CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

FIELD OF MEDICINE

CLINICAL AND EVOLUTIONARY CONSIDERATIONS UNDER TREATMENT OF PATIENTS WITH HEART FAILURE ASSOCIATED WITH CENTRAL SLEEP APNEA SYNDROME AND/OR PERIODIC BREATHING

PHD THESIS ABSTRACT

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Introduction

In developed countries, chronic heart failure (CHF) is a common disease, affecting at least 1-2% of the adult population (1). Patients with CHF still have an unfavorable prognosis despite significant advances in therapy: more than half of elderly patients and/or those hospitalized for heart failure die within 5 years of diagnosis (2,3).

Sleep apnea syndrome, whether predominantly obstructive (OSA) or predominantly central (CSA), represents an important comorbidity with a high prevalence in patients with chronic heart failure, and is associated with a more reserved prognosis. The prevalence of sleep-disordered breathing (SDB) reaches up to 75% among patients with CHF and may be even higher among patients with acute decompensated heart failure (4,5). OSA is considered an independent risk factor that increases morbidity and mortality in CHF (6), while CSA is often reported in association with Cheyne-Stokes respiration (CSR); this appears to be more of a marker of CHF severity, reflecting left ventricular dysfunction (6,7). All phenotypes of sleep apnea are associated with increased sympathetic activity, leading to unfavorable conditions in the context of CHF, including stimulation of the renin-angiotensin-aldosterone system, tachycardia, or peripheral vasoconstriction (8,9).

As a result, sleep apnea syndrome (SAS) is considered a potential therapeutic target in CHF, according to the Working Group of the European Respiratory Society (10). Patients with CHF and SAS may have less manifest symptomatology. The absence of typical symptoms such as snoring, apnea, or daytime sleepiness makes diagnosis and treatment difficult in these patients. Patients' complaints related to nocturnal sleep are often considered secondary to chronic heart failure rather than comorbid sleep apnea (11). Studies have shown that although most patients with CSA-CSR do not complain of subjective excessive daytime sleepiness, treatment improves sleep quality and objective daytime sleepiness (11,12). Therefore, a high level of suspicion is necessary to detect the presence of CSA-CSR.

CSA-CSR has been associated with increased mortality, especially in the heart failure population (13). Risk factors for CSA in patients with heart failure include male sex, higher functional class according to the New York Heart Association, lower left ventricular ejection fraction (LVEF), hypocapnia upon waking (partial pressure of arterial carbon dioxide (PaCO2)

less than 38 mmHg), higher prevalence of atrial fibrillation, higher levels of B-type natriuretic peptide, and frequent nocturnal ventricular arrhythmias (14).

OSA and CSA remain frequently underdiagnosed conditions. Questionnaires such as STOP-BANG, Epworth, and Berlin may not be sufficient for risk assessment in patients with heart failure and SAS, regardless of the presence or absence of SAS (15). Relevant sleep monitoring (through portable polygraphy or ideally attended polysomnography) should be widely used in the clinical diagnosis of SDB, especially for high-risk patients.

The treatment of SAS with positive airway pressure (PAP) in patients with heart failure can improve the apnea-hypopnea index (AHI), cardiac function, quality of life, and heart transplant–free survival (16,17). Treatment modalities for SAS in heart failure are not supported by strong evidence, particularly in the case of chronic heart failure with reduced LVEF (HFrEF). While treating OSA with continuous positive airway pressure (CPAP) is supported by non-randomized/cohort studies reporting a reduction in mortality (18,19), pressure treatment for CSA remains controversial, especially for patients with HFrEF (10,20,21). It is not known whether improving LVEF and reducing inflammatory mediators translate into a significant reduction in symptoms, morbidity, or mortality in these patients (22).

Moreover, a low adherence rate to CPAP is reported (23). Despite improving device comfort and sleep-related quality of life, adherence to CPAP generally varies between 30 and 60%, with a noncompliance rate reaching up to 50% after the first year (23,24).

Interest in sleep pathology has considerably increased in recent years in Romania, with the establishment of numerous functional sleep laboratories in major pneumology centers. Romanian research must rely on a multidisciplinary clinical partnership. However, at the beginning of the third millennium, central sleep apnea syndrome remains a nearly unknown condition, often underdiagnosed or diagnosed late (25).

The necessity for further research is essential to better understand this pathology and to develop more effective therapeutic strategies. This doctoral thesis aims to address CSA from a clinical perspective, as well as the challenges encountered in the diagnostic and treatment process of this complex pathology, since it is not a highly addressed condition in Romania. The thesis is structured into two parts: theoretical considerations and personal contribution. The

theoretical considerations reflect the current level of knowledge about CSA and its bidirectional impact with CHF, as well as the effect of PAP treatment on patients with CSA-CHF association.

The personal clinical contribution consisted of investigating sleep apnea syndrome in 333 adult subjects known to have stable heart failure and suspected of sleep apnea. They were evaluated by polygraphy or nocturnal cardiorespiratory polysomnography over 60 months, from January 1, 2016, to December 31, 2021. The general objectives of this study included:

1. The proportion of newly diagnosed sleep apnea and its forms (central, obstructive, mixed) in a population of patients with stable heart failure, optimally treated pharmacologically, regardless of LVEF value, who were referred to a sleep laboratory.
2. The effect of CPAP treatment on patients with CSA-CHF association, depending on whether sleep apnea was suppressed by CPAP or not (defining unsuppressed sleep apnea as a residual AHI $\geq$ 15 events per hour) at 3 months.
3. CPAP therapy adherence at 12 months, given that there is currently no standard approach for managing and ameliorating CSA.

The results of this work provide evidence regarding the novelty of the subject, include Romania in the ongoing research of CSA-CHF association, and phenotype based on left ventricular dysfunction, the limitations encountered in analyzing this population, and future perspectives. The presented data and discussion of results are based on an updated bibliography.

The information in this paper has been presented at national and international conferences and published in specialized journals indexed in international databases.

GENERAL PART

The prevalence of SDB in patients with HF varies according to the subtype of HF: up to 53% in HFrEF and 48% in HFpEF (2). Among SDB, CSA is more prevalent in patients with HF than in those without HF. The prevalence of CSA ranges from 29% to 40% in patients with HFrEF. In contrast, the prevalence of CSA in HFpEF remains less well established, with studies often reporting a higher incidence of OSA (51%) compared to CSA (17%) in patients with HFpEF (26). Compared to men, women exhibit a lower prevalence of SDB in HF (11).

As cardiac function deteriorates, SDB contributes to the instability of respiratory control and the reduction of upper airway patency (9). CSA in heart failure is caused by low cardiac output, delayed circulatory flow, increased sympathetic activity, and/or pulmonary congestion, which triggers hyperventilation (27). Nocturnal hypoxemia and increased sympathetic activity contribute to the progression of heart failure. Sleep can present a sensitized apneic threshold induced by hypercapnia, where elevated CO2 levels lead to excessive ventilatory compensation, resulting in hypocapnia and lowering PaCO2 below the apneic threshold (28). The chronic state of hyperventilation and increased response to hypercapnia make resting PaCO2 close to the apneic threshold, leading to central apnea (29). In patients with HF, CSA usually presents as Cheyne-Stokes respiration (CSR). This ventilation pattern can occur during sleep, wakefulness, and physical exercise (30). The pathogenesis of CSA-CSR is similar to that of CSA but is associated with a worse prognosis (31).

The negative impact of CSA in patients with HF leads to unfavorable clinical outcomes, including increased post-hospitalization mortality in patients with decompensated HF and an increased risk of malignant atrial and ventricular arrhythmias (28). CSA also increases the risk of repeated cardiac-related hospitalizations in patients with HF (32). Both OSA and CSA serve as independent predictors for increased morbidity and mortality in HF (33,34). CSA may also be a risk factor for inducing the onset of HF, indicating a bidirectional relationship between CSA and HF (35).

SDB is common, currently affecting approximately 1 billion people worldwide and up to 40% of patients with cardiovascular diseases (9). In patients with HF (both HFpEF and

HFrEF), the prevalence of SDB rises to 50% (36). It is noteworthy that HF is associated with a high occurrence of CSA, while the severity of CSA is related to cardiac function (8).

Based on clinical considerations, HFpEF can be classified into 4 phenotypes: “elderly phenotype,” “pulmonary hypertension phenotype,” “coronary artery disease phenotype,” and “obese phenotype” (37). These cannot always be clearly differentiated, as their characteristics overlap, and it is not clear whether they can evolve from one to another (24). Phenotyping patients with SDB and HF indicated that older, hypoxemic, obese patients with HFpEF might benefit most from ASV therapy (18,38).

Evidence regarding the benefit of treating CSA in patients with HF is limited and mainly based on small observational studies or post-hoc analyses. Treating comorbidities that increase the risk of negative outcomes can improve clinical results in patients with HF, regardless of specific HF therapies (39). Medical therapy can help minimize volume overload and improve residual functional capacity, thereby reducing the symptomatic burden of SDB (40).

According to the currently suggested therapeutic algorithm for CSA-CSR in HF, CPAP is the primary treatment option for symptomatic patients after ensuring optimal HF treatment. For patients with persistent CSA under CPAP (AHI $\geq$ 15 events per hour), ASV may be a more effective therapy. However, ASV is currently contraindicated in patients with a left ventricular ejection fraction $\leq$ 45% (10).

A significant concern associated with PAP devices is the low adherence rate. Despite improvements in device comfort and sleep-related quality of life, adherence to CPAP generally varies from 30 to 60%, with a non-compliance rate reaching up to 50% after the first year of treatment. Current therapeutic regimens for treating central sleep apnea syndrome (CSAS) are limited by low compliance and variable efficacy, making it difficult to mitigate the increasing burden of CSAS-IC association.

Tailoring therapies to individual patients based on the stage and subtype of heart failure (HF) may help alleviate the burden of CSAS in this population. Additionally, the development and subsequent validation of questionnaires specifically designed for patients with both HF and CSAS could aid in early detection. New therapies, such as transvenous phrenic nerve stimulation, which operates continuously throughout the night and is independent of patient compliance, may offer a better alternative for patients who are non-adherent to CPAP or for whom ASV therapy may be contraindicated.

PERSONAL CONTRIBUTIONS

General Research Methodology

To obtain the necessary bibliographic materials, the main sources used were online medical databases (PubMed, Scopus, The Cochrane Library), specialized journals, medical websites (clinicaltrials.gov, ersnet.org), international registries, and specialty books. The research included three studies conducted on patients with chronic heart failure (CHF) and suspected sleep-related breathing disorders (SRBD), subsequently confirmed with central sleep apnea syndrome (CSAS). The studies were conducted at the Sleep Laboratory of the "Marius Nasta" Institute of Pneumology in Bucharest, between January 1, 2016, and December 31, 2022. Patients were consecutively enrolled and met the selection criteria.

The diagnosis of CHF was based on medical history and was verified and documented in the medical records. Heart failure was classified according to left ventricular ejection fraction (LVEF) into: Heart failure with reduced ejection fraction (HFrEF), Heart failure with mildly reduced ejection fraction (HFmrEF), and Heart failure with preserved ejection fraction (HFpEF).

The diagnosis of SRBD was confirmed polygraphically according to the AASM 2014 manual. Patients provided informed consent for voluntary participation in the study. The study record included: Socio-demographic data: gender, age, residence; Exposure to smoking, alcohol, coffee; Anthropometric data: neck circumference, waist circumference, body mass index (BMI); Clinical parameters: ventricular rate, oxygen saturation (SaO_2), blood pressure; Daytime and nighttime symptomatology; Personal history of comorbidities; Daytime sleepiness questionnaires (Epworth); Additional investigations: spirometry, cardio-pulmonary radiography, arterial blood gas analysis, polygraphic and echocardiographic parameters.

Investigation Methods

Polysomnography (PSG) and cardiorespiratory polygraphy (PG) were used to diagnose SRBD. PSG included recording nasal-oral airflow, snoring, heart rate, oxygen saturation, thoraco-abdominal movements, and brain electrical activity. PG was performed using Porti 7 and Alice Night One devices. Apnea, hypopnea, and respiratory events were classified according to the AASM manual. The apnea-hypopnea index (AHI) was used to assess the severity of SRBD, and polygraphic parameters were analyzed to validate the diagnosis.

Patients diagnosed with moderate-to-severe SRBD were administered continuous positive airway pressure (CPAP) treatment or non-invasive ventilation (BiPAP, ASV). Titration was performed to establish the optimal treatment pressure, monitor compliance, and evaluate treatment effectiveness through analysis of CPAP device memory cards.

Statistical Analysis

The data were processed using IBM SPSS and Microsoft Excel. The analysis included parametric and non-parametric statistical tests, logistic regression models, ROC curves, and correlation assessments. Statistical tests employed included Kolmogorov-Smirnov, Shapiro-Wilk, t-test, ANOVA, Mann-Whitney, Wilcoxon, Kruskal-Wallis, $\chi 2$, Pearson, and Spearman tests. Results were considered statistically significant for $p < 0.05$.

Conclusions and Impact

The studies assessed the prevalence and clinical characteristics of patients with HF and OSA vs. HF and CSAS, as well as risk factors for SRBD among CHF patients. Additionally, the prospective analysis of CHF patients with CSAS at baseline (clinical, sleep parameters) and the impact of CPAP treatment on AHI and therapy adherence were examined. A secondary objective in the prospective study was survival and the risk of cardiovascular exacerbation. Results were presented at national congresses and published in specialized literature.

Study 1 - Prevalence of Sleep Apnea in a Population of Patients with HF and Their Clinical and Polysomnographic Characteristics

Hypothesis and Objectives

There is growing interest in treating comorbidities and optimizing risk factors in patients with heart failure (HF), including obstructive sleep apnea (OSA), which is more prevalent in these patients than in the general population. The aim of this study was to determine the proportion of newly diagnosed sleep apnea and its forms in a population of HF patients, regardless of left ventricular ejection fraction (LVEF), optimally treated pharmacologically and referred to a sleep laboratory. We evaluated the clinical phenotype of different types of sleep-disordered breathing, focusing on central sleep apnea (CSA) and risk factors within each group.

Material and Method

The study was conducted as a single-center, retrospective study over a period of 5 years (January 1, 2016 - December 31, 2020), at the Sleep Laboratory of the "Marius Nasta" Institute of Pneumology in Bucharest. Patients were clinically and paraclinically evaluated, completing the study form and specific questionnaires (Epworth Sleepiness Scale). Sleep apnea was categorized as: OSA (obstructive sleep apnea syndrome) - AHI > 5 events/hour with predominance of obstructive events, CSA (central sleep apnea syndrome) - AHI > 5 events/hour with predominance of central events, Mixed Sleep Apnea (MSA).

Data on LVEF, NYHA class, etiology of heart failure, and chronic medication were collected. To be included in the study, patients had to be over 18 years old, have a diagnosis of chronic heart failure treated according to current guidelines, NYHA class II-IV, and newly diagnosed sleep apnea.

Characteristics of the Studied Population

The study population included adult patients, predominantly male (male-to-female ratio 2.15:1), 88% of whom were classified as NYHA class II and III, with a mean left ventricular ejection fraction (LVEF) of 38% and a mean duration of heart failure diagnosis of 5 years. All patients received optimal pharmacological treatment.

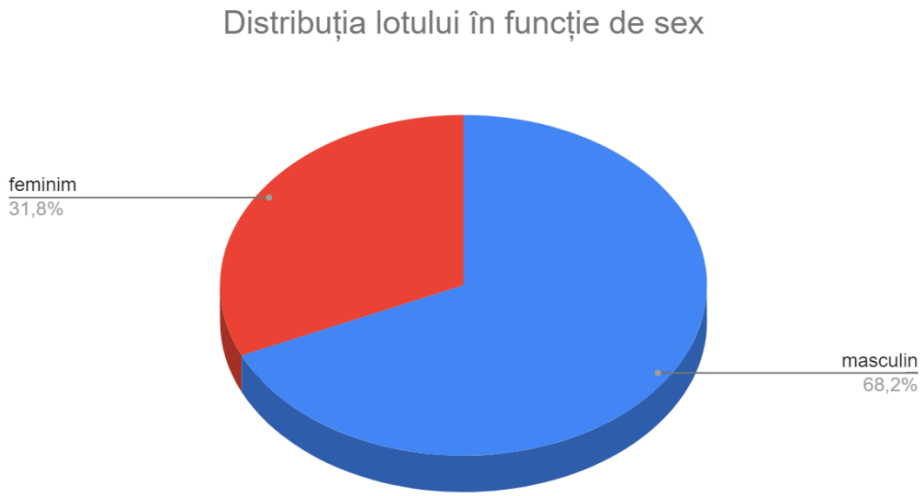

Figure 6.1. Distribution of the study cohort by sex.

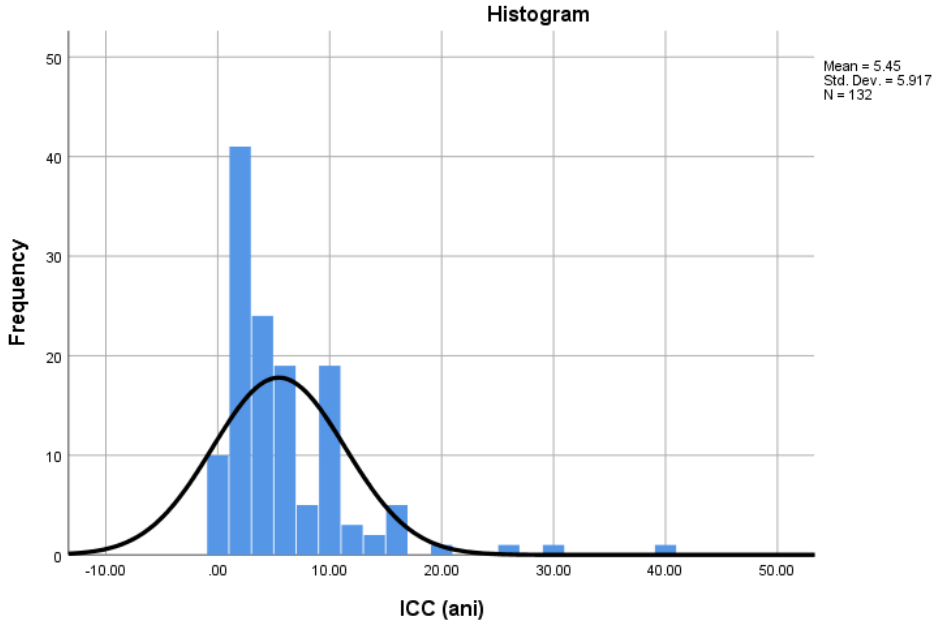

Figure 6.2. Distribution of the population based on duration of heart failure diagnosis.

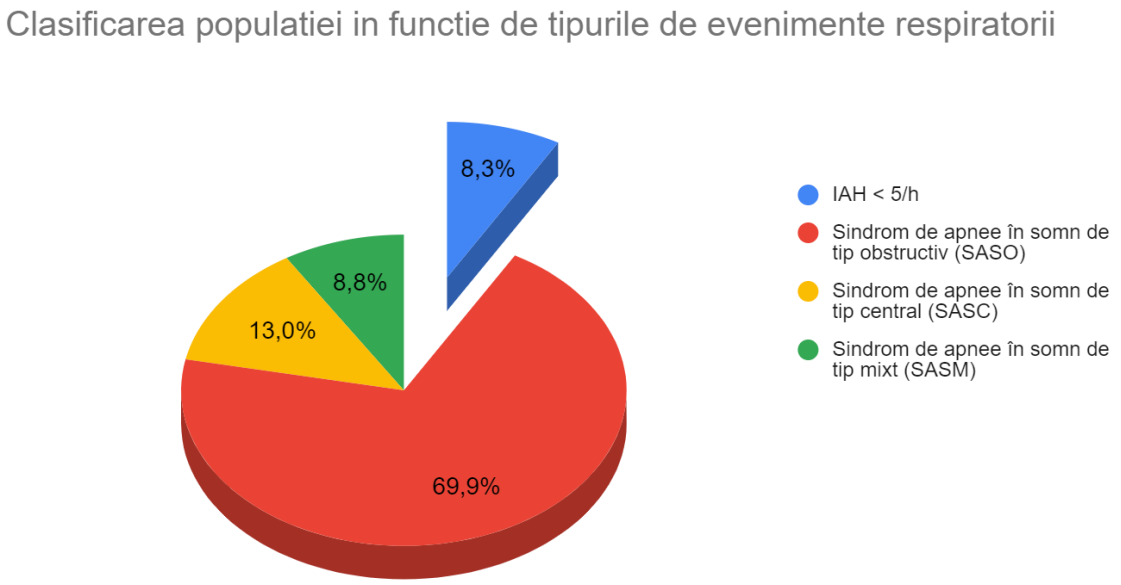

Figure 6.3. Classification of the population according to type of SDB.

Obstructive sleep apnea syndrome (OSAS) was the most common sleep-disordered breathing, present in 69.9% of patients.

Prevalence and profile of patients with central sleep apnea syndrome (CSAS).

- Central sleep apnea syndrome was less common, with a prevalence of 13%.
- Patients with CSAS were older, with lower BMI, lower LVEF, and higher prevalence of atrial fibrillation.
- They also received more beta-blockers and fewer diuretics compared to OSAS.
- Mean LVEF of 35%, distinctive phenotype with reduced LVEF.
- The studied population was highly symptomatic, with 93% reporting snoring, and over 50% having more than 5 typical symptoms of sleep apnea syndrome.
- Male patients with CSAS had daytime sleepiness in proportion of 70%, lower diastolic blood pressure (DBP), lower CPAP prediction, and lower adherence to investigations.

Confirmation of diagnosis.

- Polygraphy (PG) and polysomnography (PSG) were similar in confirming SAS suspicions, with 81% of patients having their diagnosis confirmed by PG.
- The studied population was categorized into severe forms of SAS based on AHI. 84% had moderate to severe forms of SAS (AHI > 15/hour).

PSG parameters	OSAS	OSAS-CSAS	CSAS	P Value
N (%)	269 (69.9)	50 (13%)	34 (8.8%)	
AHI /h	37.87 ± 24.77	37.99 ±1 7.62	38.38 ± 22.8	**0.980**
AHIc/AHI, %	**7 ± 6**	**45 ± 14**	**78 ± 5**	***0,022, *0.41, **0.002**
Mean SaO2 medie, %	**92 ± 2**	93 ± 3	**93 ± 2**	***0.065**
Minimum SaO2, %	**78 ± 9**	**80 ± 8**	**81 ± 7**	***0.034, ***0.05, **0.028**
Time with SaO2<90, min	92 ± 78	**51 ± 34**	**50 ± 35**	***0.039, **0.001**

- **Table 6.1. PG/PSG Parameters in Patients with OSAS, CSAS, and OSAS+CSAS.** AHIc-Central apnea index (defined as AHIc/AHI≥50%), AHI-apnea-hypopnea index, SaO2-arterial oxygen saturation. *p<0.05 OSAS versus OSAS-CSAS, **p<0.05 CSAS versus OSAS, ***p<0.05 OSAS-CSAS versus CSAS.

Prediction and CPAP titration.

• 78.1% of patients had a positive prediction for CPAP, but only 65.6% underwent APAP titration procedure.

• Mean residual AHI of 23/h and AHI reduction by only 5 events/h after the first night of PAP treatment.

• No hypoventilation observed.

• Mean CPAP pressure was 9 cmH2O.

Discussions.

The study revealed a high prevalence of SAS in patients with HF and the need for personalized treatment strategies. CSAS prevalence was 13%, associated with more impaired left ventricular function and higher prevalence of atrial fibrillation. Patient education and continuous support are crucial for improving treatment adherence and clinical outcomes.

Limitations.

The study was limited by its retrospective nature, variable data quality, and low patient follow-up rate. Other limitations include lack of access to patients' personal records and variability in qualitative variables.

Conclusions.

The study highlighted the importance of diagnosing and treating SAS in HF patients, emphasizing the high prevalence of SAS in this population. Gender differences observed and the need for personalized treatment strategies suggest the need for increased attention in managing these patients. The study also underscores the need to improve infrastructure and facilitate access to medical services to ensure proper diagnosis and treatment.

Future Perspectives.

Further Research: Additional prospective studies on larger samples are needed to validate and extend the findings of this study.

Focused Studies on Specific Subtypes: Further investigation into differences between CSAS subtypes (based on FEVS) or other parameters to personalize and optimize therapeutic strategies for each subtype.

Diagnostic and Treatment Protocols: Development and implementation of standardized protocols including comprehensive evaluation and management of CSAS in the HF population.

Monitoring: Use of advanced technologies for monitoring and treating CSAS that could provide more effective alternatives for non-compliant CPAP patients.

Patient Education and Support: Development of educational and support programs for patients to improve treatment adherence and, consequently, clinical outcomes.

Study 2 - The Effect of CPAP Treatment in Patients with HF-CSA Based on the Suppression or Non-Suppression of Residual AHI by CPAP at 3 Months of Treatment

Heart failure (HF) represents an advanced stage of heart disease associated with a high mortality rate. Both obstructive sleep apnea (OSA) and central sleep apnea (CSA) are common in patients with HF and are linked to unfavorable prognosis. Continuous positive airway pressure therapy (CPAP) can improve cardiac function and clinical outcomes. The aim of this study was to evaluate the impact of unsuppressed sleep apnea (residual AHI ≥15 events/h) under CPAP therapy in patients with HF and CSA.

Material and Method

The study included 36 patients with HF and moderate to severe sleep apnea, monitored at the Sleep Laboratory of the "Marius Nasta" Institute in Bucharest. Patients were divided into two groups: Suppressed Group: Residual AHI <15 events/h under CPAP therapy vs. Non-Suppressed Group: Residual AHI ≥15 events/h under CPAP therapy.

Inclusion criteria were:

Known diagnosis of HF with mildly reduced left ventricular ejection fraction (LVEF) documented on echocardiography. NYHA Class II - IV.

Clinical stability and optimal medical therapy.

Diagnosis of moderate to severe sleep apnea (AHI ≥15) by PG or PSG at baseline.

Polysomnography under PAP therapy at 3 months of treatment.

Exclusion criteria included:

Age under 18 or over 80 years.

Decompensated HF, recent coronary interventions, significant valvular diseases, untreated neoplasms, severe respiratory pathologies.

Patient refusal to provide informed consent.

Results.

Population: Adults, non-sleepy, with 47% classified as NYHA Class III-IV, having mild to moderate ventricular dysfunction (55% with LVEF below 55%) and average BNP over 100 pg/ml.

HF Etiology: Ischemic and with atrial fibrillation.

Unsuppressed AHI group (Figure 7.1). Older patients with more frequent atrial fibrillation, higher LVEF, and lower adherence to CPAP.

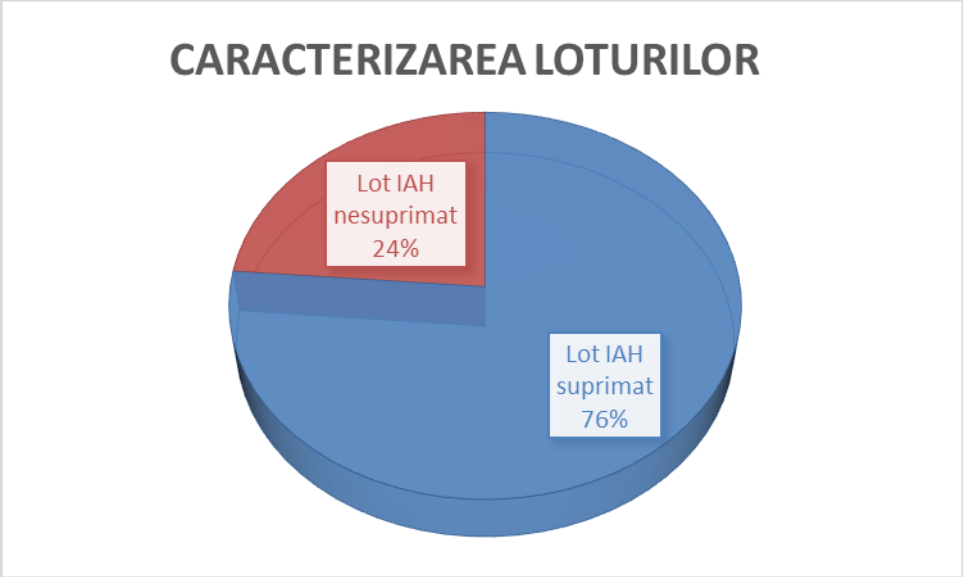

Figure 7.1. Characterization of patient cohorts based on post-PAP treatment AHI values.

Impact of CPAP: significantly positive on sleep parameters and oxygenation. It led to AHI reduction, improvement in NREM and REM sleep, as well as increased minimum SpO_2, indicating better sleep quality and respiratory function.

Effectiveness after 3 months of treatment: CPAP was more effective in the suppressed AHI group in reducing apnea-hypopnea events and improving sleep quality (Tables 7.1 and 7.2).

PSG parameters	Diagnosis	During CPAP treatment	P
TST (min)	322.8 ± 79.1	336.8 ± 79.6	0.137
Sleep Efficiency (%)	78 ± 3.24	83 ± 4.44	0.899
Arousal Index/h	41.2 ± 19.4	15.6 ± 10.7	**<0.001**
NREM sleep (%)	5.8 (12.1)	12.5 (11.1)	**<0.001**
REM sleep (%)	9.7 ± 8.4	16.8 ± 5.6	**<0.001**
AHI /h	44.1 ± 17.4	5.2 ± 3.8	**<0.001**
%central/total AHI	27.6 (55.1)	36.9 (68.5)	**<0.001**
%TST SO_2<90% (%)	17.4 (43.7)	0.7 (1.6)	**<0.001**
Minimum SaO_2 (%)	75.3 ± 13.8	96.3 ± 1.6	**<0.001**

Table 7.2. PSG Parameters under PAP Therapy in Patients with Suppressed AHI. *AHI, Apnea-Hypopnea Index; REM, Rapid Eye Movement; SO_2, Oxygen Saturation; TST, Total Sleep Time. Data are presented as mean ± standard deviation or median (interquartile range). p for comparison between parameters at diagnosis and parameters during CPAP therapy.*

Left ventricular function: There were no significant changes observed in left ventricular function between patients with suppressed AHI and those with non-suppressed AHI after CPAP treatment.

Parameters	Diagnosis	During CPAP treatment	P value
TST (min)	309.6 ± 94.4	341.6 ± 95.6	0.369
Sleep Efficiency (%)	70 ± 6.24	78 ± 4.14	0.062
Arousal Index /h	43.6 ± 20.0	17.6 ± 8.4	**<0.001**
NREM sleep (%)	0 (2.6)	12.0 (21.5)	**0.039**
REM sleep (%)	9.6 ± 5.8	18.3 ± 7.0	**0.004**
AHI /h	51.6 ± 14.2	21.3 ± 7.5	**<0.001**
%central/total AHI	81.6 (28.7)	86 (38.6)	**0.023**
%TST SO_2<90% (%)	19.1 (45.7)	2.1 (7.7)	**0.002**
SpO2 SO_2 (%)	75.6 ± 13.0	84.9 ± 4.5	**<0.001**

Table 7.3. PSG Parameters under PAP Therapy in Patients with Non-Suppressed AHI. *AHI, apnea-hypopnea index; REM, rapid eye movement; SO_2, oxygen saturation of hemoglobin; TST, total sleep time. Data presented as mean ± standard deviation or median (interquartile range). p for comparison between parameters at baseline and during CPAP therapy.*

Discussion.

Non-suppressed apnea under CPAP is associated with a worse prognosis in patients with HF and SAS, characterized by atrial fibrillation presence and therapy discontinuation. CPAP effectively reduced AHI and improved sleep and oxygenation parameters, but its impact on cardiac function was comparable between groups. The study underscores the importance of continuous monitoring and CPAP treatment adjustments to maintain optimal AHI levels.

CPAP is an effective treatment for improving sleep and reducing apnea in patients with moderate-severe SAS and HF. Continuous monitoring and treatment adjustment are essential to maintain optimal AHI levels and improve prognosis in HF patients. Identification of other predictors for CPAP effectiveness could aid in treatment personalization using modern monitoring technologies, including portable devices.

Strengths:

• Baseline and 3-month follow-up sleep study.

• Polysomnography performed after 3 months of CPAP use.

• Effects of CPAP on LV function and NT-proBNP analyzed.

Study 3 - CPAP Therapy Adherence at 12 Months and Cardiovascular Risk Assessment with and without CPAP Treatment

Introduction.

Continuous positive airway pressure therapy (CPAP) can improve cardiac function and clinical outcomes in patients with obstructive sleep apnea (OSA) and central sleep apnea (CSA). However, low adherence to CPAP and variable effectiveness are major obstacles. This study aimed to evaluate adherence to CPAP treatment among patients with CSA and the risk of cardiovascular exacerbation after 12 months of follow-up.

Material and Methods.

Starting from January 1, 2018, patients with heart failure (HF) and moderate to severe central sleep apnea (CSA) were monitored at the Sleep Clinic of the "Marius Nasta" Institute of Pneumology in Bucharest. The study included 40 patients divided into two groups: Compliance group - patients who used CPAP for at least 4 hours per night, at least 70% of the time; Control group - patients who refused to use CPAP during the first year after diagnosis.

Inclusion criteria were stable HF (NYHA class II-IV), diagnosis of CSA (AHI ≥15 events/hour), and agreement to undergo CPAP treatment. Exclusion criteria were age under 18 or over 80 years, decompensated HF, untreated neoplasms, severe respiratory pathologies, and refusal to sign informed consent.

Results.

This study evaluated the effect of CPAP therapy on patients with central sleep apnea and heart failure over a 12-month period. Patients were divided into two subgroups: those with suppressed apnea-hypopnea index (AHI) and those with non-suppressed AHI. The study monitored various parameters of sleep, oxygenation, and cardiac function.

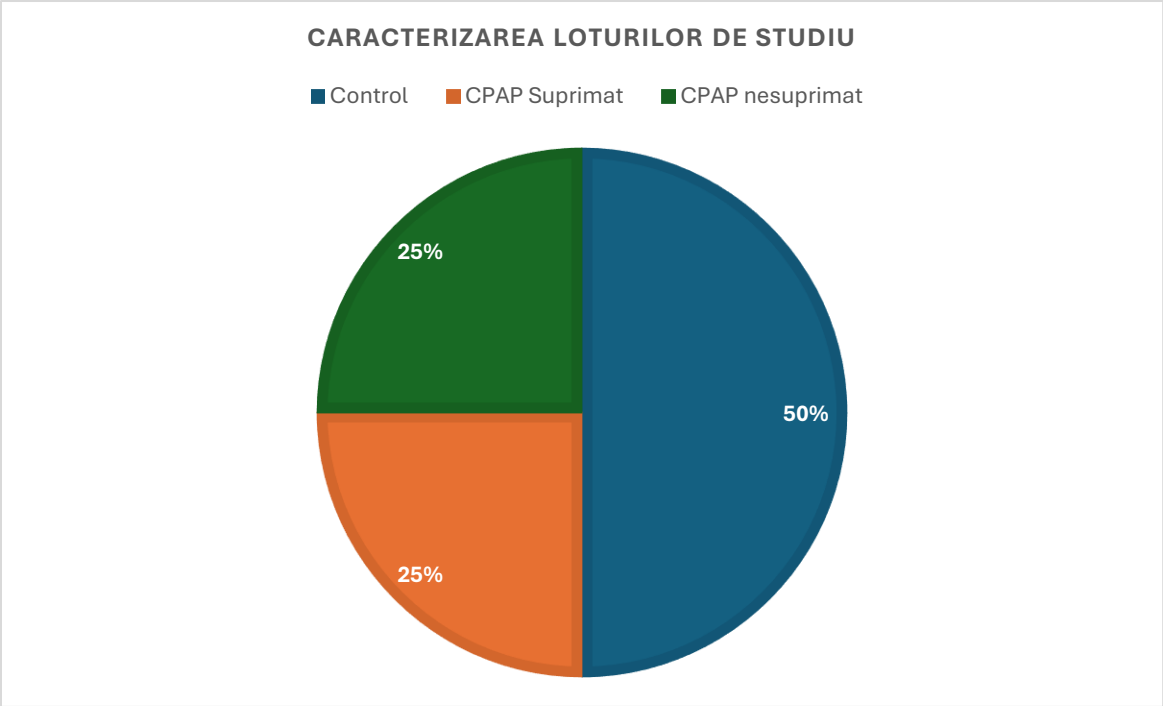

Figure 8.1. Characterization of Study Cohorts.

Out of the initial 40 patients, only 10 patients (27.72%) were compliant after 12 months of CPAP therapy. Among these, 5 patients had a suppressed AHI (<15 events/hour), while 5 patients had a non-suppressed AHI (≥15 events/hour). The control group included 10 patients who did not use CPAP.

****Demographic and Clinical Characteristics:****

There were no significant differences between groups in terms of age, sex, body mass index, NYHA class, cause of cardiomyopathy, blood pressure, LVEF, and average SpO2 during sleep.

The proportion of males was overwhelming in all groups (>90%).

Medication use was similar across groups.

****Sleep Parameters and CPAP Utilization:****

Total sleep time and sleep efficiency were similar between groups.

AHI significantly decreased in both CPAP groups, but was more pronounced in the suppressed AHI CPAP group.

CPAP pressure at 3 and 12 months increased slightly without statistical significance.

Compliance was better in the suppressed AHI CPAP group, with a higher percentage of patients using CPAP for more than 4 hours/day.

****CPAP Effectiveness:****

CPAP caused a significant reduction in AHI in both CPAP groups, with a more pronounced reduction in the suppressed AHI CPAP group.

Left ventricular ejection fraction (LVEF) significantly increased in the suppressed AHI CPAP group, suggesting additional cardiac benefit of CPAP use.

****Hospitalizations and Mortality:****

At 12 months, no patients in the suppressed AHI CPAP group reported cardiovascular-related hospitalization, while 1 patient in the non-suppressed AHI CPAP group required hospitalization for cardiovascular decompensation due to SARS-CoV-2 infection.

Discussion.

Left ventricular ejection fraction (LVEF) did not change significantly in the control group and non-suppressed AHI CPAP group, but increased significantly in the suppressed AHI CPAP group. This suggests an additional cardiac benefit of CPAP use in reducing central sleep apnea.

Some findings may be influenced by the small number of study subjects, suggesting the need for further studies with a larger sample to confirm these conclusions.

These findings indicate that CPAP use, when compliant and well-monitored, can have significant benefits for patients with CSA, both in reducing apnea severity and improving cardiac function.

This approach is crucial as patients with HF and CSA often present with multiple comorbidities that can significantly affect the efficacy and adherence to various treatments. In the absence of a standardized global protocol, it is imperative to investigate various therapeutic strategies to determine the most effective management methods for these patients. Assessing treatment adherence and the risk of cardiovascular exacerbation provides essential information for tailoring therapeutic interventions and optimizing clinical outcomes in this vulnerable population. (42)(43)

Despite improvements in device comfort and sleep-related quality of life, CPAP adherence generally varies from 30 to 60%, with non-compliance rates reaching up to 50% after the first year of treatment (23,24).

Factors associated with long-term CPAP non-compliance are described in the literature concerning any respiratory disorder, but nothing has been reported regarding comorbid CSA and HF. Thus, moderate to severe sleep apnea, poor sleep efficiency during CPAP titration, small nasal volume and high nasal resistance, concurrent use of sedatives, CPAP use under 4 hours per night in the first 2 weeks of treatment, difficulties experienced during the first night, psychological traits, claustrophobia, misunderstanding of therapy importance and instructions, or the partner's sleep affected by a patient can influence both compliance and long-term prognosis.

Treatment methods aren't supported by a high level of evidence. Moreover, CPAP has been demonstrated to be harmful in CSA patients. In the SERVE-HF study context and in anticipation of the ADVENT-HF results, ICFER management optimization is recommended to enhance the ASC practice (C-grade experts' recommendation based on six studies, including a total of just 67 patients).

Additional randomized clinical trials are needed to better elucidate the outcomes of these interventions for patients with all forms of IC, including ICFEP and advanced ICFER, and the predictive implications that may have for other cardiovascular outcomes and mortality.

Strengths

• Patients were instructed to use the CPAP device for at least 4 hours per night.

• Long study duration.

• The effects of CPAP on LVEF and NT-proBNP were evaluated at 3 months of treatment.

Future Perspectives

• **Continuous monitoring and patient support** are essential to ensure consistent CPAP use and maximize clinical benefits.

• **Further research** is needed to investigate the use of modern monitoring technologies and other types of positive airway pressure.

• **Patient phenotyping** and evaluation of predictive factors for CPAP effectiveness and management optimization to improve clinical outcomes in this vulnerable population.

• The study emphasizes the importance of **personalized treatment based on each patient's characteristics** and the need for further research to improve therapeutic strategies for patients with CSA and HF.

LIST OF PUBLISHED SCIENTIFIC WORKS

Articles published in specialty journals:

1. **Borcea CI,** Deleanu OC, Mihălțan FD. The Profile of Romanian patient with central sleep apnea and heart Failure. Internal Medicine 2021 vol. XVIII No.5 - www.srmi.ro 10.2478/inmed-2021-0181. https://intapi.sciendo.com/pdf/10.2478/inmed-2021-0181
2. **Borcea CI**, Mihălțan FD, Deleanu OC. Central sleep apnea in patients with heart failure: whom to screen and how to treat? – A brief review. Pneumologia 2020; 69(3):142-150. https://intapi.sciendo.com/pdf/10.2478/pneum-2021-0003
3. Mihălțan F, Constantin A, **Borcea C**, Coşei V, Oros M. Sleep in COVID 19 period. Internal Medicine 2020 vol. XVII No.3 - https://sciendo.com/article/10.2478/inmed-2020-0116

Published works at national and international conferences and book chapters on the topic of the doctoral thesis:

1. Mihălţan F, **Oprea C,** Cosei V, Oros M, Deleanu O. Introduction to sleep medicine - 8 th Central European Sleep Training Course. 21-25 noiembrie 2016, București
2. **Deleanu OC, Borcea CI, Zaharia AM.** Sindromul de apnee în somn central și respirația Cheyne-Stokes: ce este nou? - 10 ani de Somnologie Clujeană: trecut, prezent și viitor. Workshop național cu participare internațională. 23-25 martie 2017, Cluj-Napoca.
3. **Borcea CI.** Diagnosticul sindromului de apnee în somn - Congres UMF. 29-31 mai 2017, Palatul Parlamentului, București.
4. **Borcea CI.** Clinical case: pulmonology - The International Medical Students' Congress of Bucharest. 6-10 December 2017, București.
5. **Borcea CI, Deleanu OC.** Apneea de somn centrală la pacienții cu insuficiență cardiacă congestivă - lecții din studiile recente - Ziua Mondială a Somnului. 16 martie 2018, București.
6. **Mihălţan F, Oprea C.** VNI în sindromul de apnee în somn de tip central şi insuficienţa cardiacă cronică - Workshop Național: Managementul Modern în insuficienţa respiratorie - Ventilaţia Non invazivă în practica pneumologului. 30-31 martie 2018, Cluj-Napoca.

7. **Deleanu OC, Borcea CI.** Sindromul de apnee în somn de tip central și insuficiența cardiacă: ce este nou? - A VII-a Conferință Managementul Bolilor Pulmonare. 22-23 iunie 2018, Hotel Ramada Parc, București.
8. **Deleanu O, Borcea C.** Sindromul de apnee în somn de tip central și respirația Cheyne-Stokes - Prima Ediție a Școlii de Vară de Somnologie. 6-7 iulie 2018, Oradea.
9. **Oprea C, Deleanu O.** Poligrafia versus Polisomnografia - Conferința medicală "SOMNOLOGIA la școală", British School of Bucharest. 28 septembrie 2018, București.
10. **Borcea CI.** Sindromul de apnee în somn și insuficiența cardiacă: ce este nou? - A VIII-a Conferință Managementul Bolilor Pulmonare. 12-13 iunie 2019, București.
11. **Borcea CI, Deleanu OC, Mihălțan F.** Polisomnografia - Webinar-ul Școala de Vară de Somnologie și Ventilație Non-Invazivă, ediția a II-a. Eveniment online, 18-19 septembrie 2020.
12. **Mihălțan F, Borcea C.** Somnologia - rolul în prevenția și managementul bolilor cronice - Medicina Stilului de Viață și Bolile Cronice: Prevenție dar și Tratament. 25 noiembrie 2020, București.
13. **Borcea C.** Tulburările respiratorii în timpul somnului: de la teorie, la practică - Al X-lea Congres Bolile Cronice Netransmisibile. 19-20 februarie 2021, Online, sub egida Academiei Române „Bolile Cronice Netransmisibile și COVID-19".
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17. Mihălţan F, **Borcea C.** Aderența la tratament CPAP - "Abordarea disciplinar integrată a sindromului de apnee în somn" din cadrul Campaniei Sănătatea Somnului. 18 mai 2023, Hotel Phoenicia, București.

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20. **Borcea C**, Mihălţan F. Aderența la CPAP în SASO: o problemă eternă! - Zilele Spitalului Clinic CF Iași. 13-15 decembrie 2023, Iași.
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