Research Article (Araştırma Makalesi)

Impact of Adaptive Servo-Ventilation in Heart Failure Patients

Kalp Yetmezliği Tanılı Hastalarda Adaptif Servoventilasyon Tedavisinin Etkileri

Esra YARAR[1], Behiye Deniz KOSOVALI[2], Nazan BAYRAM[3], Meral UYAR[3], Ayten FILIZ[3]

[1] Kahramanmaraş Necip Fazıl City Hospital, Chest Diseases Clinic, Kahramanmaraş, Türkiye
[2] Ankara City Hospital, Intensive Care Unit, Ankara, Türkiye
[3] Gaziantep University, Department of Chest Diseases, Gaziantep, Türkiye

Özet

Amaç: Kronik kalp yetmezliği olan hastalarda obstrüktif apne, santral apne ve Cheyne-Stokes solunumu (CSR) gibi uykuya bağlı solunum bozuklukları (SRBD) görülebilir. SRBD kalp yetmezliğinin prognozunu etkileyebilir. Çalışmanın amacı, kalp yetmezliği olan hastalarda uykuya bağlı solunum bozukluklarını ortaya çıkarmak ve yeni bir tedavi modalitesi olarak adaptif servo-ventilasyonun (ASV) etkilerini göstermektir.

Gereç ve Yöntem: Bu prospektif çalışmaya kalp yetmezliği olan 32 hasta dahil edildi. Bir gece polisomnografi (PSG) yapıldı.

Bulgular: PSG sonuçlarına göre SRBD oranı %96.7 idi. Apne-hipopne indeksi (AHİ) >5 olan tüm hastalara sürekli pozitif hava yolu basıncı (CPAP) ve ASV titrasyonları önerildi. Demografik ve klinik özellikler, semptomlar, PSG bulguları, Cheyne-Stokes solunumu (CSR) varlığı, ekokardiyografi sonuçları kaydedildi. ASV titrasyonu öncesi ve sonrası solunum fonksiyon testleri, yürüme testleri yapıldı, transferrin ve pro-BNP konsantrasyonları belirlendi. AHİ'ye göre gruplarda 30 hastanın 18'inde şiddetli obstrüktif uyku apne sendromu (OUAS), 4'ü orta OUAS, 5'i hafif OUAS ve 2'si santral uyku apnesi (CSA) olarak tanımlandı. Obstrüktif apne, santral apne, AHİ, uyarılma ve SpO2 min değerlerinde, PSG ve CPAP, ASV titrasyonlarında anlamlı düzelme saptandı (sırasıyla p=0,001, p=0,016, p=0,001, p=0,015 ve p=0,008). ASV ile tüm CSR'lerin ortadan kaldırıldığı belirlendi. ASV titrasyonu pro-BNP sonrası yürüme mesafesi ve FVC değerleri anlamlı olarak değiştiği saptandı (sırasıyla p=0,036, p=0,018 ve p=0,018).

Sonuç: Sonuç olarak, CPAP ile devam eden ancak bir gecelik ASV uygulaması ile ortadan kaldırılan CSR ve santral apneler belirlendi. ASV'nin ayrıca pro-BNP'yi azalttığı ve FVC ve yürüme mesafesi değerlerini önemli ölçüde artırdığı ortaya konuldu.

Anahtar Kelimeler: Santral uyku apne sendromu, Kalp yetmezliği, Polisomnografi, Non invaziv ventilasyon, Obstrüktif uyku apne sendromu (OUAS)

Abstract

Objective: Sleep-related breathing disorders (SRBD) as obstructive apnea, central apnea, and Cheyne-Stokes respiration (CSR), can be seen in patients with chronic heart failure. SRBD can influence the prognosis of heart failure. We aim to reveal sleep-related breathing disorders in heart failure patients and display the effects of adaptive servo-ventilation (ASV) as a new therapeutic modality.

Materials and Methods: In this prospective study, 32 patients with heart failure were included. One night polysomnography (PSG) was done.

Results: According to the results of PSG, the SRBD ratio was 96.7%. Continuous positive airway pressure (CPAP) and ASV titrations were offered to all patients with an apnea-hypopnea index (AHI) > 5. Demographics, clinical properties, symptoms, PSG findings, Cheyne-Stokes respiration (CSR), and echocardiography results were recorded. Before and after ASV titration, pulmonary function tests and walking tests were performed, and concentrations of transferrin and pro-BNP were recorded. In the groups according to the AHI, severe obstructive sleep apnea syndrome (OSAS) in 18 of 30 patients, four moderate OSAS, five mild OSAS, and two central sleep apnea (CSA). PSG and, CPAP, ASV titrations were done in 7 male and one female patient that obstructive apnea, central apnea, AHI, arousal, and SpO2 min values had significant improvements (p=0,001, p=0,016, p=0,001, p=0,015 and p=0,008 respectively). We determined all CSRs were eliminated with ASV. After ASV titration pro-BNP, walking distance, and FVC values changed significantly (p=0,036, p=0,018, and p=0,018 respectively).

Conclusion: As a result, we determined CSR and central apneas persisted with CPAP but were eliminated with a one-night ASV application. ASV also decreased pro-BNP and increased FVC and walking distance values significantly.

Keywords: Central sleep apnea syndrome, Cardiac Failure, Polysomnography, Non invasive ventilation, Obstructive Sleep Apnea Syndrome (OSAS)

Correspondence: Esra YARAR, Kahramanmaraş Necip Fazıl City Hospital, Chest Diseases Clinic, Kahramanmaraş, Türkiye

Phone: +90 5057468402 **e-mail:** yararesra81@gmail.com

ORCID No (Respectively): 0000-0002-9593-4441, 0000-0001-9385-6542, 0000-0002-4692-2639, 0000-0002-3664-548X, 0000-0003-4049-5389

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INTRODUCTION

Sleep-related breathing disorder is one of the important factors leading to the generation and progression of heart failure. Obstructive sleep apnea syndrome (OSAS) is characterized by obstructive apneas seen in patients with heart failure but also central sleep apnea syndrome (CSS) characterized by central apneas and Cheyne-Stokes respiration (CSR) seen in about 40% of these patients. CSS with CSR triggers recurrent hypoxia attacks leading to arrhythmia (1). In patients with chronic heart failure (CHF), apnea, hypopnea, and hyperpnea attacks, sleep disturbances, arousals, intermittent hypoxemia, hyper- and hypocapnia, and intrathoracic pressure changes are frequently seen and related to sleep disorders. These sleep disturbances have many unfavorable effects on the cardiovascular system (CVS) especially such as CHF, hypertension, and coronary arterial disease (CAD). Therefore, treatment and diagnosis of sleep-related disorders lead to favorable effects on morbidity and mortality of CHF patients (2).

The gold standard therapy in sleep-related disorders is positive airway pressure therapy. This therapy aims to form a mechanic stent by positive airway pressure (CPAP/BPAP) thus making open upper airway (3). Adaptive servo-ventilation (ASV) is a new treatment modality recommended in CHF-CSR therapy. ASV gives variable pressure according to the patient's pressure-demand (hyperpnea, hypopnea, and apnea) and suppresses the CSR. ASV application treats excess fatigue and sleepiness by preventing central apneas, hypopneas, arousals, and sleep fragmentation seen during sleep and improves cardiac functions and quality of life. Therefore it is effective in preventing cardiovascular pathologies such as angina pectoris and arrythmias (4).

This study aims to determine polysomnography findings in heart failure patients and evaluate the effectiveness of ASV treatment compared with CPAP treatment.

MATERIALS AND METHODS

In this study, 9 women and 23 men with an average age of 56±9,6 years were admitted to pulmonology and cardiology outpatient clinics between February 2011 and June 2012 in Gaziantep University Hospital. Patients of chronic heart failure with appropriate medical therapy, NHYA I-IV and in echocardiography ejection fraction (EF) <50% were included in the study. All patients are informed about the procedure and the study as decided in the Helsinki declaration. This study was done with the confirmation of Gaziantep University Medical School Medical Ethic Committee on 16.12.2010 number 12/2010-24.

Inclusion criteria: >18 years, signed the informed consent form, and diagnosed with chronic heart failure.

Exclusion criteria: <18 years, not signed the informed consent form, and diagnosed with unstable angina or unstable arrhythmia.

All patients' physical examination was done and also neck circumference, weight, and height were calculated as weight/height2 (kg/m2). In echocardiography, left ventricular ejection fraction (EF), left ventricle (LV), left atrium (LA) diameters, pulmonary artery pressures (PAP), interventricular septal thickness (IVS), tissue doppler mitral currents (E, E') and aortic root thickness were calculated by one cardiology. Patients were taken to polysomnography (PSG). For patients with AHI >5 and accepted titration, PSG was repeated with CPAP and ASV. EPAP was started from 5 cmH2O and gradually increased and CPAP titrations were done automatically. The average EPAP in our patients was 7±0.9 (6-9) cmH2O. Six-minute walking test (6MWT), pulmonary function test (PFT), routine biochemistry, complete blood count, arterial blood gases, pro-BNP, and transferrin measurements done before PSG and after ASV. At first, all patients were taken to PSG for one night. In a week, titrations with CPAP and ASV were done. On the morning of titration, 6MWT and PFT were repeated. NT-pro-BNP was measured with the Elecsys 2010 (Roche, Germany) method. Before blood tests and PSG, patients are recommended not to take caffeinated beverages and foods. Patients were taken to the laboratory at 8:30 pm. Electroencephalographic (C4A1, C3A2, F3A1, F4A2, O1A1, and O2A2), bitemporal electrooculographic, submental, electromyographic, and electrocardiographic electrodes were placed. Thoracic and abdominal pneumobands with pressure transducers were placed to record movement changes. Pulse oximetry took records from the fingertips up to the test end. Records were taken with a Viasys Sleep Lab Pro (Viasys Healthcare/Germany) device. Scoring was done according to the 2007 AASM by one pulmonologist as 30 seconds epochs. Failure to follow the flow of air for at least 10 seconds is called apnea, a decrease of nasal airflow with ≥30% for 10 seconds with ≥4% desaturation or a decrease of nasal airflow with ≥50% for 10 seconds with ≥3% desaturation called hypopnea. Central apnea syndrome was defined as the total of central apneas and hypopneas constituting ≥50% of all apneas and hypopneas (3).

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. Categorical variables were presented as numbers and percentages, numerical variables were presented as mean, standard deviation, median, minimum,

and maximum. When the numeric variable fulfilled the condition of normal distribution, for independent groups Student-t test was used in binary comparisons. If not Mann Whitney U test was used. In the study of the relationship between numerical variables, if the normal distribution was fulfilled Pearson correlation analysis, if not Spearman correlation analysis was used. In patients who underwent follow-up (the subject number was less), dependent variables were analyzed with Freadman subscription repeated measures analysis of variance. Results were interpreted according to the Bonferroni correction to the alpha level of significance (to increase the reliability of p in 3 group comparisons). Statistical significance was considered as p< 0,05.

RESULTS

In our study, 9 (28.1%) women and 23 (71.9%) were male and the average age of patients was 56,9±9,6 years. Smoking was in 12 (37.5%) of our patients. When symptoms were asked, snoring at 68.8%, apnea at 40.6%, daytime sleepiness at 81.3%, dyspnea at 50%, and fatigue at 18.8% were detected. When concomitant disease distribution was assessed, coronary artery disease (CAD) at 43.8%, diabetes mellitus (DM) 31.3%, and hypertension (HT) 50% were seen. General properties are shown in **Table 1**.

The average AHI in our patients was 39,3±25,8. Average SpO_2 min was assessed as 73.9±10.5% **(Table 2)**.

Table 1. General properties

Age *Av.±SD (min-max)*		56,9±9,6 (36-65)
Gender n (%)	Women	9 (28.1)
	Men	23 (71.9)
Cigarette n (%)		12 (37.5)
Cigarette *Av.±SD (min-max)*		22,6±11,6 (5-50)
Symptom	Snoring n (%)	22 (68.8)
	Apnea n (%)	13 (40.6)
	Daytime Sleepiness n (%)	26 (81.3)
	Dyspnea n (%)	15 (50.0)
	Fatique n (%)	6 (18.8)
Comorbidity	CAD n (%)	14 (43.8)
	DM n (%)	10 (31.3)
	HT n (%)	16 (50)
	Dislipidemia n (%)	3 (9.4)
	Other n (%)	8 (25)
Comorbidity	>2	10 (31.3)

CAD: Coronary Artery Disaese, DM: Diabetes Mellitus, HT: Hypertension

Table 2. PSG findings

	Av.±SD (min-max)
OA (n)	87,8±102,3 (0-385)
CA (n)	30,6±53,1 (0-210)
AHI (number/hour)	39,3±25,8 (1-90)
Arousal (n)	19,5±12,2 (50-80)
SpO_2 min (%)	73.9±10.5 (47-90)
Sleep Efficiency (%)	73.3±18.9 (10-95)
Sleep time (hour)	5,1±1,6 (0,2-7,1)

OA; Obstructive Apnea, CA; Central Apnea, AHI; Apnea Hypopnea Index, SpO_2 min; Minimum Oxygen Saturation

Two patients' PSG records were not included in our data because of insufficient sleep. In the patients, the frequency of sleep-related respiratory disturbances was found as OSAS 90% and CAS 6.7%. In 30 patients, 18 were severe, 4 were moderate, 5 were mild OSAS and 2 were CAS, 1 patient had normal PSG. Cheyne-Stokes respiration (CSR) was detected in 14 (43.8%) patients. No significance was determined between CSR and non-CSR patients in PSG findings (p>0,05).

A total of 3 patients (1 CPAP and 2 ASV) took therapy at home. One patient had heart transplantation, one patient was died in the intensive care unit, 2 patients were moved to the outskirts and could not come again, remaining patients incompatible with the devices and control appointments. This is because of congestive heart failure.

For patients that had PSG, CPAP, and ASV titrations, the average age of 56,4±8,7 years 7 males and 1 female had statistical significance in OA, CA, AHI, arousal, and SpO_2 min values (p=0,001, p=0,016, p=0,001, p=0,015, p=0,008 respectively). With CPAP titration, the numbers of OA and CA were decreased, with ASV titration all OA and CA were eliminated **(Table 3)**.

In subgroup comparisons, there were significant difference in OA and AHI in PSG findings, in CA, arousal and SpO_2 min in CPAP and ASV titrations **(Table 4)**.

Wilcoxon test. With Bonferroni correction alpha sinificance level p<0,016. If there is no value under significance level, the smallest p value accepted as significant.

In **Figure 1** comparisons of Polysomnography, CPAP and ASV titrations were shown.

There was a significant decrease in pro-BNP between before PSG and after ASV in patients with and without CSR (p=0,036), on the other hand, transferrin levels had no significant difference.

There were significant differences in 6MWT and FVC values before PSG and after ASV (p=0,018 and

Table 3. PSG, CPAP and ASV values comparisons

	PSG Av.±SD (median)	CPAP Av.±SD (median)	ASV Av.±SD (median)	p*
OA (n)	92,3±123,7 (47)	21,5±27,7 (8)	1,0±2,8 (0)	0,001
CA (n)	37,0±72,4 (5,5)	11,8±20,2 (2,5)	0,0 (0)	0,016
AHI (number/hour)	34,8±22,5 (29)	13,9±13,1 (10,5)	4,6±2,8 (5)	0,001
Arousal (n)	21,3±14,1 (19)	7,5±4,8 (6)	7,25±2,1 (7,5)	0,015
SpO_2 min (%)	70.1±14.8 (70.5)	85.1±4.1 (84.5)	85.6±4.4 (85)	0,008
Sleep Efficiency (%)	81.0±10.0 (83)	74.8±13.6 (81)	80.1±8.9 (78.5)	0,497
Sleep Time (hour)	5,7±0,8 (5,6)	5,1±1,0 (4,9)	5,5±0,4 (5,4)	0,419

PSG: Polysomnography, CPAP: Continuous Positive Airway Pressure, ASV: Adaptive Servo-ventilation, OA: Obstructive Apnea, CA: Central Apnea, AHI: Apnea Hypopnea Index, SpO_2 min: Minimum Oxygen Saturation
* Freadman repeated scale variance analysis

Table 4. PSG, CPAP titration and ASV titration sub-group comparisons

	PSG vs. CPAP	PSG vs. ASV	CPAP vs. ASV
OA (n)	p=0,012	p=0,012	p=0,075
CA (n)	p=0,237	p=0,028	p=0,043
AHI (number/hour)	p=0,012	p=0,012	p=0,058
Arousal (n)	p=0,036	p=0,018	p=1,000
SpO_2 min (%)	p=0,025	p=0,012	p=0,609
Sleep Efficiency (%)	p=0,237	p=0,888	p=0,237
Sleep Time (hour)	p=0,207	p=0,799	p=0,206

PSG: Polysomnography, CPAP: Continuous Positive Airway Pressure, ASV: Adaptive Servo-ventilation, OA: Obstructive Apnea, CA: Central Apnea, AHI: Apnea Hypopnea Index, SpO_2 min: Minimum Oxygen Saturation

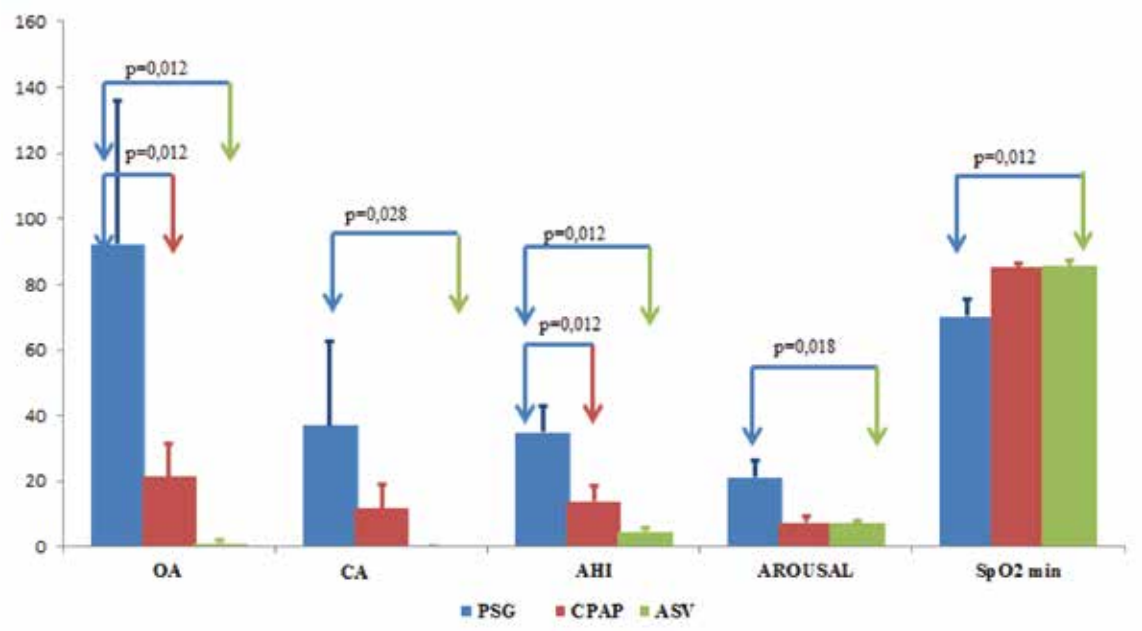

Figure 1. Comparison in PSG, CPAP and ASV

PSG: Polysomnography, CPAP: Continuous Positive Airway Pressure, ASV: Adaptive Servo-ventilation, OA: Obstructive Apnea, CA: Central Apnea, AHI: Apnea Hypopnea Index, SpO_2 min: Minimum Oxygen Saturation

p=0,018 respectively). The change in FVC was an 8.7% increase on average. There was no significant difference in patients with and without snoring, daytime sleepiness, and fatigue symptoms. SpO2 min was significantly decreased in patients with apnea and dyspnea (respectively p=0,029 ve p=0,010).

In a study of the relationship between complete blood count and routine biochemistry, there was only a negative significant difference between SpO2 min and urea and creatinine.

In the relation of PSG with echocardiography, there was a significant difference between OA with IVS diameter and PAP positively; CA with EF negatively, CA with LV diameter positively; AHI with LA diameter positively; length of sleep with LV diameter positively (p=0,023 p=0,046 p=0,013 p=0,017 p=0,046 p=0,021 respectively).

In men OA, AHI, arousal, sleep efficiency, and length of sleep values were detected significant compared with the females (p=0,038 p=0,048 p=0,003 p=0,034 p=0,019 respectively).

DISCUSSION

In our study, according to PSG, OSAS and CAS were diagnosed with chronic heart failure. Sleep-related respiratory diseases were detected in 97.6% of our study group. A statistically significant decrease was detected in central apneas with one-night ASV in comparison to one-night CPAP application in these patients. Obstructive apnea and AHI were more suppressed with ASV compared with CPAP but there was no significant relation. This could be because the number of patients was less to constitute a significant difference. After one night of ASV therapy, a significant decrease in pro-BNP values and an increase in the 6-minute walking test and FVC values were detected. A decrease in exercise capacity was a known property in chronic cardiac failure patients. Studies are showing an increase in FVC value after medical and CPAP therapy (5,6).

Wittmer et al. reported that CPAP therapy caused a significant increase in FEV1 and FVC. After CPAP therapy, increases in FEV1 14% and FVC 16% were detected (5). In the studies, it was stated that ASV therapy causes a decrease in excessive daytime sleepiness, a significant decrease in plasma pro-BNP and urinary metadrenalin excreations, decrease in AHI compared to oxygen, CPAP and BiPAP therapies, increase in length of slow wave and REM sleep time, suppression of CSR and in some studies eradication of all CSRs, significant increase in LVEF, significant improvement in life quality and physical performance (4, 5, 7, 8, 9). Yoshihisa et al., similar to our study, figured out significant decrease in levels of BNP with one-night ASV therapy was decreased cardiac afterload, arousal index and so decreased myocardial damage (10). Teschler et al., compared one-night O_2 (2 L/min), CPAP (average 9 cmH_2O), BiPAP (average 13.5/5.2 cmH2O), ASV (average 7-9 cmH_2O), and no therapy in patients with cardiac failure, NYHA III and had optimal medical therapy. ASV therapy had a significant decrease in AHI and

arousal index. Therefore, one-night ASV therapy, suppressed CSR seen in CHF and caused more improvement in sleep quality by lengthening slow wave and REM sleep compared to CPAP and oxygen therapy (8). Similarly, in our study, ASV titration resulted in a significant decrease in AHI, arousal index, and SpO2min but contrary to the study, no significant difference was seen in sleep efficiency and total sleep time. When compared to CPAP, ASV eliminated obstructive and central apnea and increased SpO_2 min significantly. All CSRs are eradicated with the use of ASV.

Pepperell et al. showed a significant decrease in plasma BNP and urinary met-adrenalin excretions and a decrease in daytime sleepiness with ASV therapeutic group in 30 patients with CHF and CSR, NYHA II-IV in a randomized, controlled, prospective study of two groups, one was 1 month therapeutic (n=15) and the other was sub-therapeutic (n=15) (7).

Hastings et al. examined 6 months of ASV therapy on dyspnea score, AHI, LVEF, and plasma BNP levels in 11 male patients with CHF and AHI> 15. When 8 patients rejected ASV therapy classified as the control group, 6 months of ASV therapy significantly decreased AHI, and increased LVEF but not in BNP levels (11).

Vogt-Labner et al., compared ASV and oxygen (2 L/min) therapies in 20 patients with NYHA III, who had CSR and CHF, according to sleep and life quality, cardiac functions in the randomized controlled study for 3 months. The study determined that in the ASV arm CSR was eliminated and cardiac functions, life quality, and physical performance improved significantly (12).

Philippe et al., compared the effectiveness and compliance of CPAP and ASV in 25 patients with CSR and CHF, NYHA II-IV, according to AHI, life quality, and LVEF in a randomised study. As a result of the study, it was shown that both CPAP and ASV decreased AHI, but only with ASV, CSR was eliminated. Therefore, compliance was similar in both groups in the 3rd month, but in the 6th month the ASV group was better than CPAP, and also life quality in the 6th month improved with ASV. Important point of this study, only with ASV therapy, significant improvement in LVEF is provided (4).

Oldenburg O. et al. examined the effects of ASV on CSR and CHF parameters in 29 male patients with CSR and CHF taking optimal medical therapy and NYHA II-IV. This study showed improvement in sleep-related respiratory disturbances and cardiopulmonary exercise tests with ASV and also, average 5,7 month-ASV therapy provided a significant increase in LVEF and a significant decrease in pro-BNP concentration (13).

In our study, with one-night ASV therapy, we showed a significant decrease in pro-BNP levels. This effect could be due to a decrease in cardiac output, so with long-term ASV treatment, this effect would be more prominent and could have important impacts on morbidity and mortality. Therefore, ASV therapy provided a significant increase in the 6-minute walking test and FVC values.

Although in our study inefficient number of patients was a restriction in the evaluation of acute effects, it was the important result that only one-night ASV therapy provided a significant decrease in serum pro-BNP levels and eradicated all CSRs in all patients. In the study, when AHI, arousal, sleep efficiency, and total sleep time were evaluated, according to gender, men had an increased number of obstructive apnea, AHI, arousal, sleep efficiency, and sleep time compared with women. Similar studies had no similar data, some studies had only male patients in the population (4,11). This situation could be due to heart failure is seen mostly in male patients (14).

Canada Positive Airway Pressure Study (CANPAP), evaluated 258 CSR and CHF patients who had or did not have CPAP therapy for 2 years randomly. In the CPAP group, more improvement was assessed in the 6-minute walking test compared with the control group. However, no significant difference was found in hospitalization, quality of life, or survival without transplant (15). On the other hand, no effect of CPAP was shown on the first night of therapy in the improvement of central respiratory disturbances (15).

ACC/AHA 2022 chronic heart failure guideline informed that CPAP therapy caused improvement in left ventricular structure and function in patients with systolic dysfunction had OSAS and also CSR (16). Thanks to these studies, it's hoped that ASV therapy would find a place in the guidelines, provide more information about the effectiveness and reliability of these approaches, and be directive in the assessment of patients who would have received the greatest benefit from therapy.

Study restrictions were few number of patients and the titrated number of patients was also fewer than expected. Therefore, several patients who had home-device were insufficient for the statistical analysis and the average follow period could not reach to expected. Another restriction of our study, there was no echocardiographic assessment after one night of CPAP and ASV application. The other restriction, it was not a randomized controlled study.

In conclusion, we found sleep-related respiratory disturbances at a rate of 96.7% in chronic heart failure

patients. OSAS was 90% and CAS was 6.7%. In chronic heart failure patients, one night ASV application, in the acute phase, compared to CPAP, eradicated Cheyne-Stokes respiration and had more improvement in AHI, obstructive apnea, and central apnea. Improvement in pro-BNP, FVC values, and exercise capacity were evaluated after one night of ASV application. Chronic heart failure patients were incompatible in hospital visits and device use compared with other patients. More long-term, randomized, controlled, prospective studies are needed for the assessment of the effects of ASV treatment on morbidity and mortality and also the diagnosis of sleep-related respiratory disturbances in chronic heart failure patients.

Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of the Gaziantep University Medical School Medical Ethic Committee on 16.12.2010 number 12/2010-24.

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