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Sleep-related breathing disorders in patients with heart failure with reduced and mildly reduced ejection fraction: main types and their dependence on heart failure etiology

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Aim. To identify and study the nature of sleep-related breathing disorders (SBDs) in a cohort of hospitalized patients with heart failure (HF) with reduced and mildly reduced ejection fraction (EF), as well as to clarify the relationship between SBD type, etiology and severity of HF.

Material and methods. The study included 117 patients with HF with reduced and mildly reduced ejection fraction hospitalized at the National Medical Research Center for Therapy and Preventive Medicine from 2019 to 2021. All patients underwent clinical and paraclinical examination, including cardiorespiratory sleep study. Patients were divided into three groups according to the type and severity of SBD: no or mild SBD, predominantly with obstructive sleep apnea (OSA) and predominantly with central sleep apnea (CSA). Severity of SBD and clinical data were compared between these groups.

Results. A total of 5 patients (4,27%) did not have any SBDs, while 47 (40,17%) were diagnosed with CSA, and 65 (55,56%) — OSA of varying severity. The proportions of patients with moderate and severe CSA and OSA differed insignificantly and amounted to 35,9% (n=42) and 44,4% (n=52), respectively. There were following proportions of diseases related to HF: coronary artery disease (41,88%), non-ischemic cardiomyopathy (26,5%), arrhythmogenic cardiomyopathy (15,38%) and other causes (16,24%) (hypertension, myocarditis, heart defects). We found that reduced EF <40%, end-diastolic volume >210 ml, and ventricular ectopy (>300 extrasystoles/day) were associated with CSA, and body mass index >30 kg/m^2 was traditionally associated with OSA.

Conclusion. More than half of HF patients with reduced and mildly reduced EF have SBDs. Decreased LVEF and ventricular ectopic activity are associated with CSA, while increased body mass index is associated with OSA. Consideration of SBD risk factors may improve patient phenotyping for individualized therapy.

Keywords: sleep-related breathing disorders, obstructive sleep apnea, central sleep apnea, heart failure.

Relationships and Activities: none.

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Heart failure (HF) is one of the most common causes of cardiovascular morbidity and mortality and is a global health problem affecting people in different countries.

The prevalence of chronic heart failure (CHF) in Russia in the general population is 7%, including with clinical manifestations — 4,5%, increasing in older age groups [1]. Since studies usually only

Table 1
Characteristics of the included patients (M±SD; Me)

Parameter	All patients (n=117)
Age, years	61 (±12,76)
Male sex, n (%)	99 (84,6%)
BMI, kg/m^2	30,99 (±6,46)
BPs/BPd, mm Hg	123,38/75,42 (±18,95/11,23)
CAD, n (%)	49 (42%)
AF (persistent and permanent), n (%)	47 (40,2%)
AF (paroxysmal), n (%)	15 (12,8%)
COPD, n (%)	15 (13%)
ICD, n (%)	22 (19%)
NYHA class III, n (%)	61 (52%)
NYHA classIV, n (%)	5 (4,3%)
CRTD, n (%)	4 (3%)
LVEF, %	34,026 (±9,44)
LVEF <35%, n (%)	62 (53%)
PASP, mm Hg	38,83 (±16,22)
NT-proBNP, pg/ml	2259,3 (±3118,6)
Hemoglobin, g/l	144,6 (±16,2)
Mean HR, bpm	71,5 (±13,8)
ACE inhibitor/ARA, n (%)	60 (51%)
Sacubitril/Valsartan, n (%)	35 (30%)
Beta-blockers, n (%)	90 (80%)
Diuretics, n (%)	77 (66%)

Abbreviations: ARA — angiotensin II receptor antagonists, BPs/BPd — systolic/diastolic blood pressure, ACE — angiotensin-converting enzyme, CAD — coronary heart disease, ICD — implanted cardioverter-defibrillator, BMI — body mass index, LV — left ventricle, PASP — pulmonary artery systolic pressure, HR — heart rate, EF — ejection fraction, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CRTD — cardiac resynchronization therapy defibrillator, NT-proBNP — N-terminal pro-brain natriuretic peptide, NYHA — New York Heart Association.

include identified cases of HF, the true prevalence is likely to be higher [2]. Despite therapeutic progress, the mortality rate among patients with CHF remains very high, accounting for 12% per year among patients with severe CHF in the Russian Federation (RF). This necessitates early identification of risk groups prone to sudden death and frequent hospitalizations to prevent serious complications and death.

Breathing-related sleep disorders (BRSDs) have been shown to be one of the factors affecting poor prognosis in HF and are also associated with an increased risk of CHF in patients. The Sleep Heart Health Study, which included 6424 men and women, found that obstructive sleep apnea (OSA) contributed to HF onset, regardless of other known risk factors. Data on the BRSD prevalence in patients with CHF in the RF are limited, which prevents practitioners from understanding the relevance of the problem and the need to treat BRSDs.

It is noteworthy that BRSDs in CHF is much more common than in the general population (more than one third of patients with a stable HF, with an increase in occurrence in decompensated HF [3]). The most common types of BRSD are OSA, central sleep apnea (CSA) (including Cheyne-Stokes respiration (CSR)), and mixed sleep apnea, which combines first two sleep disorders.

The main links in BRSD pathogenesis, such as repeated episodes of hypoxia and reoxygenation, as well as sympathetic activation associated with frequent waking up, contribute to HF progression [2]. The bidirectional pathogenetic relationship between HF and BRSD suggests that BRSD may be a modifiable risk factor in HF and have potential therapeutic value. Attention to the diagnosis and treatment of BRSD in patients with HF can improve outcomes and lead to a clinical stabilization and an increase in the quality of life.

In the present study, we studied the occurrence of different BRSD types in a cohort of patients with HF with reduced and mildly reduced ejection fraction (EF) admitted to the hospital. The relationship between the type of BRSD, etiology and severity of HF was also analyzed.

Material and methods

The study was conducted among patients hospitalized at the National Medical Research Center for Therapy and Preventive Medicine from 2019 to 2021. Patients with NYHA class II-IV HF and mildly reduced or reduced EF were included. The study included 117 patients, predominantly men (84,6%), with a mean age of 61 years (±12,76). The study protocol was approved by the Ethics Committee of the National Medical Research Center for Therapy and Preventive Medicine (protocol № 01-06/20 dated February 4, 2020). All participants signed written informed consent. The exclusion criteria were refusal to participate in the study, class IV angina, acute coronary syndrome, stroke (within 30 days before screening), resynchronization therapy (<3 months before and after screening), implanted left ventricular (LV) assist device/inclusion in heart transplant waiting list.

All patients underwent standard clinical and paraclinical examination including history collection, physical examination, laboratory tests (complete blood count, biochemical blood profile, N-terminal pro-brain natriuretic peptide (NT-proBNP)), echocardiography, Holter monitoring, and a 6-minute walk test. Clinical information collected for analysis included age, sex, anthropometry, blood pressure,

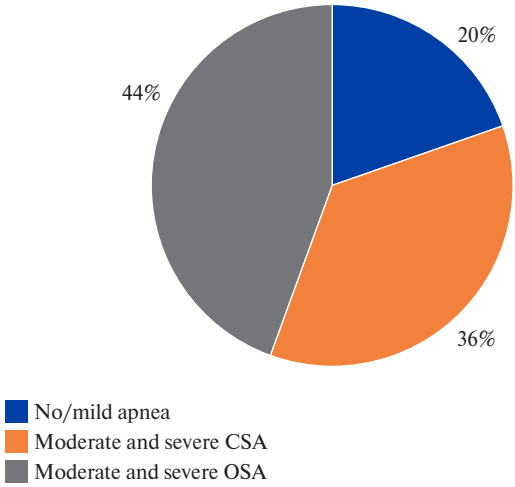

Figure 1. Distribution of groups depending on the type of BRSD and apnea severity.
Abbreviations: OSA — obstructive sleep apnea, CSA — central sleep apnea.

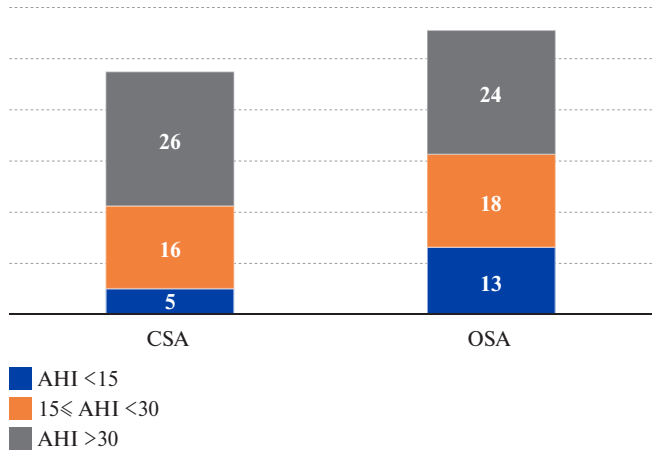

Figure 2. Severity of BRSD (N=112).
Abbreviations: AHI — apnea-hypopnea index, OSA — obstructive sleep apnea, CSA — central sleep apnea.

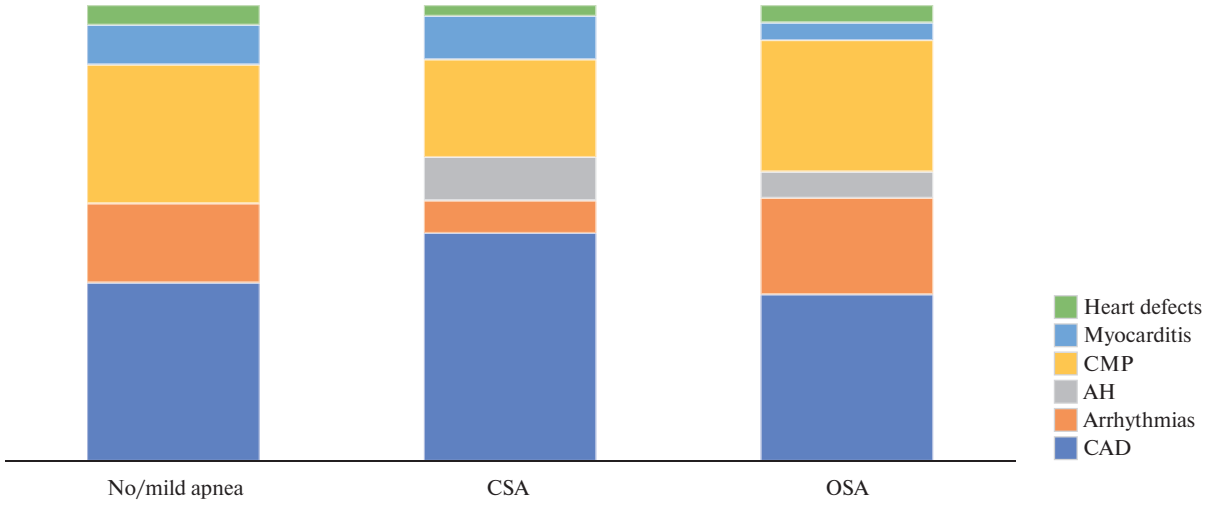

Figure 3. Etiology of HF in patients.
Abbreviations: AH — hypertension, CAD — coronary heart disease, CMP — cardiomyopathy, OSA — obstructive sleep apnea, CSA — central sleep apnea.

Epworth Sleepiness Scale, comorbidity profile, medications taken. All patients were prescribed standard therapy in accordance with national and international guidelines for HF treatment.

In order to identify BRSD, cardiorespiratory monitoring (CRM) was performed, manufactured by Meditek, Russia. During the study, the following indicators were recorded: respiratory tract airflow, chest and abdominal breathing efforts, arterial oxygen saturation, heart rate. The analysis was performed automatically using standard software and then corrected manually by a sleep medicine specialist. BRSD were determined in accordance with the criteria of the American Academy of Sleep Medicine [4]. Sleep apnea was defined as an airflow decrease by ⩾90% for at least 10 s, hypopnea — a decrease in airflow by ⩾30% for at least 10 s, accompanied by oxygen desaturation for at least 3%. CSA was diagnosed in the cessation of airflow without respiratory effort, while OSA was defined in the collapse of upper airways and sustained respiratory efforts. The criterion for CSA or OSA diagnosis in a patient was one or another type of apnea in more than 50% of all respiratory events. The severity of BRSD was defined as the number of events per hour of sleep (Apnea/Hypopnea Index (AHI)) as follows: 5-14 events per hour — mild, 15-30 events per hour — moderate, and >30 events per hour — severe.

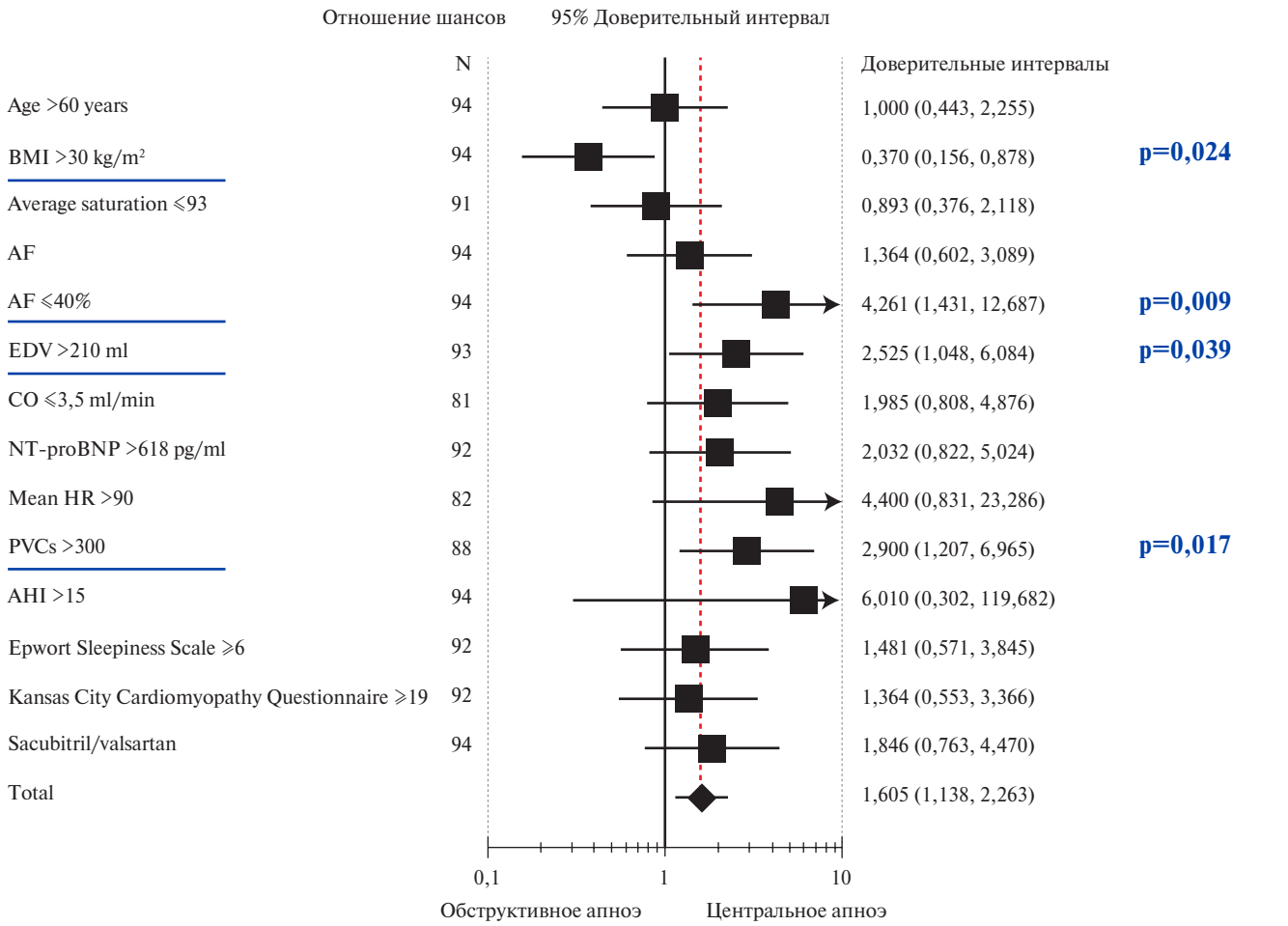

Figure 4. Clinical and laboratory parameters associated with BRSD in patients with HF.
Abbreviations: PVC — premature ventricular contraction, AHI — apnea-hypopnea index, BMI — body mass index, EDV — end-diastolic volume, KCCQ — Kansas City Cardiomyopathy Questionnaire, LV — left ventricle, CO — cardiac output, HR — heart rate, EF — ejection fraction, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, NT-proBNP — (a cut-off value of 618 pg/ml was taken based on statistical analysis — 25 quartile for CSA).

The statistical program Statistica (version 25.0) was used to analyze the obtained data. (StatSoft Inc). Results are presented as means (M) and standard deviations (SD) or median (Me, quartile (Q) 25 — quartile 75) for quantitive variables and absolute values and percentages for categorical variables. Scores were compared using the Mann-Whitney U-test. The analysis of qualitative variables and contingency tables were performed using the Pearson chi-square test. Results were considered significant at $p<0,05$.

Results

The general characteristics of included patients are presented in Table 1. Out of 117 patients, men predominated (n=99 (84,6%)). The mean age of included patients (Me, Q25-Q75) was 61 years (50-69). Patients had early-stage obesity (M±SD, 31±6,5). The mean LVEF (M±SD) was 34,026±9,44%. More than half of the patients (53%) had an LVEF <35%. The largest proportion of patients had NYHA class III HF (52,14%). There were 4,3% of patients with severe heart failure (NYHA class IV).

Atrial fibrillation was present in 53% (n=62) of patients, while permanent or persistent atrial fibrillation — in 40,2% of patients (n=47).

In 19% of patients, a cardioverter-defibrillator was implanted, and in 3% — a cardiac resynchronization therapy defibrillator was implanted. A total of 80% (n=90) of patients received baseline HF therapy, while 30% of the total number of patients (n=35) received angiotensin II receptor antagonists in combination with a neprilysin inhibitor (sacubitril/valsartan).

According to CRM, only 5 patients (4,27%) did not register any BRSD. Forty-seven (40,17%) were diagnosed with CSA, and 65 people (55,56%) — with OSA. The proportions of patients with moderate

and severe CSA and OSA differed insignificantly and amounted to 35,9% (n=42) and 44,4% (n=52) respectively (Figure 1).

Based on CRM, patients were divided into 3 groups: without BRSD (group I), predominant OSA (group II), and predominant CSA (group III) (Figure 1). In patients with CSA and OSA, moderate and severe sleep apnea predominated, as evidenced by AHI (Figure 2).

Among HF causes, the largest proportion in all three groups was coronary artery disease (CAD) (41,88% of the total), non-ischemic cardiomyopathy (26,5%), arrhythmogenic cardiomyopathy (15,38%) and other causes (16,24%), which included hypertension, myocarditis, heart defects (Figure 3). A large proportion in all three groups were patients with CAD. Arrhythmogenic cardiomyopathy (predominantly atrial fibrillation) was the only cause of HF, which showed a tendency to differ between groups, which is widely represented in the group of patients with OSA compared with patients with CSA (p=0,057).

Pearson chi-square test was used to evaluate the significance of various associations of the main severity parameters of HF with CSA and OSA (Figure 4). It was found that reduced EF <40%, end-diastolic volume (EDV) >210 ml and ventricular ectopy count (>300/day) were associated with CSA, while body mass index >30 kg/m^2 was traditionally associated with OSA.

Discussion

The data obtained in our study confirm the results of a few previous studies devoted to BRSD prevalence in patients with HF. Registered BRSD rates in patients with systolic HF remain high. This applies to both OSA and CSA with CSR. The registry by Schla HF with 6876 patients with stable HF with reduced EF [5] found that almost half of the patients in this registry had moderate and severe CSR. Two large epidemiological studies of populations with HF that assessed the prevalence of apnea were published in 1999 [6] and 2007 [7]. In the first study, among 450 patients with HF, patients with OSA and CSA-CSR with AHI ⩾10 eps/hour accounted for 38% and 33%, respectively. In a 2007 study, among 700 patients with HF (LVEF <40%) and AHI ⩾15 eps/hour, 36% had OSA and 40% — CSA-CSR. It is obvious that the use of different AHI thresholds for diagnosing BRSD determines the difference in its prevalence. It is worth noting that the study by Oldenburg O, et al. included patients with lower EF (<40%), which may explain the prevalence of CSA [7]. However, different threshold values for BRSD severity do not significantly affect the high incidence of BRSD among HF patients with reduced EF. In a very recent study by Wang T, et al., the prevalence of BRSD in patients with HF remains at the level obtained in previous studies [8]. Our data on BRSD representation among HF patients complement the existing literature and are among the first in the Russian Federation [9, 10], showing that previously recorded prevalence rates are most likely not outdated and dependent on HF therapy.

For example, in the study by Yumino D, et al. despite the widespread use of beta-blockers and spironolactone in the treatment of HF, the prevalence of BRSD remains high [11]. At the same time, the ENTRESTO-SAS study demonstrates the high efficacy of therapy with an angiotensin II receptor antagonist in combination with a neprilysin inhibitor (sacubitril/valsartan) (for 3 months) on the severity of CSA and gives hope for a possible effect of this therapy on CSA severity [12].

The proportion of patients with OSA in our study exceeds that in similar studies [6]. Inconsistencies in most cases can be explained by the difference in the studied populations (patients of different HF classes), as well as the methodology used to diagnose BRSD (polysomnography against CRM).

In our work, we have demonstrated the relationship between ventricular ectopic activity and CSA. According to the data obtained, it was more often observed in the CSA group, which may be due to the relationship between ventricular arrhythmias and significant myocardial dysfunction in HF [13].

It is interesting to analyze the hypotheses about the relationship between HF etiology and the type and severity of BRSD. In our study, the leading cause of HF in patients with both OSA and CSA was CAD. The data obtained are consistent with the previously identified wide prevalence of BRSD in patients with ischemic HF [14, 15]. A decrease in systolic function as a result of cardiomyocyte necrosis leads to edema and its subsequent participation in the development of both OSA and CSA.

In most large studies, a significant relationship between HF etiology and BRSD type has not been identified [5, 7, 16]. In a recent 2022 study according to Wang T, et al. [8] the prevalence of BRSD was relatively low in patients with arrhythmogenic HF. On the contrary, our results revealed a trend towards a significant relationship between arrhythmogenic HF and OSA. Probably, the discrepancies are due to the methodology of patient selection and the interventions performed in the hospital. In other earlier works, the prevalence of BRSD in arrhythmic HF was not reported [5, 7, 16].

Several previous studies have shown that the severity of HF is closely related to the prevalence and severity of BRSD and, in particular, CSA, and the development and severity of CSA, in turn,

reflect the severity of cardiac dysfunction. CSA is often associated with elevated brain natriuretic peptide levels, low LVEF, and the prevalence of CSA increases with increasing severity of HF [6, 17, 18].

The results of our study demonstrated that the presence of CSA is associated with worse structural and functional cardiac parameters, as assessed by echocardiography. Patients with CSA had more severe systolic (lower LVEF) LV dysfunction and enlarged chambers (EDV >210 ml). The study by Sin DD, et al. [6] also found lower LVEF in patients with CSA than those with OSA. Oldenburg O, et al. also found lower LVEF in patients with CSA, but the difference was not significant [7]. However, it should be noted that not all researchers have observed an association between CSA and the severity of LV dysfunction. Schulz R, et al. [16] found no difference in LVEF among patients with CSA compared with patients with OSA or without BRSD. Carmona-Bernali C, et al. [19] also did not confirm significant differences in echocardiographic parameters (LVEF, LV EDV). In our study, there were no significant differences in the EF value between the groups of patients with OSA and without BRSD, which once again confirms the hypothesis of more severe cardiac dysfunction in patients with CSA.

We failed to identify a significant association with NT-proBNP level and the type of BRSD, which can be explained by the small sample size and the obviously higher level of NT-proBNP in patients with atrial fibrillation [20], whose representation in the OSA group was high.

Research limitations. Limitations are related to the methodology for BRSD diagnosis. CRM was used to establish the diagnosis. Thus, the entire recording time was evaluated, not just the sleep time, which could lead to an underestimation of BRSD severity.

Conclusion

In this work, one of the first attempts in the Russian Federation was made to assess the representation of various BRSD types in patients with HF with mildly reduced and reduced EF. BRSD has been shown to remain widespread in HF patients despite advances in HF treatment. In our study, more than half of patients with HF with reduced and mildly reduced EF had severe OSA or CSA. We evaluated the relationship of OSA and CSA with clinical and paraclinical characteristics of HF. Decreased LVEF and ventricular ectopic activity are associated with CSA, while an increase in body mass index is associated with OSA. This once again emphasizes the importance of diagnosing BRSD in patients with HF, as well as further sleep studies. It is also necessary to evaluate the treatment of different types of sleep apnea, which we plan to evaluate in our next publication. Algorithms for managing patients with a combination of BRSD and HF should be developed.

Relationships and Activities: none.

References

1. Russian Society of Cardiology (RSC). 2020 Clinical practice guidelines for Chronic heart failure. Russian Journal of Cardiology. 2020;25(11):4083. (In Russ.) doi:10.15829/1560-4071-2020-4083.
2. Van Riet EES, Hoes AW, Limburg A, et al. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail. 2014;16(7):772-7. doi:10.1002/EJHF.110.
3. Suda S, Kasai T, Matsumoto H, et al. Prevalence and Clinical Correlates of Sleep-Disordered Breathing in Patients Hospitalized With Acute Decompensated Heart Failure. Can J Cardiol. 2018;34:784-90. doi:10.1016/j.cjca.2018.03.006.
4. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146:1387-94. doi:10.1378/CHEST.14-0970.
5. Arzt M, Woehrle H, Oldenburg O, et al. Prevalence and Predictors of Sleep-Disordered Breathing in Patients With Stable Chronic Heart Failure: The SchlaHF Registry. JACC Hear Fail. 2016;4:116-25. doi:10.1016/j.jchf.2015.09.014.
6. Sin DD, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160:1101-6. doi:10.1164/ajrccm.160.4.9903020.
7. Oldenburg O, Lamp B, Faber L, et al. Sleep-disordered breathing in patients with symptomatic heart failure. A contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail. 2007;9:251-7. doi:10.1016/J.EJHEART.2006.08.003.
8. Wang T, Yu FC, Wei Q, et al. Prevalence and clinical characteristics of sleep-disordered breathing in patients with heart failure of different left ventricular ejection fractions. Sleep Breath. 2022. doi:10.1007/S11325-022-02611-4.
9. Medvedeva E, Korostovtseva L, Bochkarev M, et al. The Prognostic Role of Polysomnography Parameters in Heart Failure Patients with Previous Decompensation. J Clin Med. 2022;11:3656. doi:10.3390/JCM11133656.
10. Medvedeva EA, Korostovtseva LS, Sazonova YV, et al. Obstructive sleep apnea syndrome in congestive heart failure: Cardiologist perspective. Russian Journal of Cardiology. 2018;(1):78-82. (In Russ.) doi:10.15829/1560-4071-2018-1-78-82.
11. Yumino D, Wang H, Floras JS, et al. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. J Card Fail. 2009;15:279-85. doi:10.1016/J.CARDFAIL.2008.11.015.
12. Passino C, Sciarrone P, Vergaro G, et al. Sacubitril-valsartan treatment is associated with decrease in central apneas in patients with heart failure with reduced ejection fraction. Int J Cardiol. 2021;330:112-9. doi:10.1016/J.IJCARD.2021.02.012.
13. Bitter T, Westerheide N, Prinz C, et al. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. Eur Heart J. 2011;32:61-74. doi:10.1093/EURHEARTJ/EHQ327.

14. Javaheri S. Sleep disorders in systolic heart failure: A prospective study of 100 male patients. The final report. Int J Cardiol. 2006;106:21-8. doi:10.1016/j.ijcard.2004.12.068.
15. Wang T, Yu FC, Wei Q, et al. Sleep-disordered breathing in heart failure patients with different etiologies. Clin Cardiol. 2022;45(7):778-785. doi:10.1002/CLC.23840.
16. Schulz R, Blau A, Börgel J, et al. Sleep apnoea in heart failure. Eur Respir J. 2007;29(6):1201-5. doi:10.1183/09031936.00037106.
17. Calvin AD, Somers VK, Van Der Walt C, et al. Relation of Natriuretic Peptide Concentrations to Central Sleep Apnea in Patients With Heart Failure. Chest. 2011;140:1517-23. doi:10.1378/CHEST.10-2472.
18. Ohmura T, Iwama Y, Kasai T, et al. Impact of Predischarge Nocturnal Pulse Oximetry (Sleep-Disordered Breathing) on Postdischarge Clinical Outcomes in Hospitalized Patients With Left Ventricular Systolic Dysfunction After Acute Decompensated Heart Failure. Am J Cardiol. 2014;113:697-700. doi:10.1016/J.AMJCARD.2013.10.048.
19. Carmona-Bernal C, Ruiz-García A, Villa-Gil M, et al. Quality of life in patients with congestive heart failure and central sleep apnea. Sleep Med. 2008;9:646-51. doi:10.1016/J.SLEEP.2007.11.008.
20. Zhao X, Li H, Liu C, et al. NT Pro-BNP can be used as a risk predictor of clinical atrial fibrillation with or without left atrial enlargement. Clin Cardiol. 2022;45:68-74. doi:10.1002/CLC.23760.