8.1	0.312
Diastolic dysfunction (%)	92.1	83.0	0.007
Elevated LVFP (%)	54.4	41.0	0.019

*Continuous variables are expressed as mean ± SD, statistics by unpaired Student´s *t* test. Comparison of groups by chi-squared test (two tailed). *Definition of abbreviations:* CAD=coronary Artery Disease; LV=Left Ventricular; OSA=Obstructive Sleep Apnea; IVS=Interventricular Septum; LVPW=Left Ventricular Posterior Wall; LVDD=Left Ventricular Diameter in Diastole; LVDS=Left Ventricular Diameter in Systole; RWT=Relative Wall Thickness; LVMI=Left Ventricular Mass Index; LA=Left Atrium (M mode); é=Tissue Doppler of early diastolic ventricular filling; E/A=peak flow velocity in early diastole/peak flow velocity in atrial contraction; E/é=peak flow velocity in early diastole/medial é- velocity; LVEF=Left Ventricular Ejection Fraction; LVFP=Left Ventricular Filling Pressure; PASP=Pulmonary Artery Systolic Pressure; †Measurements were performed in 163 OSA and 62 non-OSA patients with detectable tricuspidalis regurgitation.

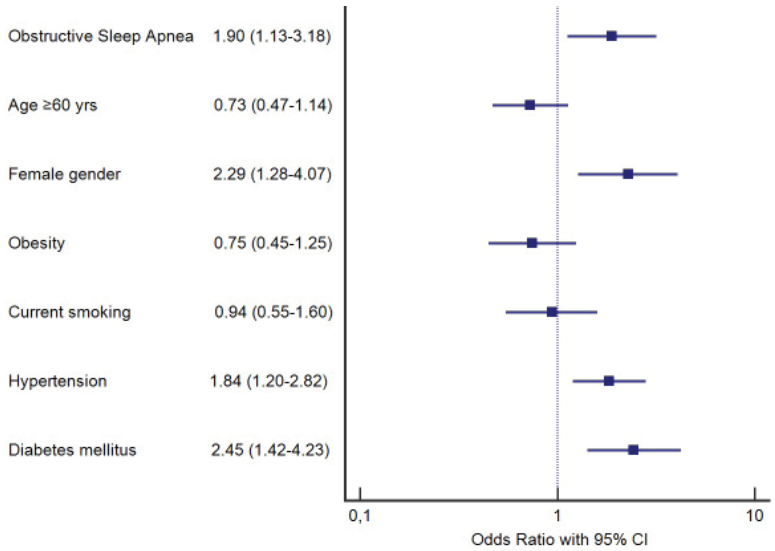

Figure 6. Multivariate regression analysis of the clinical variables associated with worse diastolic function in patients with revascularized coronary artery disease and preserved left ventricular ejection fraction. CI, confidence interval.

Paper IV

Effect of CPAP treatment on diastolic function in coronary artery disease patients with non-sleepy obstructive sleep apnea after three months and one year

In this selected group of 171 patients, CPAP prescription had no significant impact on the measured diastolic function parameters left atrial diameter or myocardial relaxation velocity, or on the ratio of early diastolic mitral flow to myocardial relaxation velocity (E/é) in the ITT population. In the on-treatment analysis, for CPAP usage of at least four hours per night, there were no significant changes three months after the study start, while there was a trend for an increase in the mean é velocity after one year whereas there was a decrease in the mean é velocity among patients with lower CPAP usage or no CPAP. For the categorical variables in the multivariate model, CPAP usage of at least four hours per night was associated with a 2.3-fold increase in the é tissue velocity after one year; an even stronger association was found for CPAP usage of at least five hours per night after adjustment for age, female gender, BMI and left atrial diameter at baseline (Table 5).

Table 5. Multivariate logistic regression analysis of CPAP usage associated with an increased é velocity after 12 months adjusted for age, female, sex, BMI and left atrium diameter at baseline in coronary artery disease patients with non-sleepy obstructive sleep apnea

	Odds Ratio	95% Confidence Interval	p Value
CPAP hours per night	**1.18**	**1.04-1.34**	**0.012**
CPAP usage ≥3 hours/night	1.80	0.86-3.74	0.117
CPAP usage ≥4 hours/night	**2.25**	**1.04-4.86**	**0.039**
CPAP usage ≥5 hours/night	**3.09**	**1.30-7.32**	**0.010**

Definition of abbreviations: BMI=body-mass-index; CPAP=continuous positive airway pressure; é=tissue doppler of early diastolic ventricular filling.

Paper V

Effect of CPAP in patients coronary artery disease and obstructive sleep apnea on long-term adverse cardiovascular outcomes

In this main primary endpoint paper, median follow-up time until mortality, loss to follow-up, or the end of the study was 57 months (range 6.5–90.2). All patients were included in the ITT analysis for primary outcomes; 16 patients died, and one was lost to follow-up (Figure 3).

Comparison between polygraphy and polysomnography

Overnight PSG in hospital was performed after the baseline cardiorespiratory PG recordings were made (median 29 days, range 5-146 days). The mean total sleep time recorded during PSG was shorter (372±92 minutes) compared with the estimated

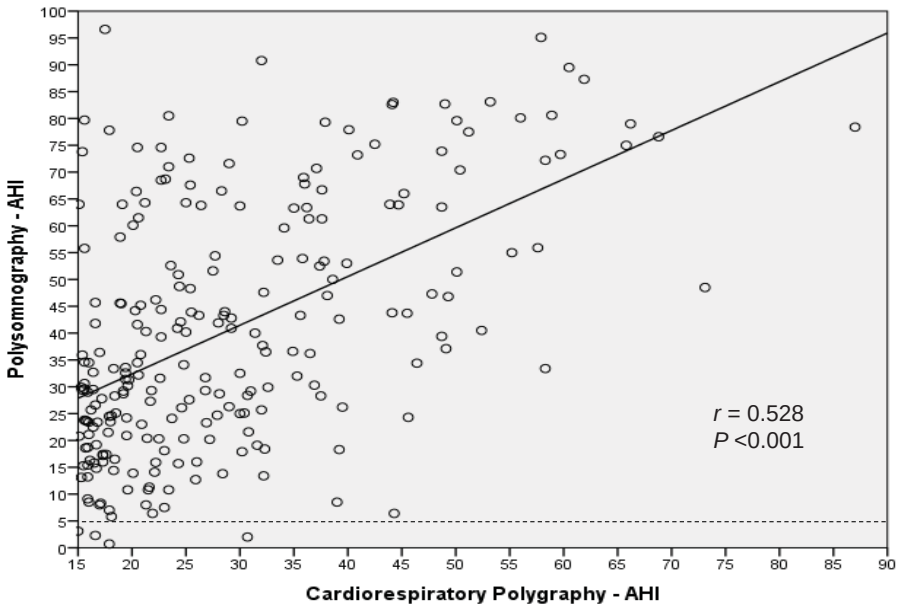

Figure 7. Apnea-hypopnea index (AHI) in OSA patients based on polygraphy versus polysomnography.

sleep time during the PG recording (424±63 minutes; p<0.001). Time spent in the supine position was shorter (30.7±25.3%) with home PG than with PSG (35.7±27.8%; p=0.011). Average AHI values were, as expected, higher (40.4±22.9) in PSG than in PG (28.9±13.3; P<0.001) because home PG recordings usually underestimate AHI due to recording time exceeding actual sleep time. As illustrated in Figure 7, there was a linear correlation between AHI values in PG and PSG (r=0.528; P<0.001). On the other hand, among patients who had an AHI ≥15 on home-based PG, 23 had mild OSA (AHI ≥5 to <15), and four did not have OSA (AHI<5) according to PSG. However, the repeated PG recordings and data from the CPAP devices in treated patients supported the initial group allocation.

CPAP compliance

Among OSA patients allocated to CPAP at baseline, 49 returned the device within two years. Of the non-sleepy OSA patients randomized to no CPAP, three wanted to start CPAP at baseline, and 22 during the amended follow-up period because they had reached the nonfatal endpoints or completed the initial three-year follow-up (or both), or because they had developed daytime sleepiness. As shown in Table 6, compliance with CPAP varied between an average of 4.4 hours per night (first month) and 6.9 hours per night (year five) for those who continued with their CPAP treatment. The average nights of CPAP use varied between 69% (first month) to 78% (year five) of the time intervals of the study in patients who were still on treatment.

Table 6. CPAP compliance data over time in 122 revascularized patients with coronary artery disease and obstructive sleep apnea (patients who returned the devices are excluded)

	Number of patients on CPAP	Number of CPAP devices checked	CPAP use (hours/night)	CPAP use (% nights/period)	CPAP level in 95th percentile (cmH_2O)	Residual AHI (events/hour)
At 1 month	105	98	4.4 (2.3)	70.4 (29.8)	9.3 (2.2)	9.5 (2.4)
At 3 months	92	88	5.1 (2.1)	73.4 (25.9)	9.7 (1.6)	6.2 (5.1)
At 6 months	83	79	5.5 (1.9)	71.6 (27.4)	9.9 (2.8)	6.2 (4.9)
At 1 year	76	73	5.8 (1.7)	76.6 (24.1)	9.5 (1.6)	5.9 (4.3)
At 2 years	70	67	6.0 (1.7)	74.0 (24.9)	9.6 (2.9)	5.4 (3.6)
At 3 years	55	53	6.1 (1.8)	74.5 (22.6)	9.2 (1.7)	6.0 (3.4)
At 4 years	35	33	6.2 (1.7)	73.4 (22.6)	8.7 (1.7)	5.4 (2.8)
At 5 years	21	12	6.9 (1.2)	78.0 (16.4)	10.4 (5.1)	4.5 (3.4)
At 6 years	11	9	6.6 (1.3)	69.1 (19.1)	9.5 (2.4)	5.0 (2.4)

Values are mean (standard deviation). *Definition of abbreviations*: AHI=apnea hypopnea index; CPAP=continuous positive airway pressure; OSA=obstructive sleep apnea.

Outcomes

Intention-to-treat population

In the whole non-sleepy group, 49 patients reached the combined endpoint during follow-up (22 in the CPAP group, and 27 in the no-CPAP group), and the incidence of the composite endpoint was 4.65 (95% CI 4.56–4.73) per 100 person-years; 4.18 (95% CI 2.75–6.35) per 100 person-years in the CPAP group vs 5.21 (95% CI 3.57–7.60) per 100 person-years in the no-CPAP group (p=0.449). As illustrated in Figure 8, the cumulative incidences of the primary endpoint did not differ significantly. Univariate predictors of adverse outcomes were diabetes mellitus and former revascularization, while CABG at baseline was protective (Table 7). In the multivariate analysis, diabetes mellitus (HR 2.05; 95% CI 1.06–3.98; P=0.034) and former revascularization (HR 3.29; 95% CI 1.77–6.10; P<0.001) were significantly associated with increased risk for the composite endpoint, whereas CABG at baseline (HR 0.30; 95% CI 0.12–0.75; P<0.001) was associated with reduced risk.

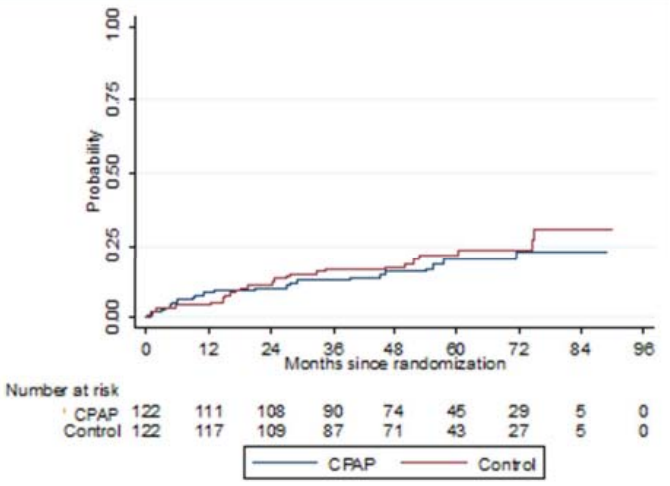

Figure 8. Cumulative incidences of the composite endpoint in the intention-to-treat population. Definition of abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio; OSA, obstructive sleep apnea.

Table 7. Cox regresson analysis of baseline covariables associated with risk for adverse cardiovascular outcomes in revascularized patients with coronary artery disease and obstructive sleep apnea without daytime sleepiness in the intention-to-treat analysis (n=244; 49 patients reached the composite endpoint)

	Univariate			Multivariate		
	Hazard Ratio	**95% CI**	***P* Value**	**Hazard Ratio**	**95% CI**	***P* Value**
CPAP assignment vs. no-CPAP	0.80	0.46–1.41	0.449	0.62	0.34–1.13	0.120
Age	1.02	0.98–1.05	0.372	1.01	0.98–1.05	0.474
Females vs. males	0.48	0.17–1.33	0.155	0.43	0.15–1.23	0.114
Apnea-hypopnea index	1.00	0.98–1.02	0.783	0.99	0.97–1.01	0.363
Body mass index	1.01	0.94–1.09	0.753	0.99	0.91–1.08	0.802
CABG vs. PCI	0.38	0.17–0.84	0.017	0.30	0.12–0.75	0.010
Current smoking	1.29	0.63–2.67	0.485	1.78	0.80–3.96	0.156
Hypertension	1.09	0.60–1.96	0.776	1.59	0.81–3.12	0.176
Diabetes mellitus	1.92	1.06–3.47	0.030	2.05	1.06–3.98	0.034
Acute myocardial infarction	1.02	0.58–1.79	0.947	1.03	0.54–1.94	0.937
Previous PCI or CABG	3.36	1.91–5.93	<0.001	3.29	1.77–6.10	<0.001
Pulmonary disease	1.39	0.50–3.85	0.532	0.95	0.33–2.74	0.925
Left ventricular ejection fraction	0.99	0.96–1.02	0.594	0.99	0.96–1.02	0.513

Definition of abbreviations: CABG=coronary artery bypass grafting; CI=confidence interval; CPAP=continuous positive airway pressure; PCI=percutaneous coronary intervention.

On-treatment population

In the on-treatment analysis, there was a significant between-group difference in a comparison based on CPAP usage: among the group who used CPAP at least four hours per night a total of six events were recorded, whereas among those with less than four hours per night or no CPAP the total was 43 events, with an HR of 0.29 and 95% CI 0.10–0.86 with covariable adjustments (Table 8).

Table 8. Cox regression analysis of the association between time-dependent CPAP usage (hours/night) and adverse cardiovascular outcomes in 244 revascularized patients with coronary artery disease and obstructive sleep apnea without daytime sleepiness (49 patients reached the composite endpoint)

	Univariate			Multivariate*		
	Hazard Ratio	**95% CI**	***P* Value**	**Hazard Ratio**	**95% CI**	***P* Value**
CPAP usage ≥3 hours/night	0.64	0.31–1.33	0.234	0.91	0.16–5.13	0.911
CPAP usage ≥4 hours/night	0.43	0.18–1.02	0.057	0.29	0.10–0.86	0.026
CPAP usage ≥5 hours/night	0.43	0.17–1.09	0.075	0.34	0.10–1.12	0.075

Definition of abbreviations: CPAP=continuous positive airway pressure, CI=confidence interval. *Adjusted for age, gender, body mass index, apnea hypopnea index, current smoking, pulmonary disease, hypertension, diabetes mellitus, acute myocardial infarction, revascularization type at baseline, former revascularization, and left ventricular ejection fraction at baseline.

DISCUSSION

Interpretation of the main results

In this thesis, undiagnosed OSA was highly prevalent among revascularized CAD patients, and the majority of these individuals did not report daytime sleepiness. The occurrence rate of OSA, based on a cut-off level of AHI ≥15, was higher than the prevalence of the traditionally recognized risk indicators for CAD. Moreover, CAD patients with concomitant OSA demonstrated a more severe comorbidity profile compared to CAD patients without OSA (Paper II).

Regarding cardiac function, based on the echocardiographic diastolic parameters, OSA was independently associated with worse diastolic function in terms of signs of an elevated LVFP. There was an almost twofold increase in risk of having an elevated LVFP, adjusted for the confounding factors (Paper III). These findings in the first two papers support the current literature suggesting an independent relationship between OSA and CAD in clinical cohorts; furthermore, the findings give additional insights into predictors of OSA in a CAD population, and different aspects of diastolic function in CAD with concomitant OSA.

When addressing the causal relationship, the papers presented in this thesis found no significant reversibility or improvement following three months to one year of CPAP treatment in non-sleepy CAD patients with OSA in the ITT population in this RCT (Paper IV). Neither was there a significant reduction in adverse cardiovascular outcomes after prescription of CPAP to all CAD patients with OSA regardless of daytime sleepiness (Paper V). Thus, our results do not confirm that all CAD patients with non-sleepy OSA should be prescribed CPAP. Screening for OSA, however, seems to be reasonable in order to take into consideration OSA as a confounding factor in secondary prevention models. The main question of this thesis was whether CPAP is an effective method of reducing adverse cardiovascular outcomes in CAD patients who are otherwise non-sleepy. The answer to this question remains maybe, given the positive effect in CPAP-adherent patients. In this context, there are two main issues to highlight: first, the sample size of the entire study population necessary to achieve a high evidence level in an RCT, and second, CPAP usage in terms of hours per night and percentage of the time period, as these aspects are still poorly described in the current literature.

Was the sample size large enough to address the primary research questions?

As summarized in the Methods chapter, there were no prior RCTs regarding the impact of CPAP treatment in CAD patients with non-sleepy OSA. It might therefore be argued that there is no justification for the risk reduction in the primary endpoint from 25% to 12%, which is a large effect for a clinical trial, particularly for a non-pharmaceutical intervention. At the time of the interim analysis, we realized that the original sample size calculation was overly optimistic, given that CPAP adherence in

patients with CAD and non-sleepy OSA was also lower than initially expected. Furthermore, for practical and financial reasons it was not possible to increase the sample size substantially.

What is the optimal CPAP adherence in order to achieve beneficial cardiovascular effects in coronary artery disease patients with non-sleepy obstructive sleep apnea?

According to the literature, four hours of nightly CPAP use for 70% of the nights is considered adequate adherence to therapy in sleep clinic cohorts[169]. This translates into an average CPAP use of 2.8 hours every night. A previous report by Weaver et al. in 2007 suggested that the thresholds for mean duration of overnight CPAP use in achieving improvement were 4 hours for ESS scores, 6 hours for the Multiple Sleep Latency Test, and 7.5 hours for Functional Outcome of Sleep Questionnaire scores[170]. There is as yet no consensus regarding "effective" adherence to CPAP treatment for cardiovascular endpoints. In a recent report by Thunström et al. addressing the impact of CPAP as add-on treatment to an antihypertensive agent to achieve optimal blood pressure control, at least four hours of CPAP usage increased the proportion of patients with adequate blood pressure control from 13% to 39%[21]. This level of CPAP hours every night seems to be a reasonable minimal adherence level also in CAD patients with non-sleepy OSA (Paper IV and Paper V).

Was the study cohort representative?

The study population was recruited in the two hospitals Skövde and Lidköping cardiology outpatient clinics after revascularization with CABG or PCI. A total of 1291 patients were invited to participate in the study, of whom 32 patients with known OSA diagnosis were excluded and 1259 were eligible for the study. In the sleep screening study there were 662 participants, 52.7% of the eligible patients. The patients who declined to participate were slightly older, the proportion of women was higher, and they had more often undergone CABG compared to the investigated group. There were no statistically significant differences regarding comorbidities except for lung disease, which was more frequent in the screened group. Thus, we consider the patients in our cohort representative, since they had similar comorbidities compared to the patients who did not undergo sleep recording.

Is the definition of obstructive sleep apnea adequate?

As the RICCADSA trial was started in 2005, the sleep apnea scoring was based on the AASM definitions from 1999. The group allocation was based on the cardiorespiratory sleep recordings, even if PSG measurements had been performed in the OSA group before the randomization. In the protocol, these measurements would be scored by an independent observer later during the recruitment period for post-hoc analyses of the PG and PSG results, and the post-hoc comparisons of the sleepy and non-sleepy OSA phenotypes. As the AASM rules have been modified several times during the period this thesis covers, rescoring of the baseline and follow-up sleep recordings according to the AASM criteria from 2007 and 2012 would provide interesting data and are part of the planned future work of our research group.

Is the epworth sleepiness scale a reliable tool for group allocation based on excessive daytime sleepiness?

About one-third of patients with OSA in this CAD cohort had excessive daytime sleepiness as defined by an ESS score of at least 10. Compared with a general population, this number is relatively high but still low compared to the sleep clinic cohorts. The ESS is a simple tool and may not reflect real sleepiness of clinical importance. However, this is the most commonly used tool globally in clinical practice. Objective sleepiness tests, such as the Multiple Sleep Latency Test[171], are time-consuming and not feasible to run for large-scale cardiac populations. To date, there are no specific subjective sleepiness questionnaires adapted to patients with cardiovascular diseases. Hypothetically, ESS could be less effective at determining whether patients have daytime sleepiness if they have concomitant CAD, since these patients could have difficulties separating fatigue caused by their CAD and sleepiness caused by their OSA.

Is obstructive sleep apnea a forgotten risk factor for coronary artery disease?

As described in detail in the Introduction of this thesis, there is accumulating research evidence for an independent association between OSA and CVD, particularly hypertension and also CAD. In a recent study of 500 subjects from five different cardiology subspecialty outpatient clinics (100 patients in each), the prevalence of OSA, based on a questionnaire followed by a portable home-sleep recording with a cut-off level of AHI ≥15, was reported to be 66%, varying from 50% (in the hypertension group) to 80% (in the heart failure group)[172]. A recent review of available studies accumulating 2324 patients with CAD, demonstrated an OSA prevalence of around 47%[173]. In spite of the differences in the diagnostic procedures (full PSG or PG) as well as different AHI or ODI cut-off values for definitions of OSA, there seems to be enough evidence to warrant overnight sleep screening in individuals with CAD, given that concomitant OSA may worsen long-term outcomes. Thus, OSA seems to be a more recognized factor now compared with the recognition of this condition in previous years. Indeed, in the current national guidelines of the Swedish Society of Cardiology, OSA is mentioned among factors to be considered for secondary prevention, and it is recommended to refer patients for a diagnostic investigation at the first suspicion of OSA[97].

What is the association between obstructive sleep apnea and diastolic dysfunction in coronary artery disease?

In our relatively large cross-sectional cohort of CAD patients with preserved LVEF, OSA was associated with worse diastolic function adjusted for the traditionally recognized risk indicators. The prevalence of diastolic dysfunction, including the mildest degree (enlargement of left atrial diameter or decreased é tissue velocity) was 90% in the whole population with preserved LVEF. This high prevalence may be attributed to pathophysiological mechanisms, due to myocardial ischemia per se or its risk factors in CAD[121]. Regarding the other comorbidities associated with diastolic dysfunction, previous studies have shown more pronounced abnormalities of the left ventricular mass index and left atrial remodeling in hypertensive patients[103,174]. This is supported in our cohort, where hypertension was associated with worse diastolic function in the

multivariate analysis. In addition, our results, with an almost 2.5-fold increase in risk among diabetes patients, support previous reports regarding an independent relationship between diabetes mellitus and diastolic dysfunction[175]. OSA has been shown to be associated with echocardiographic measurements of concentric hypertrophy[176] as well as insulin resistance, neurohormonal activation, increased oxidative stress and systemic inflammation[173,177], which all have been suggested as explanatory mechanisms for the development of diastolic dysfunction.

Are the methods that were used to define diastolic dysfunction adequate?

Echocardiography parameters measuring diastolic dysfunction have been debated for a long time. In the data presented in this thesis, diameter rather than volume of the left atrium on Echocardiography was reported because that was the clinical praxis in our hospitals at the time of the study start in 2005. However, we applied the recommended sex-stratified cut-off values for the definition of a dilated left atrium[163] used in our practice at the time, a condition that has been suggested to predict heart failure mortality in patients with chronic CAD[110]. Additionally, we relied on the well-validated parameters of diastolic dysfunction, such as tissue Doppler velocities, which have been shown to predict future heart failure hospitalizations[110,111]. Since E/é alone has been shown to have limited sensitivity to diagnose an elevated left ventricular filling pressure[178,179], we applied the combination of E/é values and the enlargement of LA parameters, as also suggested previously[116].

Is CPAP treatment feasible in coronary artery disease patients with non-sleepy obstructive sleep apnea?

Many CAD patients with OSA do not experience daytime sleepiness, and it has been suggested that non-sleepy OSA patients are less motivated to adhere to CPAP treatment because they do not see any benefits from this therapy[180]. Nonetheless, overall adherence in the current CAD population did not differ markedly from long-term adherence rates in sleep clinic cohorts[181]. This is confirmed by an observational study of a sleep clinic cohort with CAD that found comparable adherence to CPAP in sleepy and non-sleepy patients[182]. A larger RCT addressing the impact of CPAP treatment on incident hypertension and cardiovascular events in non-sleepy OSA patients from sleep clinics reported that 64% of patients were using CPAP for at least four hours per night after a median four-year follow-up[15]. Data from the SAVE trial suggest a lower CPAP compliance rate than in this study (RICCADSA), despite an initial one-week run-in phase with sham CPAP to exclude noncompliant patients before randomization[183]. Using this approach, 15% of the eligible patients were excluded before the randomizations in that report from the ongoing SAVE trial, thus possibly identifying those who were better suited for CPAP treatment.

Are the definitions that were used to detect the cardiovascular endpoints adequate?

The review by an ICEC was based on a previously described definition of the endpoints[165]. This definition was applied in the HOT study[166] as well as in other trials. The ICEC review included all data from hospital records and death certificates up to the

end of May 2013 and was blinded to group allocation and personal identity. Overall mortality was based on the death certificate. Thus, the definitions used and the independent blinded evaluation assessed for the endpoints increase the quality of the data reported in this thesis.

Does treatment with CPAP improve diastolic function in coronary artery disease?

In Paper IV, routine prescription of CPAP to patients with CAD and non-sleepy OSA with preserved LVEF did not result in a statistically significant improvement in echocardiographic measures of diastolic dysfunction. The worse diastolic function as well as enlarged LA diameter demonstrated in Paper III were not reversed with CPAP in the ITT population. However, on-treatment analysis based on CPAP usage of at least four hours per night was significantly associated with an increase in the é tissue velocity after adjustment for confounding factors. The neutral result in the ITT population may be due to several factors. The study patients had CAD and often hypertension and diabetes as well, conditions which cause fibrosis that reduces long axis function and may persist despite currently available treatments[184,185]. Moreover, other cardiac treatments than CPAP for OSA were administrated on clinical indications and were not controlled for in the statistical analyses. In addition, seen as a lifelong pathophysiological process, one year may be too short a period for intervention in order to demonstrate an improvement in cardiac function.

How should we interpret the improvement in the é tissue velocity in CPAP-compliant coronary artery disease patients with obstructive sleep apnea?

As é is a fairly stable parameter and deteriorates with increasing age, this finding should be interpreted cautiously. Nevertheless, the literature includes studies showing that improvements in é are possible following an effective antihypertensive treatment in hypertension[186]. Weight reduction in obese patients[187] as well as physical training in patients with heart failure and preserved LVEF[188] have also been found to improve é. It should also be emphasized that increased LA size seemed to inhibit the improvement in é in the multivariate analysis, and the proportion of subjects with increased LA size was higher in the group allocated to CPAP treatment. The clinical relevance of the increased é in the CAD patients with OSA who were complaint with CPAP treatment needs further long-term evaluation in the current cohort with regard to, for instance, hospitalizations for cardiac failure.

Does treatment with CPAP improve long-term outcomes in non-sleepy obstructive sleep apnea?

In our cohort, routine prescription of CPAP to patients with CAD and non-sleepy OSA did not significantly reduce the long-term cardiovascular event rate in the ITT population. A significant reduction in adverse outcomes was seen only after adjusting for baseline comorbidities and CPAP adherence. So, as discussed in the beginning of this chapter, CPAP adherence is crucial for a beneficial impact of this treatment. However, getting non-sleepy patients to comply with CPAP is challenging. Baseline differences in comorbidities between groups may also have influenced the findings.

As randomization was not stratified by comorbidities, and there was a higher proportion of patients with AMI, diabetes mellitus, and hypertension in the CPAP group, this might weaken a true effect of CPAP treatment, making the effect non-significant.

How should we treat obstructive sleep apnea in coronary artery disease patients if they do not accept CPAP treatment?

As summarized in the Introduction chapter, CPAP is not the only treatment option for OSA. Indeed, in a recent RCT, adherence to a weight loss regimen and CPAP resulted in incremental blood pressure reductions compared with either intervention alone[189]. There is also accumulating evidence for a beneficial impact of mandibular advancement devices on blood pressure in OSA patients[190,191]. Moreover, given the emergence of new mechanical and pharmacological interventions in sleep medicine[192], improved "personalization" of OSA therapy may be possible through better characterization of individual patient pathophysiology.

What are the ethical dilemmas in the design of randomizing an obstructive sleep apnea patient to no treatment during a long period?

Due to the serious acute cardiovascular responses during obstructive events, it has been argued that it is unethical to design long-term RCTs in OSA patients[138]. On the other hand, long-term follow-up studies do not always support an adverse impact of the disorder and are not prospectively controlled for the confounding factors such as high age, obesity, insulin resistance, hyperlipidemia, smoking and life-style habits; thus, a real causal relationship between OSA and CAD has not yet been readily confirmed. Moreover, long-term adherence to CPAP treatment in CAD patients with concomitant OSA without daytime sleepiness was yet not proven in the planning phase of this thesis. Indeed, a previous study[182] addressed the issue in a sleep clinic cohort in OSA subjects with CAD, suggesting a comparable compliance between sleepy and non-sleepy patients at one-year follow-up. However, since these patients were recruited from a sleep clinic cohort, they all had some form of complaints, though not significant daytime sleepiness, and could therefore have benefitted from the CPAP treatment. The issue in a cardiac clinic population is quite different, as the subjects themselves are not actively seeking for a referral but being considered for a screening procedure. When screening is carried out, OSA is usually diagnosed as a "laboratory" rather than a "clinical" disorder. For those CAD patients who do not have complaints related to OSA symptoms, it may therefore constitute a challenge to convince them to be treated "by a mask on the face" as a kind of "chronic cardiovascular treatment". The issue becomes even more complicated if such an intervention would adversely affect the patient's quality of life. Thus, despite a very high occurrence of OSA in CAD patients, these high-risk subjects were not routinely being screened for OSA by cardiologists, and treatment with CPAP is not being considered either in clinical practice.

Strengths of the thesis

One of the strengths of this thesis, which represents 10 years' work, is its randomized controlled design for patients with CAD and non-sleepy OSA with only 1 lost to follow-up (Paper V). Although the inclusion rate for eligible patients for sleep screening was only 53%, the inclusion design was consecutive, and there were no significant

differences in baseline characteristics with regard to comorbidities in revascularized patients who were included in the RICCADSA trial compared to those not eligible or those who declined to participate, as described in Paper II.

This thesis adds to previous knowledge in several aspects. It is a randomized controlled study of CAD patients with non-sleepy OSA and, to date, the first one reported in literature within this field of research. Many of the previous cardiac function studies are limited to sleepy OSA patients without structural CVD, and their CPAP follow-up included only compliant patients[120,193]. In contrast to previous studies, our study (Paper III, Paper IV) included a population more affected by an advanced heart disease, CAD, and also included non-sleepy OSA patients, a more common condition than sleepy OSA in cardiac populations. The primary endpoints were evaluated by an independent clinical event committee, blinded to patient identities and group allocation. A data and safety monitoring board reviewed the protocol and monitored a random 10% selection of the database for baseline clinical data and follow-up procedures, including CPAP adherence and primary endpoints. CPAP adherence rates were obtained from the devices and registered consecutively in the patient records by the sleep clinic nurses, who were not involved in the trial management.

Limitations of the thesis

Almost half of the CAD patients who were eligible for the sleep study chosed not to participate. Reasons for declining were long journeys, in-hospital procedures, and lack of sleep complaints or being too tired after the mechanical revascularization. Their lack of sleep complaints might be interpreted as low probability of having OSA. However, this does not seem to be the case for CAD patients as almost two-thirds of the OSA group did not report significant sleep complaints. Subjective tiredness following the mechanical revascularization might also mask excessive daytime sleepiness and symptomatic OSA. Since there were no statistically significant differences between the screened and non-screened groups with regard to BMI, obesity, current smoking, and comorbidities other than a lower prevalence of lung disease among the screened group, our sleep study cohort was relatively representative for the revascularized CAD patients in this region during the inclusion period.

Other limitations are acknowledged as follows: First, the trial was a single-center trial with two sites, which limits generalizability of results across geographic regions. Second, “non-sleepy” OSA relied on an ESS threshold which may not reflect objective sleepiness, as discussed above. Third, the trial was underpowered for the ITT arm regarding the primary endpoints partly due to the fact that CPAP adherence in patients with CAD and non-sleepy OSA was lower than initially expected. Fourth, revascularized CAD patients were a heterogeneous group, including both PCI and CABG, and both acute/subacute and elective PCI, and the apparent treatment effect was smaller than anticipated due to an optimistic first assumption. Fifth, the trial was open-label, and had no placebo control arm. On the other hand, there is no true sham CPAP or other appropriate placebo for CPAP in a long-term trial in CVD patients. Finally, results of the on-treatment analysis must be interpreted cautiously, as device usage is patient-driven and self-selection bias cannot be excluded.

CONCLUSION

This thesis emphasizes that OSA is common in CAD and also suggests that OSA is associated with a worsening of DD in patients with CAD. Prescription of CPAP treatment did not significantly reduce the long-term cardiovascular event rate in patients with CAD and non-sleepy OSA, nor did it improve DD among the evaluated echocardiographic parameters of DD in the patients with preserved LVEF. Nonetheless, when the patients were compliant with CPAP treatment, and after adjustment for baseline comorbidities, significant beneficial effects were found.

FUTURE ASPECTS

There are several interesting research questions that need to be addressed in the future:

- Is there an association between the degree of OSA and outcome among patients with various cardiovascular manifestations?
- How should we increase the feasibility of treatment with CPAP among patients who do not have symptoms?
- How should patients with various cardiovascular diseases and OSA but without symptoms be treated in the future? Should they have CPAP? Or other treatment, such as mandibular advencement therapy? Should treatment be individualized?
- How does treatment with CPAP among patients with a cardiovascular disease and OSA but without symptoms influence their quality of life?
- What are the mechanisms behind the association between the presence of OSA and various cardiovascular manifestations among patients with and without a cardiovascular disease?
- Which OSA phenotypes benefit the mostly from CPAP treatment? Sleepy or non-sleepy patients? Those with severe desaturations? Those with comorbidities?
- Would the outcomes be different if the hypopnea criteria from 2007 and 2012 would be applied?
- Which inflammatory markers are of importance in CAD with OSA for long-term outcomes?
- What is the natural course of an untreated OSA in CAD patients?

We plan to address some of these questions through sub-analyses of the RICCADSA data, thereby further expanding the body of knowledge concerning how OSA and CAD are associated.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Med sömnapné avses mer eller mindre fullständiga andningsuppehåll under sömnen. Sådana uppehåll har visats leda till sänkt syremättnad i blodet. Detta i sin tur tros kunna leda till syrebrist i olika organ i kroppen. Under de senaste två decennierna har ett ökande intresse riktats mot sambandet mellan förekomst av sömnapné och olika manifestationer av hjärt- och kärlsjukdomar.

Denna avhandling fokuserar på patienter med kranskärlssjukdom (åderförkalkning i hjärtats kärl). Tidigare forskning har hävdat att sömnapné påskyndar åderförkalkningsprocessen i hjärtats kärl och därigenom på ett ogynnsamt sätt påverkar prognosen. Det har också visats att behandling med kontinuerlig övertrycks andning under natten med hjälp av en apparat och en mask (CPAP = Continuous Positive Airway Presssure) skulle kunna förbättra prognosen för patienter med sömnapné (under förutsättning att de har symptom i form av dagtidssömnighet). Huruvida behandling med CPAP även skulle kunna ha gynnsamma effekter bland patienter med sömnapné som inte har dagtidssömnighet är inte känt. Det har också föreslagits att förekomst av sömnapné i ett långsiktigt perspektiv skulle kunna påverka hjärtfunktionen på ett ogynnsamt sätt. Ett speciellt intresse har riktats mot den del av hjärtfunktionen som speglar hjärtats fyllnadsfas (när de båda kamrarna fylls med blod i sin vilofas). Denna del av hjärtats funktion kallas för hjärtats diastoliska funktion (diastole = hjärtats fyllnadsfas). Det är ovanstående frågor som belyses i denna avhandling.

Patientmaterialet är insamlat i Skaraborg under tidsperioden december 2005 till december 2012. Samtliga patienter med en diagnostiserad kranskärlssjukdom som under denna tidsperiod har genomgått behandling med antingen kranskärlskirurgi eller så kallad ballongdilatation har utgjort studiens bakgrundspopulation. Båda dessa behandlingar siktar till att återställa hjärtats blodförsörjning. Det är dessa patienter som har tillfrågats om eventuellt deltagande i studien. De som har sagt ja till deltagande har i första hand fått genomgå en undersökning, sömnregistrering, som kallas för polygrafi och som innebär att patienten under natten i sitt eget hem får kartlagt om han/hon har sömnapné. Detta fastställs utifrån givna kriterier som i praktiken innebär att om det föreligger mer än 15 andningsuppehåll per timme så föreligger sömnapné.

De patienter som uppfyllde kriterierna för sömnapné har fått genomgå en mera utvidgad undersökning på sjukhus för ytterligare kartläggning. Samtidigt har de tillfrågats om de vill delta i en undersökning som skall belysa huruvida behandling med CPAP skulle kunna minska risken för nya hjärt-kärlhändelser och eventuellt också gynnsamt påverka hjärtfunktionen. Undersökningen har genomförts i form av en randomiserad studie där den icke sömniga patienten lottas till att antingen behandlas med CPAP eller ej. Hälften av patienterna lottas till behandling och hälften lottas till att inte få någon behandling. De sömniga patienterna erbjöds CPAP. De som inte hade sömnapné fick också vara med i en ytterligare kontrollgrupp.

Totalt var det 1259 patienter som uppfyllde kriterierna för att kunna delta i studien dvs de hade behandlats med någondera av de två metoder som återskapar ett tillfredställande blodflöde genom hjärtat. Av dessa så var det 662 dvs 53% som tackade ja

till deltagande. Det är dessa 662 patienter som utgör själv grunden till den studie som ligger till grund för min avhandling.

Av dessa 662 så var det 422 (64 %) som uppfyllde kriterierna för sömnapné. Detta innebär att mer än två av tre patienter som behandlas med kranskärlskirurgi eller ballongdilatation för sin kranskärlssjukdom har sömnapné. Denna så kallade ”nya riskfaktor” bland kranskärlssjuka visade sig vara vanligare än samtliga tidigare kända riskfaktorer. Faktorer som ökade sannolikheten för att patienterna skulle ha sömnapné var ökande ålder, att vara man, ökande vikt (uttryckt som Body Mass Index d.v.s. kroppsvikt dividerat med kroppslängd i kvadrat), samt ökande grad av sömnighet under dagen.

Studien visade att det fanns ett samband mellan förekomst av sömnapné och hjärtats funktion under fyllnadsfasen, när hjärtmuskeln slappnar av. Mätningar av denna funktion görs med hjärtultraljud där storlek av hjärtrummen mäts och funktioner värderas. Flödeshastigheter och i rörelser i vävnadens längsriktning mäts också med hjälp av dopplersignaler. Således var en nedsatt funktion under fyllnadsfasen vanligare bland patienter som hade sömnapné (54 %) jämfört med de som inte hade sömnapné (41 %). Utöver sömnapné så var följande faktorer associerade med en ökad risk för nedsatt funktion under hjärtat fyllnadsfas: att vara kvinna, högt blodtryck och diabetes.

Studien kunde inte visa att patienter som lottats till behandling med CPAP under ett års uppföljning fick en bättre hjärtfunktion (i fyllnadsfasen) jämfört med de patienter som inte lottats till behandling med CPAP. Tyvärr och som förväntat så följde inte alla patienter som lottats till behandling med CPAP de behandlingsrekommendationer som givits. När man specialstuderade de patienter som följt riktlinjerna och använt CPAP mer än fyra timmar per natt så framkom resultat som antydde en förbättrad hjärtfunktion under ett års uppföljning jämfört med övriga patienter.

Studien kunde inte visa att patienter som lottats till behandling med CPAP hade en lägre risk att drabbas av en ny hjärt-kärlhändelse (definierat som antingen död i hjärtkärlsjukdom, hjärtinfarkt, stroke eller ny åtgärd med ballongdilatation eller kranskärlskirurgi) jämfört med de som inte lottats till dylik behandling. Totalt så var det 22 patienter i behandlingsgruppen och 27 i kontroll gruppen som fick en ny hjärtkärlhändelse och denna skillnad var inte signifikant. Precis som vid studierna av hjärtfunktionen så fann man att de patienterna som använt sin CPAP när de sover hade minskad risk att få nya hjärt-kärl händelser. Denna risk skilde sig signifikant från övriga patienter.

Mina viktigaste fynd kan sammanfattas enligt följande: Bland patienter som kräver operation eller ballongdilatation för sin kranskärlssjukdom så har två av tre sömnapné. Det är alltså fullt möjligt att sömnapné är den vanligaste riskfaktorn bland dessa patienter. Hjärtats funktion i fyllnadsfasen förefaller att vara sämre bland patienter som har sömnapné. Däremot så kunde vi inte visa att rutinförskirvning med CPAP förbättrade prognosen för patienter med kranskärlssjukdom och sömnapné utan dagtidssömnighet. Det fanns dock gynnsamma effekter om patienterna var följsamma vid behandlingen.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to those who, in many different ways, contributed to the completion of this thesis.

In particular I would like to thank:

Yüksel Peker, my supervisor for introducing me into research work, and for great enthusiasm, support and kindness throughout my PhD studies.

Johan Herlitz, my co-supervisor, for excellent support in cardiologic research, through ups and downs, and for all enthusiasm.

Erik Thunström, for enthusiasm and valuable cooperation during our PhD studies, and for help with Endnote.

Jan Ejdebäck, for being my co-supervisor.

Lennart Welin, for dedicated work in the independent endpoint committee.

Magnus Johansson and *Cecilia Wallentin Guron,* for valued support in the echocardiograghic papers in this thesis.

Mikael Dellborg, for tremendous help and support in every way.

Annika Rosengren, for kindly support through the last years of my PhD studies.

Björn Cederin, for important help in including patients.

Salmir Nasic, for expert statistical help in the papers and through the years.

Karl Wegscheider and *Christine Eulenburg*, for dedicated help with statistical analysis in Paper V.

My co-authors Harun Uzel, Mustafa Saygin, and *Anders Kallryd*, on the papers in this thesis.

Marina Modin, for data monitoring.

Lennart Bergfeldt, for excellent mentoring and support during the last year of my PhD studies.

Jan Borén and *Hans Carlsten*, for active support during the last year of my PhD studies.

Eija Magnusson, for excellent work in the RICCADSA study.

Eva Thydén, for tirelessly finding solutions to problems in a skillful way.

Lena Andersson, Helena Landberg, Anna Stålkrantz and *Alen Salkic*, for valuable work in the RICCADSA trial and a lot of data entry.

The staff at the cardiology outpatient clinics SKaS in Lidköping and Skövde, for recruiting all the patients.

The staff at the Sleep Medicine Units SKaS in Lidköping and Skövde, for taking care of all the patients sleep matters.

Paul Murphy, for scoring the in-hospital PSG recordings.

Henrik Hamnered, for skilled clinical help.

The staff at the Department of Clinical Physiology SKaS, Skövde, for all the dedicated echocardiographic work.

Maria Ström, for valuable work in the echocardiographic reproducibility test.

Colleagues in the Department of Cardiology Skövde, for exercise testing the patients.

All the secretaries at the Department of Medicine SKaS Lidköping, for skillful help.

Catriona M Chaplin, CMC Scientific English for Publication*,* for excellent linguistic editing of this thesis.

Ann-Catrin Ekelund at Library SKaS Lidköping, for help with finding research material and much more besides.

Per Ola Enander, Barbro Lundquist, Gunnar Johansson, Hanna Olsson, Martin Karlsson, my colleagues at the Cardiology section in Lidköping, and *all colleagues* in the Department of Medicine SKaS Lidköping, for kindly supporting me.

Magnus Peterson, for fruitful discussions and support through the years.

Fredric Sahlin, for encouraging and supportive discussions.

Carina Karlsson, for giving me the opportunity for research time.

All the staff at the Department of Medicine, Ward 4, for an attentive and committed approach to patient care.

Lizzie Sörstrand Lilljegren and Åke *Lilljegren*, for unconditional help and love through the years.

Jan Persson, for always believing in me.

Katarina and *Dag Thuvesen*, for always being there in a loving way.

Birgitta Frylinger, for encouraging me to persevere.

Carina Karlsson and *Jim Schultheiss*, for being close and supportive despite the long distance.

My very good friends *Maria* and *Thor Bleeker, Jenny Landström* and *Jonas Danielsson, Victoria* and *Fredrik Wettervik, Ylva Kjellén* and *Greger Ivarsson*, for encouraging friendship.

Karin and *Roger Lundgren* for friendship and the fact that you are always there for us.

Charlotta Göthe and *Joakim Svensson*, for friendship and all the extra afternoon lunches for the girls through the years.

Christer Glantz, for your love and wonderful support.

Hillevi, Kerstin, and *Elisabeth Glantz*, for your love and for being so brave and dedicated in everything you do. That makes everything worth it.

Funding and research grants. This thesis was supported by the Swedish Research Council, the Swedish Heart-Lung Foundation, and research fund at Skaraborg Hospital, "Agreement concerning research and education of doctors" of Västra Götalandsregionen (ALF), Skaraborg Research and Development Council, the Heart Foundation of Kärnsjukhuset, ResMed Foundation and ResMed Ltd. ResMed Sweden provided some of the sleep recording devices and technical support. None of the funders had any direct influence on the design of the study, the analysis of the data, the data collection, drafting of the manuscript, or the decision to publish.

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“Går allt detta an, Albert?”
Han sade ändå intet. Men i hela uttrycket av hans ansikte låg detta svar:
“Det går an”.

Ur boken Det går an av Carl Jonas Love Almqvist, 1839