İstanbul Med J 2019; 20(3): 176-87
DOI: 10.4274/imj.galenos.2018.79837

Assessment of the Efficacy of Interventions for the Treatment of Sleep Respiratory Disorder in Chronic Heart Failure Patients: A Systematic Review

Kronik Kalp Yetersizliği Hastalarında Uykuda Solunum Bozukluğunun Tedavisi İçin Kullanılan Girişimlerin Etkinliğinin Değerlendirilmesi: Sistematik Derleme

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ABSTRACT

One of the most important problems of heart failure (HF) patients is sleep disturbance. In HF patients with obstructive and central sleep apnea, hypoxia, hypercapnia and over-excitation of the sympathetic system are observed. As a result, negative intrathoracic pressure and left ventricular afterload increase. Treatment of sleep respiratory disorders in chronic HF patients is important for the prognosis of the disease. Therefore, in this systematic review, we aimed to evaluate the efficacy of interventions used for the treatment of sleep respiratory disorder in chronic HF patients.

Cochrane Library, Scopus, Springer Link, Science Direct, Clinical Key, PubMed, Turkey Citation Index and EBSCO databases were searched for studies between June 2017-August 2018. When all studies were examined, out of 2.691.006 studies published between 2007-2017, 16 randomized controlled trials that met inclusion criteria were included in the study. In these studies, treatment interventions for treatment groups with sleep respiratory disorder included continuous positive airway pressure (CPAP), bi-level positive airway pressure, adaptive servo-ventilation (ASV), atrial overdrive pacing, home oxygen therapy, slow breathing exercise device and structured physical exercise. When the study results are examined, CPAP treatment improved daytime sleepiness and left ventricular ejection fraction (LVEF) but did not provide significant improvement on quality of life, and that ASV treatment reduced apnea-hypopnea index, provided improvement in LVEF and cardiac function, and reduced ventricular ejection fraction. However, further research is needed to fully demonstrate the efficacy of interventions for the treatment of sleep respiratory disorder in chronic HF patients.

Keywords: Sleep apnea, obstructive sleep apnea, central sleep apnea, heart failure

ÖZ

Kalp yetersizliği hastalarının en önemli sorunlarından birisi uyku bozukluğudur. Obstrüktif ve santral uyku apnesi şikayeti olan kalp yetersizliği hastalarında hipoksi, hiperkapni ve sempatik sistemin aşırı uyarılması söz konusudur. Bunun sonucunda negatif intratorasik basınç ve sol ventrikül ard yükü artar. Kronik kalp yetersizliği hastalarında uyku bozukluğunun tedavisi hastalığın prognozu için önemlidir. Bu nedenle bu sistematik derleme çalışmasında, kronik kalp yetersizliği hastalarında uykuda solunum bozukluğunun tedavisi için kullanılan girişimlerin etkinliğinin değerlendirilmesi amaçlandı.

Cochrane Library, Scopus, Springer Link, Science Direct, Clinical Key, PubMed, Türkiye Atıf Dizini ve EBSCO'da yer alan çalışmalar Haziran 2017-Ağustos 2018 tarihleri arasında incelendi. Tüm çalışmalar incelendiğinde, toplam taranan 2.691.006 veriden 2007-2017 yılları arasında yayımlanmış, kronik kalp yetersizliği ve uykuda solunum bozukluğu olan (sol ventrikül ejeksiyon fraksiyon ≤%45, apne-hipopne indeksi >10/saat), en az 3 ay takip edilmiş hastaların dahil edildiği 16 randomize kontrollü çalışma araştırmaya dahil edildi.

Çalışmalarda uykuda solunum bozukluğu olan girişim grubu için tedavi girişimleri olarak devamlı pozitif havayolu basıncı, iki seviyeli pozitif havayolu basıncı, adaptif servo-ventilasyon, overdrive pacemaker, evde oksijen tedavisi, yavaş solunum egzersizi cihazı ve yapılandırılmış fiziksel egzersiz girişimi uygulandığı tespit edildi. Çalışma sonuçları incelendiğinde, devamlı pozitif havayolu basıncı tedavisinin gündüz uykuluk durumunu ve sol ventrikül ejeksiyon fraksiyonu iyileştirdiği, ancak yaşam kalitesi üzerine anlamlı iyileşme sağlamadığı, adaptif servo-ventilasyon tedavisinin apne-hipopne indeksini azalttığı, sol ventrikül ejeksiyon fraksiyonda ve kardiyak fonksiyonlarda iyileşme sağladığı, ventrikül atım sayısını azalttığı tespit edilmiştir. Ancak kronik kalp yetersizliği hastalarında uykuda solunum bozukluğunun tedavisi için uygulanan girişimlerin etkisinin tam olarak ortaya konulabilmesi için daha fazla araştırmaya ihtiyaç olduğu ortaya çıkmaktadır.

Anahtar Kelimeler: Uyku apnesi, obstrüktif uyku apnesi, santral uyku apnesi, kalp yetersizliği

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Cite this article as/Atıf: Uysal H, Oruçoğlu HB. Assessment of the Efficacy of Interventions for the Treatment of Sleep Respiratory Disorder in Chronic Heart Failure Patients: A Systematic Review. İstanbul Med J 2019; 20(3): 176-87.

Received/Geliş Tarihi: 28.08.2018
Accepted/Kabul Tarihi: 12.11.2018

Introduction

Heart failure (HF) is defined as a structural or functional cardiac disorder that causes the heart not to provide enough oxygen to meet the metabolic needs of the tissues despite the normal filling pressures. Approximately 1-2% of the adult population in developed countries has HF. The prevalence of HF is reported to be 10% or more in individuals aged 70 years and older (1).

Sleep disorder is one of the most important problems of HF patients. Hypoxia, hypercapnia and over-excitation of the sympathetic system are present in HF patients with obstructive and central sleep apnea (CSA). As a result, negative intrathoracic pressure and left ventricular afterload increase. Determination of the degree of sleep disturbance by polysomnography (PSG) and administration of oxygen therapy, continuous positive airway pressure (CPAP), bi-level (BI) PAP for the treatment of obstructive sleep apnea (OSA) and adaptive servo-ventilation methods (ASV) for the treatment of nocturnal hypoxemia during the night are recommended in patients with HF (1).

The degree of SRD is determined by PSG and OSA and/or CSA classification is done. The hourly apnea-hypopnea index (AHI) between 5-15 is classified as mild OSA, between 15-30 as moderate OSA, and >30 as severe OSA. In the literature, it has been shown that patients with OSA with an AHI value of >20 have increased risk of morbidity and mortality if not treated (2). The diagnostic criteria of primary CSA syndrome are as follows: a) At least one of the following from frequent arousals and awakenings during sleep, excessive daytime sleepiness and awakening short of breath; b) PSG shows ≥5 central apneas per hour of sleep, representing >50% of total respiratory events in the AHI; and c) the disorder is not better explained by another current sleep disorder, a medical or neurologic disorder, medication use, or a substance use disorder. The diagnostic criteria of Cheyne-Stokes respiration (CSR) include ≥5 central apneas-hypopneas during sleep and monitoring crescendo-decrescendo cycle over a period of at least 10 minutes (3).

The gold standard treatment of OSA is PAP. The aim of the treatment of SRD is to ensure that the upper airway remains open during sleep and to regulate quality of breathing and sleep. However, the patient benefits from this treatment during the time she/he uses the device. For this reason, it is recommended that the patient should use the device over 70% and more than 4 hours during the night (2,3).

As reviewed in the literature, the treatment of sleep disturbance in chronic (C) HF patients is important for the prognosis of the disease. Therefore, the aim of this systematic review was to evaluate the efficacy of interventions for the treatment of SRD in CHF patients.

Methods

This systematic review was planned and carried out as a descriptive study to evaluate the efficacy of interventions used for the treatment of SRD in CHF patients. The following steps were used in systematic review. The framework of the study was based on (population, intervention, comparator, outcome and study design) (4). These steps are described in detail in Table 1.

Inclusion criteria were RCTs published between 2007-2017, including patients with CHF and RSD (OSA, CSA) (left ventricular ejection fraction (LVEF) ≤45%, AHI >10/hour) followed for at least 3 months (Table 1).

All of the RCTs included in the study were evaluated by two researchers using an appropriate quality assessment checklist (5). The results of the evaluation were discussed and the publications prepared according to the RCT criteria were included in the study.

In data extraxtion analysis, one of the researchers first examined the researches included and collected data on the findings and characteristics of the research. The second researcher then checked the accuracy of this data. Data extraction steps were carried out by the authors. The data extraction steps and the findings are explained in detail in Table 2.

In this study, the answer to the question "Which interventions are effective in the treatment of SRD in patients with CHF?" was investigated.

No funding was received during the research. Researchers used their own means throughout the study. The researchers took part in each phase of the study according to the timetable. The timetable of the study was carried out as follows:

1. Preparation of the research protocol: 07/06/2017

2. Scanning period: June-September 2017

3. Analysis: October 2017-March 2018

4. Article writing: April-August 2018

In the study, keywords were selected in accordance with the research topic (Figure 1) and electronic scanning was performed. In the selection of keywords, attention was paid to the scanning of the full text of RCTs, in which the effectiveness of interventions used in the treatment of CHF patients diagnosed with SRD.

Cochrane Library, Scopus, Springer Link, Science Direct, Clinical Key, PubMed, EBSCO and Turkey Citation Index electronic databases were used for scanning. Medline, EMBASE, Ovid and CINAHL databases were not used because they could not be accessed. When all the studies recorded according to inclusion criteria were examined, 16 publications from total scanned 2.691.006 data were included in our study (Figure 1) (6).

Table 1. Inclusion and exclusion criteria

Inclusion criteria
- Published between 2007-2017
- Followed for at least 3 months
- Randomized controlled trials
- Diagnosed with chronic heart failure
- LVEF ≤45%
- Diagnosed with CSA and/or OSA
- AHI >10/hour
- Diagnosis of sleep respiratory disorder by polysomnography
- Research in English and Turkish
- Full texts
- Studies on specified keywords
Exclusion criteria
- Studies not published in Turkish and English
- Unpublished thesis studies
- Reviews
- Abstracts
- Conference summaries, protocols, case reports, *in vitro* studies
- Ongoing study findings

LVEF: left ventricular ejection fraction, CSA: central sleep apnea, OSA: obstructive sleep apnea, AHI: apnea-hypopnea index

<table>
<tr><td colspan="2">Number of articles scanned by keywords: 2.691.006</td></tr>
<tr><td>Keywords
English: Heart failure, chronic heart failure, polisomnography, sleep disorders, sleep apnea, sleep quality, obstructive sleep apnea, central aleep apnea.
Turkish: Kalp Yetersizliği, kronik kalp yetersizliği, polisomnografi, uyku uyku bozukluğu, uyku apnesi, uyku kalitesi, obstruktif uyku apnesi, santral uyku apnesi.</td><td>Number of articles scanned by words in databases
CLINICAL KEY: 95.666
COCHRANE LIBRARY: 573
EBSCO: 1098
SCIENCE DIRECT: 1.071.673
SCOPUS: 530.056
SPRINGER LINK: 705.691
PUBMED: 286.854
TURKIYE CITATION INDEX: 803</td></tr>
<tr><td rowspan="2">Therapy initiatives for sleep-disordered breathing included in the study: CPAP, BIPAP, Adaptive Servo Ventilation (ASV), atrial overdrive pacemaker, oxygen therapy at home (HOT), slow breathing exercise device (RESPERATE) and physical exercise therapy: 16</td><td>Exclusion criteria
Unpublished and not followed for at least 3 months between 2007 and 2017: 13.454
Other than randomized controlled study: 18.802.898
Patients without a diagnosis of chronic heart failure: 161.479
Patients without AHI> 10 / s: 26.908
Studies other than Turkish and English: 20.212
Unpublished thesis studies: 47.089
Reviewes: 316.200
Conference etc. abstracts, protocols, case reports, in-vitro studies: 282.565
Ongoing studies: 20.181</td></tr>
<tr><td>A study that was evaluated for 4 weeks was removed. (Staniforth et al. 1998)</td></tr>
<tr><td colspan="2">Studies in accordance with the inclusion criteria: 16</td></tr>
</table>

Figure 1. Flow Chart

Staniforth et al. (6) European Heart Journal 1998; 19: 922-8.

In the studies, CPAP, BIPAP, ASV, overdrive pacemaker, home oxygen therapy (HOT), slow breathing exercise device (RESPERATE) and structured physical exercise interventions were applied as treatment interventions for the group with SRD (Tables 2, 3). In addition, in the studies evaluated, it was found that symptom evaluation scales such as Epworth Sleepiness Scale (ESS), Pittsburg Sleep Quality Index (PSQI), Fatigue Severity Scale, and disease-specific quality of life scales such as Minnesota Living with HF Questionnaire (MLHFQ) and Chronic HF Questionnaire (Q), and SF-36 general quality of life scale, mental status and motor function assessment tools were used (Table 2).

Results

The randomized controlled trials included in the study were mostly conducted with male CHF patients who were 60 years of age and over and who had a diagnosis of OSA and CSA (AHI >10/hr., LVEF ≤45%) (Table 2).

In a study evaluating the effect of CPAP therapy on cardiac functions in CHF patients with OSA, it was reported that CPAP treatment improved LVEF compared to those treated with fake-CPAP (placebo) treatment. However, no significant difference was found in the cardiological variables and quality of life of patients in both the intervention and placebo groups. The authors stated that the improvement in LVEF would not necessarily improve cardiological symptoms (7). However, Khayat et al. (8) stated that, contrary to this study, BIPAP treatment was more effective on improvement in LVEF than CPAP. Bradley et al. (9) reported that CPAP treatment, in addition to medical treatment, improved the CSA and nocturnal oxygenation compared to medical treatment only, and that the CPAP group had more improvement in their functional capacity (six minutes walking distance-6MWD) (p=0.016) (Table 2).

In the study of O'Connor et al. (10), in which the effectiveness of ASV therapy was evaluated, it was found that ASV treatment added to the optimal medical therapy in patients with moderate-to-severe sleep apnea did not improve cardiovascular (CV) outcomes over 6 months, and that functional capacity in both control and intervention group did not differ. However, Arzt et al. (11) reported that ASV treatment added to medical therapy was an effective treatment for CSA and OSA, and that it improved cardiac function compared to medical therapy only in patients with sleep apnea. Similarly, in another study conducted in 2012, it was found that ASV significantly reduced central, periodical various respiratory disorders (12). In another study, it was found that ASV treatment at home caused a mild improvement in sleep fragmentation and improved sleep efficiency in CHF patients with CSA or OSA (13). However, Cowie et al. (14) stated that ASV treatment in addition to medical therapy did not improve outcomes, increased risk of CV death, and had no beneficial effect on quality of life and HF symptoms (Table 2).

Kasai et al. (15) found a significant increase in functional capacity (6MWD) in the ASV-mode group compared to the CPAP-mode group. Priefert et al. (16) found that ASV therapy for patients with EF <40% lower ejection fraction (HFrEF) and SRD provided significant improvement in AHI at 12 weeks compared to the group treated with medical therapy only. In the same study, it was found that ASV treatment had an effect on nocturnal ventricular and supraventricular arrhythmias and the number of ventricular beats was less in the ASV treated group compared to the control group (Table 2).

Kawecha-Jaszcz et al. (17) found that the use of slow breathing device at home in patients with stable chronic systolic HF tended to reduce sleep disturbance and predominantly narrow central apnea, improve functional capacity and systolic left ventricular function. In one study, the authors stated that CPAP treatment titrated automatically at night in patients with OSA and CHF improved the daytime sleepiness, but did not improve other quality of life measures or severe CHF markers (Table 2) (18).

In another study, daytime sleepiness was found to be better in the CPAP group than the BIPAP group. In the same study, quality of life, functional capacity and blood pressure (BP) changes were found to be better in the BIPAP group than in CPAP (8). Similarly, Egea et al. (7) reported that CPAP therapy did not show a significant improvement in cardiological changes and quality of life except daytime sleepiness (Table 2).

Nakao et al. (19) reported that nocturnal oxygen therapy for 12 weeks at home improved SRD and had a positive effect on functional capacity in chronic HF patients with CSA (Table 2).

Suna et al. (20) found that exercise training administered to the intervention group significantly improved poor sleep quality in patients with HF followed by a disease management program for 12 weeks (Table 2).

As a result of the studies, only one RCT evaluated the effect of atrial overdrive pacemaker treatment on SRD in systolic HF patients with OSA and the intervention was found to reduce AHI safely (Table 2) (21).

Table 2. Characteristics of the studies included in the systematic review

Source and sleep respiratory disorder type	Method-randomization	Gender-sampling	Duration	Other evaluation tools	Age	Findings	Results
Egea et al. (7) OSA	- RCT, multi-center, - Plasebo (fake-CPAP) (n=32) - CPAP (n=28)	- Mostly male - A total of 60 patients - OSA (AHI >10/h) - CHF (LVEF <45%)	3 months	- ESS - SF-36 - NYHA classification - Borg dyspnea scale - 6MWT	CPAP: 64 Fake-CPAP: 63 (mean)	- A 30% improvement in LVEF compared to baseline in the CPAP group, less than 30% improvement in placebo. - In contrast to the placebo group, significant improvement in AHI ($p<0.001$) and SaO_2 ($p=0.002$) in the CPAP group	- CPAP treatment has been shown to be beneficial in CHF patients with SRD. - No difference was found between the two groups except for ESS index in the cardiac variables and quality of life tests
Khayat et al. (8) OSA	- RCT pilot study, - BIPAP (n=13), CPAP (n=11)	- Female and male mixed group - Total 24 patients - Stable LV systolic dysfunction - NYHA class II-III, - CHF (LVEF LV 45%) - Not hospitalized in the last 3 months and medication was unchanged. - New OSA	3 months	- ESS - 6MWT - MLHFQ - Weekly device memory check for treatment compliance assessment	BIPAP=51.3 CPAP=54.8 (mean)	- AHI was not changed in both groups (p=0.24). - Compliance with the treatment device is slightly higher in the BIPAP group. In the CPAP group, the ESS score was higher (p=0.38). Heart rate changes in CPAP group more effective (p=0.42). - MLHF, 6MWD, SBP and DBP improved in the BIPAP group	BIPAP treatment was found to be more effective than CPAP in the treatment of LVEF in patients with LV dysfunction and OSA. Further studies have been proposed to evaluate the mechanisms behind this effect
Smith et al. (18) OSA	RCT, double blind, placebo control, diagonal design. - Automatically adjusted CPAP (at least 6 hours per night) - CPAP (n=12) - Fake-CPAP (n=11) (placebo) (1:1)	- Mainly male - Total 23 patients - NYHA class II-IV - Stable, symptomatic CHF (LVEF <45%) - OSA (AHI ≥15/h)	6 weeks	- Clinical evaluation - TTE - CPET - 6MWT - Neurohormonal markers - OSLER test - ESS - Quality of Life Assessment	61 (mean)	- In case of daily sleepiness with CPAP, there was no objective improvement (OSES p=0.63), there was improvement in subjective assessment (ESS) (p=0.04). No significant difference was found between CPAP treatment and fake-CPAP in the evaluation of -LVEF, exercise capacity and quality of life ($p>0.05$)	- CPAP treatment improved subjective daily sleepiness, but did not improve other quality of life measures or CHF markers. The symptomatic benefit in this patient group is the alleviation of OSA rather than the improvement in cardiac function
Randerath et al. (12) OSA CSA	- RCT, parallel group, double blind, single center clinical study. - CPAP (n=34) or ASV (n=36) + optimal medical treatment - Optimal medical treatment	- Mainly male - CHF (LVEF ≥20%) - NYHA class II and III-AHI ≥15/hr - Central rate 80% - Obstructive rate 20%-50%	1 year	- ECO at the baseline, 3rd, 12th months - CPET - proBNP - MLHFQ - After 6 and 9 months, quality of life data was received by telephone.	CPAP=67.4 ASV=65.3 (mean)	- Both methods have significantly improved total AHI. - Approximately 50% of patients with CPAP have decreased central respiratory disability, and with ASV treatment, there is a better reduction in AHI than CPAP. - Compared to CPAP treatment at 12th month follow-up, there was an improvement in periodic and different respiratory disorders and proBNP levels with ASV treatment	It has been proven that ASV (compared to CPAP in patients with mild to moderate HF during a 12-month period) is effective in suppressing central, periodic, different respiratory disorders more effectively and obstructive events in an equally effective manner. Patients showed improvement in BNP levels

Table 2 contiuned

Kasai et al. (15) CSA	- RCT, prospective, single-center, single-blind study. - CPAP mode or ASV mode	- Gender not specified. - Total 74 patients - NYHA ≥II - CHF (LVEF <50%) - AHI ≥15/h	3 months	- PSG - BMI - ABG - CV variables - 6MWT - ECHO - LVEF - SF-36 quality of life assessment	CPAP: 65.8 ASV=64.3 (mean)	- Significant reduction in plasma proBNP level in the ASV mode group. The decrease in UNE and increase in 6MWD are significantly higher in the ASV group. Significant reduction in LV end-systolic diameters in the LV group	ASV treatment has been shown to improve underlying dysfunction in non-CPAP-induced CSA Japanese male HF patients. Effective suppression of CSA has been shown to be useful in improving cardiac function. It is recommended to investigate the long-term effects of CSA treatment with ASV
Bradley et al. (9) CSA	RCT, open-label, multi-center (11-center) operation. - CPAP + optimal medical treatment (n=128) - Optimal medical treatment (n=130) at least 6 hours of CPAP use at home during the night	- Mainly male Total of 258 patients - NYHA class II-IV - At least one medical treatment - Stable CHF (LVEF <40%) - CSA	3 months	- Radionuclide angiography resting LVEF - 6MWT - Life Quality Survey Atrial natriuretic peptide and plasma norepinephrine levels were measured at -3 centers	18-79	In the CPAP group, 6MWD increased more at three-month follow-up (p=0.016). There is no significant difference between the two groups in the Chronic Heart Failure Questionnaire A significant increase in LVEF in the CPAP group (p=0.02). - Plasma norepinephrine level decreased significantly (p=0.009)	- CPAP improved central sleep apnea, nocturnal oxygenation, left ventricular function, sympathetic nerve activity, and submaximal exercise performance. - The CANPAP study did not show a beneficial effect of CPAP on morbidity or mortality in patients with central sleep apnea and heart failure. There was no significant difference in mortality rates between the two groups
Hetzenecker et al. (13) OSA CSA	- RCT, multi-center, parallel group - ASV (BIPAP-ASV) + medical treatment (n=32) - Optimal medical treatment (n=31) (1:1)	- Mainly male - Total 63 patients - Severe sleep apnea - CHF	12 weeks	- Actigraphy device (wrist) - BMI - Resting heart rate - NYHA - proBNP	- ASV=64 - Control=65 (mean)	- Significant greater reduction in sleep fragmentation index compared to the control group and significantly improved sleep efficiency and proBNP decrease in the ASV group (p=0.062)	The study showed that ASV treatment at home could reduce sleep disruption and improve sleep quality in CHF patients with severe CSA or OSA
O'Connor et al. (10) OSA	- RCT, multi-center clinical study - ASV - General care control group (1:1)	- Mostly male - Reduced or preserved EF - AHI ≥15/h - Hospitalized HF patients	6 months	- BMI - NYHA - LVEF - proBNP - ESS - SaO2 - 6MWT	62 (mean)	- There was a significant decrease in baseline in both groups in AHI (p=0.0001). - 6MWD was similar in both groups (p>0.05)	It was found that ASV treatment, which was added to the optimal medical treatment compared to those receiving only optimal medical treatment, did not improve CV outcomes over a 6-month period.

Table 2 contiuned

Cowie et al. (14) CSA	- RCT, Multi-center, parallel group, event-based study. - ASV + medical treatment (n=666) - Medical treatment (n=659)	- Mainly male - Symptomatic CHF (LVEF CHF 45%) - Hospitalized at least 1 time within 2 years, - NYHA II, III or IV - CSA (AHI ≥15/h, >50% of apnea or hypopnea event and central AHI ≥10/hr)	-Evaluation on first 2 weeks, 3 and 12 months - On the 6th and 12th months, phone contact. -Total 31 months follow-up	- NYHA classification - 6MWT - EQ-5D - MLHFQ - ESS	69 (mean)	- SRD was better controlled during ASV treatment. - AHI 6,6/h, ODD 8,6/h - Mortality and CV mortality for all causes were higher (29.3%, 24.0%) than in the control group, respectively (34.8%, 29.9%) in the ASV group ($p<0.05$)	- In addition to guideline-based medical therapy, the treatment of ASV was found not to improve results. - It was found that ASV increased the risk of CV death (34%) and had no beneficial effect on quality of life or HF symptoms. These results were seen despite effective control of central sleep apnea during treatment of ASV
Arzt et al. (11) OSA CSA	- RCT - ASV (BIPAP) + optimal medical treatment (n=37) - Optimal medical treatment (n=35) (1:1)	- Mostly male - Total 72 - Stable CHF (LVEF) 40%) (in the last 4 weeks) - NYHA class II-III - AHI≥20/hr	12 weeks	- SF-36 - MLHFQ - proBNP - Creatinine - GFR - Fatigue severity scale - ESS	- ASV=64 - Control=65 (mean)	- Moderate improvement in LVEF in both groups ($p>0.05$). - In the ASV group, AHI and central AHI significantly decreased ($p<0.001$). - Significant increase in mean arterial SaO_2 in the ASV group ($p=0.001$). - Further decline in BNP in the ASV group, and an increase in GFR ($p>0.05$). - Quality of life and symptom scores were similar in both groups ($p>0.05$)	The study showed that ASV is an effective treatment for both CSA and OSA in CHF patients. It has been shown that ASV treatment decreases BNP levels in CHF patients with SRD, thus improving cardiac functions
Lyons et al. (22) OSA CSA	- RCT, multi-center, multinational, parallel group, open label, single blind - ASV + standard medical treatment - Standard medical treatment - 430 OSA and 430 CSA patients	- Men and women - Stable HFrEF (LVEF 3 45) for at least 3 months - SRD (AHI≥15/h)	In a maximum period of 5 years; basal, 1st, 3rd and 6th months and every 6 months: PSG In 6 months: - ECHO - proBNP - 6MWT	- Physical examination - 6MWT - MLHFQ - ESS	18 years and over	- OSA in HFrEF patients is more common than CSA. - ASVmV improves the CSA, but there is no difference in the first evaluation between those who are not using ASV mode. - Secondary evaluation of the ASV mode for all causes and increased mortality and morbidity in CV	According to the results of the ADVENT-HF study, data are provided to improve the quality of life and decrease the morbidity and mortality in patients with OSA and HFrEF treated with ASV. The information obtained from the ADVENT-HF study will provide important information in the treatment of patients with HFREF and CSA in the SERVE-HF study

Table 2 contiuned

Priefert, et al. (16) OSA CSA	- RCT, multi-center, controlled, parallel, open label. - ASV (BIPAP-ASV) + optimal medical treatment at night (n=37) - Optimal medical treatment (n=35)	- Mostly male - A total of 72 patients - Stable HFrEF - SRD	12 weeks	- PSG - NYHA - Pulse - LVEF - BP - BMI - EEG - EOG - EMG - SaO_2 - Single channel ECG	- Control=67 - ASV=65 (mean)	- Significant improvement in AHI/hr. ($p<0.001$), obstructive AHI/hr. ($p=0.003$) and central AHI/hr. ($p<0.001$) in ASV group. - Further improvement in total sleep time (min.) ($p=0.259$) and mean SaO_2 (%) ($p=0.0031$) in the ASV group. - The number of single, multiple and double VEAs in ASV group was less ($p>0.05$). - Decreased heart rate (min) in the treatment of ASV, but no significant difference between the groups ($p>0.05$)	In the study, it was stated that ASR treatment could be applied in patients with HFrEF and SRD. It is recommended to repeat the study with larger patient groups
Nokao et al. (19) CSA	- RCT, open label, multi-center operation. - HOT (3 liters oxygen therapy per minute (with 92% density) with nasal cannula + optimal medical treatment - Optimal medical treatment	- Mostly male - Short term: 30 HOT, 33 controls in total 63 - Long term: 26 HOT, 25 controls total 51 - A total of 107 patients - CSA - Symptomatic, stable CHF (LVEF, 45%) - NYHA II-III - At least 5 episodes of apnea-hypopnea with ≥5/hr. reduction in ODI and 5 hours of sleep	Baseline and 12-week evaluation with two-channel real-time Holter device at night	- PSG - NYHA classification - Pulse - LVEF - proBNP - SaO_2 - Specific Activity Scale (Mets) - QoL scale	- HOT=65.3 - Control=66.5 (mean)	- Significant improvement in AHI ($p<0.01$), a significant decrease in CAI ($p<0.05$) in the HOT group. - Significant improvement in ODI ($p<0.01$), increase in functional capacity ($p<0.01$), further improvement in LVEF ($p>0.05$), greater reduction in VEAs ($p>0.05$), further improvement in NYHA ($p=0.02$) in the HOT group	- HOT has been shown to improve SRD, quality of life, and cardiac function in patients with CHF and CSA. The efficacy of HOT on ventricular arrhythmias has not been demonstrated. Further studies have been proposed
Kawechka-Jaszcz et al. (17) CSA	- RCT, cross design, open label - Slow Respiratory Exercise (SRE) with + RESPERATE + optimal medical treatment - The standard care group	- 86 male, 24 female with a total of 110 stable HF patients (LVEF <40%). - NYHA class I-III - A 24-hour Holter with sinus rhythm - Those who have the ability to apply breathing exercises after training	10-12 weeks	- PSG - Ambulatory cardiorespiratory device (Emblatta Gold) - ECHO - 6MWT - NYHA - BP - BMI - Laboratory tests	23-87 64.5 (mean)	- Significant decrease in global AHI in the SRE group ($p=0.043$), - Significant increase in LVEF ($p=0.03$) and 6MWD ($p<0.001$)	- In stable systolic CHF patients, SRE was found to reduce narrow central apnea and hypopnea in SRD, improving functional capacity and systolic LVEF. It is stated that the SRE device can be used successfully as a home-based rehabilitation tool in CHF patients

Table 2 contiuned

Sharafkhaneh et al. (21) OSA	- RCT - Atrial overdrive pacemaker - CPAP	- 15 men - Medium-severe OSA with pacemaker applied 46 months ago - Stable systolic HF (LVEF <55%)	Pacemaker implanted 46 months before the study	- ESS	74 (mean)	- Decrease in AHI (7±7.9) and total stimulation index (17±16.8) with CPAP treatment. - Improvement at nocturnal SaO_2	- Atrial overdrive pacemaker has been shown to reduce AHI safely. - Although atrial overdrive pacemaker is not as effective as CPAP in the treatment of OSA, it may play a therapeutic role in patients with systolic cardiac dysfunction with other treatment modalities
Suna et al. (20) OSA CSA	- RCT (sub-study) - Disease training program + structured physical exercise training (n=54) - Self-management support program (+52), which includes disease training program + standard exercise recommendations	- Mostly male - A total of 106 patients	12 weeks	- PSQI - 6MWT - GDS - BMI - Resting heart rate	- Control=62 - Intervention=61 (mean)	- Significant improvement in sleep disturbance ($p<0.01$), sleep duration, drowsiness during the day, sleep efficiency habit scores were not significantly different in the intervention group. - PSQI-Subjective sleep quality and global scores significantly improved in the intervention group ($p<0.01$)	In the second week of 12-week follow-up, heart failure patients visited by the exercise physiologist were found to have improved sleep quality

CAI: Central apnea index, ASVmV: ASV mode set in minute ventilation, BMI: body mass index, EEG: electroencephalography, EOG: electrooculography, EMG: electromyography, VEA: ventricular premature beats, proBNP: brain natriuretic peptide, GFR: glomerular filtration rate, UNE: norepinephrine amount in 24-hour urine, 6MWD: 6 minutes walking distance; CPET: cardiopulmonary exercise test, MLHFQ: minnesota living with heart failure questionnaire, EQ-5D: euroQol group 5-dimension self-report questionnaire, GDS: geriatric depression scale, SRD: sleep respiratory disorder

Effect of Adaptive Servo-ventilation Methods and Continuous Positive Airway Pressure on Mortality

Two studies published in 2015 showed that there was no significant difference between the ASV treatment group and the medical treatment group in terms of quality of life or changes in HF symptoms (14), and that ASV treatment increased the risk of death due to all reasons and CV death ($p<0.05$) (14). In contrast to these studies, the ADVENT-HF study showed that treatment with ASV in HFrEF patients improved health-related quality of life and reduced morbidity and mortality (22) (Tables 2, 3).

Discussion

One newly defined factor that is considered to contribute to morbidity and mortality in CHF is SRD. Sleep respiratory disorder is usually defined as OSA and CSA (23).

As a result of the polysomnographic examination, the presence of more than 5 AHIs indicates the presence of OSA. For the diagnosis of OSA with AHI, excessive daytime sleepiness and cardiac disorders are expected. It has been shown that the risk of morbidity and mortality increases especially when AHI is more than 20 (2).

Non-invasive mechanical ventilator devices used in the treatment of PAP include CPAP, Auto CPAP (APAP), BIPAP, Auto BIPAP, BIPAP-ST (/Auto), volume cycle ventilator (AVAPS/IVAPS), and Servo-Ventilator (/Auto). The first treatment option for the treatment of SRD is CPAP. The aim of the treatment of SRD is to ensure that the upper airway remains open during sleep and to regulate ventilation and sleep quality (2). This method has been shown to significantly improve symptoms such as snoring, morning headaches and daytime sleepiness in many studies. It is stated that BIPAP treatment should be considered for the treatment of CSA in CHF patients to normalize AHI when it does not respond to adequate CPAP, ASV and oxygen treatments. However, it is also emphasized that ASV treatment is indicated for the treatment of CSA (23).

As a result of the evaluations made in this study, treatment interventions for CHF patients with OSA and CSA included mostly CPAP (7-9,12,18) and ASV (10-16,22), as well as BIPAP (8), overdrive pacing (21), oxygen therapy with nasal cannula (6,19), slow breathing training (17) and exercise training (20).

In these studies, the CPAP treatment for the treatment of CHF patients with OSA was found to improve LVEF (7) and daytime sleepiness (7,8,18), and ASV treatment was also found to improve AHI (10,11,16), reduce obstructive events, improve respiratory distress (12) and quality of life (22), increase oxygen saturation (11,16) and sleep time, reduce ventricular premature stroke and mean heart rate (16) (Tables 2,3).

Table 3. Treatment interventions for the treatment of sleep respiratory disorders

Author and Type of Sleep Respiratory Disorder	CPAP	BIPAP	ASV	PM	Oxygen Treatment	Slow Respiratory Exercise	Physical Exercise
Egea et al. (7) (OSA)	- LVEF (+) - Sleepiness (+) - QOL (-) - Functional capacity (-)	-	-	-	-	-	-
Smith et al. (18) (OSA)	- Sleepiness (+) - QOL (-) - CV markers (-)	-	-	-	-	-	-
Khayat et al. (8) (OSA)	Sleepiness (+)	- LVEF (+) - QOL (+) - Functional capacity (+) - Blood pressure (+) - AHI/hour (-)	-	-	-	-	-
Bradley et al. (9) (CSA)	- LVEF (+) - Sympathetic nerve activity (+) - Nocturnal SaO_2 (+) - Mortality for all causes (-)	-	-	-	-	-	-
Hetzenecker et al. (13) (OSA, CSA)	-	Sleep quality (+)	-	-	-	-	-
Lyons et al. (22) (OSA)	-	-	QOL (+) Mortality for all causes (-) Morbidity (-)	-	-	-	-
O'Connor et al. (10) (OSA)	-	-	AHI (+) CV symptom (-) Functional capacity (-)	-	-	-	-
Cowie et al. (14) (OSA)	-	-	QOL (-) CV symptom (-) CV mortality (-)	-	-	-	-
Randerath et al. (12) (OSA, CSA)	-	-	OSA (+) CSA (+) NT-proBNP (+)	-	-	-	-
Kasai et al. (15) (CSA)	-	-	NT-proBNP (+) UNE (+) Functional capacity (-) LV end-systolic diameters (+)	-	-	-	-
Arzt et al. (11) (OSA, CSA)	-	-	NT-proBNP (+) AHI / hour (+) Mean SaO_2 (+) GFR (+) LVEF (-) QOL (-) Symptom scores (-)	-	-	-	-

Table 3 contiuned

Priefert et al. (16) (OSA, CSA)	-	-	AHI / hour (+) Obstructive AHI / hour (+) Central AHI / hour (+) Sleep time (+) Mean SaO_2 (+) VEA (+) Mean heart rate (+)	-	-	-	-
Sharafkhaneh et al. (21) (OSA)	-	-	-	AHI/hour (+)	-	-	-
Nokao et al. (19) (CSA)	-	-	-	-	CSA (+) QOL (+) Functional capacity (+) VEA (+) AHI / hour (+) LVEF (+)	-	-
Kawecha-Jaszcz et al. (17) (OSA, CSA)	-	-	-	-	-	OSA (+) CSA (+) Functional capacity (+) Systolic LVEF (+)	-
Suna et al. (20) (OSA, CSA)	-	-	-	-	-	-	Sleep quality (+)

Improvement (+), No improvement: (-), OSA: Obstructive sleep apnea, CSA: central sleep apnea, LVEF: left ventricular ejection fraction, QOL: quality of life, SaO2: oxygen saturation, AHI: Apnea-Hypopnea index, VPB: ventricular premature beats, UNE: norepinephrine in 24-hour urine, BNP: brain natriuretic peptide, PM: pacemaker

The American College of Cardiology/American Heart Association 2013 guide states that CPAP may be useful for improving functional status and increasing LVEF in HF patients with sleep apnea (Evidence B) (24). Similarly, HF Society of America (2010) guideline also recommends the use of CPAP therapy in HF patients with a diagnosis of PSG-documented OSA to improve daily functional capacity and quality of life (25). The treatment of OSA with CPAP showed decrease in sympathetic flow and BP during sleep. The results of studies describing the effect of long-term CPAP treatment on BP in patients with OSA are not very impressive. Most studies have reported a reduction in systolic or diastolic pressure between 2-10 mmHg after several weeks of CPAP treatment. These studies have shown that the effect of CPAP treatment on BP in patients with OSA is modest and variable (26).

In patients with HF, CSA appears as CSR, a periodic respiration resulting in a long apnea or hypopnea. CSA, which is quite common in HF, is seen in 30-50% of patients. CPAP treatment aimed at normalizing AHI is shown as the first treatment to be considered for CHF patients (23). CPAP treatment intervention for the treatment of HF patients with CSA has been found to improve nocturnal oxygenation, LVEF, sympathetic nerve activity and functional capacity (9), however, in the same patient group, ASV treatment has been found to decrease plasma proBNP (12,15), the amount of norepinephrine in 24-hour urine (UNE), left ventricular end systolic diameter (15), in central AHI and to increase functional capacity (16). Improvement in LVEF is associated with improvement in plasma BNP levels (Table 2,3) (27). For this reason, BNP levels were also examined in the studies in which ASV and CPAP treatments were used. In contrast, Hastings et al. (27) found no change in BNP levels in ASV-treated patients compared to the control group.

Adaptive servo-ventilators work primarily with the BIPAP principle. ASV is indicated in the presence of CSR on PSG in patients with predominant congestive HF (EF <40%) (2). However, it has been reported that ASV treatment is indicated for normalizing AHI and for the treatment of CSA syndrome associated with CHF (23). In a non-randomized study, 11 patients were treated with ASV in addition to medical treatment for 6 months, and only medical treatment was applied to the comparison group. At the end of 6 months, AHI hourly event decreased significantly compared to the baseline (p=0.001) and there was also a significant improvement in sleep efficiency (p=0.01), LVEF (p=0.04), daytime sleepiness (p=0.001) and quality of life (p=0.005) in the ASV group (28).

BIPAP is not the first treatment option in patients with OSA, but it is stated that it can be the first choice in non-invasive methods in patients with hypoxemia-hypoventilation syndromes who can not tolerate CPAP treatment and who are not able to exhale against high pressure (2). As a result of the evaluations, only one study has applied BIPAP therapy in CHF patients with OSA and improvement was observed in LVEF, quality of life and functional capacity (8).

American Academy of Sleep Medicine (2011) states that administered oxygen therapy at night is indicated for the treatment of CSA in patients with CHF (29). In patients with HF, additional nocturnal oxygen therapy is administered through nasal cannula for the treatment of CSA. Data from some small-sample, short-term studies suggest that oxygen therapy with nasal cannula improves AHI, exercise capacity and LVEF, and decreases BNP level and sympathetic nervous system activity (23). In a small sample study with CHF patients with CSA (LVEF <45%, mean age 65 years, AHI >5/hour), oxygen therapy at night was shown to improve exercise capacity, cardiac function, and cardiac sympathetic nerve activity (30). In the light of the findings of our study, two studies in the literature (6,19) reported that oxygen therapy for the treatment of CHF patients with CSA improved SRD (6,19), LVEF (19) and had a positive effect on ventricular arrhythmias (19). One of the studies showed that oxygen therapy improved quality of life and functional capacity (17), but the other study (6) did not achieve the same effect (Table 2). When the literature is examined, it has been shown that night oxygen therapy through nasal cannula have no positive effect on daytime sleepiness, sleep quality, quality of life or cognitive functions. Unlike CPAP and ASV, nighttime oxygen therapy was found not effective in eliminating upper airway obstruction, which may be accompanied by central apneas. In the light of these findings, it is stated that oxygen therapy can be used only if pressure-assisted treatments are ineffective or patients cannot tolerate these treatments (23,31-33).

In the literature, it has been hypothesized that atrial overdrive pacemaker therapy can increase cardiac filling and decrease pulmonary obstruction by increasing the heart rate, thus reduce or prevent CSA formation. In some small sample studies, atrial overdrive pacemaker therapy has been shown to reduce the number of CSA attacks, improve oxygen saturation, and reduce stimulation in HF patients (23,34,35). In another study, it was reported that atrial overdrive pacemaker treatment in CSA did not provide any improvement (36). In this study, it was determined that atrial overdrive pacemaker treatment in CHF patients with OSA provided significant reduction in AHI in a single RCT (Table 2) (21).

Conclusion

Sleep disorder is a common problem in HF patients. In the studies performed within the systematic review, the effectiveness of medical treatments and interventions for sleep disturbance in HF patients were evaluated. When the efficacy of the interventions was examined, it was observed that the addition of CPAP to medical therapy improved CSA and nocturnal oxygenation and increased 6MWD. The use of CPAP improved daytime sleepiness and LVEF with regular use in HF patients with OSA, but no effect on quality of life was observed. ASV treatment added to medical therapy also improved CSA and OSA with regular use. ASV alone was effective in reducing respiratory distress and sleep apnea, and it reduced AHI, improved LVEF, and reduced ventricular pulse. The use of ASV increased 6MWD compared to CPAP. When CPAP and BIPAP were evaluated, CPAP was effective in improving sleep quality and quality of life, while BIPAP was more effective in improving quality of life, functional capacity and BP. In addition to these interventions, the physical exercise program has been shown to be effective in improving sleep quality.

Ethics

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - H.U., H.B.O.; Design - H.U., H.B.O.; Supervision - H.U.; Resources - H.U., H.B.O.; Materials - H.U., H.B.O.; Data Collection and/or Processing - H.U., H.B.O.; Analysis and/or Interpretation - H.U., H.B.O.; Literature Search - H.U., H.B.O.; Writing Manuscript - H.U., H.B.O.; Critical Review - H.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support**.**

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