Aus dem medizinischen Zentrum für Innere Medizin,
Schwerpunkt Pneumologie
des Fachbereichs Medizin der Philipps-Universität Marburg

Atrial fibrillation in heart failure patients with and without sleep-disordered breathing

Inaugural-Dissertation zur Erlangung des Doktorgrades der
gesamten Humanmedizin
dem Fachbereich Medizin der Philipps-Universität Marburg

vorgelegt von

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Marburg 2023

Angenommen vom Fachbereich Medizin der Philipps-Universität Marburg am: 17.07.2024

Gedruckt mit Genehmigung des Fachbereichs Medizin

Dekanin: Prof. Dr. Denise Hilfiker-Kleiner

Referent: Prof. Dr. Med. Ulrich Koehler

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1. Introduction:

1.1. Heart Failure

1.1.1. *Definition and epidemiology*

Ambiguity and a lack of standardization plague the currently available definitions of heart failure (HF) (Braunwald, 2013). A definition released by the Heart Failure Society of America defined HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue (2013 ACCF/AHA guideline). From the middle of the 20th century onward, a series of investigations convincingly revealed that the incidence of HF had not risen among White populations. Interestingly, the uptick in hospitalizations was attributed to the improved survival rates post HF diagnosis. This, in turn, contributed to a larger pool of individuals living with HF who were prone to recurrent hospitalizations (Aniel *et al.*, 2002)(Roger *et al.*, 2004).

Furthermore, a growing recognition of the heterogeneous nature of the HF syndrome emerged. Notably, it was acknowledged that HF could manifest with either preserved or reduced left ventricular ejection fraction (EF) (2017 ACC/AHA). In a majority of studies, around 50% of HF cases were identified as HF with preserved EF. Regrettably, therapeutic trials struggled to pinpoint effective treatments for this particular manifestation of HF (Dunlay, Roger and Redfield, 2017). Statistics show that more than 10 million individuals in Europe and 23 million worldwide are suffering from HF (Mosterd and Hoes, 2007) . Approximately 10 million people exhibit myocardial weakness without symptoms. In Germany, HF is one of the most common reasons for consultation in general practitioner practices and the leading cause for hospital admissions (Fink and Haidinger, 2007). The epidemiology in populations related to HF in terms of age, sex, race, and ethnicity disparities. HF's incidence and prevalence increase with age, often within the context of multiple health issues in older individuals. Women are about twice as likely as men to develop HF with preserved ejection fraction (HFpEF). Studies rarely present stratified data based on race or ethnicity. The clinical outcome analysis highlights excess risk of hospitalizations and deaths among Black individuals, especially

in younger age groups while the data on HF incidence in Hispanic and Latine individuals are limited. In the South Asians population, a high burden of atherosclerotic cardiovascular disease and associated risk factors were reported (Roger, 2021).

1.1.2. *Etiology*

HF can result from an array of diverse cardiac conditions, hereditary predispositions, and systemic diseases, often presenting with multifactorial etiologies. The prevalence of these underlying factors exhibits significant disparities between high-income and developing nations (Yusuf *et al.*, 2014). The Global Burden of Disease Study outlines a comprehensive spectrum of 17 primary HF etiological factors, with a considerable proportion, approximately two-thirds, attributed to ischaemic heart disease, chronic obstructive pulmonary disease, hypertensive heart disease, and rheumatic heart disease. While the quantification of right-sided HF associated with chronic obstructive pulmonary disease has been attempted, the limitations in available data necessitate further research endeavors (Hawkins *et al.*, 2009). The distribution of HF's causal contributors displays distinctive patterns across socioeconomic strata. Specifically, regions characterized by greater economic affluence experience heightened prevalence of ischaemic heart disease and chronic obstructive pulmonary disease as prominent etiological contributors to HF. Conversely, regions with limited economic resources predominantly confront the impact of hypertensive heart disease, rheumatic heart disease, cardiomyopathy, and myocarditis as primary drivers of HF incidence and prevalence (Vos *et al.*, 2012).

1.1.3. *Causes and risk factors*

Notably, hypertension, diabetes, sedentary lifestyle, hyperlipidemia, and tobacco usage have all been identified as factors linked to the onset of HF. These associations are often mediated through the conduit of coronary disease. Furthermore, certain risk factors, such as diabetes or obesity, demonstrate a direct correlation with HF. In recent times, these factors, acknowledged contributors to HF's development, are increasingly being recognized for their intricate involvement through diverse physiological pathways (Ebong *et al.*, 2014). Multimorbidity prevalent in elderly HF populations underscores the coexisting and interacting nature of traditional cardiovascular risk factors. A recent case-control study scrutinized risk factors and comorbidities, revealing higher prevalence rates of various risk factors in HF patients compared to controls, as displayed in Figure 1.

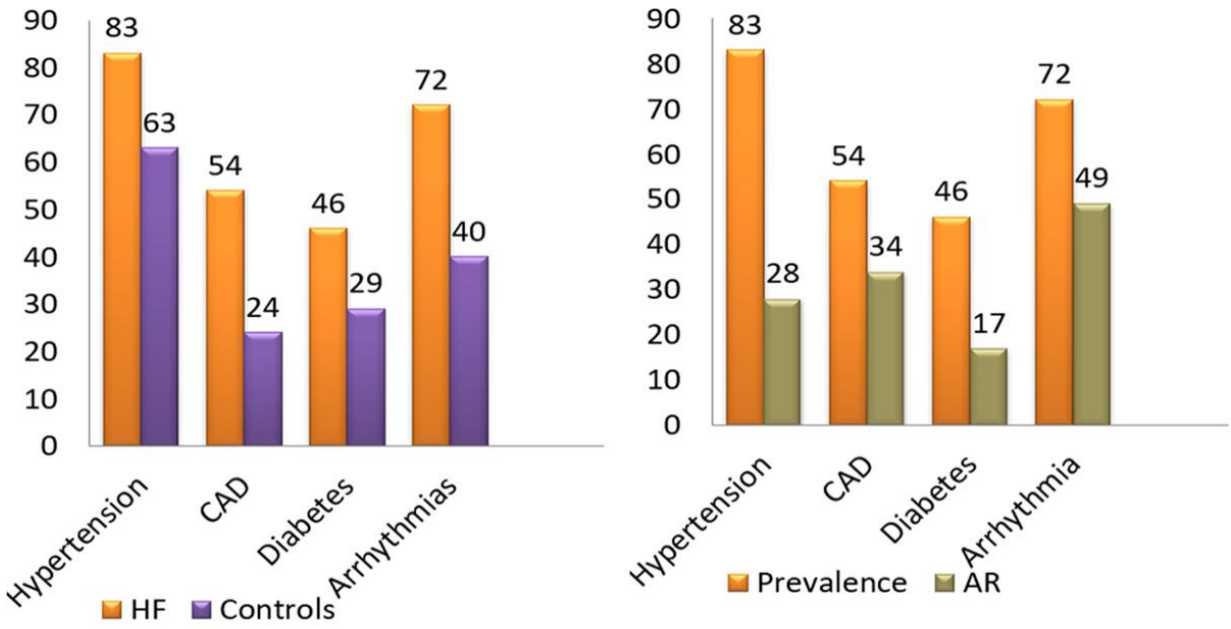

Figure 1. Prevalence and attributable risk of comorbidities in HF (Roger, 2021) .

This trend remained consistent across cases with the exception of hypertension, irrespective of EF. Specifically, cardiometabolic risk factors such as diabetes and obesity exhibited stronger associations with HF in younger age groups. Noteworthy was the significant role played by cardiac arrhythmias in HF genesis, warranting further inquiry. The concept of attributable risk emerged, quantifying absolute exposure impact by assessing excess disease risk in exposed versus unexposed individuals. Crucial for population health, this metric offered insights into the potential disease reduction achieved if the considered risk factor were eliminated. While complete eradication may be implausible, this metric allowed envisioning outcomes attainable through partial risk factor mitigation in the population (Chamberlain *et al.*, 2020).

1.1.4. ***Pathophysiology***

Complexes mechanisms underscore the pathophysiology of HF, these mechanisms reduce the progressive deterioration of the heart's ability to pump blood effectively. This identified the endotypes of HF which are categorized into systolic HF (reduced EF) and diastolic HF (preserved EF). In systolic HF, coronary artery disease, heart attacks, or cardiomyopathies can lead to a reduction in the heart's ability to contract and pump blood efficiently due to the weakness in the heart muscle. While in diastolic HF an impairment

of the heart muscle to relax limited its ability to efficiently pump blood, in clinical condition such as hypertension and ventricular hypertrophy the heart loss its ability to relax and fill the heart during the diastolic phase (Arrigo *et al.,* 2020) (Kirali K *et al.*, 2017).

Multi-mechanisms can help in maintain cardiac output and contractility to compensate for its inability to efficiently pump blood. Three major mechanisms are included such as a). Increase in left ventricular (LV) volume (dilation) and mass (hypertrophy) b). Increase in systemic vascular resistance (SVR) secondary to sympathetic activation and increased catecholamine release c). Activation of the renin-angiotensin-aldosterone (RAAS) and vasopressin (ADH) systems. Altogether, the compensation mechanisms can ultimately worsen the condition over time (Kirali K *et al.*, 2017).

1.1.5. ***Diagnosis***

The clinical presentation of HF includes symptoms like shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea. Fatigue and edema are common, while right-sided HF can lead to abdominal distention and pain. In advanced stages, tachycardia, pedal edema, increased jugular venous pressure, abnormal lung sounds, and S3 gallop become apparent. Less frequent signs include hepatojugular reflux and ascites. Recent research highlights microvascular dysfunction and oxygen supply issues in HF patients, prompting the consideration of therapeutic strategies to enhance muscle microvascular and oxidative function (Watson, Gibbs and Lip, 2000) (Heart Failure Society of America, 2010) (Poole *et al.*, 2012).

The assessment of HF involves many approaches, including a comprehensive physical examination and blood tests. These tests involve a complete blood count, urinalysis, and a detailed metabolic profile assessing serum electrolyte levels, blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function, and thyroid-stimulating hormone. Additionally, Natriuretic peptides (NPs) have emerged as golden biomarkers for HF over the past decade. Although the NPs levels impacted by other cardiovascular conditions such as valvular heart disease, ischemia, and hypertension, as well as non-cardiac factors like age, renal function, anemia, pulmonary disorders, and sepsis, it is still used as predicting factor in HF. NPs don't replace the need for cardiac imaging; their interpretation must align within the clinical context (Inamdar and Inamdar, 2016).

As per the proposed categorization of HF stages, Stage A pertains to individuals harboring risk factors for HF without apparent symptoms, encompassing conditions such as hypertension, diabetes, familial predisposition to cardiomyopathy, or exposure to cardiotoxins. Stage B signifies pre-HF individuals who lack ongoing HF symptoms yet exhibit evidence of structural heart anomalies, abnormal cardiac function, or elevated biomarkers. The progression to Stage C entails the presence of current or previous HF symptoms originating from structural or functional cardiac aberrations. Lastly, Stage D signifies advanced HF, characterized by severe symptoms, recurrent hospitalizations despite optimal treatment (Guideline-Directed Medical Therapy), and potential consideration for advanced interventions like transplantation, mechanical circulatory support, or palliative care, see Figure 2.

Furthermore, the NYHA functional classification is pivotal for assessing symptoms and functional capacity in symptomatic (Stage C) and advanced (Stage D) HF patients. This classification ranges from Class I (no activity limitations) to Class IV (symptoms even at rest). It's crucial to range from Class I (no activity limitations) to Class IV (symptoms even at rest). It's crucial to determine NYHA class at diagnosis and during treatment to track progress.

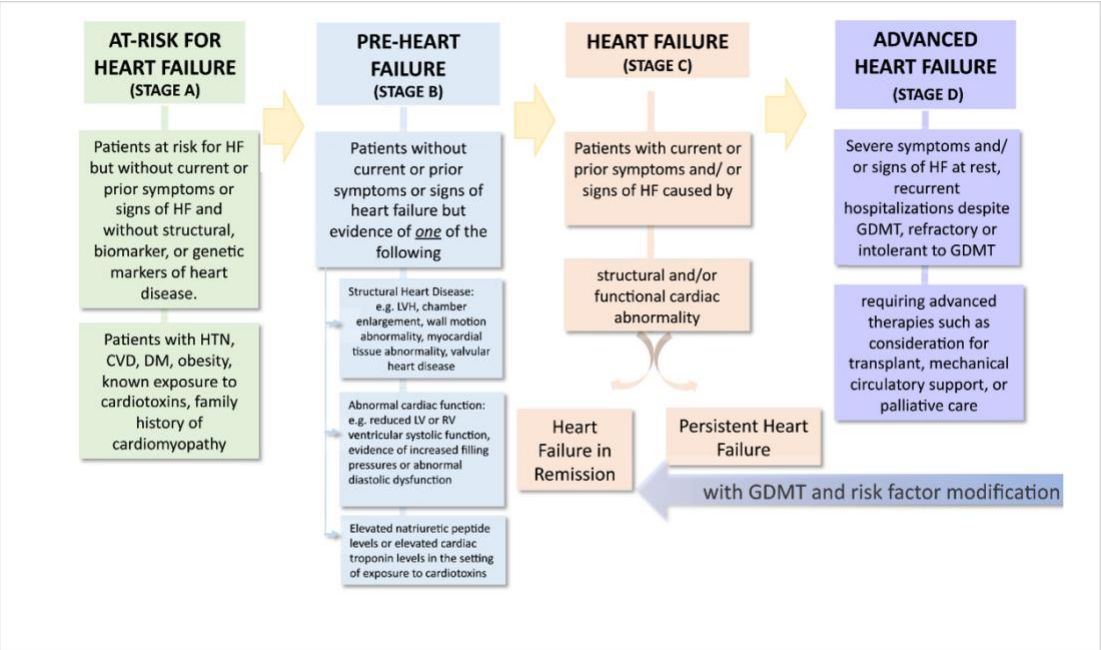

Figure 2. Stages in the development and progression of HF. CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; GDMT, guideline-directed medical therapy (Bozkurt *et al.*, 2021).

For instance, a patient with symptomatic HF (Stage C) who becomes asymptomatic can be designated as NYHA Class I. Worsening class correlates with a poorer prognosis. Any symptomatic HF patient (NYHA Class II–IV) should optimize treatment (Bozkurt *et al.*, 2021). More details on the NYHA class were summarized in Table 1.

Table 1: NYHA Classification in HF.

NYHA Functional Classification	
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain.
IV	Symptoms of HF at rest. Any physical activity causes further discomfort.

1.1.6. ***Treatment***

The major aims of HF treatment are improving prognosis and symptom relief. Moreover, for the in-hospital patients, goals also include reducing hospital stays, preventing organ damage, and managing coexisting conditions that impact prognosis.

The comprehensive treatment approach entails diligent monitoring of oxygen levels, with attention to PaO2 below 60% or SaO2 below 90%. Noninvasive positive pressure ventilation (NIPPV) is selectively deployed to mitigate respiratory distress and circumvent intubation (Inamdar and Inamdar, 2016).

According to the 2021 European Society of Cardiology ESC Guidelines for the diagnosis and treatment of acute and chronic HF, the therapeutic regimen aims to improve survival in HF patients and compensate for the reduction in left ventricular ejection fraction (LVEF) and the risk of HF hospitalizations. A combination of medications is recommended for HF patients, including renin-angiotensin-aldosterone (RAAS) inhibitors, angiotensin receptor-neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitors (ACE-I), beta-blockers, and mineralocorticoid receptor antagonists (MRA). These drugs considered as first-line treatments for HFrEF management;

adjustments in the treatment should be considered if contraindicated or not tolerated. Additionally, drug doses can be adjusted to the maximum allowable dose. The guidelines still recommended to change from ACE-I to ARNI, if a combination of ACE-I, beta-blocker, and MRA was unable to control the symptoms. Although, ARNI is considered as a primary treatment option instead of ACE-I. Angiotensin-receptor blockers (ARBs) continue to be a replacement if the patient developed a tolerance against ARNI or ACE-I. To reduce the risk of mortality attributed to cardiovascular diseases or the decline in heart function in patients with HFrEF, the sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin add on therapy is recommended. The HFrEF patients treated with ACE-I/ARNI, a beta-blocker, and an MRA may benefit from the SGLT2 in the presence or absence of diabetes.

Furthermore, in select cases, Digoxin is employed to provide a moderate boost to cardiac output, alleviate HF symptoms, and curtail hospitalization instances. The administration of anticoagulants is judiciously tailored to abate the risk of thromboembolism. Inotropic agents are cautiously employed to optimize organ perfusion, alleviate congestion, elevate cardiac output, and moderate neuro-humoral activation in the context of HF characterized by reduced EF (Inamdar and Inamdar, 2016).

1.2. Sleep-disordered breathing

Sleep-disordered breathing (SDB) is gaining more attention recently as an outcome of HF. It's viewed as a risk factor inducing the progression of cardiac dysfunction. More than 50% of HF patients are suffering from SDB. However, a substantial number of patients with SDB still go undetected within current medical practice. Risk factors including age, obesity, lower EF and AF are independently inducing the occurrence of SDB (Pearse and Cowie, 2016).

SDB consists of three major subtypes, obstructive sleep apnea (OSA), central sleep apnea (CSA), or a blend of the two. Within the context of OSA, the collapse of the pharynx occurs during sleep, resulting in upper airway obstruction and frequently accompanied by snoring. This condition is preceded by risk factors such as obesity, a shortened neck structure, and retrognathism (a condition where the jaw is positioned farther back than usual) (Elias *et al.*, 2012).

HF introduces a rostral shift of fluid during sleep. The nocturnal shift of fluid towards the upper body region plays a contributory role in the development of both OSA and CSA in patients with HF. The magnitude of fluid migration within the overnight

period is not only associated with the severity of sleep apnea but also impacts the predominant type of sleep apnea experienced. This migration is closely linked to the level of leg edema and the duration of time spent in a sitting position. Due to its opposite correlation with physical activity, it impacts the lifestyle fostering the onset of sleep apnea in HF patients by facilitating weight gain and promoting the retention of fluid in dependent areas (Yumino *et al.*, 2010).

In Cheyne-Stokes respiration also known as CSR, characterized by alternating breathing intensities and frequent central apnea, is observed in a significant proportion of HF patients, particularly those with reduced LVEF and AF. The combination of heightened chemosensitivity and delayed circulation, rather than just delayed circulation alone, is implicated in its pathogenesis. Potential contributors to increased chemosensitivity include elevated pulmonary pressures, fluid shifts during sleep, or carotid body abnormalities. This phenomenon's association with intermittent hypoxemia and catecholamine surges exacerbates underlying HF, often leading to paroxysmal nocturnal dyspnea in affected patients (Hahrokh and Avaheri, 1999) (Spaak *et al.*, 2005) See Figure 3.

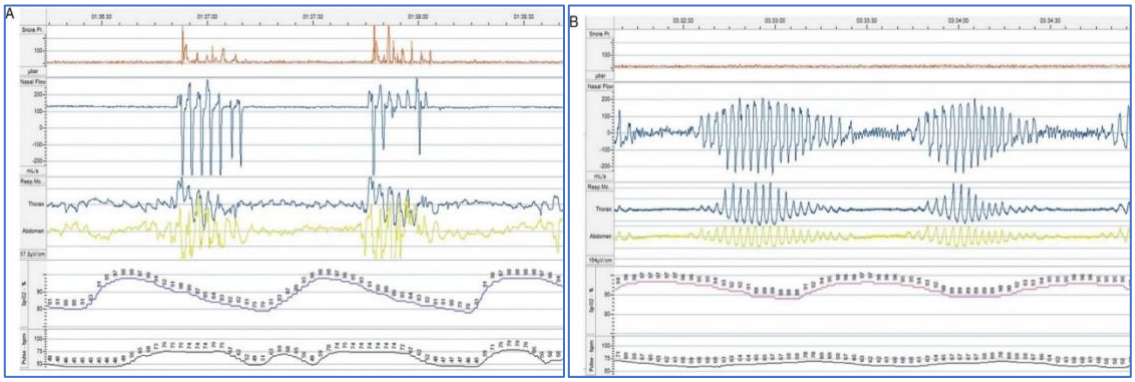

Figure 3. (A) Severe OSA on sleep polygraphy. Note the persistence of respiratory effort during apnea and the marked swings in heart rate and oxygen saturation. (B) Severe CSA on sleep polygraphy. Note the absence of respiratory effort during apnea (Pearse and Cowie, 2016)

1.2.1. *Diagnosis and treatment*

The out-clinic patients commonly seek attention at sleep clinics due to concerns about excessive daytime sleepiness (EDS) or prompted by their partner's complaints regarding their snoring noise or witnessed apneic episodes during sleep. Snoring, though prevalent in the general population (35–45% of men, 15–28% of women), often leads to social disruption, necessitating medical intervention. Excessive daytime sleepiness, related to

disrupted sleep from frequent arousals, is a common issue but can be challenging to differentiate from other forms of tiredness. The Epworth Sleepiness Scale (ESS) serves as a practical tool for subjective assessment. Witnessed apneic events and nocturnal choking, frequently reported by bed partners, contribute to clinic referrals; however, these accounts may not always accurately reflect actual respiratory events. Female patients with OSA may report fewer apneic events, and the differentiation of such episodes from other causes of nocturnal breathlessness is crucial (Schlosshan and Elliott, 2004).

Within the clinic, polysomnography (PSG) is used as a definitive diagnostic method for SDB. This procedure usually demands hospital admission and the presence of a skilled technician throughout the night. However, its implementation is resource-intensive, costly, and the diverse array of methodologies, tools, and diagnostic standards utilized across various sleep centers introduces complexity into the assessment and interpretation of PSG data, making comparisons challenging (Chesson *et al.*, 1997). Full polysomnography (PSG) encompasses two distinct dimensions: the observation of diverse respiratory parameters to gauge respiration, and the monitoring of cortical brain activity to ascertain sleep presence and its specific stage (Chesson *et al.*, 1997).

Continuous positive airway pressure (CPAP) is a recognized treatment for OSA, and its benefits extend to HF patients. It prevents pharyngeal collapse in OSA, while in HF, it aids pulmonary function, reduces intrathoracic pressure swings, and lowers blood pressure. CPAP's positive effects on cardiac preload, afterload, and overall function are noteworthy, demonstrated by improved right ventricular systolic function and exercise capacity, contributing to reduced mortality in HF patients with preserved EF (Pearse and Cowie, 2016), CPAP is demonstrated in Figure 4.

The management of CSA in HF patients is less well-defined than in OSA. The standard treatment of HF, including diuretics, beta-blockers, and cardiac resynchronization therapy, can improve CSA. Oxygen therapy has shown benefits in reducing sympathetic drive, increasing oxygen saturation, and improving LVEF in HF patients with CSA. Nasal continuous positive airway pressure (CPAP) treatment has also been effective in improving CSA, LVEF, oxygen saturation, and walking distance. Research is required to determine the impact of SDB management on HF prognosis (Yoshihisa and Takeishi, 2017).

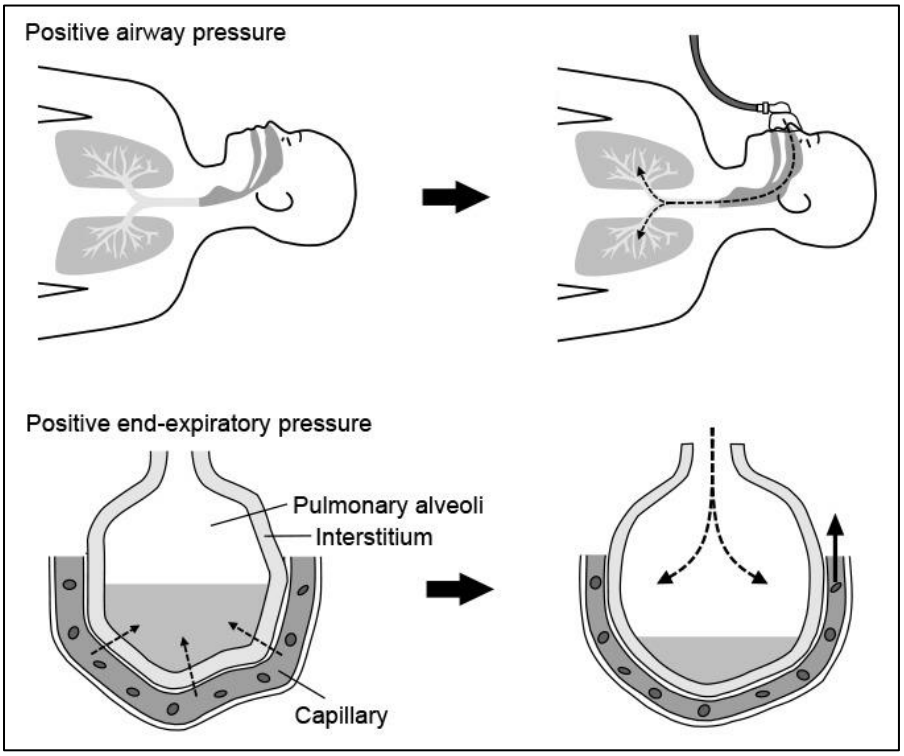

Figure 4. Effect of positive airway pressure. Upper panels: Positive airway pressure widens an upper airway and pulmonary alveoli. Lower panels: Positive end-expiratory pressure expands pulmonary alveoli, decreases pulmonary fluid and improves congestion and gas exchange in patients with HF (Yoshihisa and Takeishi, 2017).

1.2.2. ***The links between HF, SDB, and arrhythmia***

OSA can exacerbate HF progression through many mechanisms including negative intrathoracic pressure, enhancing preload and afterload, sympathetic activation, endothelial dysfunction, vasoconstriction, and adverse changes in myocardial function and fibrosis (Spaak *et al.*, 2005) (Dimsdale *et al.*, 1995).

In contrast, CSA is generally seen as a consequence of HF, linked to increased sympathetic activation, blood pressure fluctuations, hypoxemia, and endothelial stress, along with elevated C-reactive protein levels. Both OSA and CSA elevate sympathetic activity, which contributes to peripheral vasoconstriction, tachycardia, and renin–angiotensin–aldosterone system activation, making SDB a potential therapeutic target in HF management. Additionally, patients with SDB are at greater risk of malignant ventricular arrhythmia, with OSA patients more likely to experience implantable cardioverter defibrillator (ICD) therapies at night due to increased sympathetic activity, intrathoracic pressure variations, and haemodynamic disruptions (Pearse and Cowie, 2016). The links between the cardiac progression and SDB are clarified in Figure 5.

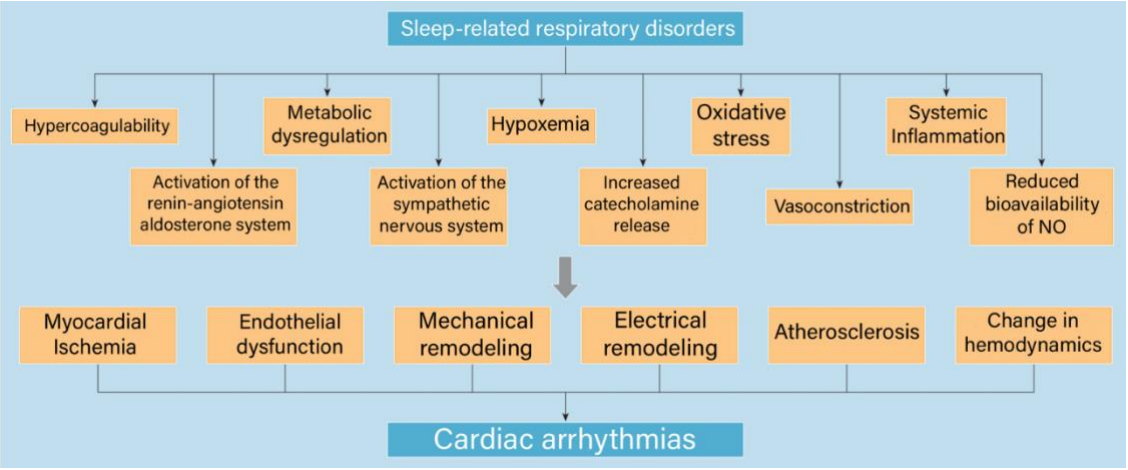

Figure 5. Effect of SDB in inducing recurrent hypoxemia, sympathetic nervous system activation, and catecholamine release. This in turn predisposes to cardiac arrhythmias via vasoconstriction, regional ischemia, oxidative stress, reduced endothelial function, increased inflammation and metabolic dysregulation (Bitter, Horstkotte and Oldenburg, 2011).

From a pathophysiological perspective, the emergence of bradyarrhythmias in the context of apnea is primarily attributed to a vagal-mediated cardioinhibitory reflex. This reflexual response is largely precipitated by respiratory efforts aimed at overcoming pharyngeal obstruction, a phenomenon commonly referred to as the Müller maneuver. Remarkably, the mechanism underlying this vagal reflex appears to be intrinsically connected to the active struggle against airway obstruction. Notably, the employment of nasal ventilation therapy has demonstrated significant efficacy in the management of bradycardic arrhythmias associated with OSA. This therapeutic approach holds the potential to address the root cause of vagal reflex-mediated bradyarrhythmias by ensuring adequate ventilation and preventing respiratory-induced perturbations. In a broader clinical context, the consistent application of CPAP therapy tailored to address OSA-associated bradyarrhythmias has exhibited the capacity to obviate the requirement for pacemaker interventions, underscoring its potential as an efficacious non-invasive intervention strategy, see Figure 6.

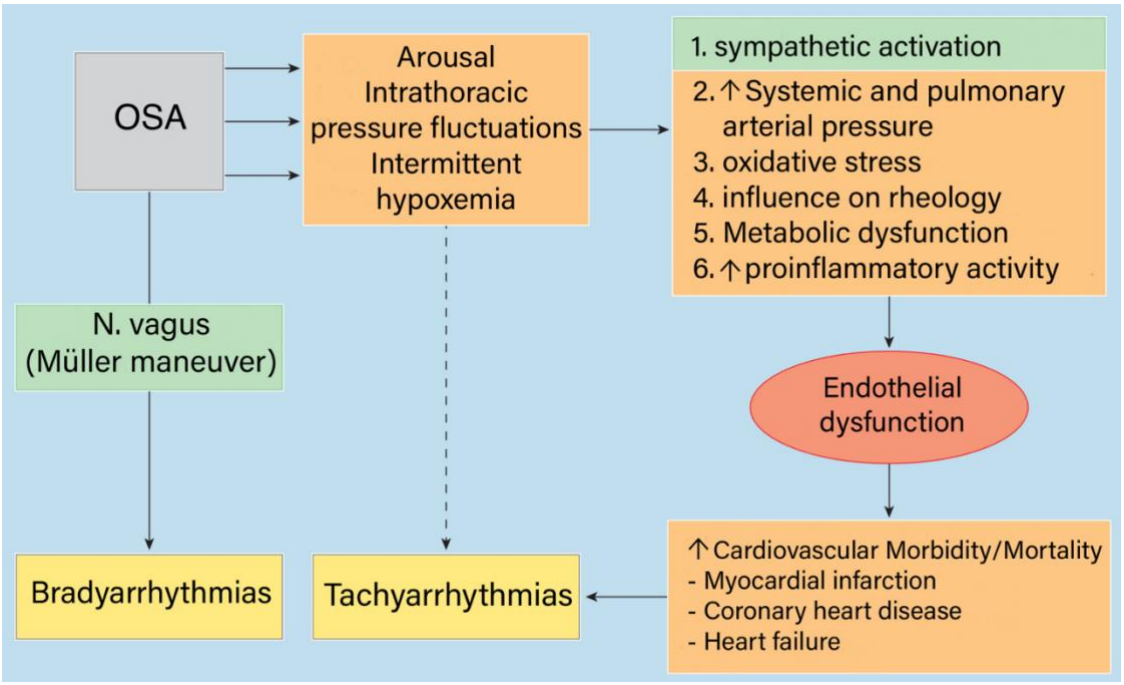

Figure 6. Bradyarrhythmias in OSA (Koehler *et al.*, 2011).

Ventricular arrhythmias are primarily evident in patients with cardiovascular comorbidities such as coronary artery disease, hypertensive heart disease, dilated cardiomyopathy, and chronic HF of any etiology, often accompanied by obstructive sleep apnea (OSA) or central sleep apnea with Cheyne-Stokes respiration (CSA-CSR). In individuals with chronic HF and CSA-CSR, ventricular arrhythmias are prominently observed during the hyperventilation phase. The pathogenesis of these arrhythmias is linked to an elevated sympathetic tone, serving as a triggering mechanism(Koehler *et al.*, 2011), all details are clarified in Figure 7.

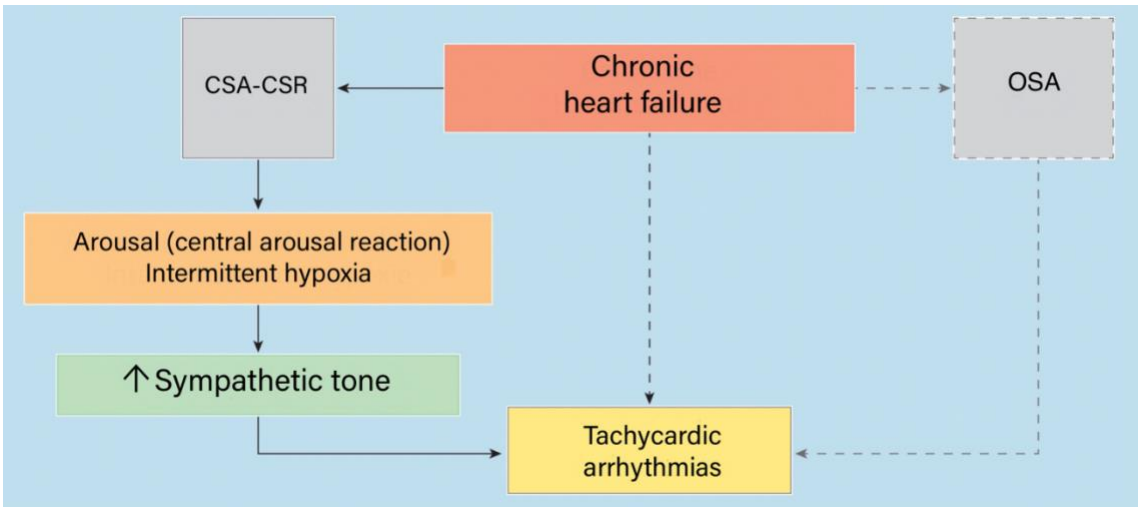

Figure 7. Tachycardic cardiac arrhythmias in OSA and CSA/CSR (Koehler *et al.*, 2011)

1.2.3. *AF and HF*

AF is the most common arrhythmia in clinical practice, responsible for about one-third of cardiac rhythm disturbance-related admissions. The prevalence of AF is estimated to be 2.5% in the middle-aged general population in Germany (Schnapel et al 2012). Hospital admissions for AF have risen by 66% in the past 20 years due to factors including population aging, increased prevalence of chronic heart disease, and enhanced monitoring leading to higher rates of diagnosis (Anter, Jessup and Callans, 2009).

The coexistence of AF and HF can be partially explained by shared risk factors such as age, hypertension, diabetes, obesity, and structural heart conditions. These factors lead to cellular, electrophysiological, and neurohormonal changes that predispose the heart to both AF and myocardial failure. The relationship between AF and HF's pathophysiology is still being researched, but AF can contribute to HF development or progression. Elevated resting heart rate and irregular heart rate responses during exercise lead to reduced diastolic filling time and cardiac output. Additionally, impaired atrial contractile function worsens matters, especially in patients with diastolic dysfunction. Studies show that the onset of AF in HF patients correlates with worsened functional class, cardiac index, and exercise capacity, and restoration of sinus rhythm can improve these parameters (Kareti *et al.*, 2005) (Pozzoli *et al.*, 1998) (Gosselink *et al.*, 1994). This is clarified in Figure 8.

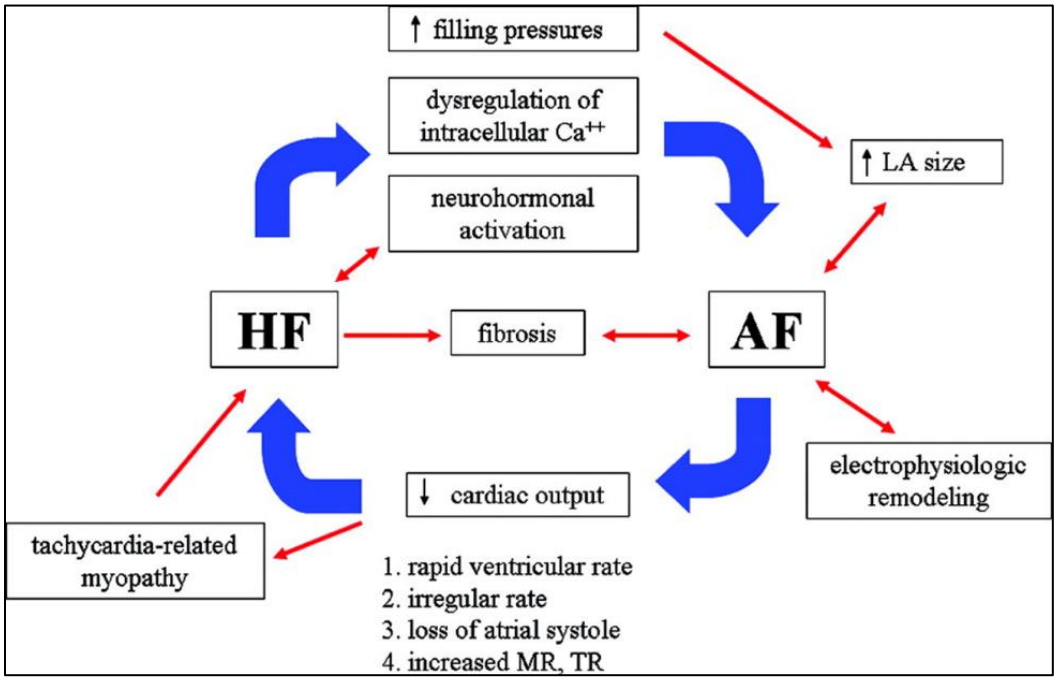

Figure 8. AF and HF: a vicious pathophysiological cycle. LA indicates left atrial; MR, mitral regurgitation; and TR, tricuspid regurgitation (Anter, Jessup and Callans, 2009).

Shared risk factors and comorbidities, including age, male sex, hypertension, congestive HF, and coronary artery disease, are common to both AF and SDB. OSA, a form of SDB, potentially contributes to AF development through intermittent hypoxia, recurring arousals, and negative intrathoracic pressure. These mechanisms elevate sympathetic nerve activity, oxidative stress, and may lead to electrical and mechanical remodeling in atria and the left ventricle. Patients with OSA show documented electrical and cardiac mechanical changes, further indicating a heightened susceptibility to AF (Wolk, Kara and Somers, 2003) (C Digby and Baranchuk, 2012) (Arias and Sánchez, 2007).

Evidence consistently shows that patients with OSA are less likely to maintain sinus rhythm after AF treatment with radiofrequency catheter ablation. For instance, recent research revealed a significantly higher risk of AF recurrence after ablation in patients with OSA compared to those without. Untreated OSA doubles the risk of AF recurrence after electrical cardioversion. OSA's adverse effects on AF recurrence extend beyond electrical interventions; patients with severe OSA have a lower response rate to antiarrhythmic drug therapy compared to those with mild OSA (Lavergne *et al.*, 2015). In patients with permanent AF and HF, a single overnight session of overdrive ventricular pacing demonstrated efficacy in decreasing central apnea events (Bordier, Maurice-Tison and Ramana, 2012). Similarly, restoration of sinus rhythm through electrical cardioversion led to a reduction in central respiratory events, with the number of patients experiencing CSA decreasing from 53 to 23 after cardioversion (Fox *et al.*, 2016) . Notably, in individuals with drug-refractory persistent AF, radiofrequency catheter ablation yielded a notable decrease in AHI, and a significant correlation was established between the ablation outcome and the percent change in AHI (Naruse *et al.*, 2012).

2. Hypothesis:

The association between HF and SDB has been established. Thus, our research was focusing on the links between the AF and SDB in patients suffering from HF.

We hypothesis that prevalence/occurrence of AF in HF patients may differ among the SBD different phenotype including OSA and CSA.

3. Materials and Methods:

3.1.Patient Cohort and Data Collection

In the period spanning from August 2007 to June 2011, a comprehensive observational investigation was conducted with the aim of examining the prevalence of AF and SDB among a specific cohort of 302 patients who had been diagnosed with HF. These patients were selected from the standard procedural flow of the cardiology ward at University Hospital in Marburg, with the objective of encompassing a diverse representation of HF cases within the study population.

Inclusion Criteria:

The selection process for participants in this study adhered to specific inclusion criteria to ensure the representative nature of the HF cohort under investigation. The following criteria were applied:

- Inpatient Status: Participants were exclusively recruited from the pool of inpatient admissions.
- Age Range: Individuals aged 18 to 80 years were considered eligible for participation.
- Echocardiographic EF: Patients with an echocardiographically determined EF of 50% or less were included.
- NYHA Functional Classification: Inclusion spanned across NYHA functional stages 1 to 4

Exclusion Criteria:

To establish the integrity of the study cohort, the following exclusion criteria were employed:

- Age Limitations: Individuals below 18 years or above 80 years of age were not considered for participation.
- Cognitive Capacity: Individuals with limited cognitive capacity or those unable to provide informed consent were excluded.
- Malignancy: Patients with known malignancies, except for basal cell carcinoma, were excluded.
- Severe Liver Dysfunction: Individuals with severe liver dysfunction were excluded from the study.
- Progressive Renal Insufficiency: Participants with progressive renal insufficiency,

indicated by a serum creatinine level exceeding 3 mg/dl, were excluded.

- Substance Abuse: Patients with a history of alcohol and/or substance abuse were excluded.
- Infectious Diseases: Individuals with HIV infection, infectious hepatitis, or other severe infectious diseases (e.g., tuberculosis, pneumonia) were not included.
- Acute Mental Illness: Individuals experiencing severe acute mental illnesses, such as acute psychosis, were excluded.
- Pre-existing Sleep-Related Breathing Disorders: Participants with known SDB were not considered.
- Concurrent Participation in Clinical Trials: Individuals concurrently participating in other clinical studies were excluded to prevent potential confounding effects.

3.2.Anthropometric Data and Lifestyle Factors

Anthropometric data, encompassing age, gender, and Body Mass Index (BMI), calculated as the ratio of body weight (kg) to height (m)^2, were acquired from all enrolled patients. Furthermore, patients' medical histories were elicited to identify pre-existing conditions, and the current quantity of cigarette consumption was quantified in "pack years."

3.3.Subjective Daytime Sleepiness Assessment

To gauge subjective daytime sleepiness, participants completed the "Epworth Sleepiness Scale (ESS)" questionnaire, yielding valuable insights into their perceived levels of somnolence.

3.4.Blood Pressure Measurement

Blood pressure measurements, both systolic and diastolic, were extracted from clinical examination findings performed by attending physicians at the time of admission.

3.5.Cardiac Catheterization and Coronary Angiography

For patients with available data, the results of left heart catheterization and coronary angiography were meticulously documented to provide additional insights into the cardiovascular status.

3.6.Diagnostic Approaches

3.6.1. *Electrocardiogram (ECG)*

The 12-lead resting electrocardiogram (ECG) was performed on all patients as part of the diagnostic protocol. It was used to identify the presence of sinus rhythm or AF. ECG recordings were obtained during the period of stay and carefully evaluated by a qualified medical professional.

3.6.2. *Cardiorespiratory polysomnography*

For the evaluation of sleep-related breathing disorders, cardiorespiratory polysomnography was employed as the diagnostic modality. The data acquisition and storage were facilitated through the utilization of the SOMNOcheck 2 R&K ambulatory polysomnography system, manufactured by Weinmann, Hamburg, Germany (refer to Figure 9).

Figure 9. SOMNOcheck 2 R&K System. Source: Company Weinmann.

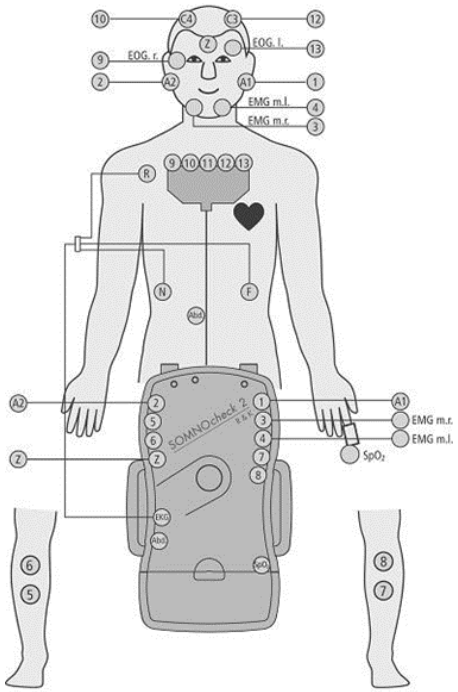

Figure 10. Applying and positioning electrodes., Source: Company Weinmann.

After a comprehensive discussion of the procedural framework, an independent measurement session was conducted during the nocturnal period between 22:00 and 6:00 hours. Proficiently trained staff affixed the monitoring apparatus within the designated patient quarters (refer to Figure 10). The instrumentation facilitated the capture of multiple physiological parameters, encompassing nasally derived airflow, thoracic and abdominal excursion magnitudes, the spatial orientation of the patient, and a spectrum of pertinent sleep parameters.

The following sleep parameters were meticulously recorded and quantified: Total In Bed (TIB) time, Total Sleep Time (TST), average oxygen saturation (mean SaO2), the duration of time with oxygen saturation below 90% (SaO2 < 90%), the arousal index, proportions of non-rapid eye movement (NREM) sleep stages 1-4, rapid eye movement (REM) sleep, sleep latency, sleep efficiency, and periodic limb movement (PLM) index. Furthermore, the classification of breathing disturbances encompassed the assessment of various indices and occurrences, including the overall Apnea-Hypopnea Index (AHI), Obstructive Apnea-Hypopnea Index (OAHI), and Central Apnea Index (CAI).

The depth of captured data extended beyond mere quantification, encompassing insights into the characteristics and manifestations of diverse breathing disorders. By adeptly amalgamating this multifaceted dataset, our study was able to achieve a comprehensive evaluation of sleep parameters and breathing irregularities, contributing

to a holistic understanding of the subject condition.

The analysis of polysomnographic data was carried out through computer-assisted visual examination by trained personnel at the Sleep Medicine Center Marburg.

3.7.*Definition of Sleep-Related Breathing Events*

The categorization and characterization of sleep-related breathing events were established in accordance with established medical criteria. These definitions are pivotal for precisely classifying various forms of SDB. The sleep structure was recorded according to the recommendations of (Rechtschaffen and Kales, 1968). Respiration was classified following the international guidelines of the AASM for obstructive or central apneas and hypopneas (American Academy of Sleep Medicine, 2005).

The following criteria were employed:

- Apnea: An apnea event was identified as a cessation of breathing lasting for a duration equal to or exceeding 10 seconds.
- Obstructive Apnea: A classification of obstructive apnea was assigned when the criteria for apnea were met, concomitant with observable respiratory efforts, as evidenced by thoracoabdominal movement.
- Central Apnea: The distinction of central apnea was established when apnea criteria were fulfilled, but no associated thoracoabdominal movement was detected.
- Hypopnea: Hypopneic events were characterized by a reduction in airflow exceeding 50% (or thoracoabdominal movements) that persisted for a duration of 10 seconds or more. In addition to airflow reduction, these events were coupled with a decrease in oxygen saturation exceeding 4% and/or an arousal response.
- Classification of Hypopneas: Hypopneas were subcategorized based on their origin. Those marked by increasing thoracoabdominal movement and concurrent snoring during reduced airflow were considered of obstructive origin. Conversely, hypopneas lacking respiratory effort were designated of central origin.
- Mixed Apnea: The classification of mixed apnea was attributed to events where apnea criteria were met. Notably, the initial phase of these events exhibited an absence of respiratory effort, succeeded by a subsequent resumption of respiratory effort during the latter part of the Cheyne-Stokes breathing, while not assigned a separate classification, was encompassed within the spectrum of central events.

These precise definitions and classifications provide a foundation for the accurate identification and differentiation of sleep-related breathing events, contributing to a comprehensive characterization of the observed phenomena within the study population. We implemented two distinct AHI cutoff values (5 and 15 events per hour of sleep) to assess the prevalence of these disorders within the cohort of HF patients under investigation.

A classification scheme was employed to ensure precision in categorization. Patients were allocated to the CSA/CSR group if central sleep-related breathing abnormalities exceeded 50% of the cases observed. In parallel, the OSA group encompassed patients exhibiting more than 50% of either obstructive or mixed sleep-related breathing abnormalities.

To provide a quantitative gradation of the severity of sleep apnea, AHIs within specific ranges were employed. Sleep apnea was classified as mild when the AHI ranged from 5/h to 14/h. Subsequently, an AHI falling within the interval of 15/h to 29/h was designated as moderate, while a pronounced AHI surpassing 30/h was indicative of severe sleep apnea. Importantly, an AHI value below 5/h was stratified as clinically inconsequential, thereby emphasizing its limited clinical significance within this context.

This methodological framework ensured a thorough assessment of the diverse range of sleep-related breathing abnormalities encountered within the realm of HF patients. The application of multiple cutoff values and the subsequent gradation of severity allowed for a comprehensive evaluation, enabling a refined exploration of the intricate interplay between HF and sleep disorders.

3.8.Statistical Analysis:

All data underwent statistical analysis at university hospital Marburg, and results were reported as mean ± standard deviation, as customary. Basic data pertaining to AHI cutoff values of ≥ 5/h and ≥ 15/h, categorized into CSA/CSR, OSA, and No SDB groups, were subjected to a preliminary Kolmogorov-Smirnov test to assess normal distribution. Subsequently, they were evaluated using ANOVA. In instances where normal distribution was not established, ANOVA on ranks (Kruskal-Wallis) was performed as an alternative.

To characterize the correlation between variables, the Spearman's rank correlation test was employed. Statistical significance was defined as a p-value < 0.05 for all conducted tests.

4. Results:

4.1.Patient Characteristics

A total of 302 patients were screened for study inclusion. Thirteen patients were excluded from the flowchart for the reasons mentioned, see Figure 11. Among the 289 patients, 219 (75.78%) were male, and 70 (24.22%) were female. The average age was 60.6 (±13.79) years, with a mean BMI of 27.7 (±5.10) kg/m². Table 2 displays the clinical parameters of the patients.

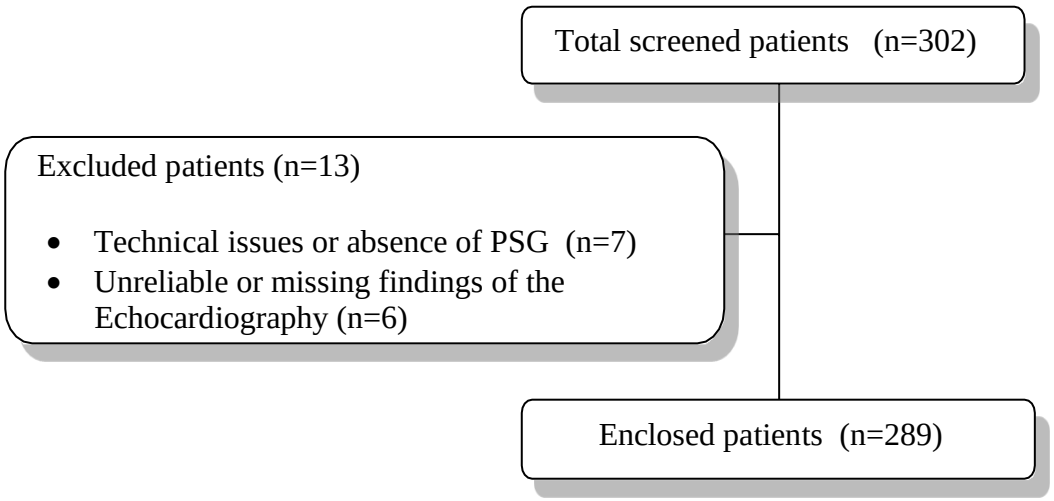

Figure 11: Flowchart of Patient Recruitment.

Table 2. Patient characteristics, n= 289

	Mean ± SD
Age (Years)	60,6 ±13,79
Height (m)	1,7 ± 0,09
Weight (kg)	84,4 ± 19,54
BMI kg/m²	27,7 ± 5,10
Blood pressure RR_Systole mmHg (n=261)	123,5 ± 18,24
Blood pressure RR_Diastole mmHg (n=261)	77,4 ± 11,59
ESS (n=281)	6,3 ± 3,66
EF in Echocardiography in %	33,8 ± 10,12

4.2.Distribution of risk factors among patients

The LVEF demonstrated significant impairment, averaging 33.8% (±10.12). Daytime sleepiness assessed via ESS yielded an average score of 6.3 (±3.66). The enrolled patients exhibited the distribution of the following pre-existing conditions or risk factors (Table 3).

Table 3. Distribution of pre-existing conditions/risk factors, n= 289

Pre-existing condition	Yes	No	Unknown
Arterial hypertension	197 (68,16%)	90 (31,14%)	2
Diabetes mellitus	79 (27,33%)	208 (71,97 %)	2
heart attack	86 (29,75%)	202 (69,89%)	1
Coronary heart disease	132 (45,67%)	155 (53,63%)	2
COPD	34 (11,76%)	240 (83,04%)	15
Presence of pretibial edema	88 (30,44%)	198 (68,51%)	3
Smoking	157 (54,32%)	128 (44,29%)	4

4.3.The NYHA classification of HF among the patients

We then delineate the categorization of HF among the patient cohort. It is noteworthy that eighty percent of the patients were evenly distributed between NYHA classes II and III (Figure 12).

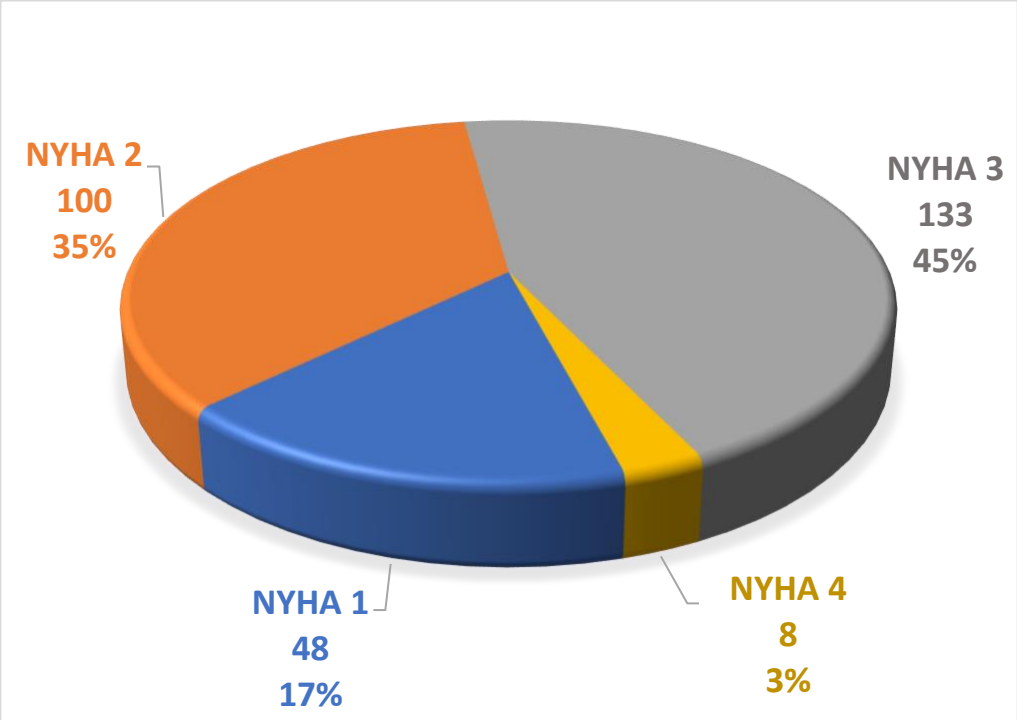

Figure 12. Distribution of NYHA classes I-IV, n=289

4.4.Atrial Fibrillation

The presence of AF was discerned in a subset of the cohort, specifically noted in 65 patients (22.49%). Intriguingly, among this subgroup, a distinct subset of 11 patients displayed rhythms influenced by pacemaker activity. Nevertheless, it is paramount to emphasize that the underlying rhythm for this subgroup consistently remained AF, elucidating the complex interplay between cardiac pacing interventions and the enduring arrhythmic condition.

4.5.SDB analysis

Using an AHI cutoff of 5 and 15 per hour of sleep, polysomnography revealed the presence of SDB in 72% and 47% of cases, respectively. Within this context, OSA accounted for 26% and 15%, while CSA and CSR combined constituted 46% and 32% of cases. Upon application of an AHI cutoff of ≥5/h, 75 patients (26%) were identified as having OSA, comprising 58 males and 17 females. In parallel, 134 patients (46%), encompassing 114 males and 20 females, exhibited CSA and CSR. Upon application of an AHI cutoff of ≥15/h, 43 patients (15%) were identified as having OSA, comprising 35 males and 8 females. In parallel, 93 patients (32%), encompassing 83 males and 10 females, exhibited CSA and CSR.

The prevalence and specific categorization of SDB are graphically illustrated in Figures 13 and 14.

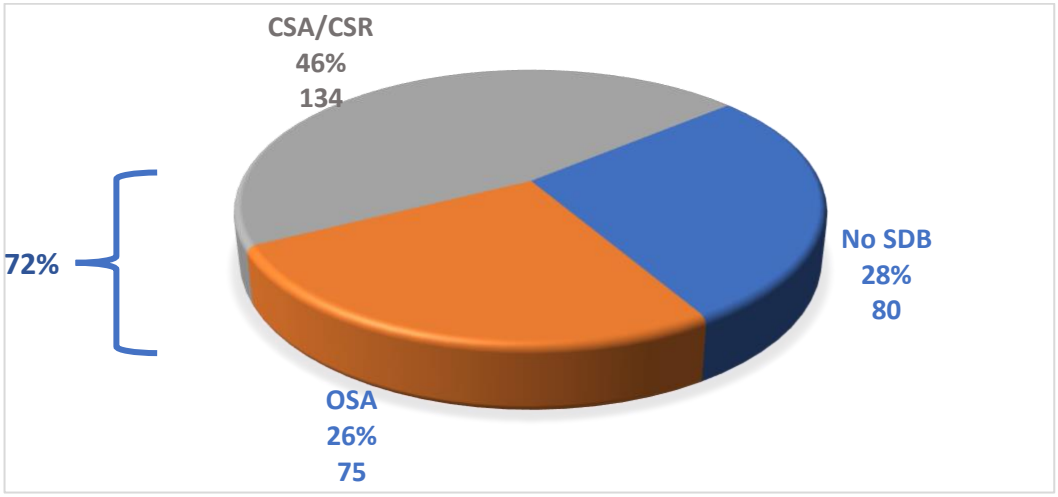

Figure 13. Frequency of SDB in the study, n=289 (AHI Cutoff ≥5/h)

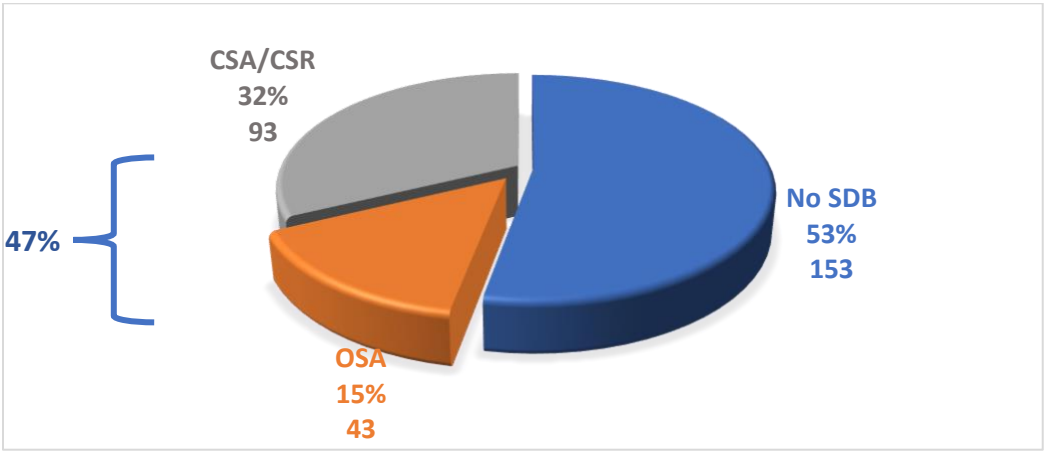

Figure 14. Frequency of SDB in the study, n=289 (AHI Cutoff ≥15/h)

4.6.Examined Sleep Parameters

The conducted polysomnography revealed the following sleep parameters, as presented in Tables 4 and 5. The TIB was notably superior in the group without sleep-related breathing disorders. The mean AHI values for SDB groups demonstrated marked pathological levels. The average mean oxygen saturation (SaO2 mean %) appeared to be comparatively more favorable in the group without SDB. Furthermore, the mean recorded duration during which oxygen saturation fell below 90% (SaO2 < 90% [min.]) was significantly prolonged in the CSA group. Additionally, the arousal index exhibited pathological values in the two SDB groups. Limited distinctions were observed among the remaining sleep parameters.

Table 4. Comparison of sleep parameters (with AHI Cutoff ≥5/h)

	OSA n= 75	CSA/CSR n=134	No SDB n=80	P value
TIB	509,8 ± 53,52	504,4 ± 48,55	521,2 ± 33,29	**0,021**
TST	317,8 ± 92,86	298,1 ± 97,53	289,1 ± 91,75	>0,05
ESS	6,6 ± 3,49	6,5 ± 3,78	5,8 ± 3,59	>0,05
AHI (n/h)	21,3 ± 15,55	27,9 ± 17,82	1,9 ± 1,54	**0,000**
SaO2 mean %	94,7 ± 3,11	94,3 ± 2,88	95,3 ± 3,32	**0,027**
SaO2 < 90% (min.)	39,3 ± 70,04	62,8 ± 85,70	42,9 ± 80,97	**0,003**
Arousal index/h	18,2 ± 9,06	16,2 ± 10,62	11,9 ± 7,86	**0,000**
Sleep efficiency	62,4 ± 17,36	59,3 ± 18,49	56,8 ± 18,03	>0,05
Sleep latency	45,7 ± 66,63	40,4 ± 45,72	51 ± 49,36	>0,05

Table 5. Comparison of sleep parameters (with AHI Cutoff ≥15/h)

	OSA n=43	CSA/CSR n=93	No SDB n=153	P value
TIB	499 ± 66,38	502 ± 53,64	519 ± 31,87	**0,014**
TST	290 ± 97,56	296 ± 97,83	311 ± 92,03	>0,05
ESS	6 ± 3,52	7 ± 3,89	6 ± 3,57	>0,05
AHI (n/h)	30 ± 15,37	36 ± 15,20	5 ± 4,32	**0,000**
SaO2 mean %	94 ± 3,16	94 ± 2,97	95 ± 3,07	**0,020**
SaO2 < 90% (min.)	53 ± 88,05	64 ± 78,85	44 ± 80,38	**0,002**
Arousal index/h	20 ± 10,09	18 ± 11,34	13 ± 7,55	**0,000**
Sleep efficiency	58 ± 18,28	59 ± 18,42	60 ± 18,01	>0,05
Sleep latency	39 ± 55,53	36 ± 41,04	52 ± 57,51	>0,05

4.7.Comparison between patients with OSA, CSA, and those without SDB

Patient characteristics across OSA, CSA, and Non-SDB Groups are detailed for comparison within Tables 6 and 7. Most of SDB-afflicted patients were of male gender. First using AHI cutoff of ≥5/h, patients with CSA displayed a greater tendency toward obesity in comparison to those with OSA or lacking SDB. Additionally, the LVEF demonstrated a higher level within the OSA group. On the other hand, considering an AHI cutoff of ≥15/h, the SDB-affected patients tended to be older and exhibited a higher prevalence of obesity in contrast to other groups. The LVEF did not exhibit any significant differences. Notably, there were no statistically significant differences observed across the three groups in terms of the ESS scores and the prevalence of AF.

Table 6. Comparison of patients with OSA, CSA, and without SDB (with AHI Cutoff ≥5/h)

	OSA n=75	CSA/CSR n=134	No-SDB n= 80	P value
Age (Years)	58,8 ± 13,83	62,3 ±13,54	59,4 ± 13,99	>0,05
Male [n(%)]	58 (77,33%)	114 (85,07%)	47 (58,75%)	**0,000**
BMI kg/m²	28,2 ± 5,73	28,1 ± 4,95	26,4 ± 4,51	**0,036***
ESS	6,6 ± 3,49	6,5 ± 3,78	5,8 ± 3,59	>0,05
EF in Echo. In %	36,3 ± 9,88	32,4 ± 9,53	33,7 ± 10,95	**0,016**
AF [n(%)]	14 (18,66%)	33 (24,62%)	18 (22,5%)	>0,05

*Significant only in comparison between CSA/CSR and No-SDB groups.

Table 7. Comparison of patients with OSA, CSA, and without SDB (with AHI Cutoff ≥15/h)

	OSA n=43	CSA/CSR n=93	No-SDB n= 153	P value
Age (Years)	61,4 ± 2,25	64,2 ± 2,50	58,1 ± 14,49	**0,004**
Male [n(%)]	35(81,39%)	83(89,24%)	101 (66,01%)	**0,000**
BMI kg/m²	28,9 ± 5,94	28,3 ± 4,82	26,9 ± 4,91	**0,045**
ESS	6,3 ± 3,52	6,5 ± 3,89	6,2 ± 3,57	>0,05
EF in Echo. in %	35,9 ± 9,42	32 ± 10,04	34,2 ± 10,27	>0,05
AF [n(%)]	9 (20,93%)	21(22,58%)	35 (22,78%)	>0,05

4.8.Comparison between patients with or without AF

The AF group demonstrated older age, coupled with an elevated occurrence of AF cases with NYHA functional classes III and IV. The prevalence of SDB was the same regardless of the AF presence or absence. Pertinently, no statistically significant differences were identified in terms of BMI, gender distribution, LVEF, coronary heart disease (CAD), and prior history of myocardial infarction between these two groups.

Table 8: Comparison of patients with and without AF (CAD: Coronary artery disease, MI: myocardial infarction)

	AF n=65	No AF n=224	P value
Age (Years)	66 ± 10,24	59 ± 14,29	**0,001**
Male [n(%)]	52 (80%)	167 (74,55%)	>0,05
BMI kg/m²	27,6 ± 5,60	27,7 ± 4,95	>0,05
EF in Echo. in %	34,3 ± 9,98	33,6 ± 10,18	>0,05
CAD	32 (49,23%)	100 (44,64%)	>0,05
MI in the med. History	22 (33,84%)	64 (28,57%)	>0,05
NYHA			**0,003***
I	7 (10,76%)	41 (18,30%)	
II	16 (24,61%)	84 (37,5%)	
III	38 (58,46%)	95 (42,41%)	
IV	4 (6,15%)	4 (1,78%)	
SDB (with AHI cutoff ≥5/h)	47 (72,30%)	162 (72,32%)	>0,05
OSA	14 (21,53%)	61 (27,23%)	
CSA/CSR	33 (50,76%)	101 (45,08%)	
SDB (with AHI cutoff ≥15/h)	30 (46,15%)	106 (47,32%)	>0,05
OSA	9 (13,84%)	34 (15,17%)	
CSA/CSR	21 (32,30%)	72 (32,14%)	

*Significant was detected only in case of NYHA III and IV.

4.9.Investigating the correlation among the selected or measured variables

The correlation analysis employing Spearman's Rho coefficient (as presented in Table 9) revealed notable relationships among various variables. Notably, Table 9 exclusively displays statistically significant correlations, all of which are marked with a positive sign, indicating a positive correlation between the examined variables. Conversely, correlations with a negative sign signify a demonstrable negative association between the compared variables. This approach efficiently highlights the distinct nature of the relationships observed in the study.

Notably, a positive correlation was established between BMI and the AHI components, both central and obstructive, as well as the average recorded duration of oxygen saturation below 90% (SaO2 < 90%). In conclusion, higher BMI values were consistently linked with elevated AHI values and a prolonged duration of oxygen desaturation below 90%.

Additionally, an increment in the New York Heart Association (NYHA) class coincided with a higher ESS score, while a decrease in the mean oxygen saturation (SaO2 mean %) correlated with an increase in ESS scores. Moreover, as expected a rise in the NYHA class and an extension of the duration of oxygen saturation below 90% were associated with a heightened prevalence of AF.

Table 9: Spearman correlations between variables

	CAI	OAHI	GAHI	SaO2 mean%	SaO2 <90% (min.)	NYHA
BMI	+	+	+	-	+	
ESS				-		+
EF	-	+				
AF					+	+

5. Discussion:

This thesis represents a significant European study investigating the prevalence of SDB and AF in HF patients. Employing a cohort of 289 patients from 302 with HF, we aim to underscore the complex association between HF, SDB, and AF, highlighting the importance of this association in both clinical practice and further basic research. The study extends our understanding of cardiovascular diseases, and it suggests that HF management may improve outcomes in individuals suffering from SDB. The study did not find a correlation between AF and OSA or CSA. Furthermore, it sheds light on the importance of having a standardized definition of SDB.

The distribution of risk factors among our cohort was heterogeneous. Notably, over 70% of the patients did not report COPD, diabetes mellitus, or heart infarction comorbidities. On the other hand, 80% of the patients were distributed between NYHA classes II and III. It is well known that NYHA is increased and associated with poorer outcomes in patients with HF. (Ahmed, Aronow and Fleg, 2006). The lower frequency of comorbidities and the predominant classification of patients into NYHA classes II and III enhance the eligibility of our results.

Similar to other studies, we used the definition of SDB according to (AASM 2005), although Bitter *et al.* applied the new standard definitions for sleep-related breathing disorders according to the American Academy of Sleep Medicine (AASM 2010) (Bitter et al 2011)

However, it is complicated to compare our study results to the previous studies due to the difference in the SDB definition and patients' criteria. For example, Javaheri *et al.,* Lanfranchi *et al.,* Macdonald *et al*., and Vazir *et al.* defined SDB by the cut-off AHI ≥15/h. On the other hand, Oldenburg et al. and Bitter *et al.* defined SDB by a cut-off AHI ≥5/h. Sin et al. used three cut-off values for his study: the AHI cut-offs ≥10, 15, and 20/h.

The prevalence of SDB in HF different between studies (49-66%) with an AHI cut-off of ≥15/h and between (66-76%) with an AHI cut-off of ≥5/h. Our study found a similar prevalence of SDB. We observed that the percentage of SDB decreased from (72%) when applying ≥15/h as cutoff compared to (47%) when applying AHI ≥5 as cutoff. Furthermore, using different devices to detect SDB within various studies introduces significant variability in the results. In our study, we applied conventional polysomnography (PSG), recognized as the "gold standard" for detecting sleep disorders. Conversely, in the majority of other studies, polygraphy was used as a

methodology. Of note, polygraphy lacks the capability to record certain hypopneas associated with arousals, primarily due to the absence of electroencephalic data (EEG). Consequently, this variability has prompted doubts about the reliability of results in other research studies. A summary of studies, including patients' number, AHI criteria, LVEF, the method used to detect SDB, and the prevalence of OSA and CSA, were depicted in Table 10.

Strikingly, the occurrence of OSA and CSA was higher when applying ≥15/h as a cutoff. OSA and CSA were more prevalent in males than females, suggesting an impact of sex on the distribution of OSA and CSA. Several studies have found that CSA patients are more likely to be male than those with OSA (Ratz *et al.*, 2018) (Bixler *et al.*, 1998). In addition, our study revealed that CSA is the dominant type of SDB in HF, with an incidence of 46% (with AHI cut-off ≥5) and 32% (with AHI cut-off ≥15). Similarly, other studies showed a higher percentage of CSA compared with OSA (Figure 15).

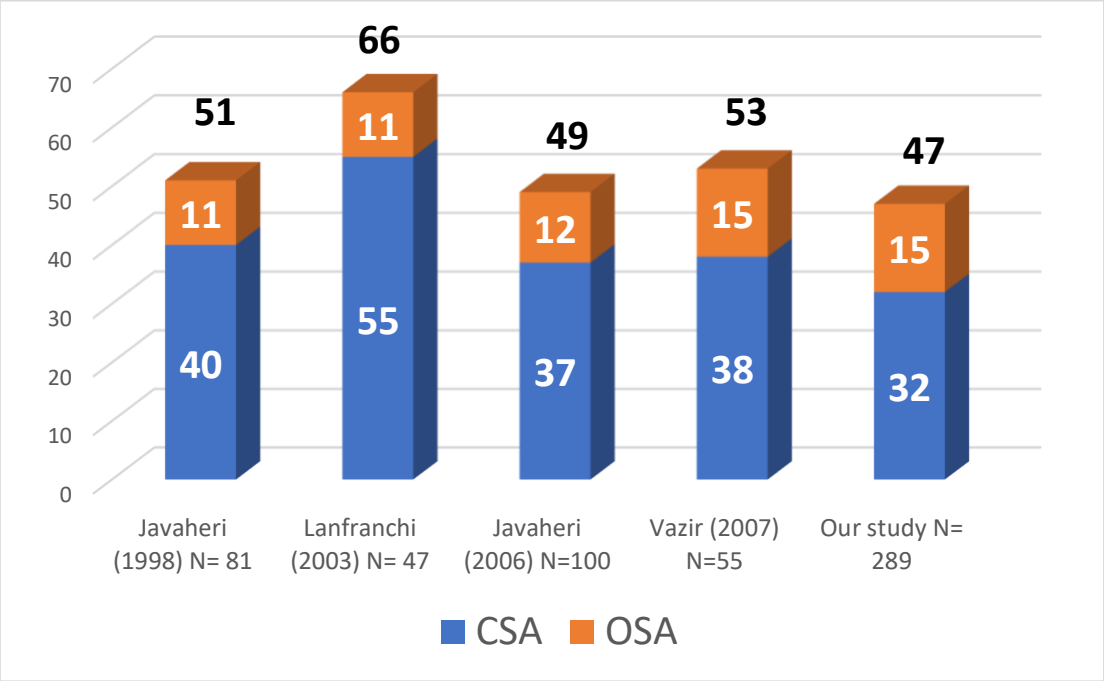

Figure 15. Frequency of SDB in HF patients (with AHI cut-off ≥15)

CSA can be higher in patients suffering from decompensated acute HF (Suda *et al.*, 2018). The occurrence of SDB in HF patients is influenced by several factors, including the bias in diagnosis, variable definitions of SDB, diverse HF severity levels, and differences in the optimization of medical therapy (Caples, Wolk and Somers, 2005). Thus, the variation should be considered when interpreting findings across studies.

In contrast, Sin *et al*. reported an increase in the incidence of OSA compared with CSA in his cohort. However, this study focused on patients visiting the sleep laboratory. This approach impacted the study outcome as it relied on a speculated general physician diagnosis of OSA, determined by symptoms like snoring and increased daytime sleepiness (Sin *et al.*, 1999). Another study demonstrated that the high level of OSA occurrence may be explained by risk factors such as age, male gender, BMI, and ethnicity (Ferrier *et al.*, 2005), or it may associate with the preserved left ventricular function (Schulz *et al.*, 2007). Applying the standard AASM definitions of SDB from 2010, a convergent proportion of OSA and CSA was observed (Bitter *et al.*, 2011).

Our data confirmed the SDB phenotype in OSA and CSA groups when comparing them to the non-SDB group after applying ≥15 or 5/h as a cutoff. The TIB, arousal index and AHI significantly increased in SDB patients (OSA and CSA) compared to non-SDB patients. The opposite was observed for SaO2 mean %, which was significantly decreased in the two SDB groups compared to the non-SDB, indicating pathological values in SDB groups.

Risk factors such as age, BMI, and comorbidities can increase the risk of SDB in HF patients. In the current study, we concluded that advanced age (>60), elevated BMI (>28 kg/m2), and male gender are considered risk factors associated with both subtypes of SDB in patients with HF.

Sin *et al.* found that OSA frequency is higher in male with higher BMI or in older female. While CSA was higher in male, patients older than 60 years, patients with AF or patients with hypercapnia while awake. In this context, Oldenburg *et al.* found that CSA is higher in male patients, old patients or patients with higher NYHA class. An association was found between EF and occurrence of CSA (Oldenburg *et al*., 2007) (Ferrier *et al.*, 2005). Additionally, older patients with HF may suffer from pulmonary hypertension compared to younger patients, which can explain the increased risk of nocturnal hyperventilation and CSA (Adir, Humbert and Chaouat, 2021).

In the context of obesity or high BMI as a risk factor for SDB in HF patients, obesity leads to the constriction of the upper respiratory muscles, resulting from the accumulation of adipose tissues. This constriction in the upper airway impacts normal breathing, leading to increases in intrathoracic pressure, inducing episodes of apnea and hypoxia (Jehan *et al.*, 2017). In addition, obesity is a risk factor strongly associated with the development of HF and cerebrovascular disease (Mallah *et al.*, 2023), which, in turn, is correlated to the occurrence of CSA. Metabolic changes and obesity can increase the

workload of the heart and promote structural changes in the heart muscle (Mallah *et al.*, 2023).

Of note, women are more susceptible to having CSA or OSA than men due to the lower apnea threshold they have or lower testosterone levels (Zhang *et al.*, 2023) (Garcia-Touchard *et al.*, 2008) (Zhou *et al.*, 2003) (Jennum and Riha, 2009). Treating pre-menopausal women with testosterone for 12 days increases their apnea threshold (Zhou *et al.*, 2003). The sex effect was noticed in the presence of HF (Sin *et al.*, 1999). Thus, this indicates the important role of gender in the development of SDB (CSA or OSA) in HF patients. On top of that, upper respiratory airways edema in patients with HF can worsen the symptoms and increase the risk of SDB development (Yumino *et al.*, 2010).

It has been shown that CSA is correlated with asymptomatic LV dysfunction. The autonomic control of cardiac muscle is correlated with the severity of CSA, which in turn increases cardiac arrhythmias (Lanfranchi *et al.*, 2003).

In recent decades, accumulating evidence indicates a possible causal association between CSA and AF. The underlying mechanism is still unclear. It is proposed that many factors induced by apnea can lead to AF, including hypoxia, changes in CO2 levels, or stimulation in sympathetic tone (Sanchez *et al.*, 2020). In our study, patients with CSA had a higher prevalence of AF compared to OSA or non-SDB, although no statistical differences were detected. The history of paroxysmal AF was not taken into consideration by our study, which may have led to the underestimation of the AF recorded cases.

Furthermore, our study noticed that AF becomes more frequent when the NYHA class is increased, and the mean recorded time in which oxygen saturation is below 90% ($SaO2 < 90\%$) is prolonged. Moreover, we have shown that the central apnea index increases with a deterioration of the LVEF, while the obstructive apnea index decreases. This negative correlation between the severity of LV dysfunction and CSA was observed by other studies (Oldenburg *et al.* 2007) (Sin *et al.* 1999) (Ferrier K *et al.* 2005).

In conclusion, our study highlights important associations between SDB and AF in HF patients. The prevalence of SDB in HF patients demonstrates significant variability across studies, underscoring the need for standardized diagnostic criteria. Notably, our findings pointed out the impact of obesity and gender on the development of SDB, suggesting that personalized approaches may be crucial in managing HF patients with sleep disorders. We also were unable to find a statistical correlation between AF and OSA or CSA. An ideal diagnostic procedure for AF should be considered in future studies. The implications

of our study extend beyond prevalence rates, emphasizing the potential clinical benefits of addressing SDB in HF management. The association between CSA and adverse cardiovascular outcomes, including heightened arrhythmias, suggests a link between HF management and the clinical outcomes of CSA patients.

Our study has three primary limitations. First, the sleep study was performed without video monitoring. However, the device used in our study is a well-known validated device for inpatients and outpatients PSG. Second, the recruited patients were from cardiology wards, thus, the occurrence in the outpatient setting may vary. Third, the evaluation of AF in HF patients depends on resting ECG or the signal from the ECG channel in the PSG. Therefore, the patients with paroxysmal AF were underestimated

Table 10: Comparison with other studies on the prevalence of SDB in HF.

	Nr. of Pat.	AHI Cutoff	Mean EF%	The used device	Prevalence of SDB (%)			Prevalence of OSA (%)			Prevalence of CSA (%)		
Javaheri 1998	81	≥ 15	22-27	**PSG** Grass 78D ®	51			11			40		
Sin 1999	450	≥ 10, 15, 20	27,3	**PSG** Various device parts	AHI ≥ 10 70	AHI ≥ 15 61	AHI ≥ 20 53	AHI ≥ 10 38	AHI ≥ 15 32	AHI ≥ 20 27	AHI ≥ 10 33	AHI ≥ 15 29	AHI ≥ 20 25
Lanfranchi 2003	47	≥ 15	unclear	**Polygraphie** Merlin ®	66			AHI ≥ 10 11			55		
Ferrier 2005	87	≥10	34	**PSG** S Series Sleep System ®	68			53			15		
Javaheri 2006	100	≥ 15	21-26	**PSG** Grass 78D ®	49			12			37		
Schulz 2007	203	≥ 10	28	**Polygraphie** Stardust II System ®	71			43			28		
Vazir 2007	55	≥ 15	30,6	**PSG** Jaeger Sleeplab ®	53			15			38		
Oldenburg 2007	700	≥ 5	28,3	**Polygraphie** Embletta ®	AHI ≥ 5 76		AHI ≥ 15 53	AHI ≥ 5 36		AHI ≥ 15 20	AHI ≥ 5 40		AHI ≥ 15 33
Macdonald 2008	108	≥ 15	20	**Polygraphie** Stardust System ®	61			30			31		
Bitter 2011	255	≥ 5, 15	25-30	**Polygraphie** Embletta ®	AHI ≥ 5 66,3		AHI ≥ 15 43,9	AHI ≥ 5 32,2		AHI ≥ 15 17,2	AHI ≥ 5 34,1		AHI ≥ 15 26,7
Our Study 2012	289	≥ 5, 15	33,8	**PSG** SOMNOcheck 2 R&K ®	AHI ≥ 5 72		AHI ≥ 15 47	AHI ≥ 5 26		AHI ≥ 15 15	AHI ≥ 5 46		AHI ≥ 15 32

6. Summary:

Background:

More than 50% of HF patients are suffering from sleep-disordered breathing (SDB). Patients with SDB are at high risk of cardiac arrhythmias, especially atrial fibrillation (AF). The aim of this study is to assess the prevalence of AF and SDB in a cohort of patient diagnosed with HF. Furthermore, it aims to investigate the potential association between AF and SDB.

Methods:

We screened a total of 289 out of 302 patients with heart failure (HF) and a left ventricular ejection fraction (LVEF) of 50% or less for sleep-disordered breathing (SDB) using cardiorespiratory polysomnography (PSG), excluding those with known SDB. Two distinct apnea-hypopnea index (AHI) cutoff values (5 and 15 events per hour of sleep) were utilized. Our investigation included various clinical parameters such as BMI, sex, age, and blood pressure. Additionally, we examined the New York Heart Association (NYHA) classification of HF and the occurrence of atrial fibrillation (AF) within our cohort. Polysomnography was employed to assess sleep parameters, including total sleep time (TIB), AHI, mean oxygen saturation (SaO2 %), SaO2 < 90%, arousal index per hour, sleep efficiency, and sleep latency. We then compared patients with SDB (obstructive sleep apnea, central sleep apnea) and those without SDB using both AHI cutoffs (≥15 and 5 events/h) for parameters such as age, BMI, Epworth Sleepiness Scale (ESS), ejection fraction (EF), and AF presence. Further analyses were conducted to explore differences in the mentioned parameters among patients with or without AF in our cohort.

The results were presented as mean ± standard deviation. Basic data underwent a preliminary Kolmogorov-Smirnov test to assess normal distribution, followed by ANOVA for normally distributed data and ANOVA on ranks (Kruskal-Wallis) in instances where normal distribution was not established. The Spearman's rank correlation test was employed to characterize the correlation between variables listed in table 9.

Results:

Among the 289 patients, 219 (75.78%) were male, and 70 (24.22%) were female. The average LVEF was 33.8%. The most of patients were evenly distributed between NYHA classes II and III. AF was found in 65 of 289 patients (22.49%). Using an AHI cutoff of 5 and 15 per hour of sleep, polysomnography revealed the presence of SDB in 72% and

47% of cases, respectively. OSA with an AHI > 5/h was present in 75 patients (26%) and 43 patients (15%) had moderate oder severe OSA with an AHI >15/h. Otherwise CSA with an AHI > 5/h was present in 134 patients (46%) and 93 patients (32%) had moderate oder severe CSA with an AHI >15/h. The levels of sleep parameters like TIB and AHI were elevated in SDB patients compared to non-SDB patients. In contrast, non-SDB patients had higher mean SaO2 levels and arousal index. Advanced age (>60), elevated BMI (28 kg/m2), and male gender were identified as SDB risk factors compared to non-SDB patients. The occurrence of SDB was similar regardless of the presence or absence of AF, suggesting a lack of correlation between AF and OSA or CSA. However, an increased prevalence of AF was observed in CSA patients.

Conclusion:

Our study determined that age, BMI, and male gender increase the risk of SDB in HF patients, emphasizing the need for personalized management. The study also revealed the importance of standardized SDB definitions, device usage, and personalized management approaches. While no direct correlation was found between AF and OSA/CSA, our findings provide valuable insights into the complex relationships among SDB, HF, and AF, highlighting potential clinical benefits in addressing SDB during HF management.

7. Zusammenfassung:

Hintergrund

Mehr als 50 % der Herzinsuffizienz-Patienten leiden an schlafbezogener Atmungsstörung (SBAS). Bei Patienten mit SBAS besteht ein hohes Risiko für Herzrhythmusstörungen, insbesondere für Vorhofflimmern (VHF). Ziel dieser Studie ist es, die Prävalenz von VHF und SBAS in einer Kohorte von Patienten mit diagnostizierter Herzinsuffizienz (HI) zu ermitteln. Außerdem soll der mögliche Zusammenhang zwischen VHF und SBAS untersucht werden.

Methoden:

Wir untersuchten insgesamt 289 von 302 Patienten mit HI und einer linksventrikulären Auswurffraktion (LVEF) von 50 % oder weniger mittels kardiorespiratorischer Polysomnographie (PSG) auf SBAS, wobei diejenigen mit bekannter SBAS ausgeschlossen wurden. Es wurden zwei verschiedene Grenzwerte für den Apnoe-Hypopnoe-Index (AHI) verwendet (5 und 15 Ereignisse pro Stunde Schlaf). Unsere Untersuchung umfasste verschiedene klinische Parameter wie BMI, Geschlecht, Alter und Blutdruck. Außerdem untersuchten wir die Klassifizierung der New York Heart Association (NYHA) für HI und das Auftreten von VHF in unserer Kohorte. Mittels PSG wurden Schlafparameter wie Gesamtschlafzeit (TIB), AHI, mittlere Sauerstoffsättigung (SaO2 %), SaO2 < 90%, Arousal-Index pro Stunde, Schlafeffizienz und Schlaflatenz ermittelt. Anschließend verglichen wir Patienten mit SBAS (obstruktive Schlafapnoe OSA, zentrale Schlafapnoe ZSA) und solche ohne SBAS unter Verwendung beider AHI-Grenzwerte (≥15 und 5 Ereignisse/h) für Parameter wie Alter, BMI, Epworth Sleepiness Scale (ESS), Ejektionsfraktion (EF) und VHF. Weitere Analysen wurden durchgeführt, um Unterschiede bei den genannten Parametern zwischen Patienten mit und ohne VHF in unserer Kohorte zu untersuchen.

Die Ergebnisse wurden als Mittelwert ± Standardabweichung angegeben. Die Basisdaten wurden einem vorläufigen Kolmogorov-Smirnov-Test unterzogen, um die Normalverteilung zu beurteilen, gefolgt von einer ANOVA für normalverteilte Daten und einer ANOVA über Ränge (Kruskal-Wallis) in Fällen, in denen keine Normalverteilung festgestellt werden konnte. Der Spearman's Rangkorrelationstest wurde verwendet, um die Korrelation zwischen den in Tabelle 9 aufgeführten Variablen zu charakterisieren.

Ergebnisse:

Von den 289 Patienten waren 219 (75,78 %) männlich und 70 (24,22 %) weiblich. Die durchschnittliche LVEF betrug 33,8 %. Die meisten Patienten waren gleichmäßig auf die NYHA-Klassen II und III verteilt. VHF wurde bei 65 von 289 Patienten (22,49 %) festgestellt. Bei Verwendung eines AHI-Grenzwerts von 5 bzw. 15 pro Schlafstunde ergab die PSG in 72 % bzw. 47 % der Fälle das Vorliegen einer SBAS. Eine OSA mit einem AHI > 5/h lag bei 75 Patienten (26 %) vor und 43 Patienten (15 %) hatten eine mittelschwere bis schwere OSA mit einem AHI > 15/h. Ansonsten lag eine ZSA mit einem AHI > 5/h bei 134 Patienten (46 %) vor, und 93 Patienten (32 %) hatten eine mittelschwere bis schwere ZSA mit einem AHI > 15/h. Die Werte von Schlafparametern wie TIB und AHI waren bei SBAS-Patienten im Vergleich zu Nicht-SBAS-Patienten erhöht. Im Gegensatz dazu hatten Nicht-SBAS-Patienten höhere mittlere SaO2-Werte und einen höheren Arousal-Index. Ein höheres Alter (>60), ein erhöhter BMI (>28 kg/m2) und das männliche Geschlecht wurden als SBAS-Risikofaktoren im Vergleich zu Nicht-SBAS-Patienten identifiziert. Das Auftreten von SBAS war unabhängig vom Vorhandensein oder Nichtvorhandensein von VHF ähnlich, was darauf schließen lässt, dass kein Zusammenhang zwischen VHF und OSA oder ZSA besteht. Allerdings wurde bei ZSA-Patienten eine erhöhte Prävalenz von VHF beobachtet.

Schlussfolgerung:

Unsere Studie ergab, dass Alter, BMI und männliches Geschlecht das Risiko für SBAS bei HI-Patienten erhöhen, was die Notwendigkeit eines personalisierten Managements unterstreicht. Die Studie zeigte auch, wie wichtig standardisierte SBAS-Definitionen, der Einsatz von Geräten und personalisierte Managementansätze sind. Obwohl kein direkter Zusammenhang zwischen VHF und OSA/ZSA gefunden wurde, bieten unsere Ergebnisse wertvolle Einblicke in die komplexen Zusammenhänge zwischen SBAS, HI und VHF und unterstreichen den potenziellen klinischen Nutzen der Berücksichtigung von SBAS bei der Behandlung von HI.

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9. Appendix

9.1. Curriculum vitae:

9.2. Publications:

1. Grimm W, Sass J, **Sibai E**, Cassel W, Hildebrandt O, Apelt S, Nell C, Koehler U. Severe central sleep apnea is associated with atrial fibrillation in patients with left ventricular systolic dysfunction. **Pacing Clin Electrophysiol**. **2015** Jun; 38 (6):706-12. doi: 10.1111/ pace.12495. Epub 2014 Sep 5. PMID: 25196395.
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3. Koehler U, Reinke C, **Sibai E**, Hildebrandt O, Sohrabi K, Dette F, Grimm W. Autonome Dysregulation und kardiale Arrhythmien bei Patienten mit obstruktiver und zentraler Schlafapnoe Autonomic dysfunction and cardiac arrhythmia in patients with obstructive and central sleep apnea]. Dtsch Med Wochenschr. 2011 Dec;136(50): 2622-8. German. doi: 10.1055/s-0031-1292852. Epub 2011 Dec 7. PMID: 22160956.

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9.3. List of academic teachers

My academic teachers in Philipps University Marburg: Professors Claus Franz Vogelmeier and Ulrich Köhler.

My academic teachers in Damaskus University: Drs. Moh. Naem Shahrour and Ghassan Ghaddban.

9.4. Acknowledgments:

I would like to take this opportunity to express my special thanks to the following people without their help the preparation of this doctoral thesis would never have been possible:

First of all, I would like to thank Prof. Dr. med. Köhler, my doctoral supervisor, for his supervision of this thesis and for his kind help and patience. The numerous discussions on an intellectual and personal level will always remain in my memory as an enriching and constructive exchange.

I would also like to thank Prof. Dr. med. Vogelmeier for his valuable support from the very beginning.

I would also like to thank Dr. Christop Nell for the statistical analysis of the data.

My special thanks go to my colleague Dr. rer. nat. Bilal Alashkar Alhamwe, without his help and advice, such a scope of work would never have been possible.

My special thanks go to my parents, Wessam and Sameer Sibai, who have made my life possible and help me pursue my goals, and they make sure I do not face any hurdles.

I am deeply indebted and grateful to my wife, Ragad Brejawi, for her incredibly helpful support and understanding during the preparation of this doctoral thesis and to whom I dedicate this thesis.

My children: Sameer, Maria and Yusuf I am always proud of you.

Thanks!

9.5. Ehrenwörtliche Erklärung: