Sleep-Disordered Breathing

in Heart Failure Patients

and its Impact on Cardiovascular Risk

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Contents

Acknowledgments

This thesis is based on studies carried out at Lovisenberg Diakonale Hospital, Oslo during the years 2006 and 2010 in cooperation with the Sleep Laboratory at the Ear, Nose and Throat Clinic.

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List of publications

I. Herrscher TE, Akre H, Øverland B, Sandvik L, Westheim AS. High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function. J Card Fail 2011 May;17(5):420-5.

II. Herrscher TE, Akre H, Øverland B, Sandvik L, Westheim AS. Clinical predictors of sleep apnea in heart failure outpatients. Int J Clin Pract 2014 June;68(6):725-30.

III. Herrscher TE, Øverland B, Sandvik L, Westheim AS, Akre H. High cardiovascular risk profile in patients with sleep apnea. Laryngoscope 2014 Jan;124(1):306-10

Abbreviations

AHI	Apnea Hypopnea Index
ASV	Adaptive Servoventilation
BP	Blood Pressure
BMI	Body Mass Index
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive Protein
COPD	Chronic Obstructive Pulmonary Disease
CSA	Central Sleep Apnea
CSR	Cheyne-Stokes Respiration
CV	Cardiovascular
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection Fraction
EMG	Electromyogram
ESS	Epworth Sleepiness Scale
HF	Heart Failure
HFPEF	Heart Failure with Preserved Ejection Fraction
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
NREM	Non-Rapid Eye Movement
NT-proBNP	N-terminal prohormone Brain Natriuretic Peptide
OGTT	Oral Glucose Tolerance Test
OSA	Obstructive Sleep Apnea
pCO2	Partial Pressure of Carbon Dioxide
PCWP	Pulmonary Capillary Wedge Pressure
PSG	Polysomnography
PG	Polygraphy
REM	Rapid Eye Movement
SDB	Sleep-Disordered Breathing

Introduction

Sleep-disordered breathing (SDB), encompassing both obstructive and central sleep apnea, occurs frequently in patients with cardiovascular (CV) disease. This thesis is based on sleep studies performed in patients with heart failure (HF), and in patients referred to the sleep laboratory, with the overall objective of evaluating the association between SDB, HF and CV risk factors.

Sleep and its impact on the cardiovascular system

Sleep is an essential physiologic process for most living organisms [1]. Based on electroencephalographic (EEG) monitoring, sleep can be divided into non-rapid eye movement (NREM) sleep, which has three defined stages, and rapid eye movement (REM) sleep [2] (Figure 1). The number and duration of different sleep stages change throughout a person's lifetime [3].

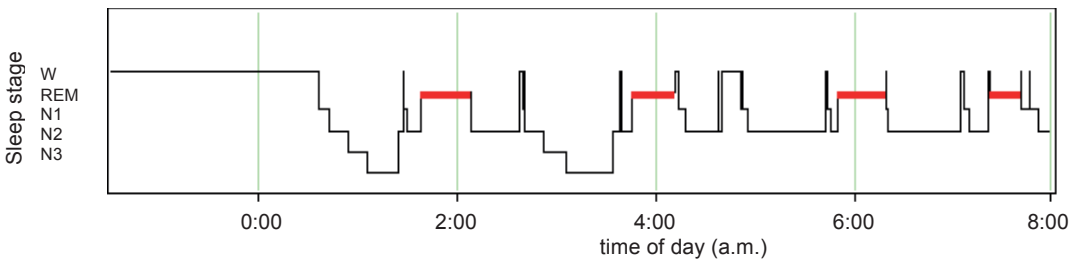

Figure 1. Example of a hypnogram for adults with awakenings.
The thick red horizontal lines show REM sleep.
Peaks with thinner lines show short awakenings.
W: awake; REM: rapid eye movement; N1,N2,N3: Sleep stages in non-rapid eye movement sleep

NREM and REM affect the CV system. NREM sleep is characterized by autonomic stability with dominance of the parasympathetic tone, whilst in REM sleep the sympathetic nervous system is activated, causing an increase in heart rate and blood pressure (BP) with the potential to provoke ischemic episodes and arrhythmias [4].

Deprivation of sleep, especially selective NREM deprivation, results in impaired cognition and vigilance [5;6]. In several studies, short sleep duration has been associated with greater adiposity [7;8]. Epidemiological studies suggest that short or long sleep duration, and difficulty in remaining sleep, are associated with the development of diabetes [9-11], and inadequate or disrupted sleep has been associated with CV disease and hypertension [12-15]. Unfortunately, most studies have not distinguished between voluntary restriction of time asleep and sleep loss or impaired sleep quality caused by pathological conditions like SDB. On the basis of the available studies it is not possible to establish a causal link between time asleep and CV disease risk.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway obstruction during sleep (Figure 2). This results in apneas and hypopneas, leading to increased respiratory effort, arterial oxygen desaturation and fragmentation of sleep.

An apnea is the absence of respiration for at least 10 seconds; a hypopnea is a decrease in tidal volume of at least 50% followed by ≥ 3% oxygen desaturation [2]. OSA is diagnosed if five or more obstructive apneas / hypopneas occur per hour of sleep, as expressed by the apnea – hypopnea index (AHI) [16]. AHI cut-off points of 5, 15 and 30 are widely used to define mild, moderate and severe OSA, respectively. Although the AHI defines the average number of breathing cessations during one night, it does not reflect the duration of apneas or

the level of oxygen desaturation, both of which provide important additional information when evaluating the severity of SDB.

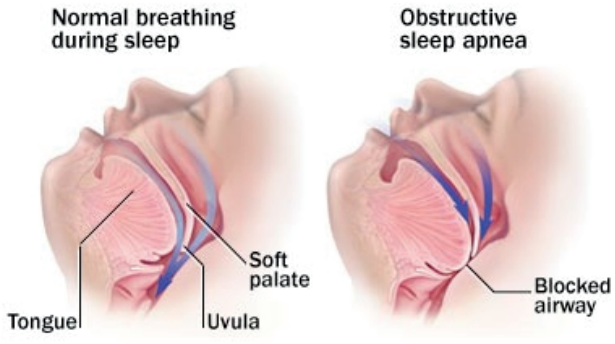

Figure 2. Illustration of the upper airway in normal breathing and in obstructive sleep apnea. Adapted from the Mayo Foundation for Medical Education and Research.

OSA is a relatively common disorder and its prevalence appears to have increased lately. [17;18]. In a recent population-based study of adults aged 30 – 65 years in Norway, the estimated prevalence of OSA was 16%, with moderate to severe OSA reported in 8% of the cohort [19]. Males had a higher prevalence than females (21% vs. 13%), with a similar distribution for moderate to severe disease (11% vs. 6%). In the Wisconsin sleep study published in 1993, the prevalence of OSA with daytime hypersomnolence (OSA syndrome) was estimated to be 4% in men and 2% in women [20].

Narrowing of the pharyngeal lumen and increased upper airway collapsibility are the main pathophysiological features in OSA patients [21]. Body mass index (BMI), male gender, increasing age, snoring and neck circumference are associated with the disease [22]. Malhotra and White estimated that roughly 70% of OSA patients are obese, and obesity may

be the only major modifiable risk factor [23]. The risk of OSA increases with increased body weight: a 10% weight gain has been shown to predict a six-fold increase in the likelihood of developing moderate to severe OSA [24]. Other risk factors associated with OSA include night time nasal congestion, smoking and alcohol consumption before sleep [25].

Untreated OSA, particularly moderate to severe disease, contributes to worse quality of life, worse cognitive performance and excessive daytime sleepiness [26-29].

Co-morbidity in obstructive sleep apnea

OSA is associated with a number of CV diseases including hypertension, diabetes, coronary artery disease, HF and stroke [30]. This association may not be due only to shared risk factors, but could also reflect a role of OSA in the etiology of these conditions [25].

The relationship between OSA and hypertension has been widely investigated. Obstructive events during sleep, together with hyperventilation while recovering breath, can result in acute changes in BP and heart rate [31]. Despite several coexisting risk factors such as obesity, some longitudinal studies have suggested that OSA is an independent risk factor for systemic hypertension, although the evidence is inconsistent [32-34]. In the latest European guidelines for the management of hypertension, OSA is characterized as a modifiable cause of refractory hypertension and should be considered in patients with a non-dipping BP profile [35].

The prevalence of type 2 diabetes is higher in patients with OSA versus non-OSA patients even after adjusting for confounding factors [36]. Correspondingly, the prevalence of OSA among patients with type 2 diabetes appears to exceed predictions of OSA in the general population [37]. OSA is a possible risk factor for developing impaired glucose metabolism and type 2 diabetes [38-40], most likely due to deteriorating insulin sensitivity [41]. In recently

published analyses from the European Sleep Apnoea Database, increasing severity of sleep apnea was associated with higher HbA1c levels in a non-diabetic cohort [42], while OSA was associated with an increased risk of concomitant type 2 diabetes and worse diabetes control in patients with type 2 diabetes [43]. Furthermore, untreated OSA has been shown to increase the incidence of coronary heart disease and HF, CV events and even all-cause mortality [44-46].

Central sleep apnea

Central sleep apnea (CSA) is characterized by insufficient or absent ventilation caused by loss of ventilatory drive. It has various manifestations, including Cheyne-Stokes respiration (CSR), high altitude-induced periodic breathing and opioid-induced central apnea, arising from different pathophysiological mechanisms. Nevertheless, significant CSA is rarely recorded in the absence of HF [47]. The most common type of CSA in patients with HF is CSR, also referred to as periodic breathing [48;49]. CSR has a characteristic crescendo / decrescendo ventilatory pattern with hypopneas or apneas occurring at the nadir of the respiratory cycle (Figure 3).

The appearance of CSR indicates instability of the respiratory control system. In healthy subjects, ventilation decreases with sleep onset and the partial pressure of carbon dioxide (pCO2) increases, keeping pCO2 above the apnoeic threshold [50]. In HF patients, increased venous return in the supine position increases pulmonary capillary wedge pressure (PCWP) and lung congestion. This can stimulate pulmonary vagal irritant receptors, resulting in reflex hyperventilation [51;52]. Most HF patients with CSA seem to have chronic hyperventilation with low pCO2 levels [53;54] In these patients, the carbon dioxide-dependent apnea threshold seems to be altered [55], facilitating apneas with decreasing pCO2. As a result, even a slight increase in ventilation, such as any kind of arousal, can

reduce pCO2 below the apnoeic threshold, which results in a central apnea. Apneas leading to rising pCO2 induce a secondary hyperventilation response in an attempt to normalize pCO2 levels. Additionally, it has been suggested that central pCO2 receptor sensitivity is increased, which elicits an inadequate ventilatory response with rising pCO2 [56]. The combination of oscillating pCO2 levels and altered chemoreceptor function leads to ongoing cycles of hypo- and hyperventilation [57;58]. Another pathophysiological factor that can impair the usual feedback mechanism is a prolonged circulation time in HF patients, expressed by the correlation between severity of systolic function and Cheyne-Stokes cycle length [59].

Like OSA, CSA with CSR is associated with increased morbidity and mortality, but it remains controversial as to whether CSR is simply an epiphenomenon in HF patients or if it contributes to morbidity and mortality [60;61].

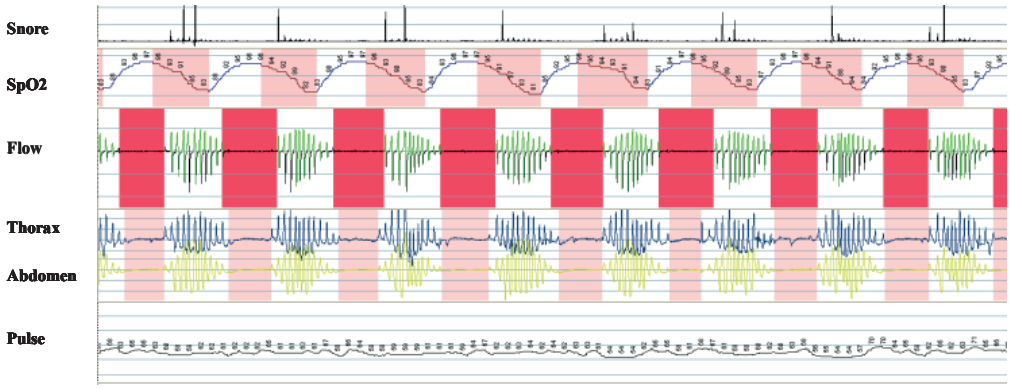

Figure 3. A 10 minutes trace from a polygraphic recording (Embletta) in a patient with Cheyne Stokes respiration.
Snore = snore signal; SpO2 = oxygen saturation; Flow = flow from nasal air pressure transducer; Thorax = thoracic movements measured with respiratory inductance plethysmography; Abdomen = abdominal movements measured with respiratory inductance plethysmography; Pulse = pulse signal

Pathophysiological aspects of obstructive sleep apnea

Patients with SDB experience a wide range of hormonal, biochemical and hemodynamic changes, each of which could affect the heart and the CV system (Figure 4).

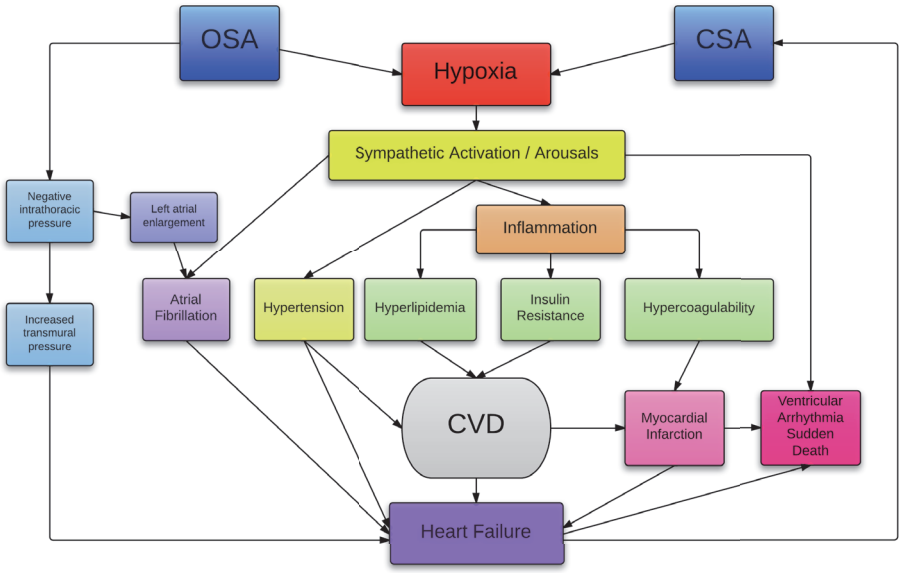

Figure 4. Pathophysiological interaction between obstructive / central sleep apnea and cardiovascular disease / heart failure.

Intermittent hypoxemia, increased respiratory effort, hypercapnia and micro-arousals are the main pathophysiological features of OSA [62]. These conditions contribute to sympathetic activation [63], expressed by increased sympathetic nerve activity even during daytime [64;65], and higher levels of circulating catecholamines [66]. Increased sympathetic activation mediated by chemoreflex activation, probably coupled with altered baroreflex responsiveness, is considered to be an important contributor to the high prevalence of hypertension in OSA [67-69].

Several studies have shown left ventricular (LV) hypertrophy to be associated with OSA even, in one study, after adjusting for BP levels [70-72]. This appears to result from increased LV afterload during obstructive apneas, combined with sympathetic activation and intermittent hypoxemia [73]. LV diastolic dysfunction and increased left atrial size, indicative of structural myocardial changes, have been detected in otherwise healthy OSA patients [74;75].

Caples and Somers have suggested that recurrent fluctuations in intrathoracic pressure in OSA could contribute to chamber enlargement of the thin-walled atria as well as to tissue stretch and remodelling at the pulmonary vein ostia, thereby promoting the development of atrial fibrillation [76]. Other pathophysiological conditions which could potentially link OSA to atrial fibrillation are autonomic imbalance, hypoxia, inflammation and hypertension [77].

Patients with OSA have a high incidence of serious arrhythmias and sudden cardiac death at night, which again may be explained by increased sympathetic activation and hypoxemia [78;79].

During an obstructive apnea, a series of acute hemodynamic changes occur: the attempt to breath against the occluded pharynx generates negative intrathoracic pressure, which augments right ventricular filling (pre-load) by increasing venous return. At the same time, hypoxemia raises pulmonary artery pressure [80], increasing right ventricular afterload. Right ventricular distension can cause septal displacement and thereby impairs LV filling [81]. Additionally, it is assumed that negative intrathoracic pressure increases LV transmural pressure, and hence afterload [82]. Several studies have shown that obstructive apneas or their simulation can reduce stroke volume and cardiac output in men [83-86], an effect that is more pronounced and sustained in HF patients [87].

Mild to moderate chronic pulmonary hypertension has traditionally been associated with OSA. However, its prevalence is relatively low and concomitant lung or heart disease is often present in this condition [88-90].

Repetitive desaturations, re-oxygenation and sleep fragmentation appear to trigger systemic inflammation, oxidative stress and procoagulant / thrombotic activity, promoting the development of atherosclerosis, dyslipidemia and CV disease which are associated with OSA [91-93]. However, co-morbidities such as obesity, diabetes, CV disease and smoking are all potential confounding factors and causality can not yet be confirmed.

Pathophysiological aspects of central sleep apnea

The key clinical significance of CSA is its association with increased mortality [48]. Indeed, CSA may even be an independent risk factor for all-cause mortality [60].

Variations in heart rate, oscillating BP and oxygen desaturation occur in CSR [94-96], but no additional intrathoracic pressure is generated during a central apnea which affects LV afterload. Repetitive nocturnal deprivation of myocardial oxygen has been proposed as a mechanism for inducing the progression of chronic HF [97]. It has been shown that HF patients with CSR have a higher sympathetic activity, as measured by urinary catecholamines, compared to HF patients without CSR [98]. However, increased total body and cardiac sympathetic nerve activity in HF patients with CSR, was subsequently found to be related to HF severity [99]. In another study, significantly higher urine and plasma norepinephrine levels in HF patients with CSR were reduced by continuous positive airway pressure (CPAP) therapy [100]. It has been demonstrated that CSR provokes ventricular ectopy in HF patients, particularly during the hyperpneic phase [101]. Severe CSR has been associated with impaired cardiac autonomic control and increased cardiac arrhythmias in HF

patients [102]. Furthermore, CSR seems to be an independent risk factor for malignant arrhythmias in this setting [103].

In summary, the failing heart in patients with CSR is repeatedly exposed to hypoxia, oscillating BP and varying heart rate, and possibly to increased sympathetic activity. These effects could theoretically contribute to the higher mortality observed in patients with CSR, but more evidence is needed to prove causality.

Obstructive sleep apnea and Cheyne-Stokes respiration in heart failure

The prevalence of SDB is generally higher in HF patients compared with the general population, but varies depending on AHI cut-off levels and inclusion criteria. In large-scale studies, SDB was present in up to 81% of stable HF patients with reduced ejection fraction (EF) [104]. Using an AHI cut-off of ≥ 15, several studies have documented moderate to severe SDB in about 50% of patients [105-108]. The prevalence of CSR is associated with increasingly symptomatic HF and lower EF [106]. Male gender, age > 60 years, hypocapnia during wakefulness and the prevalence of atrial fibrillation may be other risk factors for CSR [108]. In HF patients with preserved ejection fraction (HFPEF), up to 69% were found to have SDB; the majority had OSA [109;110].

The relationship between HF and SDB appears to be bidirectional. Pathophysiological changes associated with OSA, as described above, contribute to the onset and progression of both systolic and diastolic HF. At the same time, the pathophysiological implications of HF aggravate OSA and facilitate CSA. HF with fluid overload and overnight redistribution from the lower to the upper part of the body can contribute to pharyngeal narrowing, thus potentially increasing the severity of OSA, which can be reversed by CPAP [111;112]. Patients with OSA seem to be more susceptible to pharyngeal obstruction in response to fluid redistribution than non-OSA patients [113]. In HF patients, rostral fluid shift may

additionally accumulate in the lungs, increasing the PCWP and leading to pulmonary congestion, which can provoke hyperventilation that facilitates the development of central apneas and CSR [114].

In HF patients, the type of sleep apnea can change from predominantly obstructive at the start of the night to predominantly central events towards the end of the night. This change has been associated with a reduction in pCO2, related to overnight deterioration in cardiac function as suggested by a prolonged circulation time and an increase in periodic breathing cycle length [115]. This generates the hypothesis that not only fluid shift, but in some cases also the direct adverse cardiovascular effects of OSA, can lower cardiac output and raise PCWP sufficiently to induce CSA [114].

CSR in HF patients occurs not only at night but also during waking hours [116]. When observed during the day, it has been associated with reduced survival [117;118].

Treatment of OSA and CSA

Management of OSA should include weight reduction, which seems to reduce the severity of OSA [24;119] as well as abstinence from alcohol, which predispose to pharyngeal collapse during sleep [120].

The standard treatment for OSA is considered to be CPAP, delivered by a nasal or facial mask [121;122]. CPAP keeps the upper airway from collapsing, thus avoiding obstructive apneas and hypopneas. In patients with OSA and daytime sleepiness, CPAP significantly reduces daytime sleepiness and improves daytime function [123]. The treatment effect is well-documented in patients with hypertension [124], and CPAP has also been shown to improve insulin resistance and diabetes, especially in patients with severe OSA [125;126].

In HF patients, relatively small studies have shown that CPAP treatment can reduce LV afterload and heart rate [127], increase left ventricular ejection fraction (LVEF) and decrease sympathetic activation [128-130]. Observational studies have demonstrated that CPAP treatment was associated with reduced morbidity and mortality in HF patients with OSA [131;132], No prospective, randomized trial has yet determined whether CPAP treatment influences morbidity or mortality in non-sleepy HF patients.

The first consideration in HF patients with CSA / CSR should be to optimize HF treatment. Adequate drug therapy with beta blockers and diuretics reduces central apnea frequency, probably by lowering cardiac filling pressure [51;133]. A meta-analysis has shown that cardiac resynchronization therapy, with an implantable device when indicated, is also effective in reducing the severity of CSA [134]. Nocturnal oxygen should be considered in symptomatic HF patients with CSA but no alternative to ventilator therapy (CPAP / ASV) is currently recommended as standard treatment [135].

Although initial results were promising [136], CPAP treatment in HF patients with CSR failed to show a positive impact on mortality in the CANPAP (CANadian continuous Positive Airway Pressure) trial [137]. A *post-hoc* analysis however, revealed a benefit in survival and improvement of LVEF in the subpopulation of patients whose AHI was reduced to below 15 [138].

A novel ventilator treatment, adaptive servoventilation (ASV) therapy, introduced in 2001, was developed specifically to treat CSR [139]. ASV applies anticyclic pressure support during periods of periodic breathing in an attempt to maintain a constant breathing volume [140]. Compared to CPAP, ASV is more effective in reducing central events and patients demonstrate better compliance [141-143]. There is emerging evidence that ASV treatment can improve cardiac function and reduce arrhythmic events in HF patients with CSR [144;145]. However, there is a need for randomized, controlled trials of ASV therapy in this population to examine its effect on morbidity and mortality.

Aims of the thesis

General aims

- To investigate the association between SDB and CV disease, particularly in HF patients.

Specific aims

- To investigate the prevalence of SDB in HF patients, focusing on patients with preserved LV function (Paper I).
- To identify clinical predictors of both obstructive and central sleep apnea in HF patients (Paper II).
- To evaluate the individual CV risk profile in patients with SDB (Paper III).
- To detect undiagnosed CV disease in patients with various degrees of SDB (Paper III).

Materials and methods

Study design and population

This thesis presents material from two clinical studies with a cross-sectional study design.

Patients studied in Papers I and II were consecutively enrolled from the outpatient HF clinic of Lovisenberg Diakonale Hospital, Oslo, Norway. The HF clinic was established in order to give optimal medical treatment to patients with HF, and has specially-trained nurses working in close cooperation with cardiologists. It is included in the Norwegian Heart Failure Registry [146]. The majority of patients are referred from the cardiology department at Lovisenberg Hospital, with a minority referred directly from their primary care physicians. The diagnosis of HF is based on clinical signs and symptoms, measurement of N-terminal prohormone brain natriuretic peptide (NT-proBNP), and assessment of LV function, according to current HF guidelines [147;148].

Papers I and II included patients aged 18 to 80 years who had clinically stable HF with fully up-titrated HF medication as recommended in the HF guidelines. Patients were excluded if they had been hospitalized for any reason or had needed intravenous diuretics within the previous six weeks. Further exclusion criteria were myocardial infarction or stroke within the previous three months, and severe or very severe chronic obstructive pulmonary disease (COPD) (stage III and IV) based on lung function according to the Global Initiative for Chronic Lung Disease [149]. The inclusion period was between June 2006 and December 2008. In total, 120 patients met the inclusion criteria. Five patients refused to participate because of the inconvenience, such that 115 HF patients were enrolled in the study.

Paper III included patients from the Sleep Laboratory at Lovisenberg Diakonale Hospital, recruited during the period from October 2009 to March 2010. Patients were referred for an evaluation of SDB by their general practitioners or an Ear, Nose and Throat specialist.

Exclusion criteria were known sleep apnea, or cases in which the sleep study was being undertaken for therapeutic purposes. In total, 255 subjects were enrolled and all participants gave written informed consent.

The study protocols were reviewed and approved by the Regional Ethics committee and the Norwegian Data Inspectorate.

Study procedures

All HF patients in Paper I underwent an overnight polygraphy (PG) (Embletta, ResMed, Norway) which was performed unattended at home. Nasal airflow, thoracic and abdominal movements, pulse oximetry, body position and a three-channel electrocardiogram (ECG) were recorded continuously. In Paper III, the Reggie system (Camtech, Norway), which has an additional esophageal catheter that indirectly measures intrathoracic pressure [150], was used in addition to the Embletta. Thirty-four out of 255 patients in Paper III had an inconclusive PG or were unable to complete an unattended PG and were therefore diagnosed with an in-hospital polysomnography (PSG) (Embla, ResMed, Norway). The PSG additionally included a six-channel EEG, a two-channel electrooculogram, a submental electromyogram (EMG) and an EMG from both legs.

Data were blinded and scored at the Lovisenberg Sleep Laboratory by a qualified sleep specialist using a modified version of the 2007 American Academy of Sleep Medicine manual for the scoring of sleep and associated events [2]. An obstructive apnea was defined as ≥ 10-second pause in respiration with ongoing respiratory effort. An obstructive hypopnea was defined as a minimum 50% reduction in airflow with either a ≥ 3% oxyhemoglobin desaturation or an arousal. Arousals were diagnosed by EEG in a PSG or were classified as a presumed arousal in the PG using heart rate response as a surrogate for arousal from sleep. A central apnea was defined as ≥ 10-second pause in respiration without thoracic and

abdominal effort. The AHI was calculated based on actual sleep time (PSG) or analyzed time (PG).

The diagnosis of SDB was made if the patient had ≥ 5 apnea / hypopnea events per hour of sleep. SDB severity was graded according to guideline recommendations [16] and our clinical routine as mild (AHI 5 – 14.9), moderate (AHI 15 – 29.9) and severe (AHI ≥ 30).

CSR was diagnosed if the patient had central AHI ≥ 5 and at least three consecutive cycles of crescendo and decrescendo changes in breathing amplitude or the cyclic crescendo / decrescendo pattern lasted for at least 10 consecutive minutes [2].

Patients with both obstructive and central apneas were classified according to the dominating respiratory sleep pattern.

Evaluated parameters

Demographic and co-morbidity data were extracted from the Norwegian Heart Failure Registry [146] and from patient records. Quality of life was measured using The Minnesota Living with Heart Failure Questionnaire [151]. Daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS) [152]. All patients in Paper I had a two-dimensional echocardiographic assessment of LVEF. Patients with EF ≥ 45% were considered to have preserved EF.

Blood samples analyzing hemoglobin, CRP, creatinine, cholesterol, triglycerides, glucose, HbA1c and NT-proBNP were obtained the morning after the sleep study.

Office BP measurements in Paper III were performed with a sphygmomanometer on the upper arm using the standard technique [153]. A minimum of three BP measurements were obtained and the average of three multiple readings was used for statistical purposes.

A 12-lead ECG was performed on the same day. The ECG was analyzed manually by a single, blinded observer as described in Paper III.

In order to assess the individual CV risk, the Framingham general CV disease risk score was calculated for each patient based on the following parameters: age, gender, systolic BP, total-cholesterol, HDL-cholesterol, hypertension treatment, current smoking and diabetes. The Framingham general CV disease risk score is expressed as the 10-year risk for coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, transient ischemic attack, peripheral artery disease and HF [154;155].

Patients with a fasting glucose > 5.6 mmol/l and / or HbA1c > 5.7% were requested to perform a two-hour oral glucose tolerance test (OGTT) with a 75 g glucose load. Patients with a two-hour plasma glucose value of between 7.8 and 11.1 mmol/l were defined as having impaired glucose tolerance. Diabetes mellitus was diagnosed if fasting plasma glucose was ≥ 7 mmol/l and / or HbA1c ≥ 6.5 %, or the 2-hour plasma glucose in the OGTT was ≥ 11.1 mmol/l. Patients with a fasting glucose between 5.6 and 6.9 mmol/l and a normal OGTT were classified as impaired fasting glucose according to updated diabetes guidelines [156].

Statistical analyses

Statistical analyses were performed using SPSS software version 17.0 and 18.0 (SPSS Inc. Chicago, IL, USA). Continuous data were presented as mean ± standard deviation or as median values with 25^{th} and 75^{th} percentiles if distribution was non-normal. Differences between groups were assessed using the independent samples t-test for variables with approximately normal distribution, and the Mann-Whitney rank sum test for non-normal continuous variables. Categorical data were listed as frequencies and percentages and were compared using the Chi-square test. Both bivariate and multivariate analyses (logistic

regression) were applied to detect variables predicting sleep apnea. Linear regression analysis was used when comparing CV disease risk in different AHI classes, with log of the Framingham score as dependent variable. The log transformation was performed to fulfil the linearity assumption in linear regression analysis.

All tests were two-tailed and findings with $p < 0.05$ were considered statistically significant.

Summary of results

Paper I

High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function

We investigated the prevalence of SDB in a cohort of HF outpatients (n = 115). Patients were clinically stable and receiving fully up-titrated HF medication. Sixty-two percent had reduced EF, and 38% had HFPEF. The overall prevalence of SDB was 81% (AHI ≥ 5). Moderate to severe SDB (AHI ≥ 15) was present in 52% of cases (Figure 5). We found no differences in EF, quality of life or sleepiness between patients with and without SDB.

HFPEF patients showed almost the same prevalence of SDB as the group with reduced EF (80% vs. 82%). In HFPEF patients, however, OSA (62%) was far more frequent than CSA (18%). Compared to HFPEF patients without OSA, HFPEF patients with OSA had a higher BMI (32 ± 5.8 vs. 27.9 ± 4.1, p = 0.02) and a higher proportion had hypertension (74% vs. 35%, p = 0.01).

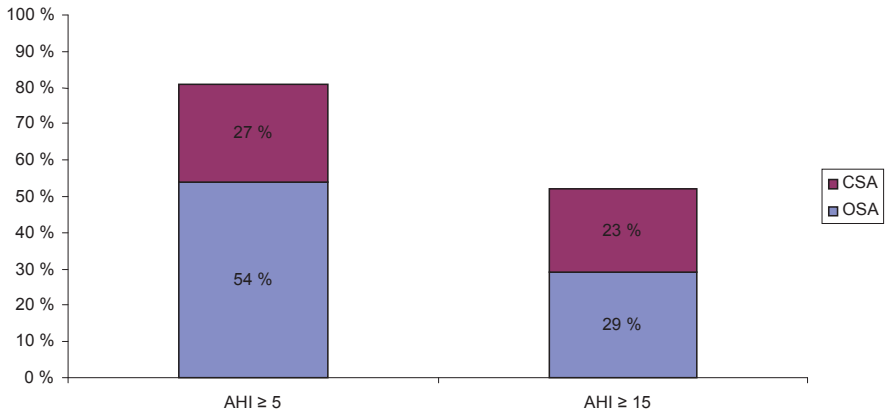

Figure 5. Prevalence of SDB in a stable HF population. N = 115

Paper II

Clinical predictors of sleep apnea in heart failure outpatients

In this paper, we aimed to identify clinical predictors of moderate to severe SDB in HF patients. The patient cohort was identical to Paper I. Fifty-two percent of patients had AHI ≥ 15. In the multivariable logistic regression model, we found that BMI ≥ 30 kg/m² was the only independent predictor of moderate to severe SDB ($p = 0.008$). Hypertension was a predictor for OSA ($p = 0.02$), while hemoglobin ≥ 15 g/dl was associated with CSA ($p = 0.002$).

Quality of life and level of sleepiness were not significantly associated with SDB. Patients with mild to moderate COPD were less likely to have SDB compared to patients without COPD ($p = 0.002$).

Paper III

High cardiovascular risk profile in patients with sleep apnea

We investigated the individual CV risk profiles of patients with SDB and the prevalence of premature and undiagnosed disease in this group. The study cohort included 255 patients referred to the Sleep Laboratory for a sleep evaluation, of whom 190 (75%) were diagnosed with SDB. All patients had predominantly OSA (AHI ≥ 5).

Patients with moderate to severe SDB (AHI ≥ 15) had a higher prevalence of known heart disease and hypertension compared with patients without sleep apnea. In addition, patients with moderate to severe SDB had a significantly higher fasting glucose, HbA1c, cholesterol to HDL-cholesterol ratio and CRP.

Patients with SDB had a higher median Framingham risk score than patients without SDB. Compared to patients without SDB, patients with severe SDB had a significantly higher Framingham score [RR 1.60 (95% CI: 1.26 – 2.05, p < 0.001)], adjusted for age and gender, representing a 60% increased risk of developing CV disease over the next 10 years.

Among participants without known hypertension, 114 were diagnosed with SDB. In this group, only 11% had optimal BP, 44% had pre-hypertension and 45% had significantly elevated BP. These results remained consistent for all AHI classes (Figure 6).

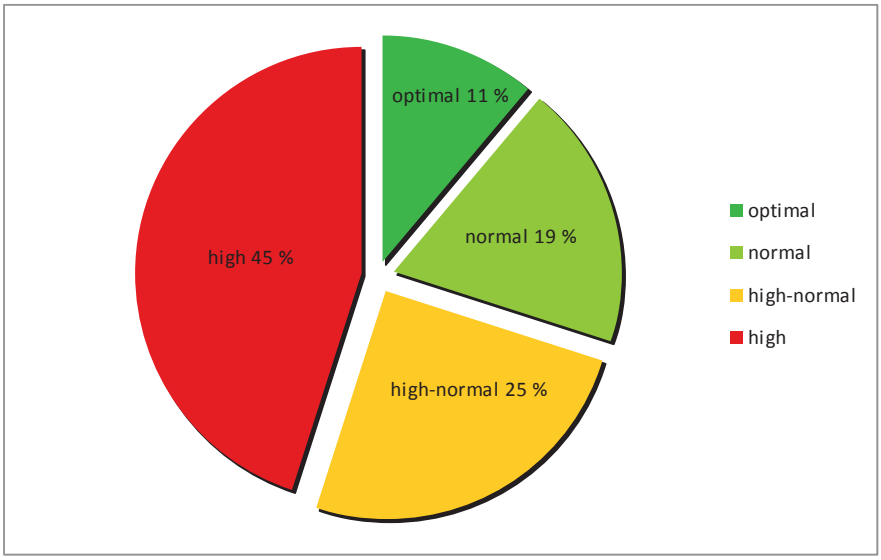

Figure 6. Blood pressure measurements in SDB patients without known hypertension

Optimal: Systolic < 120 mmHg and diastolic < 80 mmHg

Normal: Systolic 120 – 129 mmHg or diastolic 80 – 84 mmHg

High-normal: Systolic 130 – 139 mmHg or diastolic 85 – 89 mmHg

High: Systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg

Among patients without known diabetes, 171 were diagnosed with SDB. In this “non-diabetic” group, 48% had pathological glucose disposal comprising impaired fasting glucose in 38% of patients and impaired glucose tolerance in 9% of patients. One patient met the diagnostic criteria for diabetes mellitus (Figure 7). Within the “non-diabetic” group of patients who had moderate to severe SDB, 57% had pathological glucose disposal.

Twenty percent of SDB patients without known heart disease had significant ECG changes.

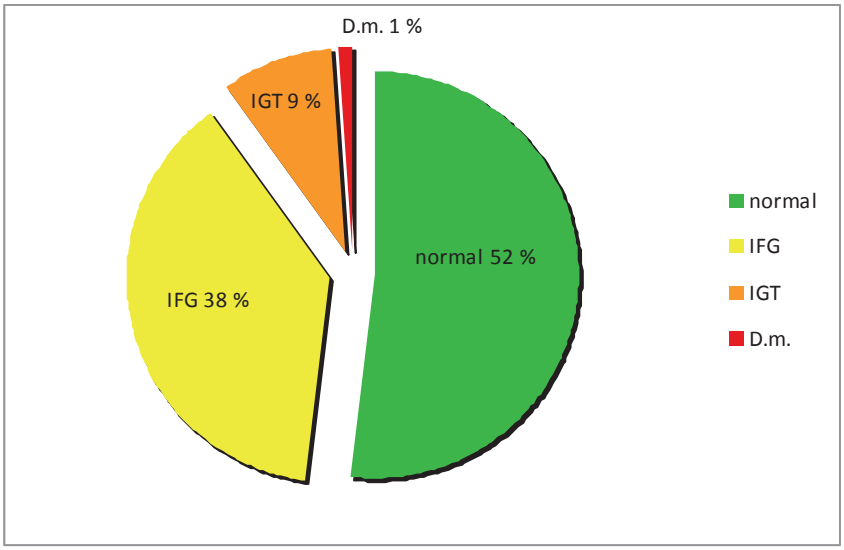

Figure 7. Glucose disposal in 171 “non-diabetic” patients with SDB

IFG: Impaired Fasting Glucose, IGT: Impaired Glucose Tolerance, D.m.: Diabetes mellitus

Discussion

Attention has recently focussed on SDB and its impact on CV disease, especially in patients with HF [30;82;157]. In this thesis we have demonstrated a high prevalence of SDB in HF outpatients. Furthermore, we have explored possible clinical predictors that could be used to select patients for referral to a sleep specialist. Moreover, we found that subjects with SDB diagnosed at the Sleep Laboratory have a significantly higher 10-year risk of developing CV disease compared to subjects without SDB. Patients with SDB also have a high prevalence of unidentified medical conditions including elevated BP, pathological glucose disposal and ECG changes.

Sleep studies

All our patients in the HF cohort were tested at home with PG, measuring nasal air flow via a nasal pressure transducer, thoracic and abdominal movements (respiratory inductance plethysmography), pulse oximetry and body position. A PSG is an overnight study, usually performed at the hospital, which in addition assesses sleep, wakefulness and muscle activity by using EEG, oculography and myography. The PSG is considered the gold standard for diagnosing sleep disorders [16], even though it is time-consuming, relatively expensive and often unavailable outside specialist centres.

In terms of scoring and calculating sleep indices, the main advantage of PSG is that the EEG recording allows an exact determination of sleep time and respiratory arousals. Without direct information on sleep, the calculated indices in a PG can be underestimated compared to a PSG. If sleep disorders other than moderate to severe OSA or CSA are suspected, or if the patient shows symptoms of daytime sleepiness or snoring and has a negative PG, a complete sleep study with PSG should be considered [158].

In Paper III, 34 out of 255 patients completed a PSG. The distribution of AHI groups was similar to PG patients, with a slightly higher percentage of patients in the severe SDB group (no SDB 18%, mild 29%, moderate 21%, severe 32%). A separate statistical analysis excluding PSG patients did not show any significant difference to the main results.

Because of the high number of patients with suspected breathing disorders at night, especially patients with CV disease, clinicians need a relatively simple and practice means to diagnose SDB. In several studies, home-based cardiorespiratory PG has been shown to diagnose breathing disorders satisfactorily during sleep compared to a PSG, and with lower costs [159-164]. Additionally, it could be available at most hospitals, enabling more patients to be studied.

Even simpler devices have been tested [165;166] and in the future may be adequate to screen patients at risk in a primary care setting before referral to a sleep specialist.

Study population

In Papers I and II, all patients were consecutively enrolled from the outpatient HF clinic at Lovisenberg Diakonale Hospital. They were referred either by their primary care physician or by the Medical Department at the hospital. The relatively high prevalence of SDB in our cohort was consistent with large-scale studies by Oldenburg and Bitter [106;109], even without the potential referral bias that tertiary centers in Germany may experience, where often only patients with more severe or complex disease are transferred to university hospitals.

The use of beta blockers has previously been shown to have a negative correlation with the prevalence of SDB [133;167;168]. In our study, we had a higher percentage of beta-blocker and angiotensin-converting-enzyme inhibitor / angiotensin receptor blocker usage compared

to prevalence studies from the USA and France [104;169]. This implies that SDB is a common condition even in a relatively unselected and well-treated HF population.

In Paper III we included patients referred to the Sleep Laboratory by their primary care practitioner or Ear, Nose and Throat specialist for an evaluation of SDB. Since at the time of the study Lovisenberg Diakonale Hospital was the only Sleep Laboratory in Oslo, we assume that there is no relevant referral bias in our study and the present data should be representative of a typical SDB population.

Sleep-disordered breathing in heart failure

The main finding in Paper I was a high prevalence of SDB in clinically stable HF outpatients treated at the HF clinic. Most prevalence data published previously were based on HF patients with reduced EF [104;106;169;170]. Our study included HF patients regardless of LV function. Sleep data on HF patients with preserved systolic function are rare. Chan et al. performed sleep studies on 20 patients with isolated diastolic dysfunction and found a SDB prevalence of 55%, using AHI > 10 as a cut-off value [110]. The first large-scale prevalence, study including 244 HFPEF patients, was published in 2009 by Bitter et al [109]. They described a SDB prevalence of 69.3%, based on an AHI cut-off value of ≥ 5, which is close to the prevalence observed in our cohort. As in our study, the majority of these patients had OSA.

OSA is considered an important risk factor for hypertension [171]. In hypertensive patients, micro- and macrovascular changes can lead to structural damage in the heart and may cause ventricular stiffness and LV hypertrophy, resulting in diastolic HF [172]. But impaired diastolic function has also been directly associated with OSA [173]. As described earlier, several pathophysiological mechanisms have been identified that could contribute to the relationship between OSA and morphological and functional changes in the myocardium.

In several studies, OSA was associated with atrial fibrillation [174;175]. It is unclear whether atrial fibrillation contributes directly to HFPEF but, notably, it occurs in two-thirds of these patients and confers a poor prognosis [176].

Randomized clinical trials investigating the effect of CPAP treatment on morbidity and mortality in HFPEF patients with OSA are still required. However, CPAP has been shown to lower BP in patients with OSA [124] and may lower the recurrence of atrial fibrillation after cardioversion and catheter ablation (pulmonary vein isolation) [177-179]. While further research is necessary to define effective strategies for medical treatment of HFPEF [180], it seems reasonable to treat co-morbidities such as hypertension and OSA.

In previously published studies, CPAP treatment of HF patients with OSA and reduced EF improved EF and quality of life [128;129;181]. In patients who had predominantly CSA with CSR, treatment with ASV appeared superior to CPAP in reducing the AHI [139] and may improve HF symptoms and cardiopulmonary performance [182;183]. However, results from randomized controlled trials are required to assess the effect of ventilation therapy on morbidity and mortality in HF patients with CSR.

In our opinion, the high prevalence of SDB in HF patients and the promising results observed positive airway pressure treatment indicate that sleep apnea should be considered as part of the diagnostic routine when managing patients with HF.

Clinical predictors of sleep-disordered breathing in heart failure

In Paper II, BMI ≥ 30 kg/m² was shown to be an independent predictor of moderate to severe SDB in HF patients. Patients with OSA had a slightly higher BMI than patients with CSA but the difference was not statistically significant. Sin et al. [108] found in their cohort that BMI was a risk factor only for OSA. As previously mentioned, HF patients with reduced EF have a high prevalence of both OSA and CSA with CSR. Additionally, mixed sleep apnea – where central apneas are followed by airway obstruction in the same apnoeic event – can occur in this group [62]. Instances where obstructive respiratory events lead to central respiratory events and *vice versa*, as well as a shift in the predominant type of SDB, were observed [115;184;185]. Thus, a significant overlap between OSA and CSA seems to be present in HF patients.

We assume that the overlap between OSA and CSA explains why obesity with a BMI cut-off of 30 kg/m² emerged as a marker to predict moderate to severe SDB of all types in our study.

Daytime sleepiness, as measured with the ESS, could not predict SDB in our cohort of HF patients. As reported in previous studies, hypersomnolence is usually not found in HF patients despite significantly reduced sleep time and poorer objective sleep quality [186-188]. This can partly be explained by increased daytime sympathetic activity [189]. Based on these findings, sleepiness (and especially ESS) cannot be recommended as a screening tool for SDB in HF patients.

Hypertension was a predictor for OSA in our HF patients. In epidemiological, cross-sectional and longitudinal studies, OSA was a risk factor for hypertension [34;190-192]. A high prevalence of OSA was found in hypertensive patients, particularly for drug-resistant hypertension [193;194]. In addition to the increased risk of becoming hypertensive, elevated BP appears more difficult to treat with coexisting OSA.

Hypertension is strongly related to LV hypertrophy but the mechanisms are complex and multifactorial [195]. We know from longitudinal studies that hypertension predisposes patients to HF [196]. LV mass is higher in hypertensive patients with a non-dipper BP profile than in those with a nocturnal BP reduction of > 10% [197]. Unfortunately, sleep data were lacking in this cohort. Several studies have shown that both systolic BP and OSA are associated with LV hypertrophy, although there is some conflicting data as to whether this association is dependent or not [70-72;197-199].

As discussed above, OSA is not only a risk factor for high BP, but may also contribute directly to deteriorating cardiac function in patients with hypertension. Therefore we suggest that HF patients with hypertension should be considered for sleep studies to rule out OSA as an underlying co-morbidity.

Hemoglobin ≥ 15 g/dl was associated with CSA in our cohort. In a sub-study of the ELITE II trial, polycythemia with hemoglobin > 15 g/dl was associated with significantly increased mortality [200]. The authors argued that polycythemic HF patients are at particular risk of thrombotic events and detrimental effects caused by the generation of oxygen-derived free radicals, but the reason for increased mortality in this polycythemic HF cohort remains unclear. Nocturnal hypoxia in HF patients with central sleep apnea has been shown to be a stimulus for erythropoietin production [201], potentially leading to higher hemoglobin levels. Patients with CSA typically suffer from more severe HF and may therefore receive more diuretic therapy than patients with OSA, which can contribute to a further increase in hemoglobin. Hypothetically, polycythemic patients in the ELITE II trial could have had a high prevalence of CSA, which would have been a possible explanation for polycythemia and an additional marker for increased mortality. Further studies are needed to investigate if there is an association between CSA and mortality in HF patients with polycythemia.

COPD is a relatively common concomitant disease in HF [202]. In our cohort, mild to moderate COPD was found to be an independent predictor for no SDB. This finding cannot

be compared to previous studies because COPD of any severity was an exclusion criteria in recently published studies of SDB prevalence in HF patients [104;106;169]. COPD in subjects with OSA seems to be as frequent as in the general population but no association has been shown between these two disorders [203;204]. To our knowledge, there are no data available regarding the coexistence of CSA with CSR and COPD.

A possible explanation for our finding of a negative association between COPD and SDB might be that COPD patients do not reach pCO2 levels that are low enough to initiate CSR cycles. Presumably, there is also an altered chemo-receptor system in this group. Further studies are needed to support this contention.

Cardiovascular risk in patients with sleep-disordered breathing

In Paper III, the Framingham general CV disease risk score was significantly higher in patients with SDB compared to the group without SDB. Adjusted for age and gender, patients with severe SDB had a 60% increase in 10-year CV disease risk. As discussed above, SDB is associated with a number of conditions and diseases which can cause and accelerate the development of CV disease. Hypertension [34;192;205], insulin resistance / diabetes and altered lipid metabolism [206-208] are particularly noteworthy in this context and account for a higher Framingham risk score. Finally, a high prevalence of smoking (up to 30% in patients with severe SDB) contributed to the higher Framingham risk score and might concurrently increase the risk of OSA [209].

A relatively high percentage of SDB patients included in our study – up to 47% of those with severe SDB – were treated for hypertension. This is consistent with results from a study by Lavie et al. [171]. Additionally, the majority of patients without known hypertension in our cohort had elevated BP. Bearing in mind that masked hypertension seems to be frequent in

OSA [210], patients diagnosed with OSA should be considered for close follow-up with repeated BP measurements.

The prevalence of known diabetes among our patients with SDB was as high as 15% in the subpopulation with severe SDB, which is slightly higher than in the Wisconsin Sleep Cohort [36]. Additionally, however, 48% of “non-diabetics” had impaired glucose metabolism and one patient met the criteria for diabetes. Impaired fasting glucose and impaired glucose tolerance put these patients at high risk for developing type 2 diabetes, and increased their CV risk [211]. Prospective studies are needed to investigate whether CPAP treatment can prevent the development of diabetes and reduce the overall CV risk in this group.

Among SDB patients without known heart disease and a mean age of 50 years, significant ECG changes were observed in 20% of cases. The changes were predominantly signs of LV hypertrophy and ST-T changes, possibly reflecting structural heart damage. These were also the main ECG findings in the Wisconsin Sleep Cohort study [212]. In a large population-based sample from the same age group (45 – 55 years), including patients with known coronary heart disease, major ECG changes were seen in < 5% of cases and minor changes in up to 8.5% [213].

Due to the frequency of ECG findings in OSA patients – even in those without known heart disease – we suggest that patients with SDB should be considered for ECG screening and referred to a cardiologist if ECG changes are present.

In 2008, the American Heart Association / American College of Cardiology stated that available evidence points to a CV benefit for CPAP treatment in OSA [157]. The main goal of the report was to improve the management of SDB in patients with CV disease. On the other hand, it seems equally important to identify and treat all medical co-morbidities in patients with SDB in order to minimize the risk of CV-related death. Thus, appropriate screening routines to detect concomitant CV disease in patients diagnosed with SDB are advisable.

Limitations

The main limitation of Papers I and II is the relatively small number of patients, especially in subgroup analyses. This applies primarily to our analyses of the possible impact of COPD on SDB and the significance of hemoglobin levels in HF patients with CSA, which need to be confirmed in larger studies. The mean age of patients with SDB was 62 years, mainly due to exclusion of patients > 80 years. Our results cannot, therefore, be extrapolated for patients over 80 years of age.

Conclusions

This thesis shows that:

- SDB is highly prevalent in HF patients.
- SDB, and in particular OSA, is a common and probably important co-morbidity in HFPEF patients.
- In HF patients, BMI ≥ 30 kg/m² is a predictor of moderate to severe SDB of all types, and could be used to stratify HF patients before referral to a sleep specialist.
- Patients with severe SDB have a 60% increase in 10-year CV disease risk, measured by the Framingham general CV disease risk score.
- Undiagnosed hypertension, pathological glucose disposal and ECG changes are highly prevalent in patients with SDB.

Future Perspectives

SDB is highly prevalent among HF patients and represents a diagnostic and therapeutic challenge for HF management. In order to decrease the number of undiagnosed cases of SDB, sleep apnea screening could be considered at primary care level and at HF clinics. This could improve the diagnosis of SDB and also reduce the number of normal sleep studies performed at sleep laboratories.

Knowledge about the impact of treating OSA with CPAP, especially CSR with ASV or other treatment options, is still limited in patients with HF. Long-term studies investigating the prognostic value of SDB treatment are required in this population, with the ultimate aim of identifying subgroups who would obtain the most benefit from intervention.

It also remains to be established whether it is reasonable to use AHI as the main treatment indicator or if different markers for hypoxia / level of desaturation should also be employed.

In the case of CSA with CSR, the results from two large randomized controlled trials are expected shortly, and will illuminate the role of ASV treatment in HF patients with reduced EF.

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