

Sleep Apnea-Hypopnea Syndromes and Heart Failure

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Heart failure (HF) and sleep-disordered breathing are conditions highly prevalent in the general population that often co-exist in the same patient. Epidemiological and pathophysiological studies indicate that there may be a causal link between sleep-disordered breathing and HF with either left ventricular systolic dysfunction or preserved ejection fraction. The presence of sleep-disordered breathing in HF patients exposes the cardiovascular system to intermittent hypoxia, sympathetic activation, and increased preload and afterload and they trigger several inflammatory, oxidative and neurohumoral mechanisms that may precipitate the progression of the disease. Although there are no available data to indicate that treating sleep-disordered breathing in HF patients reduces cardiac mortality, several studies demonstrate a significant improvement in structural and functional cardiovascular parameters. This review focuses on the clinical and epidemiological bases, the pathophysiological mechanisms and the therapeutic implications between HF and sleep apnea-hypopnea syndromes.

Key words: *Sleep apnea/hypopnea syndrome. Heart failure. Treatment with continuous positive airway pressure.*

Síndromes de apneas-hipopneas durante el sueño e insuficiencia cardíaca

La insuficiencia cardíaca (IC) y los trastornos respiratorios durante el sueño son entidades que presentan una elevada prevalencia en la población general y es frecuente la presencia de ambas en un mismo paciente. Diversos estudios epidemiológicos y fisiopatológicos indican que puede haber una relación causal entre dichos trastornos y el desarrollo del síndrome de IC, tanto asociada con la presencia de disfunción sistólica ventricular izquierda como en casos con función sistólica conservada. La presencia de trastornos respiratorios durante el sueño en enfermos con IC expone al sistema cardiovascular a hipoxemia intermitente, activación simpática y aumento de la precarga y poscarga ventricular que, a su vez, ponen en marcha una serie de mecanismos inflamatorios, oxidativos y neurohumorales que pueden favorecer la progresión de la enfermedad. Aunque aún no disponemos de datos que demuestren que el tratamiento de los trastornos respiratorios durante el sueño en enfermos con IC disminuye la mortalidad de esta población, diversos trabajos demuestran una mejoría significativa en distintos parámetros de estructura y función cardiovascular. En este trabajo se revisan las bases clínicas y los datos epidemiológicos, las relaciones fisiopatológicas y las implicaciones terapéuticas entre el síndrome de IC y los síndromes de apneas-hipopneas durante el sueño.

Palabras clave: *Síndrome de apnea/hipopnea del sueño. Insuficiencia cardíaca. Tratamiento con presión positiva continua.*

INTRODUCTION

Heart failure syndrome is a very common condition with a prevalence that has continued to rise despite major advances in diagnosis and treatment.¹ It represents a major cause of morbidity and mortality in developed

countries and is responsible for approximately 20% of hospital admissions in individuals aged more than 65 years. Its high associated morbidity and mortality alongside the extraordinary economic impact of caring for these patients make the disease a considerable public health problem.²

Consequently, new strategies must be identified that are applicable to the majority of these patients, both in terms of clinical effectiveness and financial cost. Thus, attention has been paid in recent years to the presence of sleep-disordered breathing in the general population, particularly its possible influence as a

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ABBREVIATIONS

CPAP: continuous positive airway pressure
 LVEF: left ventricular ejection fraction
 AHI: apnea-hypopnea index
 CSR: Cheyne-Stokes respiration
 CSAHS: central sleep apnea-hypopnea syndrome
 OSAHS: obstructive sleep apnea-hypopnea syndrome

causative factor and element that favors the progression of the disease in patients with heart failure.

Conceptually, there are 3 types of apnea (complete cessation of airflow) and hypopnea (partial cessation of airflow): central, obstructive, and mixed. Central apnea refers to the cessation of airflow accompanied by an absence of respiratory effort, while obstructive apnea refers to the suppression of airflow with sustained respiratory effort. Mixed apneas share characteristics of both forms. This classification allows differentiation between the 2 main types of sleep-disordered breathing encompassed by the term sleep apnea-hypopnea syndrome: obstructive sleep apnea-hypopnea syndrome (OSAHS), in which obstructive apneas are predominant, and central sleep apnea-hypopnea syndrome (CSAHS), in which most events are central in nature.

The number of apnea and hypopnea events divided by the number of hours of sleep constitutes the apnea-hypopnea index (AHI). An AHI greater than 5 is considered abnormal, and the AHI is the most widely used index to quantify the severity of the syndrome.

OSAHS is a considerable health problem, due to its high prevalence, which is estimated at around 4% and 2% in middle-aged men and women, respectively, and due to the considerable morbidity and mortality associated with the disease.³⁻⁶ Although excessive daytime sleepiness leads to the death of some of these patients as a result of workplace or traffic accidents, cardiovascular complications are the main cause of death or disability. OSAHS has been linked to various cardiovascular diseases, such as systemic hypertension, disorders of cardiac rhythm, ischemic heart disease, cerebrovascular accidents, pulmonary hypertension, and altered ventricular function and heart failure.^{4,5,7-15} The common association of OSAHS with heart failure assumes particular importance due to the high prevalence of both diseases, the overlap between various pathophysiologic mechanisms, and the possibility of applying common therapeutic measures.¹⁶

CSAHS with Cheyne-Stokes respiration (CSR) has a negative prognostic value, and unlike OSAHS, appears to be more a consequence than a cause of heart failure.

Here we review the clinical basis, epidemiology, pathophysiologic associations, and therapeutic

implications regarding the association between heart failure syndrome (and by extension, ventricular function) and sleep apnea-hypopnea syndromes, addressing OSAHS and CSAHS separately.

OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME AND HEART FAILURE

In recent years, various studies have been published indicating an association between OSAHS and heart failure. The nature of this association is still not fully clear, not only in terms of its clinical and therapeutic implications but also in relation to the pathophysiologic mechanisms involved and the true epidemiology of the phenomenon. This is due, among other reasons, to the small sample size of the published case series, the type of sleep studies performed, conceptual differences between authors, and the presence of confounders, such as obesity, hypertension, diurnal hypoxemia, and hypercapnia, and airflow limitations.

Current strategies for the assessment and treatment of patients with heart failure are restricted to assessing the alert patient. This approach assumes that the mechanisms that could contribute to the pathophysiology or progression of heart failure remain quiescent during periods of sleep. However, there are important pathophysiologic links between OSAHS and heart failure that can affect ventricular function in patients with OSAHS without primary heart disease, as well as pathophysiologic, therapeutic, and prognostic implications when a patient with heart failure also has OSAHS.

Pathophysiology

OSAHS could compromise left ventricular function through various mechanisms (Figure 1).

Ineffective respiratory effort against the occluded upper airways during apnea causes a sharp reduction in intrathoracic pressure, leading to an increase in the left ventricular transmural pressure and an increase in left ventricular afterload. Repetition of these events would favor compensatory concentric hypertrophy, with increased oxygen demand and consumption by the left ventricular myocardium.¹⁷

Continued repetition of episodes of increased ventricular wall stress could lead to activation of genes involved in the process of ventricular remodeling and give rise to varying degrees of contractile dysfunction.¹⁸ In addition, excessive negative intrathoracic pressure during apnea events can alter the relaxation properties of the left ventricle, leading to difficulties in diastolic ventricular filling.¹⁹

On the other hand, the reduction in intrathoracic pressure favors venous return towards the right atrium and from there to the right ventricle, with the consequent distension of the chamber, capable of displacing the

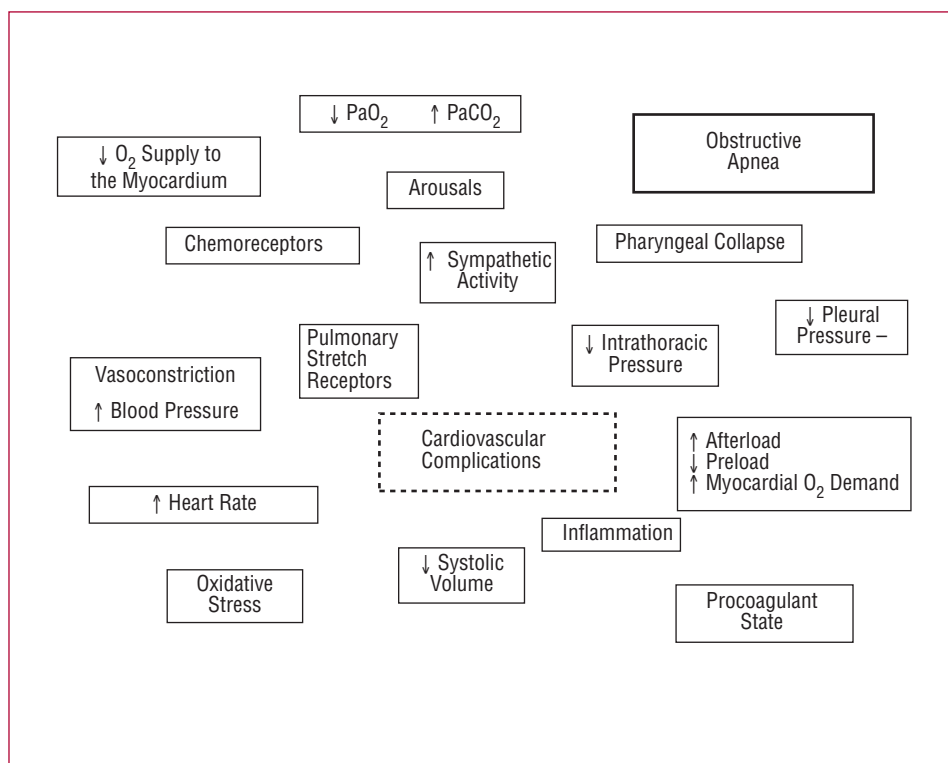


Figure 1. Pathophysiologic mechanisms initiated by repeated apneas with direct effects on the cardiovascular system.

interventricular septum towards the left during ventricular diastole. This phenomenon will impede left ventricular filling and lead to a reduction in preload.²⁰ The reduced preload and increased afterload will act synergistically to reduce systolic volume.²¹

Hypoxemia as a result of apnea affects the cardiovascular system through various mechanisms, such as reduction in oxygen supply to the myocardium, increased sympathetic nervous system activity, development of endothelial dysfunction, and procoagulant effects.

Hypoxemia leads to a reduction in the supply of oxygen to the myocardium, an effect that is even more accentuated in patients who have a limited blood supply as a result of arteriosclerotic obstructive coronary artery disease. The hypocapnia that can appear due to hyperventilation following apnea can worsen the supply of oxygen to the myocardium, both as a result of coronary vasoconstriction and shifting of the saturation curve for hemoglobin to the left. This reduced myocardial oxygen supply could affect left ventricular systolic and diastolic function. Hypoxemia also leads to increases in sympathetic activity and systemic blood pressure, alongside a sustained reduction of vagal tone.

Direct conclusive scientific evidence indicating that OSAHS can cause arteriosclerosis is still not available. However, intermittent hypoxemia and reoxygenation as a result of apnea events probably contributes to the generation of oxygen free radicals and certain cell adhesion molecules. That would give rise to reperfusion

injury and favor endothelial dysfunction, representing the onset of arteriosclerotic processes. It has also been demonstrated that hypoxemia can induce apoptosis of myocardial and endothelial cells, as well as the expression of certain genes involved in regulating the synthesis of endothelial vasodilators, such as nitric oxide, the plasma concentrations of which have been found to be reduced in patients with OSAHS.²² It has been reported that the vasodilator response is worse in individuals with OSAHS but improves with nasal application of continuous positive airway pressure (CPAP) in relation to the reduced sympathetic activity in response to this treatment.²³ Various procoagulant effects have been demonstrated in patients with OSAHS and those effects can be attenuated by treatment with CPAP. In subjects with OSAHS, increases have been found in the concentration of C-reactive protein compared with control individuals of a similar age, sex, and body mass index. These increases are proportional to the AHI.²⁴

Finally, the electroencephalographic arousals that occur at the end of an apnea event, along with hypoxemia, also increase sympathetic activity and reduce vagal tone.^{25,26}

Little is currently known about which of the described mechanisms would play the most important role in the pathophysiology of left ventricular dysfunction in patients with OSAHS. It is possible that in each patient an individual balance is established between one or another of those factors.

Ventricular remodeling plays an essential role as a final pathway common to the various factors implicated in alteration of left ventricular function as a result of apnea and hypopnea events. Hypertrophy, loss of myocytes, and excessive interstitial fibrosis play fundamental roles in this process.^{27,28}

It is currently not known what the true epidemiologic impact would be in terms of OSAHS as the cause of left ventricular dysfunction in certain patients with heart failure of unknown etiology, particularly when many of those patients are not diagnosed due to the absence of excessive daytime sleepiness.²⁹ It is also unknown in what proportion of patients with asymptomatic left ventricular dysfunction OSAHS could be the main causative factor.

Nevertheless, the pathophysiologic links between heart failure and OSAHS help to understand how in individuals with heart failure of any etiology, the development of OSAHS can favor the progression of heart failure through a variety of mechanisms and generate more severe stages of the disease with negative clinical, therapeutic, and prognostic consequences.

Essentially, the pathophysiologic mechanisms implicated in OSAHS and heart failure converge at 2 main points that would facilitate worsening of ventricular failure. Firstly, the deleterious effects of hyperactivation of the sympathetic nervous system and inhibition of the parasympathetic system on the cardiovascular system in general. Secondly, the alterations in preload and afterload and the effects of hypoxemia on the left ventricle with dysfunction due to any type of heart disease. Some of the consequences of sympathetic hyperactivity on this already diseased ventricular myocardium would include necrosis and apoptosis of myocytes, loss of sensitivity and downregulation of β -adrenoceptors, arrhythmogenesis, and increased mortality.³⁰⁻³² Stimulation of sympathetic nerve terminals in the renal system would lead to activation of the renin-angiotensin-aldosterone system, causing increased sodium retention and increased volume status,³¹ with the consequent negative effects on myocardial performance.

Verdecchia et al³³ reported a stronger association between hypertension and the development of ventricular hypertrophy when the hypertension was during sleep rather than when the patient is awake. The increased blood pressure during sleep that occurs in patients with hypertension and OSAHS compared with patients with hypertension alone would place the former at a greater risk of developing left ventricular hypertrophy.³⁴

It has been observed that dogs subjected to repeated apneas over a number of weeks develop nocturnal and diurnal hypertension, left ventricular hypertrophy, systolic ventricular dysfunction, and interstitial pulmonary edema.³⁵ Given that the cardiac output in patients with ventricular dysfunction is particularly

sensitive to increases in afterload, the most direct mechanism through which OSAHS could worsen left ventricular function would be through its effect on systemic blood pressure. Thus, when a patient with heart failure presents repeated obstructive apneas, blood pressure is increased to levels higher than those during the day.³⁶ In patients with heart failure that is stable with medical treatment, the presence of OSAHS is associated with increased daytime blood pressure proportional to the number of apnea and hypopnea events.³⁷

The repeated increases in negative intrathoracic pressure that occur during apnea events, which in patients with heart failure could reach pressures of -65 mm Hg, generate a large increase in afterload and myocardial oxygen demand. There are greater reductions in systolic volume in patients with heart failure than in control individuals with preserved systolic function.³⁸

Finally, increased concentrations of certain inflammatory mediators, production of oxygen radicals, and the development of varying degrees of endothelial dysfunction in patients with OSAHS can also promote and accelerate arteriosclerosis. Given that ischemic heart disease is the main cause of left ventricular dysfunction, OSAHS could worsen ventricular dysfunction through effects on the coronary arteries.

Epidemiology and Clinical Impact

Preliminary studies described the appearance of acute pulmonary edema during the night in some patients with OSAHS and normal left ventricular function.³⁹ It was also reported that the thickness of the left ventricular wall was greater in nonhypertensive patients with OSAHS than in healthy subjects.⁴⁰ In a larger study, left ventricular hypertrophy was identified in 41% of patients with OSAHS and it was demonstrated that hypertrophy was directly related to the AHI and the length of time during sleep in which arterial oxygen saturation (SaO_2) was less than 90%.⁴¹ The improvement in systolic and diastolic left ventricular function when obstructive apnea events are abolished reinforces the association between the 2 diseases.^{7,11,42-44} Laaban et al⁴⁵ undertook a prospective study of 169 patients with OSAHS with no known presence of heart disease and observed systolic dysfunction in 13 patients, corresponding to a prevalence of 7.7% (left ventricular ejection fraction [LVEF], 42% [6%]), having ensured that inducible ischemia was not present.

The main epidemiologic study undertaken to date analyzing the association between OSAHS and different cardiovascular diseases, the Sleep Heart Health Study,⁴⁶ demonstrated an increased risk of developing hypertension, ischemic heart disease, or cerebrovascular accidents, but the strongest association was observed

Prevalence of Sleep-Disordered Breathing in Patients With Heart Failure*

Author and Reference	No.	AHI	LVEF	Respiratory Disorders	OSAHS	CSAHS
Lofaso et al ⁵⁰	29	10	<25	9 (45%)	1 (5%)	8 (40%)
Javaheri et al ⁵²	81	15	25 (9)	41 (51%)	9 (11%)	32 (40%)
Lanfranchi et al ⁵¹	66	10	23 (6)	50 (76%)	4 (6%)	46 (70%)
Tremel et al ⁴⁷	34	10	30 (10)	28 (82%)	7 (20%)	21 (62%)
Sin et al ^{49†}	450	10	27 (16)	316 (70%)	168 (37%)	148 (33%)
Chan et al ^{54‡}	20	10	>50	11 (55%)	7 (35%)	4 (20%)

*LVEF indicates left ventricular ejection fraction; AHI, apnea-hypopnea index; OSAHS, obstructive sleep apnea-hypopnea syndrome; CSAHS, central sleep apnea-hypopnea syndrome.

†Retrospective.

‡Consecutive patients with diastolic heart failure.

with heart failure. The presence of OSAHS with an AHI of at least 11 was associated with a relative risk of 2.38 of presenting heart failure, independently of any other known risk factor.

Many studies have addressed the prevalence of sleep-disordered breathing in patients with heart failure, the majority in patients with left ventricular systolic dysfunction (Table).⁴⁷⁻⁵² The differences observed in the prevalence of respiratory disorders can be easily explained by the different values of AHI considered to define the syndrome, as well as by the different definitions for the concept of hypopnea between different authors. What is also known today is that a relatively low AHI is associated with cardiovascular complications.^{14,46,53} Irrespective of the level of AHI considered, the prevalence of sleep-disordered breathing is found to be very high (45%-82%) in patients with systolic heart failure. However, data is unavailable on the true prevalence of sleep-disordered breathing in patients with heart failure treated concomitantly with drug treatment and nondrug treatment optimized in each patient.

The main prospective study out of those mentioned included 81 men with stable heart failure (LVEF<45%), in whom polysomnography was performed, taking an AHI of at least 15 as the threshold.⁵² Of all the patients, 41 (51%) presented a moderate to severe AHI during sleep, with a mean of 44 (19). Eleven percent of patients presented OSAHS, while 40% presented CSAHS. In those 41 patients with sleep-disordered breathing, the prevalence of atrial fibrillation and ventricular arrhythmias was also significantly higher than in patients without such problems during sleep.

The study containing the largest number of patients was retrospective and included 450 patients of both sexes with a mean LVEF of 27% (16%).⁴⁹ In overall terms, the severity of OSAHS in that group was greater than that observed in the prospective study of Javaheri et al.⁵² This could be because in the study by Sin et al,⁴⁹ one of the reasons for referring patients to the sleep laboratory and therefore to be able to include

them in the study was the presence of risk factors for OSAHS, while that was not the case in the study by Javaheri et al. Of the 450 patients included in the study, 168 (37%) presented OSAHS and 148 (33%) CSAHS, with a higher prevalence of OSAHS in men (38%) than women (31%). The only independent risk factors for presentation of sleep-disordered breathing were body mass index more than 35 in men and age more than 60 years in women.

Taking an AHI of at least 10 as the threshold for disease, Chan et al⁵⁴ assessed the prevalence of OSAHS in 20 men and women with symptomatic isolated diastolic dysfunction assessed by echocardiography, and they found that 11 patients (55%) presented sleep-disordered breathing, 7 (35%) with OSAHS and 4 (20%) with CSAHS. Large epidemiology studies will be needed to determine the true prevalence of sleep-disordered breathing in patients with isolated diastolic ventricular dysfunction, since it has been observed that a large proportion of elderly patients with heart failure present isolated diastolic dysfunction and sleep-disordered breathing could be prevalent in that group. In addition, the presence of OSAHS could constitute an independent cause of diastolic dysfunction in some patients (Figure 2),⁷ and those alterations in diastolic function could also contribute to the development of pulmonary hypertension.⁸

It has been speculated that OSAHS could play a role in the pathogenesis of left ventricular failure in certain patients with heart failure of unknown etiology and that it could be a cause of heart failure. The pathophysiologic processes initiated during repeated episodes of apnea and hypopnea and that involve the cardiovascular system would also allow progression of heart failure in patients in whom the disease is initiated by any type of primary heart disease; in those patients, the respiratory events during sleep would be added either as a consequence of heart failure or independently of it.

Heart failure itself might contribute to the development of OSAHS, and not just to the development

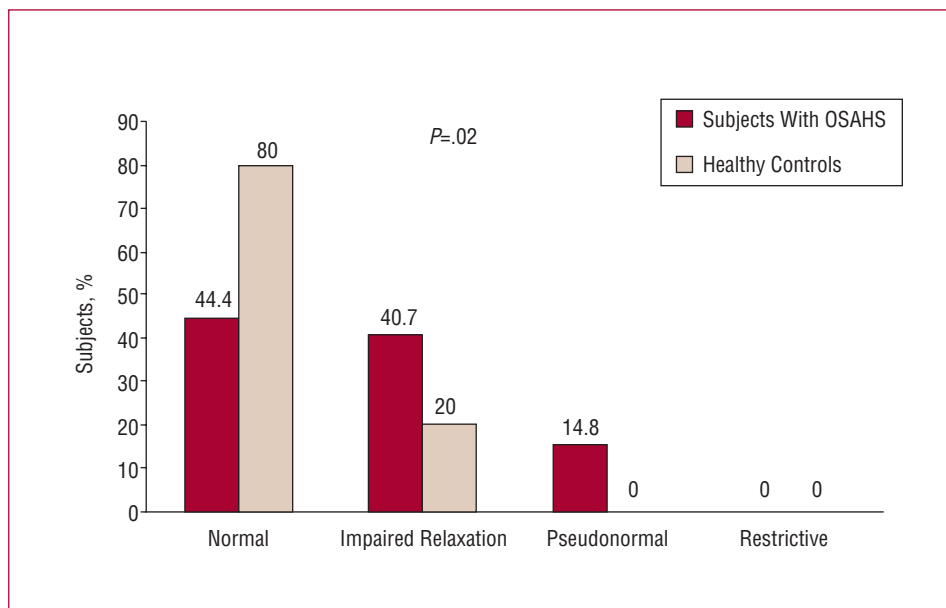


Figure 2. Distribution of the patterns of left ventricular systolic function in healthy individuals and patients with OSAHS. Adapted from Arias et al.⁷ OSAHS indicates obstructive sleep apnea-hypopnea syndrome.

of CSAHS, as will be discussed in the final part of this section. Thus, the CSR that can occur during sleep in patients with heart failure could destabilize the upper airway and predispose to collapse of the airway by reducing the dilatory muscle tone of the pharynx secondary to loss of respiratory drive in the phases of apnea. In addition, the fluid retention that accompanies heart failure syndrome could result in edema of the soft tissue of the neck and pharynx when the patient is in a sleeping position, and this could cause narrowing of the upper airway and even lead to intermittent collapse of the airway.

The clinical characteristics of OSAHS in patients with heart failure are similar to those of other patients with OSAHS but with conserved ventricular function. Thus, patients are usually obese and have a history of snoring. However, the daytime sleepiness typical of OSAHS may be absent,²⁹ suggesting that many patients with heart failure could have undiagnosed OSAHS.

OSAHS can have a particularly negative effect in patients with left ventricular dysfunction, since increased afterload as a result of obstructive apnea has a much greater effect on a ventricle with altered function than on one in which function is conserved. Thus, when individuals with left ventricular dysfunction experience a large negative intrathoracic pressure during the Müller maneuver, they have large reductions in systolic volume and cardiac output that last longer after apnea than in individuals with normal ventricular function.³⁸ In addition, the increased sympathetic activity generated in OSAHS would have very negative prognostic effects in patients with concomitant ventricular dysfunction.

Treatment

The treatment indications for OSAHS regarding its effects on the cardiovascular system, specifically in terms of its effects on left ventricular function, are still not well established. The concept of OSAHS does not only involve a certain number of apnea and hypopnea events; it is also necessary that the patient presents certain characteristic symptoms, mainly excessive daytime sleepiness. It has been reported that many of the patients in whom significant obstructive respiratory events are observed during sleep remain asymptomatic.²⁹ In addition, studies performed to date (in individuals without abnormal ventricular function) to assess the efficacy of nocturnal CPAP for the treatment of OSAHS have only demonstrated significant benefits in symptomatic patients, in whom improvements are seen in the number of apnea and hypopnea events, quality of sleep, excessive daytime sleepiness, and cognitive and neural function, along with reduced daytime and nighttime blood pressure. Such benefits have not been demonstrated when CPAP is used in patients who are asymptomatic, despite presenting an increased AHI.⁵⁵

Consequently, taking into account the pathophysiologic factors that link OSAHS with heart failure, the question arises as to whether treatment should be provided in all patients with abnormal left ventricular function who present obstructive respiratory events during sleep, irrespective of the presence or absence of symptoms. Even if it is confirmed that OSAHS is a possible cause of heart failure, it is debatable whether it is appropriate to also treat asymptomatic patients with obstructive apnea/hypopnea and without ventricular abnormality to prevent this possible complication in the long-term. Future

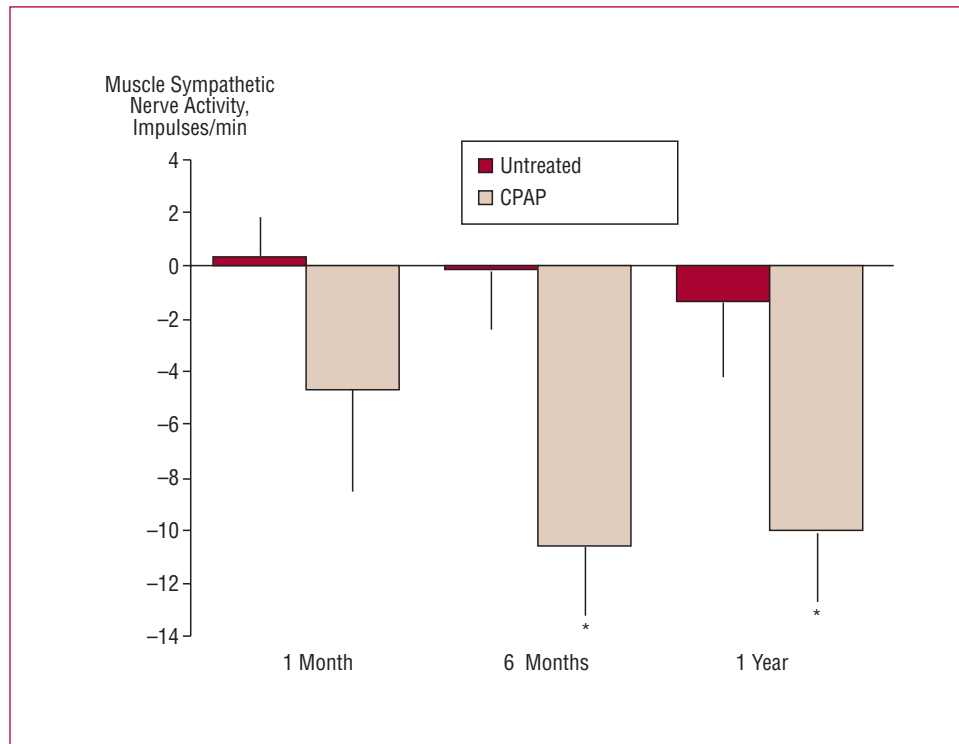


Figure 3. Muscle sympathetic nerve activity in patients with OSAHS with and without treatment using CPAP. Adapted from Narkiewicz et al.⁵⁷ CPAP indicates continuous positive airway pressure; OSAHS, obstructive sleep apnea–hypopnea syndrome.

prospective studies will be required to provide answers to these questions.

In the meantime, it seems reasonable to indicate treatment with nocturnal CPAP in patients with OSAHS and heart failure who present symptoms characteristic of this type of sleep-disordered breathing. Of course, the therapeutic approach should consider, in addition to CPAP, general measures that have been demonstrated to generate improvements of the syndrome, such as reducing body weight. It is also advisable to suspend the consumption of substances that predispose to collapse of the pharynx during sleep due to loss of muscle tone in that structure, such as alcohol and benzodiazepines.

Currently available information on the use of CPAP in patients with heart failure and OSAHS is still limited, although most studies report a favorable clinical effect of the treatment on various factors associated with the structure and function of the cardiovascular system.^{7,8,11,12,43,44} Some of the beneficial effects of applying CPAP in these patients would be reduction of sympathetic activity both during sleep and while the patient is awake^{56,57} (Figure 3), increased variability of heart rate, improved vasodilatory capacity of the endothelium, improved hypercoagulability, and improved leukocyte activation. In addition, the abolition of apnea and hypopnea events through application of CPAP prevents recurrent hypoxemia, reduces nocturnal blood pressure and heart rate, and increases the sensitivity of the baroreflex. Suppression of obstructive

apneas and arousals leads to a reduction in myocardial oxygen demand due to reduced sympathetic activity, increased intrathoracic pressure, and reduced left ventricular end-diastolic pressure, and increases coronary blood flow due to increased cardiac output, thereby increasing coronary perfusion. The effects on systolic volume are dependent upon left ventricular function. When that is normal, CPAP reduces venous return, limits ventricular filling, lowers afterload, and reduces systolic volume. In contrast, when ventricular function is abnormal and, therefore, left ventricular end-diastolic pressure is increased, the reduction in preload improves the force–length relationship of the myocardium and increases the systolic volume and cardiac output.

The study by Malone et al⁴³ was the first to assess the effects of treatment with CPAP on left ventricular function in patients with heart failure. It was an uncontrolled study of 8 patients with idiopathic dilated cardiomyopathy and OSAHS with a mean LVEF of 37%, in whom CPAP was applied over a period of 1 month. An increase in LVEF was observed that reached a mean of 49%, as well as an improvement in the functional class of the patients. However, these beneficial effects disappeared a week after suspension of treatment.

There are 2 main randomized trials available that have addressed the effect of treatment with CPAP in patients with heart failure and left ventricular systolic dysfunction.^{11,12} Kaneko et al¹¹ performed a randomized

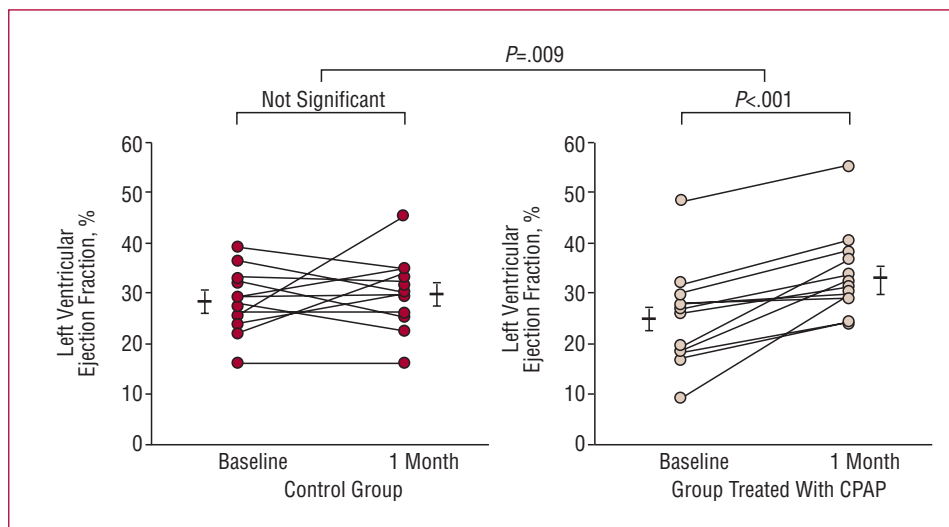


Figure 4. Response of the left ventricular ejection fraction, %, to a month of treatment with CPAP in patients with OSAHS and systolic heart failure. Adapted from Kaneko et al.¹¹ CPAP indicates continuous positive airway pressure; OSAHS, obstructive sleep apnea-hypopnea syndrome.

controlled trial of 1 month of treatment with CPAP in which 24 patients were included with heart failure due to ischemic heart disease or nonischemic dilated cardiomyopathy and OSAHS (AHI \geq 20) with optimized drug treatment of heart failure and in a stable clinical condition during the previous 3 months. In the 12 patients included in the group treated with CPAP there was a reduction in daytime heart rate and systolic blood pressure, with a 9% increase in mean LVEF (Figure 4). Mansfield et al¹² studied the effects of treatment with CPAP for 3 months in 40 patients with heart failure and OSAHS (mean AHI, 25; mean LVEF, 38%). In addition to improvements in the scores on quality-of-life questionnaires and in daytime sleepiness, after 3 months of treatment with CPAP a statistically significant increase was observed in LVEF from 38 ± 3 to $43 \pm 0\%$, as well as a reduction in the nocturnal concentration of urinary catecholamines.

Information is still lacking on the long-term benefits of treatment with CPAP in patients with OSAHS and heart failure in terms of morbidity and mortality. Data is also unavailable regarding the effectiveness of other treatments for OSAHS, such as mandibular advancement devices or surgery, in patients with heart failure.

Various studies have analyzed the effects of treatment with CPAP on left ventricular diastolic function in patients with OSAHS,^{7,42,44,58} and in all of them an improvement was observed in variables associated with diastolic function following treatment with CPAP. In addition, it has been demonstrated that subjects with OSAHS and conserved left ventricular systolic function have a worse cardiovascular response to exercise than healthy subjects, and that this reduced response is improved following treatment with CPAP.⁵⁹ The cardiovascular response could be related to the presence of abnormal diastolic function in many patients with OSAHS (Alonso-Fernández et al,

unpublished results). The main study in this field, that of Arias et al,⁷ was a randomized, placebo-controlled trial in which the presence of abnormal diastolic function was assessed in 15 healthy subjects and 27 patients with OSAHS without evidence of any type of cardiovascular disease, along with the effect of treatment for 3 months with CPAP on echocardiographic variables associated with diastolic function in the patients with OSAHS. In that study, it was concluded that OSAHS can affect left ventricular diastolic function independently of other factors and that treatment with CPAP leads to improvement in the diastolic function variables assessed; that improvement would prevent progression of diastolic function abnormalities.

CENTRAL SLEEP APNEA-HYPOPNEA SYNDROME AND HEART FAILURE

CSAHS with CSR is very common in patients with heart failure and appears to be more of a consequence than a cause of the heart failure. It is characterized by increases and decreases in tidal volume separated by periods of apnea or hypopnea without accompanying respiratory effort and has a typical duration of 30 to 60 seconds.

In some individuals with heart failure, OSAHS and CSAHS coexist, and in those cases there may be a gradual change in the type of respiratory events over the course of the sleep period, such that they may be predominantly obstructive at the beginning of sleep and central towards the end of the night.⁶⁰ One or other type of event can predominate in the same patient according to the progressive degree of left ventricular dysfunction, and over the years the presence of obstructive apnea events in individuals with heart failure may predispose them to also have CSAHS with periodic respiration.

Pathophysiology

In patients with heart failure, CSAHS is associated with hypocapnia as a result of the presence of elevated end-diastolic ventricular pressures that lead to pulmonary congestion, which in turn triggers a state of hyperventilation and of increased central and peripheral chemosensitivity. The episodes of apnea are triggered by a decrease in PaCO₂ to below the apnea threshold as a consequence of hyperventilation. At the end of the apnea episode, and as a result of increased chemosensitivity, there is an exaggerated response to oxygen desaturation and increased PaCO₂, leading to increased ventilation, with a reduction in PaCO₂, perpetuating the cyclic state of alternation between apneas and hyperventilation typically observed in patients with heart failure and CSAHS. The length of the subsequent phase of hyperventilation is inversely proportional to the cardiac output, reflecting a delay in the transmission of changes in arterial blood gases from the lungs to the peripheral chemoreceptors. This extension of the circulation time causes the breathing pattern typical of periodic respiration and, specifically, of its cycle length, although it is not responsible for triggering central apneas.

From a pathophysiologic perspective, CSAHS has some negative effects on the cardiovascular system, mainly due to 3 factors occurring during the repeated episodes of central apnea, largely shared with those mentioned for obstructive apneas:

1. Intermittent anomalies in the partial pressures of blood gases and, specifically, the presence of repeated cycles of hypoxia/reoxygenation and hypercapnia/hypocapnia. Hypoxemia can have negative effects on the cardiovascular system via mechanisms such as reduced oxygen supply to the ventricular myocardium, sympathetic hyperactivation not only during periods of sleep but also continuously while the individual is awake, development of abnormalities of vascular endothelial function, or the production of a state of pulmonary arteriolar vasoconstriction. The last of those could in turn cause increases in right ventricular afterload that in the long-term would lead to deterioration of right ventricular function, with the associated negative prognostic consequences. The generation of cycles of hypoxia and reoxygenation favors breaking the balance in the production of vasoactive substances and components of the clotting system, and this favors the development of procoagulant conditions and vasoconstriction.

2. Generation of arousals with disorganization of normal sleep states. These arousals, which are produced during the ventilatory phase and contribute to oscillations of the breathing pattern, along with the blood gas abnormalities mentioned, lead to increased sympathetic activity, and this is fundamentally important

as a negative prognostic marker in patients with heart failure. The presence of CSAHS could therefore contribute to deterioration of heart failure. A characteristic of patients with CSAHS is that despite the occurrence of arousals, snoring during sleep and excessive daytime sleepiness are not common.

3. Although to a lesser extent than obstructive apneas, following central apneas, in the hyperpnea or ventilatory phase, there is a certain increase in ventricular transmural pressure. The reduced elasticity of the lung due to congestion of the parenchyma means that the intensity of inspiratory effort is increased in the ventilatory phases, and that causes repeated reductions in intrathoracic pressure, not during the apneas but rather during the ventilatory phases, with the associated increase in afterload as a consequence of increased negative intrathoracic pressure. This increase can become hemodynamically significant, due to the greater sensitivity to small changes in afterload in patients with heart failure.

Epidemiology and Clinical Impact

The prevalence of CSAHS is much higher in patients with heart failure than in those without, and in addition, the presence of CSAHS in those patients carries with it negative prognostic implications in terms of mortality and the requirement for heart transplant,^{51,61} although epidemiologic data is still unavailable assessing groups of patients with heart failure with optimized treatment. It has been demonstrated that optimization of treatment for heart failure can reduce the severity of CSAHS by stabilizing ventilatory control of the patients. As mentioned, one of the principal mechanisms implicated in the cardiac effects of CSAHS would be the presence of sympathetic hyperactivity, and at the same time, the introduction of treatment with β -blockers in patients with heart failure has been shown to reduce mortality due to attenuation of the state of sympathetic hyperactivity displayed by these patients. In patients with heart failure and CSAHS the introduction of these drugs in the treatment has been associated with a reduction in the incidence of adverse events.⁶²

On the other hand, CSAHS in patients with heart failure has been associated with reduced physical capacity and a higher incidence of ventricular arrhythmias.^{52,63}

In the 2 main epidemiologic studies that have assessed the prevalence of CSAHS in patients with heart failure, in which 450 and 81 patients were included, the prevalence of CSAHS was 33% and 40%, respectively.^{49,52} The main risk factors for presentation of CSAHS in patients with heart failure, based on the analysis performed in the study with the largest number of patients,⁴⁹ would be male sex, hypocapnia, atrial fibrillation, and advanced age. However, obesity was not found to be a significant risk factor. It is also worth noting the low prevalence of the syndrome in women,

for as yet unknown reasons, as this could influence the increased mortality in men with heart failure.

Treatment

As heart failure is the fundamental cause of CSAHS with periodic respiration, the first therapeutic measure that should be considered in these patients is the optimization of cardiopulmonary function using the standard therapeutic measures for these individuals. Those therapeutic measures, by improving structural and functional cardiac parameters, and therefore, hemodynamic status, will improve, and in some cases even eliminate, sleep-disordered breathing, essentially by normalizing PaCO₂, increasing functional residual capacity, decreasing circulation time, and increasing the diameter of the upper airway.

In patients in whom episodes of central apnea persist despite optimization of treatment specifically aimed at improving heart failure, various forms of treatment have been studied with variable results.

Various drugs that act as circulatory stimulants, such as theophylline and acetazolamide, have been proposed as treatments for CSAHS in patients with heart failure. The first has a central action and increases myocardial contractility by acting as a cellular adenosine antagonist, and the second, an inhibitor of carbonic anhydrase, stimulates respiration by production of metabolic acidosis and also has a diuretic effect. However, the clinical safety of the drugs in this context remains to be determined and their use is not recommended.

Atrial pacing using a permanent pacemaker was initially suggested on the basis of data obtained in a randomized study involving patients with sleep-disordered breathing in whom permanent pacing was indicated and who did not have heart failure, since it was found that those in whom atrial pacing was provided at a frequency 15 beats faster than the baseline frequency displayed a reduction in the rate of both central and obstructive respiratory events of up to 50%.⁶⁴ In various subsequent randomized trials undertaken in individuals without heart failure and with obstructive apneas, no significant reduction has been observed in the rate of apneas/hypopneas,^{65,66} and currently this treatment modality is not considered indicated as a first-line treatment for sleep-disordered breathing. However, it seems reasonable that the hemodynamic improvement generated by the treatment in subjects with heart failure in whom permanent cardiac pacing is indicated could lead to a reduction in central apneas with periodic respiration in many patients.

Nocturnal nasal oxygen provision has been shown to significantly reduce the severity of CSAHS in patients with heart failure.^{67,68} Although a reduction in nighttime sympathetic activity is achieved, to date no studies have demonstrated an improvement in terms of clinical results and cardiovascular function. Mechanisms such

as increased PaCO₂, reduced ventilatory response to CO₂, and an increase in body oxygen reserves could be linked to the therapeutic effects of nocturnal oxygen therapy in this clinical context. An added problem in this type of treatment is the potential to generate hyperoxia, which would facilitate increased cellular oxidative stress, with the consequent problems which that would imply, such as increases in peripheral resistance, blood pressure, and ventricular filling pressures, as well as reducing cardiac output in those patients. As a consequence of the above, to date, clear scientific evidence is unavailable on the effects of oxygen supplementation in patients with heart failure and CSAHS and long-term results from randomized placebo-controlled trials will be needed to establish the true benefits in terms of reduction of morbidity and mortality in patients with heart failure and CSAHS.

Provision of CPAP in patients with heart failure (with elevated left ventricular end-diastolic pressures) leads to a reduction in afterload due to increased intrathoracic pressure, increases systolic volume, reduces sympathetic activity, reduces preload by lowering venous return, and thus, lowers ventricular filling pressures. In contrast, the acute response of cardiac output to treatment with CPAP in awake patients with heart failure is different in patients with atrial fibrillation and/or reduced left ventricular filling pressures, in whom application of CPAP leads to a reduction in cardiac output. However, the long-term hemodynamic effects of chronic application of CPAP in the first group of patients—those with low left ventricular filling pressures and/or atrial fibrillation—are not known.

The clinical results of applying CPAP in patients with heart failure and CSAHS are not uniform, although gradual titration of the applied pressure until high pressures are achieved (8-12.5 mm Hg) is accompanied by more favorable results, with a significant reduction in the frequency of central apneas. In those studies, nocturnal application of CPAP (1 to 3 months) in patients with heart failure and left ventricular systolic dysfunction has been shown to significantly reduce central apneas and eliminate oxygen desaturation, reduce sympathetic activity, generate a reduction in the density of ventricular extrasystoles, and even improve left ventricular systolic function.^{61,69-71} In one of those studies, 66 patients with heart failure, 29 of whom had CSAHS, were randomized to receive nocturnal CPAP over 3 months or a control situation without CPAP.⁶¹ In that study, a reduction in mortality and incidence of heart transplant was observed after a mean follow-up of 2.2 years in the group that received CPAP. In patients with heart failure and CSAHS, it was also found that there was an improvement in LVEF after 3 months of treatment with CPAP.⁶¹ The limited number of patients included in these studies, as well as the lack of optimized medical treatment of heart failure (particularly the low percentage of patients

treated with β -blockers), limit the current validity of the results. The most important study that has assessed the effects (morbidity, mortality, and cardiovascular function) of application of CPAP in patients with heart failure, reduced systolic function, and CSAHS included 258 patients who were randomized to receive CPAP plus medical treatment of heart failure or medical treatment alone.⁶² Despite demonstrating an improvement in the severity of CSAHS, left ventricular systolic function, oxygen saturation, and level of sympathetic activity in patients treated with CPAP, the study was terminated prematurely having not observed differences between the groups in terms of survival, rate of hospital admissions, or quality of life of the patients. Therefore, until new studies are performed or that study is subjected to subsequent analysis, which might allow identification of subsets of patients in whom the treatment is beneficial in terms of reduced mortality, current data are not sufficient to indicate the use of that treatment systematically in patients with heart disease and CSAHS. What is known is that the application of CPAP in this clinical context only improves cardiovascular function when a reduction is achieved in the frequency of central apneas; thus, the use of other forms of applying positive airway pressure that effectively reduce the severity of CSAHS could lead to long-term clinical benefits, although no conclusive data are as yet available.

CONCLUSIONS

The presence of sleep-disordered breathing is very common in patients with heart failure. In many of those patients, the disorder could favor progression of the disease, and in some it could even play a causative role. Treatment of sleep-disordered breathing in this population has been demonstrated to improve a number of variables associated with cardiovascular structure and function, but future randomized multicenter studies will be required to determine whether the treatment is accompanied by benefits in terms of mortality.

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