ДРУЖЕСТВО НА КАРДИОЛОЗИТЕ В БЪЛГАРИЯ
Българска кардиология
том XXX, 2024, № 3
ОБЗОРИ
REVIEWS
doi: 10.3897/bgcardio.30.e129108

ЗАСТОЙНА СЪРДЕЧНА НЕДОСТАТЪЧНОСТ, ОБСТРУКТИВНА СЪННА АПНЕЯ И ХРОНИЧНА ОБСТРУКТИВНА БЕЛОДРОБНА БОЛЕСТ – СИНДРОМ НА ТРОЙНО ПРИПОКРИВАНЕ

Г. Войнова[1], П. Калайджиев[1,2], Р. Илиева[1,2], Г. Николова[1,3], Д. Марков[1,2], С. Яков[1], Ц. Коцев[1], Н. Георгиева[1], А. Христова[1,2], Л. Шопов[1,2], Е. Кинова[1,2], А. Гудев[1,2]

[1]Кардиологично отделение, УМБАЛ „Царица Йоанна – ИСУЛ“– София,
[2]Катедра по спешна медицина, [3]Катедра по анестезиология и интензивно лечение МУ – София

CONGESTIVE HEART FAILURE, OBSTRUCTIVE SLEEP APNEA, AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE – TRIPLE OVERLAP SYNDROME

G. Voynova[1], P. Kalaydzhiev[1,2], R. Ilieva[1,2], G. Nikolova[1,3], D. Markov[1,2], S. Yakov[1], Ts. Kotsev[1], N. Georgieva[1], A. Hristova[1,2], L. Shopov[1,2], E. Kinova[1,2], A. Goudev[1,2]

[1]Cardiology Department, UMHAT “Tsaritsa Yoanna – ISUL” – Sofia
[2]Department of Emergency Medicine, [3]Department of Anesthesiology and Intensive Care, Medical University – Sofia,

Резюме. Индивидуалния подход в лечението на сърдечната недостатъчност (СН) и персонализираната медицина са основна тема през последните години на всички научни форуми. Съчетанието на хронична обструктивна белодробна болест (ХОББ) и сънна апнея (СА) допълнително усложняват клиничната картина при пациентите със СН. Припокриването и на трите заболявания изисква екип от специалисти и допълнителни терапевтични средства за по-добрия контрол и за подобряване на прогнозата. Голяма част от патофизиологичните механизми на трите заболявания се припокриват. Новите терапии за СН показват добри резултати, както при съсчтание с ХОББ, така и при СА. Неинвазивната вентилация при хоспитализация и след това за дома е утвърден метод при отделните групи. В комбинация на трите заболявания все още липсват категорични данни от рандомизирани проучвания.

Ключови думи: сърдечна недостатъчност; сънна апнея; хронична обструктивна белодробна болест; троен синдром на припокриването

Адрес за кореспонденция: д-р Гергана Войнова, e-mail: gerivoinova@gmail.com

Abstract. The individual approach in the treatment of heart failure (HF) and personalized medicine have been the main topic in recent years in all scientific forums. The combination of chronic obstructive pulmonary disease (COPD) and sleep apnea (SA) further complicates the clinical presentation in patients with HF. The overlap of all three diseases requires a team of specialists and additional therapeutic approach for better control and to improve the prognosis. A large number of the pathophysiological mechanisms of the three diseases also overlap. The novel therapies for HF have shown good results, both in COPD and CA subgroups. Noninvasive ventilation during hospitalization and at home is an established method in the individual groups. In a combination of the three diseases, definitive data from randomized trials are still lacking.

Key words: heart failure; sleep apnea; chronic obstructive pulmonary disease; triple overlap syndrome

Address for correspondence: Gergana Voynova, MD, e-mail: gerivoinova@gmail.com

Introduction

In 1985, David C. Flenely was the first to use the term “overlap syndrome” (OS) to characterize the combination of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA). Individually, the prevalence of COPD and OSA among patients with heart failure is high, with studies also revealing a high frequency of the combination of both conditions [1, 2, 3]. Patients with OSA and COPD experience significant oxygen desaturation during sleep, closely associated with a higher incidence of pulmonary hyper-

tension and changes in the structure and function of the right side of the heart compared to patients with either OSA or COPD alone. The medication therapy for COPD has no contraindications in patients with congestive heart failure (CHF) and sleep apnoea. The new medications for heart failure are beneficial for all three conditions. Treatment with positive airway pressure effectively benefits individual patient groups. For patients with OSA alone, continuous positive airway pressure (CPAP) therapy is recommended for home use, while for patients with COPD, bi-level positive airway pressure (BiPAP) therapy is recommended, as officially outlined in the 2020 American Thoracic Society Clinical Practice Guideline [4]. However, questions remain open regarding patients with triple overlap syndrome.

Obstructive sleep apnea and heart failure

OSA is characterized by repetitive and prolonged interruptions (apneas) or reductions (hypopneas) in airflow by over 50% for more than 10 seconds during sleep, accompanied by desaturation ≥ 4%, attributed to upper airway obstruction [5]. Up to 81% of patients with exacerbated heart failure are affected, as indicated by a Bulgarian study on the subject [6]. The pathophysiological mechanisms are well studied, with a pathological cycle rapidly leading to the progression of heart failure and higher rates of hospitalization and mortality. This is illustrated in Figure 1. Regardless of the causative factors, the consequences involve variable levels of blood oxygen and unstable carbon dioxide levels, along with frequent arousals and significant fluctuations in chest pressures. These fluctuations cause disruptions in the autonomic nervous system, leading to increased sympathetic activity and decreased parasympathetic function, as well as disturbances in hypothalamic-pituitary regulation. Variations in oxygen levels and subsequent reoxygenation lead to the formation of free oxygen radicals and oxidative stress, activating inflammatory mechanisms such as nuclear factor-kappa B (NF-kB) and tumor necrosis factor-alpha (TNF-α). Finally, significant changes in intrathoracic pressure can cause atrial stretching, changes in left ventricular wall pressure, and increased oxygen demand by the cardiac muscle [7].

Treatment with home CPAP therapy: Impact of therapy on sympathetic activity, left ventricular ejection fraction, rehospitalization, and mortality

Continuous positive airway pressure (CPAP) therapy is successfully used to treat OSA in patients with heart failure (HF), both acute [8] and chronic [9, 10, 11], with favorable benefits for the cardiovascular system. An important issue is the increased adrenergic activity in patients with heart failure with preserved systolic function (Fig. 2).

In the literature many single-center studies adding home CPAP therapy in HF patients show positive results. Benefits are noted regarding systolic function and left ventricular ejection fraction, improvement in diastolic function, and arterial pressure [12, 13, 14]. However, in one large study by McEvoy et al. involving over 1300 patients, no significant difference was found in ejection fraction and systolic arterial pressure, only a significant difference in diastolic arterial pressure was noted [15]. Differences in these studies may be attributed to variations in follow-up periods ranging from 6 months to 2 years and patient selection criteria. Some studies include only patients with reduced systolic function, while others, like ours, do not select patients based on this parameter. Bulgarian authors on the subject also demonstrated the benefit of adding

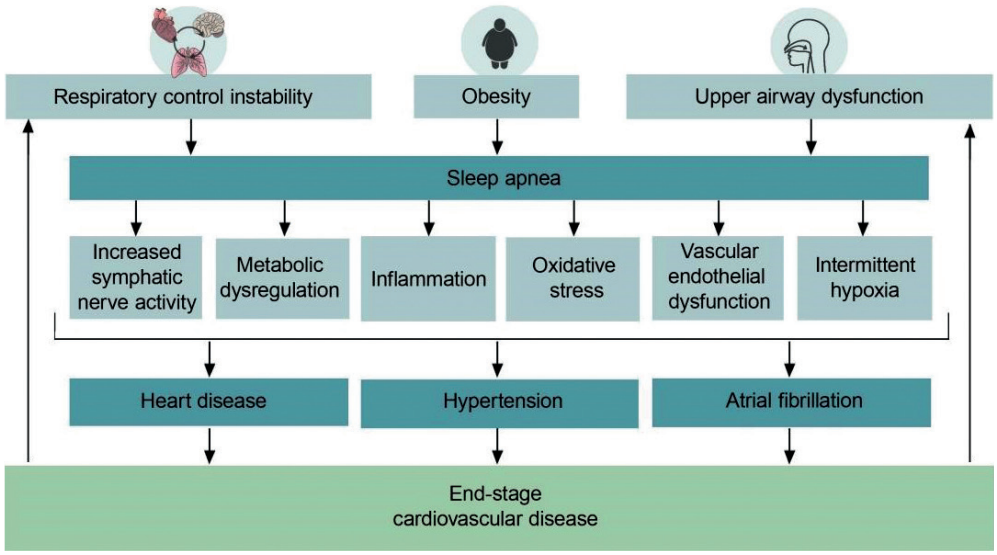

Fig. 1. Pathophysiological mechanisms of obstructive sleep apnea and heart failure

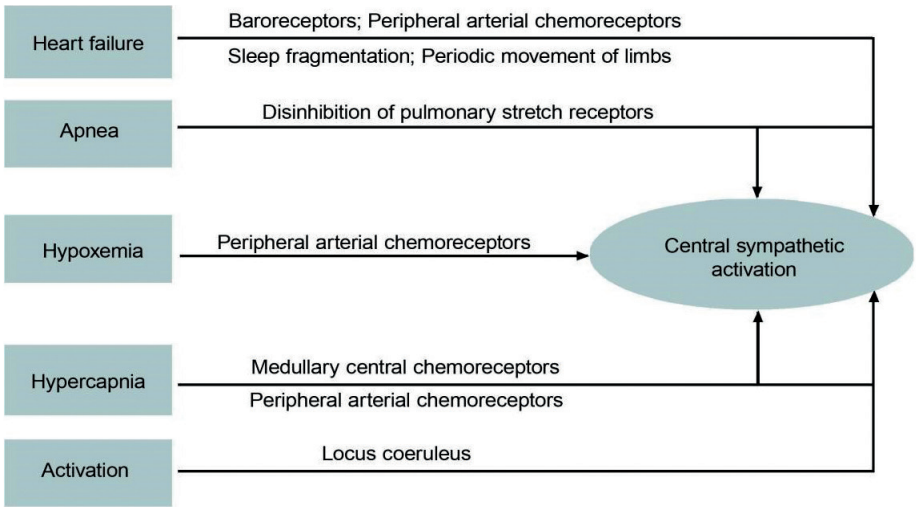

Fig. 2. Increased adrenergic activity in patients with heart failure with preserved ejection fraction

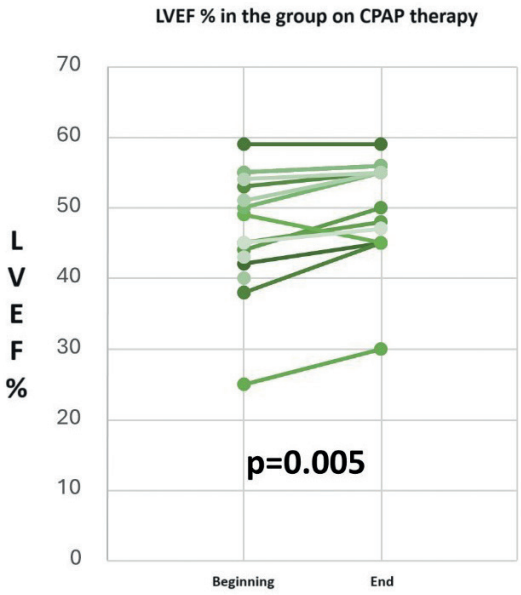

Fig. 3. Change in left ventricular ejection fraction during CPAP therapy

automatic CPAP to standard home medication therapy [16]. Individual parameters such as LVEF% (Fig. 3), body mass index (BMI), systolic and diastolic arterial pressure also influence outcomes.

Following the data published by SERVE-HF in 2015 [17], Bradley TD et al. published the results of ADVENT-HF [18] in 2023, where adaptive servo-ventilation (ASV) was used in patients with reduced systolic function. No benefits were observed in terms of hospitalization and mortality. These results practically exclude adaptive servo-ventilation as an option for non-invasive ventilation in patients with reduced systolic function. There is a lack of data from randomized trials regarding patients with preserved systolic function and sleep disorders for the use of ASV.

These differences in data necessitate large randomized trials with sham devices to confirm or refute the hypothesis of the benefit of CPAP therapy in HF patients.

The new guidelines for heart failure and the impact of new drug classes on sleep apnea

The European Society of Cardiology published its new recommendations in 2021, and just 2 years later, in 2023, an update was released [19, 20]. In 2021, the recommendations indicated sacubitril/valsartan as a Class I, Level of Evidence A medication for patients with reduced systolic function due to its ability to reduce overall mortality, cardiovascular mortality, and heart failure hospitalizations. This change was based on the PARADIGM-HF study involving 8442 patients with reduced left ventricular systolic function [21]. Subsequent analyses and studies explored the effects of sacubitril/valsartan (SV) on sleep apnea. Small prospective clinical trials reported improvements in sleep apnea episodes in patients on SV compared to those on ACE inhibitors [22]. With the 2023 update, there is a high recommendation for treating all classes of heart failure with sodium-glucose cotransporter-2 protein inhibitors (SGLT2i). Analyses regarding their impact on sleep apnea are also ongoing. Xie L et al. conducted a multicenter randomized clinical trial comparing patients with obstructive sleep apnea (OSA) and heart failure with added dapagliflozin to standard therapy and a control group, with a 3-month follow-up. Results showed benefits in sleep parameters, as well as improvement in left ventricular systolic and diastolic function, NT-proBNP levels, and left ventricular dimensions in patients receiving SGLT2i. It's worth noting that only 107 patients were included, but it provides a good direction for larger randomized trials [23]. Explaining the positive effects on breathing during sleep, improvements in hemodynamics, volume overload, and subsequently sympathetic activity in these patients can be sought. The concept of shared risk factors and pathophysiological mechanisms is supported by the fact that better treatment of heart failure also influences sleep apnea [24].

COPD AND HEART FAILURE

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are significant causes of mor-

bidity and mortality worldwide. The association between the two diseases is common and characterized by higher levels of mortality and morbidity than each disease alone. Both conditions share common risk factors such as advanced age, smoking, and systemic inflammation [25]. Obstructive syndrome is caused by chronically damaged bronchi, with interstitial and submucosal edema and fibrotic remodeling that compress and obstruct the airways. Destruction of lung tissue in alveolar walls, resulting in emphysematous bullae, leads to impaired function. Individuals with stable COPD have low-grade, chronic systemic inflammation favoring systemic atherosclerosis due to increased levels of C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), leading to the development of coronary artery disease [26]. On the other hand, acute inflammation has several cardiovascular effects: it increases neutrophil and fibrinogen levels, leading to a procoagulant state and causing disturbances in the autonomic nervous system that favor arrhythmias. COPD is often associated with pulmonary arterial hypertension, leading to right HF and eventually left HF over time.

COPD is characterized by persistent symptoms and airflow obstruction due respectively to damage to the airways and alveoli, chronic bronchitis, and emphysema, confirmed by spirometry with a post-bronchodilator test showing FEV1 (forced expiratory volume in one second)/FVC (forced vital capacity) < 70%. The severity of this airflow limitation is further classified based on post-bronchodilator FEV1 into GOLD stage 1 (FEV1 ≤ 80% predicted), GOLD stage 2 (50-80%), GOLD stage 3 (30-50%), GOLD 4 (FEV1 < 30%) [27].

Therapeutic challenges in patients with HF and COPD

Primary diagnosis is crucial. When HF is superimposed on COPD, it has a significant adverse effect on prognosis, while a secondary diagnosis of COPD in an HF patient appears to have little impact [28]. Diagnosing one from the other is a considerable clinical challenge, even when using „gold standard“ diagnostic tests, but timely identification and treatment of the underlying disease process have a significant impact on symptoms, quality of life, and, in the case of HF with reduced ejection fraction (HFrEF), long-term outcomes. Once the diagnosis of HFrEF is established, early treatment with optimal medical therapy is essential [30]. Increased attention is recommended with beta-blockers, but comorbidity with COPD should not be a reason to discontinue treatment. If there are concerns about bronchoconstriction and therapy with non-selective beta-blockers like carvedilol, switching to a cardioselective betablocker such as bisoprolol is recommended [30]. Note that most treatments for HFrEF, including loop diuretics, may also have favorable aspects in COPD in patients with both diagnoses. Subanalyses of large drug trials that inhibit sodium-glucose cotransporter proteins in the nephron (SGLT2i) also consider subgroups with COPD. In DAPA-HF, one in eight patients with HFrEF had concomitant COPD. Participants with COPD had a higher risk of hospitalization and cardiovascular mortality. The benefit of dapagliflozin was observed in both groups of patients with and without COPD [31]. Drug interactions are presented in Figure 4.

Assumptions for the use of positive airway pressure (PAP)

PAP has various effects on hemodynamics. Firstly, PAP reduces systemic venous return and right chamber preload by increasing intrathoracic pressure [32, 33, 34]. Secondly, PAP alters pulmonary vascular resistance (PVR), a major factor in right chamber overload,

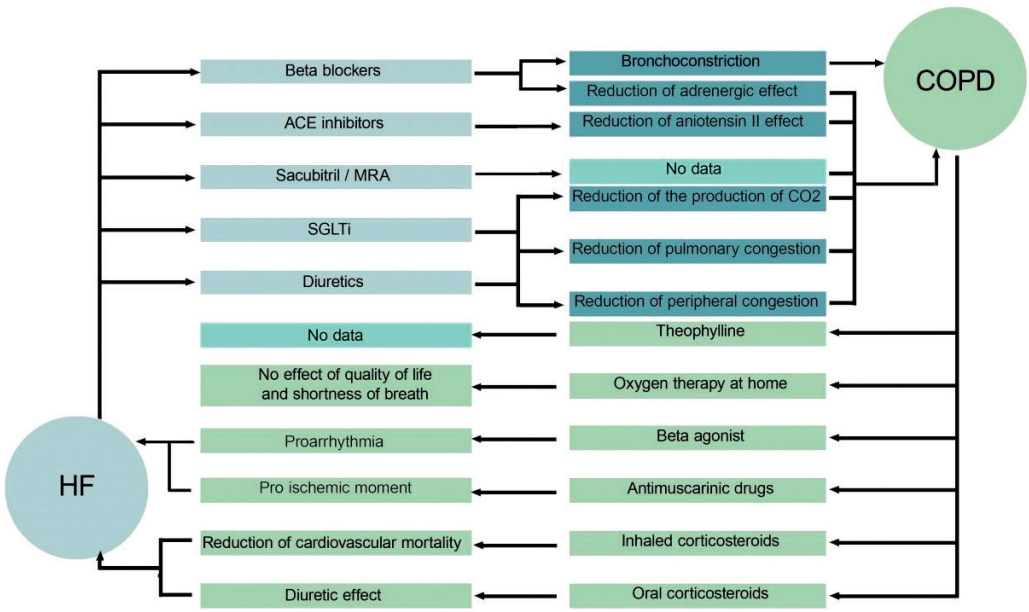

Fig. 4. Various drug interactions in HF and COPD treatment

by alternating lung volume [35]. Additionally, reducing right chamber preload and increasing right ventricular afterload leads to decreased pulmonary venous return and limitation of left chamber filling and preload. The increased intrathoracic pressure compared to atmospheric pressure creates a pressure difference between intrathoracic and extrathoracic cavities. Therefore, PAP may reduce left chamber afterload. In patients without HF, who are usually preload-dependent, reduced right chamber preload and left chamber preload in addition to increased right chamber afterload may result in a net decrease in cardiac output, while reducing left chamber afterload may result in increased cardiac output. Patients with HF are more sensitive to reduced afterload and are mainly dependent on it. PAP therapy causes a net increase in cardiac output by reducing right chamber preload, left chamber preload, and afterload, while increasing afterload may decrease cardiac output [36].

Bi-level PAP

Bi-level PAP provides two fixed levels of PAP: a higher level of pressure during inspiration (inspiratory positive airway pressure (IPAP)) and a lower level of pressure during expiration – expiratory positive airway pressure (EPAP). The level of pressure support is determined as the difference between IPAP and EPAP, and the level of IPAP plays an important role in relieving respiratory muscles, reducing respiratory work, controlling obstructive hypopnea or restricted flow, maintaining alveolar ventilation, and reducing partial pressure of carbon dioxide ($PaCO_2$). EPAP has respiratory and hemodynamic effects similar to those provided by CPAP. Additionally, BiPAP devices have several backup ventilation modes, including spontaneous breathing (S-mode), synchronized backup ventilation, and spontaneous breathing with synchronized backup ventilation (ST-mode) (Fig. 5) [37].

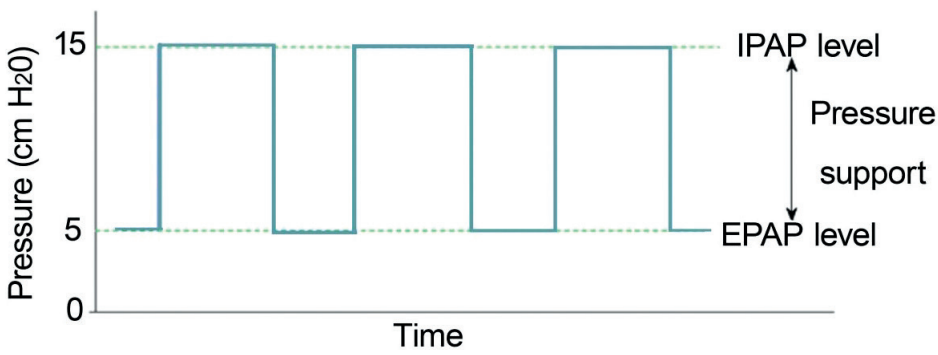

Fig. 5. Schematic presentation of Bi-level positive airway pressure

Use of PAP therapy following acute decompensation of heart failure

Studies demonstrate the efficacy of PAP therapy during hospitalization for heart failure. In such cases, BiPAP shows advantages over CPAP and better prognosis, particularly in combination with sleep apnea and COPD [38]. However, the situation regarding continuation of home therapy is different. Large randomized trials on post-discharge behavior of patients with overlapping triple syndrome are still lacking. Several retrospective studies show a clear link between cardiovascular pathology and overlapping syndrome. Adle et al. compared data from 14,300 patients with overlapping syndrome, revealing a higher incidence of heart failure and worse prognosis among these patients. Additionally, there is a high prevalence of carotid stenosis and strokes [39]. Adding BiPAP for acute decompensation with carbon retention has entered the recommendations of Intensive Care Societies as a first-line method in several guidelines, including the European Respiratory Society [40].

Mokhlesi B et al. analyzed nearly 3000 patients who received PAP without specifying the form of home therapy after hospital discharge as empirical treatment. Interestingly, every form of PAP improved the post-hospital period and reduced mortality. The main inclusion criteria were overweight and hypoventilation. The article also emphasizes the lack of randomized studies on the topic [41].

Conclusion

Based on available data on overlapping syndrome, there seems to be a significant link between heart failure, COPD, and OSA. The coexistence of all three conditions can significantly increase mortality. Compared to groups with only COPD or only OSA, patients with overlapping syndrome likely have worse diastolic function, right ventricular hypertrophy, more severe oxygen desaturation, and more frequent decompensation of heart failure. The main drug classes for both COPD and HF have rather an additive effect. Positive pressure therapy improves prognosis, both with CPAP and BiPAP, in various patient cohorts with OSA and COPD. There is insufficient definitive data on the benefit of BiPAP in treating patients with HF and overlapping syndrome. Adding such therapy after discharge would be a non-pharmacological approach with an additional effect on standard heart failure therapy.

No conflict of interest was declared

References

1. Varmaghani M, Dehghani M, Heidari E et al. Global prevalence of chronic obstructive pulmonary disease: Systematic review and meta-analysis. East. Mediterr. Heal. J. 2019;25:47-57. doi: 10.26719/emhj.18.014.

2. Zhang P, Chen B, Lou H et al. Predictors and outcomes of obstructive sleep apnea in patients with chronic obstructive pulmonary disease in China. BMC Pulm. Med. 2022;22:16. doi: 10.1186/s12890-021-01780-4.

3. Senaratna CV, Perret JL, Lodge CJ et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med. Rev. 2017;34:70-81. doi: 10.1016/j.smrv.2016.07.002.

4. Macrea M, Oczkowski S, Rochwerg B, et al. Long-Term Noninvasive Ventilation in Chronic Stable Hypercapnic Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;202(4):e74e87. doi: 10.1164/rccm.202006-2382ST.

5. D'Andrea, A, Canora A, Sperlongano S et al. Subclinical impairment of dynamic left ventricular systolic and diastolic function in patients with obstructive sleep apnea and preserved left ventricular ejection fraction. BMC Pulm Med 20, 76 (2020). https://doi.org/10.1186/s12890-020-1099-9.

6. Kalaydzhiev P, Poroyliev N, Somleva D, et al. Sleep apnea in patients with exacerbated heart failure and overweight. Sleep Med X. 2023 Feb 28;5:100065. doi: 10.1016/j.sleepx.2023.100065.

7. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardiol. 2017;69(7):841-858. doi:10.1016/j.jacc.2016.11.069

8. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation. 2000;101(4):392-7. doi: 10.1161/01.cir.101.4.392.

9. Usui K, Bradley TD, Spaak J, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. J Am Coll Cardiol. 2005;45(12):2008-11. doi: 10.1016/j.jacc.2004.12.080.

10. Hall AB, Ziadi MC, Leech JA, et al. Effects of short-term continuous positive airway pressure on myocardial sympathetic nerve function and energetics in patients with heart failure and obstructive sleep apnea: a randomized study. Circulation. 2014;130(11):892-901. doi: 10.1161/CIRCULATIONAHA.113.005893. Epub 2014 Jul 3.

11. Kaneko Y, Floras JS, Usui K, et al. Cardiovas- cular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348:1233-41.

12. Kalaydzhiev P, Somleva D, Georgieva N et al. Sleep apnea and exacerbate heart failure in overweight patients; Sleep & Breathing disorders 2023-04-20 Journal article; ERJ Open Research 2023 9: 1; doi: 10.1183/23120541.sleepandbreathing-2023.1

13. Damy T, Margarit L, Noroc A, et al. Prognostic impact of sleepdisordered breathing and its treatment with nocturnal ventilation for chronic heart failure. Eur J Heart Fail. 2012;14(9):1009-19. doi: 10.1093/eurjhf/hfs085

14. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 2000;101:392-7.

15. Johnson CB, Beanlands RS, Yoshinaga K, et al. Acute and chronic effects of continuous positive airway pressure therapy on left ventricular systolic and diastolic function in patients with obstructive sleep apnea and congestive heart failure. Can J Cardiol. 2008;24(9):697-704. doi:10.1016/s0828- 282x(08)70668-8

16. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med. 2016;375(10):919-931. doi:10.1056/NEJMoa1606599

17. Cowie MR, Woehrle H, Wegscheider K et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015 Sep 17;373(12):1095-105. doi: 10.1056/NEJMoa1506459.

18. Bradley TD, Logan AG, Lorenzi Filho G, et al. ADVENT-HF Investigators. Adaptive servoventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction (ADVENT-HF): a multicentre, multinational, parallel-group, open-label, phase 3 randomised controlled trial. Lancet Respir Med. 2024 Feb;12(2):153-166. doi: 10.1016/S2213-2600(23)00374-0

19. Theresa A McDonagh, Marco Metra, Marianna Adamo et. al. ESC Scientific Document Group, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, Eur Heart J, 2021,42(36),3599-3726, https://doi.org/10.1093/eurheartj/ehab368

20. Theresa A McDonagh, Marco Metra, Marianna Adamo et al. ESC Scientific Document Group, 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, Eur Heart J, 2023,44(37),3627-3639, https://doi.org/10.1093/eurheartj/ehad195

21. McMurray JJ, Packer M, Desai AS, et al. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 371(11):993-1004. doi: 10.1056/NEJMoa1409077

22. 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;330:112-119. doi: 10.1016/j.ijcard.2021.02.012.

23. Xie L, Li S, Yu X, et al. DAHOS Study: Efficacy of dapagliflozin in treating heart failure with reduced ejection fraction and obstructive sleep apnea syndrome – A 3-month, multicenter, randomized controlled clinical trial. Eur J Clin Pharmacol. 2024 Feb 22. doi: 10.1007/s00228024-03643-3.

24. Tanriover C, Ucku D, Akyol M et al. Potential Use of SGLT-2 Inhibitors in Obstructive Sleep Apnea: A new treatment on the horizon. Sleep Breath 2023, 27, 77-89. https://doi.org/10.1007/s11325-022-02606-1

25. Horodinschi RN, Bratu OG, Dediu GN, Pantea Stoian A, Motofei I, Diaconu CC. Heart failure and chronic obstructive pulmonary disease: a review. Acta Cardiol. 2020;75(2):97104. doi: 10.1080/00015385.2018.1559485.

26. de Miguel Díez J, Chancafe Morgan J, Jiménez García R. The association between COPD and heart failure risk: a review. Int J Chron Obstruct Pulmon Dis. 2013;8:305-12. doi: 10.2147/COPD.S31236.

27. Agusti A, Celli BR, Chen R, et al. Pocket guide to COPD diagnosis, mangement, and prevention. 2019. Available at www.goldcopd.org

28. Ehteshami-Afshar S, Mooney L, Dewan P, et al. Clinical characteristics and outcomes of patients with heart failure with reduced

ejection fraction and chronic obstructive pulmonary disease: insights from PARADIGM-HF. J Am Heart Assoc. 2021;10(4):e019238. doi: 10.1161/JAHA.120.019238

29. Canepa M, Straburzynska-Migaj E, Drozdz J, et al. ESC-HFA Heart Failure Long-Term Registry Investigators. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. Eur J Heart Fail. 2018;20(1):100-110. doi: 10.1002/ejhf.964

30. Cotton S, Devereux G, Abbas H, et al. Use of the oral beta blocker bisoprolol to reduce the rate of exacerbation in people with chronic obstructive pulmonary disease (COPD): a randomised controlled trial (BICS). Trials. 2022;23(1):307. doi: 10.1186/s13063-022-06226-8

31. Dewan P, Docherty KF, Bengtsson O, et al. Effects of dapagliflozin in heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: an analysis of DAPAHF. Eur J Heart Fail. 2021;23(4):632-643. doi: 10.1002/ejhf.2083. Epub 2021 Jan 18.

32. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol. 1957;189(3):609-15. doi: 10.1152/ajplegacy.1957.189.3.609.

33. Pinsky MR. Determinants of pulmonary arterial flow variation during respiration. J Appl Physiol Respir Environ Exerc Physiol. 1984;56(5):1237-45. doi: 10.1152/jappl.1984.56.5.1237.

34. Pinsky MR. Instantaneous venous return curves in an intact canine preparation. J Appl Physiol Respir Environ Exerc Physiol. 1984;56(3):765-71. doi:10.1152/jappl.1984.56.3.765.

35. Whittenberger JL, Mcgregor M, Berglund E, Borst HG. Influence of state of inflation of the lung on pulmonary vascular resistance. J Appl Physiol 1960; 15: 878-882.

36. Kato T, Suda S, Kasai T. Positive airway pressure therapy for heart failure. World J Cardiol. 2014;6(11):1175-91. doi: 10.4330/wjc.v6.i11.1175.

37. Pancer JP, Swick TJ, Wise MS. American Academy of Sleep Medicine. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep. 2006 Mar;29(3):375-80. doi: 10.1093/sleep/29.3.375.

38. Konikkara J, Tavella R, Willes L et al. Early recognition of obstructive sleep apnea in patients hospitalized with COPD exacerbation is associated with reduced readmission. Hosp Pract. 2016;44(1):41-47 https://doi.org/10.1080/21548331.2016.1134268.

39. Adler D, Bailly S, Benmerad M, et al. Clinical presentation and comorbidities of obstructive sleep apnea-COPD overlap syndrome. PLoS One. 2020 Jul 9;15(7):e0235331. doi: 10.1371/journal.pone.0235331.

40. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426. doi: 10.1183/13993003.02426-2016.

41. Mokhlesi B, Masa JF, Afshar M, et al. The Effect of Hospital Discharge with Empiric Noninvasive Ventilation on Mortality in Hospitalized Patients with Obesity Hypoventilation Syndrome. An Individual Patient Data Meta-Analysis. Ann Am Thorac Soc. 2020;17(5):627-637. doi: 10.1513/AnnalsATS.201912-887OC.