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АНАЛИЗ НА ЕХОКАРДИОГРАФСКИТЕ ПРОМЕНИ ПРИ ПАЦИЕНТИ С ЦЕНТРАЛНА СЪННА АПНЕЯ ЛЕКУВАНИ СЪС SGLT2i

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ANALYSIS OF ECHOCARDIOGRAPHIC CHANGES IN PATIENTS WHIT CENTRAL SLEEP APNEA TREATED WITH SGLT2i

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Резюме.

Въведение: Остра декомпенсирана сърдечна недостатъчност (ОДСН) често се свързва с централна сънна апнея (ЦСА), която влошава клиничната картина и качеството на живот. При пациенти с ОДСН, ЦСА допринася за повтаряща се нощна кислородна десатурация, повишен индекс на апнея-хипопнея (AHI) и чести епизоди на Чейн-Стоукс дишане, влошавайки прогнозата. Ехокардиографското наблюдение е от съществено значение за тези пациенти, осигурявайки надеждна оценка на сърдечната функция с течение на времето. Инхибиторите на натриево-глюкозния котранспортер-2 (SGLT2i), първоначално разработени за диабет, показват ползи за бъбречната функция, подобряват симптомите при сърдечна недостатъчност и са ефективни при сънна апнея, което предполага мултиорганна протекция. **Цел:** Да се оцени ефектът от терапията със SGLT2i върху ехокардиографските параметри и тежестта на сънната апнея при пациенти с ЦСА и ОДСН с намалена систолна функция. **Материал и методи:** Проведено е проспективно кохортно проучване с 162 пациенти, включващо тези с фракция на изтласкване < 40%, NT-proBNP > 900 pg/ml и AHIcentral > 5. Изключени са пациенти с краен стадий на бъбречно заболяване, клас IV сърдечна недостатъчност по NYHA, ХОББ или тежка дихателна недостатъчност. За оценките са използвани ApneaLink™ и подробен ехокардиографски запис, като пациентите са проследявани три месеца след започване на SGLT2i терапията. **Резултати:** От 52-ма пациенти, отговарящи на включващите критерии, 48 завършиха проучването. Регистрират се сигнификанти ехокардиографски промени. Диастолната функция се подобрява значимо с намаление на съотношението E/e' от 14.74 ± 2.57 до 13.64 ± 2.18, p = 0.002, както и функцията на дясна камера, показано с намаления в RVOT от 39.25 ± 4.01 до 38.32 ± 3.59, p = 0.004 и s-PAP от 41.26 ± 5.74 до 40.07 ± 5.20, p = 0.001. TAPSE също се подобрява от 18.37 ± 2.17 mm до 18.87 ± 1.96 mm, p < 0.001, а съотношението s-PAP/TAPSE отразява по-добра ефективност на дясната камера променяйки се от 0.46 ± 0.11 до 0.48 ± 0.10 в края на проследяването, p < 0.001. Показателите за сънна апнея също показват подобрение с намаления в AHI от 21.35 ± 4.91 до 18.33 ± 4.75, p = 0.015, централния AHI от 13.16 ± 3.70 до 10.04 ± 3.57, p < 0.001 и епизодите на Чейн-Стоукс дишане от 33.70 ± 11.20 до 26.58 ± 9.95, p < 0.001. Индексът на кислородна десатурация (ODI) намалява от 24.29 ± 7.01 до 17.91 ± 5.90, p < 0.001, а нивата на NT-proBNP, които показват тежестта на сърдечната недостатъчност, се намаляват от 1574.89 ± 652.80 pg/ml до 1250.35 ± 484.26 pg/ml, p < 0.001. **Заключение:** Терапията със SGLT2i води до съществени подобрения в ехокардиографските показатели, особено на тези, отразяващи функцията, заедно със значителни намаления в тежестта на ЦСА и кислородната десатурация при пациенти с ОДСН. Тези резултати подкрепят потенциала на SGLT2i като ефективна терапевтична опция, налагайки допълнителни проучвания за дългосрочните ползи върху сърдечно-съдовата система.

Ключови думи: инхибитори на SGLT2; ехокардиографски промени; централна сънна апнея

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Abstract.

Background: Acute decompensated heart failure (ADHF) is often associated with central sleep apnea (CSA), which exacerbates cardiovascular strain and impacts quality of life. In ADHF patients, CSA contributes to recurrent nocturnal oxygen desaturation, elevated apnea-hypopnea index (AHI), and frequent Cheyne-Stokes respiration episodes, increasing health risks. Echocardiographic monitoring is essential in these patients, providing reliable assessment of heart function over time. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially developed for diabetes management, have shown benefits for renal function, sleep apnea symptoms, and heart failure outcomes, suggesting potential for multifaceted treatment. **Purpose:** To evaluate the effects of SGLT2i therapy on echocardiographic parameters and sleep apnea severity in patients with CSA and ADHF with reduced systolic function (HFrEF). **Material and methods:** We conducted a prospective cohort study with 162 patients, including those with an ejection fraction < 40%, NT-proBNP > 900 pg/ml, and AHIcentral > 5. Exclusions were patients with end-stage renal disease, NYHA class IV heart failure, COPD, or severe respiratory failure. ApneaLink™ and echocardiograms were used for assessments, and patients were followed for three months post-initiation of SGLT2i. **Results:** Among the 52 eligible patients, 48 completed the study. Echocardiographic improvements were significant, particularly in diastolic function with a reduction in the E/e' ratio (from 14.74 ± 2.57 to 13.64 ± 2.18, p = 0.002) and right heart function, as shown by decreases in RVOT (from 39.25 ± 4.01 to 38.32 ± 3.59, p = 0.004) and s-PAP (from 41.26 ± 5.74 to 40.07 ± 5.20, p = 0.001). TAPSE also improved (from 18.37 ± 2.17 mm to 18.87 ± 1.96 mm, p < 0.001), and the s-PAP/TAPSE ratio reflected better right heart efficiency (from 0.46 ± 0.11 to 0.48 ± 0.10, p < 0.001). Sleep apnea metrics also showed improvement, with reductions in AHI (from 21.35 ± 4.91 to 18.33 ± 4.75, p = 0.015), central AHI (from 13.16 ± 3.70 to 10.04 ± 3.57, p < 0.001), and Cheyne-Stokes respiration episodes (from 33.70 ± 11.20 to 26.58 ± 9.95, p < 0.001). Oxygen desaturation index (ODI) decreased (from 24.29 ± 7.01 to 17.91 ± 5.90, p < 0.001), and NT-proBNP levels, indicating heart failure severity, were reduced (from 1574.89 ± 652.80 pg/ml to 1250.35 ± 484.26 pg/ml, p < 0.001). **Conclusion:** SGLT2i therapy led to substantial improvements in echocardiographic measures of diastolic and right heart function, along with significant reductions in CSA severity and oxygen desaturation in ADHF patients. These findings support the potential of SGLT2i as an effective treatment option, meriting further study for long-term benefits on cardiac and respiratory health.

Key words: SGLT2 inhibitors; echocardiographic changes; central sleep apnea

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Introduction

Acute decompensated heart failure (ADHF) represents a critical health burden with substantial morbidity, mortality, and economic impact, driven by frequent hospitalizations, intensive treatment requirements, and high readmission rates, particularly when complicated by central sleep apnea (CSA) [1]. CSA is especially concerning in ADHF, as it leads to recurrent nocturnal oxygen desaturation, elevated AHI, and frequent Cheyne-Stokes respiration episodes, all of which contribute to adverse clinical outcomes and heightened mortality risk [2]. Echocardiographic monitoring is essential in managing these patients, providing insights into cardiac function, pulmonary pressures, and hemodynamic changes, especially since right ventricular dysfunction and elevated pulmonary pressures are commonly seen in ADHF and worsened by CSA [3].

SGLT2i initially developed for diabetes management, have emerged as an effective treatment for heart failure, offering benefits such as enhanced diuresis, anti-remodeling effects, and reductions in heart failure-related mortality and hospitalizations [4]. Recent studies indicate that SGLT2i may also reduce CSA severity by improving cardiac efficiency, reducing neurohormonal activation, and stabilizing respiratory function during sleep [5]. Echocardiographic monitoring, assessing changes in parameters of the left ventricle, left atrium, and diastolic function, as well as evaluating alterations in the right ventricle and pulmonary systolic pressure, is an established method for tracking the efficacy of therapeutic intervention [6]. SGLT2i therapy may provide a multifaceted approach for ADHF patients with CSA, enhancing both cardiac function and respiratory stability.

Aim

To assess the 3-month impact of SGLT2 inhibitor therapy on cardiac and respiratory parameters in patients with acute decompensated heart failure and reduced ejection fraction. This study investigates improvements in CSA severity and evaluates cardiac function changes through echocardiographic indicators, including systolic and diastolic function, right ventricular outflow tract (RVOT) size, systolic pulmonary artery pressure (s-PAP), TAPSE, and the TAPSE/s-PAP ratio.

Material and Methods

Study Design

A total of 162 patients with ADHF were screened for inclusion in this single-center, prospective cohort study at the cardiology department of University Hospital "Tsaritsa Yoanna – ISUL" in Sofia, conducted from 2021 to 2023. Patients were observed over a 3-month

period after initiating SGLT2i therapy to assess changes in echocardiographic and sleep apnea parameters. Among the initial cohort, 52 patients met the criteria outlined in Table 1.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Acute decompensated heart failure with New York Heart Association (NYHA) class II/III	1. NYHA class IV or terminal heart failure
2. NT-proBNP > 900 pg/ml	2. Acute respiratory failure
3. Central apnea-hypopnea index (AHIcentral) > 5	3. Acute coronary syndrome (ACS)
4. Ejection fraction, % (EF) < 40%	4. End-stage kidney disease
5. Naive patients on SGLT2i therapy	5. Terminal liver insufficiency
6. Signed informed consent	6. Chronic Obstructive Pulmonary Disease (COPD)
	7. Lack of informed consent

In-Hospital Measurements and Follow-Up

During hospitalization, after obtaining informed consent and with approval from the institutional ethics committee of the Medical University of Sofia (Protocol 2100 from 27.04.2021), we conducted NT-proBNP measurements, echocardiographic assessments, and sleep apnea screening. Echocardiography was performed using a Philips EPIQ 7 system, while sleep apnea screening utilized the ApneaLink™ respiratory monitoring system by ResMed [7]. Out of 52 eligible patients, 2 declined follow-up, and 2 passed away during the study period, resulting in a total of 48 patients who completed the follow-up and were included in the analysis. Fig. 1

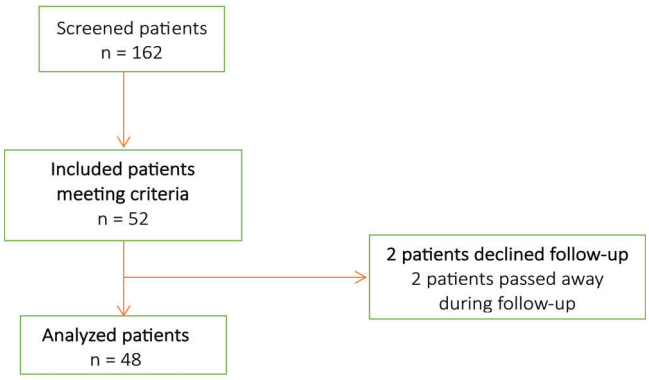

Fig. 1. Study flow chart

Statistical Analysis

Data were analyzed using SPSS software (version 26.0). Descriptive Statistics: Results are presented as means ± standard deviations for continuous variables and as percentages for categorical variables. Normality Test: The Shapiro-Wilk test was used to check for normal distribution of data. Non-parametric tests were used if normality was not achieved. Changes Over Time: Paired t-test was used for comparing pre- and post-therapy measurements when data followed a normal distribution. The Wilcoxon signed-rank test was applied for dependent variables when normal distribution was not achieved. Analyses were conducted using SPSS, with additional regression and graphical analyses performed using GraphPad Prism (version 9) where necessary.

Results

Patient Demographics and Clinical Characteristics

Out of the 162 patients studied, 52 patients (32%) exhibited AHIcentral > 5 and AHIobstructive < 15 per hour. The mean age of the cohort was 69 years, with a standard deviation of ± 8.64. Regarding gender distribution, males outnumbered females, with a ratio of 33 to 15. No significant change in body mass index (BMI) was observed from baseline to the end of therapy 27.612 ± 4.78 vs. 27.504 ± 4.65 (p = 0.51). Ischemic heart disease was the leading cause of heart failure, accounting for 64% of cases. Diabetes mellitus was present in 65% of patients (n=31), while atrial fibrillation was observed in 69% (n=33). In terms of concomitant therapy, ACE inhibitors or ARNi were administered to 83.3% (n=40) of the patients, diuretics to 85% (n 41), beta-blockers to 92% (n 44), and MRA to 45.8% (n=22). The data are presented in Table 2.

Table 2. Patient Demographics and Clinical Characteristics

Demographics and Clinical Characteristics	N
Sex f/m	15/33
Age, years	69.00 ± 8.64
Ischemic / Non ischemic	31/17
Diabetes mellitus, %	64.6%
Atrial fibrillation, %	68.8%
ACE/ARNi, %	83.3%
MRA, %	45.8%
Diuretics, %	85.4%
β-blockers, %	91.7%

Mean ± SD
ACE/ARNi – angiotensin-converting enzyme inhibitors/ angiotensin receptor-neprilysin inhibitors, MRA – mineralocorticoid receptor antagonists

Hemodynamic and Left Ventricular Function Parameters

Among the studied parameters, significant changes were observed in the mean values of E/e′ and NT-proBNP. The E/e′ ratio showed a notable decrease from 14.74 ± 2.57 to 13.64 ± 2.18 (p = 0.002), indicating improvement in diastolic function. NT-proBNP levels also significantly decreased from 1574.89 ± 652.80 to 1250.35 ± 484.26

(p < 0.001), suggesting an improvement in the clinical status of the patients. Fig. 2

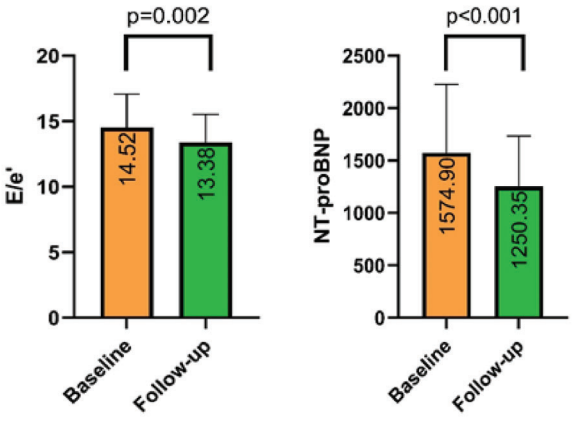

Fig. 2. Changes in E/e' Ratio and NT-proBNP Levels at Baseline and Follow-up

With respect to EF, there was an observed trend toward improvement, with an increase from 35.42 ± 4.29 to 35.72 ± 4.35; however, this change did not reach statistical significance (p = 0.052), indicating only a tendency for improved systolic function. No significant changes were observed in LVEDV and LAVi throughout the study period, indicating stable structural heart parameters. LVEDV remained consistent, with values of 190.74 ± 18.03 at baseline and 189.48 ± 17.39 at follow-up (p = 0.353), suggesting that left ventricular filling volume was unaffected. Similarly, LAVi showed minimal variation, recorded at 43.97 ± 2.95 at baseline and 43.99 ± 3.05 at follow-up (p = 0.920). These results indicate that structural cardiac parameters left ventricular and left atrium were preserved in the studied population.

Changes in Right Ventricular and Pulmonary Pressure Parameters

Based on the observed data, notable changes were recorded in specific parameters associated with right ventricular function and pulmonary pressure, indicating potential improvements in cardiac dynamics following intervention. The RVOT diameter showed a slight but statistically significant reduction from 39.25 ± 4.01 mm to 38.32 ± 3.59 mm (p = 0.004). The RAA presented a marginal decrease, from 22.014 ± 3.05 cm² to 21.72 ± 2.81 cm², though this change did not reach statistical significance (p = 0.095).

TAPSE, a key indicator of right ventricular systolic function, demonstrated a significant increase from 18.37 ± 2.17 mm to 19.04 ± 1.85 mm (p < 0.001), suggesting improved contractile performance of the right ventricle. s-PAP decreased from 41.26 ± 5.74 mmHg to 40.07 ± 5.20 mmHg (p = 0.001), indicating a favorable effect on pulmonary pressures. Additionally, the s-PAP/TAPSE ratio, an index often used to assess right ventricular function relative to pulmonary pressure, slightly increased from 0.46 ± 0.11 to 0.48 ± 0.10 (p < 0.001), reinforcing the observed enhancement in right ventricular performance. Fig. 3

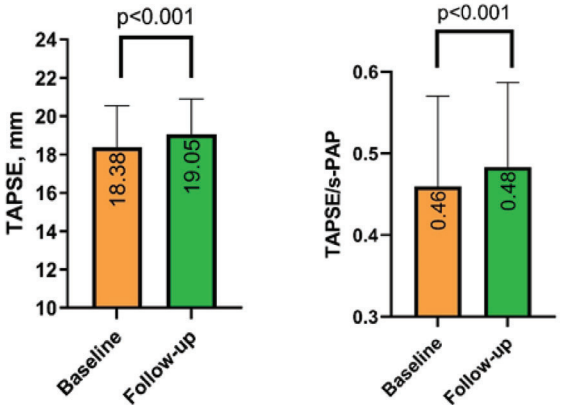

Fig. 3. Changes in TAPSE and TAPSE/s-PAP ratio at Baseline and Follow-up

Improvements in Sleep Apnea Severity and Respiratory Patterns

AHI, a primary measure of sleep apnea severity, decreased from 21.35 ± 4.91 to 18.33 ± 4.75 (p = 0.015), suggesting a reduction in overall apnea events per hour. Additionally, the presence of Cheyne-Stokes respirations showed a marked decline from 33.70 ± 11.20 to 26.58 ± 9.95 (p < 0.001), reflecting improvements in the regularity of respiratory patterns during sleep. AHIcentral also demonstrated a notable reduction, from 13.16 ± 3.70 to 10.04 ± 3.57 (p < 0.001), which may indicate a decreased frequency of central apneas. In contrast, the AHIobstructive showed minimal change, with values of 5.52 ± 2.36 before and 5.63 ± 2.32 after the intervention (p = 0.404), indicating that the primary improvements were centered on central, rather than obstructive, apnea events. ODI, which reflects the frequency of oxygen level drops during sleep, decreased significantly from 24.29 ± 7.01 to 17.91 ± 5.90 (p < 0.001), suggesting a better maintenance of blood oxygen levels throughout the night. Fig. 4.

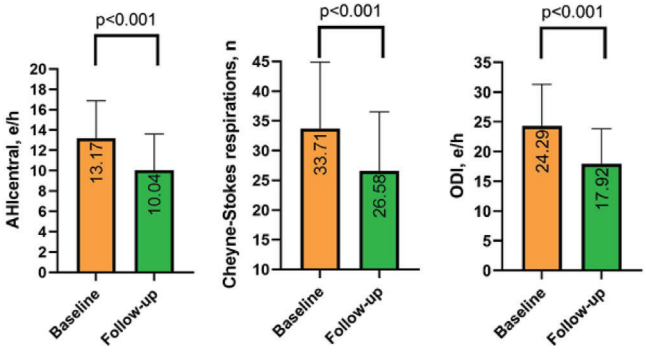

Fig. 4. Changes in AHIcentral events per hour, Cheyne-Stokes respirations and ODI – oxygen desaturation index events per hour at Baseline and Follow-up

Discussion

This study investigates the potential benefits of SGLT2i in patients with both HF and CSA, conditions that frequently co-occur and significantly diminish quality of life. Our findings reveal a high prevalence of CSA among HF patients, particularly in males, consistent with established data on the epidemiology of this comorbidity [8, 9]. In HF, CSA exacerbates hemodynamic stress and can drive adverse remodeling, emphasizing the need for effective management strategies [10, 11].

Non-pharmacological therapies, including CPAP and Adaptive Servo-Ventilation (ASV), have been explored as treatment options for CSA in HF populations. However, their effectiveness has been somewhat limited. CPAP has demonstrated variable success in stabilizing respiratory control, with some studies suggesting only moderate improvements [12]. Terziyski and Draganova [8] have provided insights into the complex pathophysiology of CSA in HF and the specific challenges associated with Cheyne-Stokes respiration, noting the intricate clinical demands of treating this patient group. CPAP has shown some benefits in improving heart rate variability, but overall efficacy in this context remains uncertain, as supported by findings from Terziyski et al. [13]. Moreover, the SERVE-HF trial linked ASV therapy to higher mortality rates among certain HF patients, raising important concerns about ASV's safety and efficacy in treating CSA in these cases [10]. Given these limitations, there is an increasing interest in alternative therapeutic options, such as SGLT2i, which have demonstrated promising cardiovascular benefits and may offer a more comprehensive treatment strategy for patients with HF and CSA [5, 14].

Our study shows that echocardiographic indicators of structural changes, such as LVEDV, LAVi, RAA, and RVOT, remained relatively stable, suggesting that SGLT2i therapy did not significantly impact cardiac structure over the study period. In contrast, several functional parameters—including EF, E/e', s-PAP, TAPSE, and the TAPSE/s-PAP ratio—demonstrated notable improvements. These enhancements in functional performance could be attributed to a reduction in respiratory strain, primarily due to fewer episodes of Cheyne-Stokes respiration and a decrease in desaturation events, which have a direct impact on the workload and efficiency of the right heart [8, 9].

The improvements observed in right ventricular function and pulmonary pressures align with existing research, which indicates that SGLT2 inhibitors can help reduce ventricular preload and alleviate pulmonary congestion, ultimately supporting right ventricular contractility [15,16]. Studies also suggest that by modulating fluid balance and neurohormonal activity, SGLT2i may improve hemodynamics and thus mitigate the effects of CSA on cardiac function, providing a comprehensive benefit to patients with HF and CSA [17, 18]. These results support SGLT2i therapy as a potentially valuable intervention for improving functional cardiac performance without compromising structural integrity [19].

In our study, we found that SGLT2i therapy yielded more notable benefits for respiratory parameters associated with CSA than with OSA. This observation is supported by Tanriover et al.'s 2023 meta-analysis, which documented improvements in AHI and oxygen saturation in OSA patients treated with SGLT2i, although with a lesser effect than that observed in CSA [20]. Similarly, SGLT2i demonstrated positively impacted right ventricular function and pulmonary pressures in patients with OSA [21]. Convincing evidence also highlights the efficacy of Sacubitril-valsartan in reducing central apnea events and improving CSA-related respiratory parameters, as shown by Jaffuel et al. in the ENTRESTO-SAS study. Their findings suggest that Sacubitril-valsartan may exert these effects by reducing neurohormonal activation and pulmonary congestion, which are key factors driving central respiratory instability in HF [22].

The observed differences in outcomes for CSA and OSA with SGLT2i therapy can be attributed to variations in study design and cohort characteristics. Notably, the largest cohort specifically studying CSA consists of only 101 patients, as seen in the research by Jaffuel et al. [22]. In contrast, the larger randomized trials examining the effects of SGLT2i, such as those with dapagliflozin and empagliflozin, conduct sub-analyses primarily based on clinical criteria without consistently incorporating polysomnographic evaluation to diagnose and monitor sleep apnea in HF patients. Studies like the DAPA-HF and EMPEROR-Reduced trials, which have set the foundation for understanding SGLT2i's cardiovascular benefits, largely relied on clinical symptomatology and biomarkers rather than objective sleep assessments [18, 19]. This difference in approach may account for the nuanced understanding of SGLT2i's effects on respiratory parameters, particularly when comparing CSA and OSA outcomes.

Our study shows that SGLT2i therapy significantly benefits respiratory parameters linked to CSA, more so than OSA. This is seen in the reduction of AHIcentral and Cheyne-Stokes respiration episodes, suggesting a positive effect on central respiratory control in HF patients. These improvements likely result from SGLT2i's autonomic modulation, reducing sympathetic activity and stabilizing respiratory drive to decrease central apnea episodes [5, 22].

Additionally, the anti-inflammatory properties of SGLT2i may further support respiratory stability by counteracting inflammation-driven disruptions in brainstem respiratory centers, which contribute to apnea-hyperpnea cycles in HF. The lack of effect on OSA indices reinforces that SGLT2i targets CSA mechanisms, rather than the structural factors causing OSA. This aligns with findings from larger HF studies that support the role of SGLT2i in enhancing autonomic and inflammatory pathways specific to CSA [22, 23, 24, 25].

Limitations

A key limitation of this study is the relatively small sample size, which may limit the broader applicabili-

ty of our findings. The complex care needs of HF patients with concurrent sleep apnea, compounded by multiple comorbidities, require intensive monitoring and follow-up, presenting logistical and resource demands. Additionally, ethical considerations precluded the inclusion of a control group, as withholding SGLT2i treatment was not feasible. The need for repeat polysomnography to accurately assess sleep apnea severity also posed a limitation, given its resource-intensive nature, which restricts its practicality in routine settings. Furthermore, the short follow-up period limits insight into potential long-term structural changes, highlighting the importance of future studies with extended durations to fully assess the stability of these improvements.

Conclusion

In conclusion, our findings indicate that SGLT2 inhibitors provide notable benefits for HF patients with CSA, improving functional cardiac parameters and reducing central apnea severity. Enhanced right ventricular function, pulmonary pressures, and oxygenation highlight SGLT2 inhibitors' potential to address the complex relationship between cardiac and respiratory systems in this population. Further randomized studies with larger samples and longer follow-ups are needed to confirm these benefits and clarify underlying mechanisms, ultimately guiding more effective therapies for this high-risk group.

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