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SYSTEMATIC REVIEW

Effects of CPAP on cardiorespiratory outcomes in patients with obstructive sleep apnea and heart failure: a systematic review

Efeitos da pressão positiva contínua nas vias aéreas nos desfechos cardiorrespiratórios em pacientes com apneia obstrutiva do sono e insuficiência cardíaca: uma revisão sistemática

Efectos de la presión positiva continua en las vías aéreas en los resultados cardiorrespiratorios en pacientes con apnea obstructiva del sueño e insuficiencia cardíaca: una revisión sistemática

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ABSTRACT | Obstructive sleep apnea (OSA) is a public health problem with a great economic impact. It is estimated that the prevalence of patients with OSA ranges from 4% to 6% of men and 2% to 4% of women in the general population. Strong evidence suggests that both sleep disorders and heart failure (HF) are related. Continuous positive airway pressure (CPAP) is the gold standard non-pharmacological treatment for this population. However, there is still a gap in the literature and its effects in patients with OSA and HF are not entirely clear. This study aimed to evaluate, by randomized clinical trials, the effects of positive pressure on cardiorespiratory function in patients with OSA and HF. Randomized clinical trials were included, with publication in the MEDLINE, PEDro, Cochrane Library, SciELO and PubMed databases and the risk bias was assessed using the PEDro scale. Six articles were included in this study, involving 165 participants. Our findings demonstrate that CPAP in the treatment of OSA in patients with HF promotes an increase in left ventricular ejection fraction, oxygen saturation and a reduction in blood pressure, apnea/hypopnea indices and awakenings from sleep during the night. We conclude that treatment with CPAP promotes an improvement in cardiorespiratory outcomes in patients with OSA and HF, improving the prognosis and reducing the risk of sudden death. However, their data must be cautiously interpreted considering the bias of the studies and their limitations.

Keywords | Continuous Positive Airway Pressure; Obstructive Sleep Apnoea; Heart Failure; Systematic Review.

RESUMO | A apneia obstrutiva do sono (AOS) é um problema de saúde pública de grande impacto econômico. Estima-se que a prevalência de portadores de AOS seja de 4% a 6% entre os homens e de 2% a 4% entre as mulheres da população em geral. Há fortes evidências de que os distúrbios do sono e a insuficiência cardíaca (IC) estão relacionados. A pressão positiva contínua nas vias aéreas (CPAP) é o tratamento não farmacológico padrão ouro para essa população. No entanto, ainda há uma lacuna na literatura, e seus efeitos em pacientes com AOS e IC não estão plenamente estabelecidos. Assim, o objetivo deste estudo foi avaliar através da revisão de ensaios clínicos randomizados os efeitos da CPAP na função cardiorrespiratória em pacientes com AOS e IC. Foram incluídos seis ensaios clínicos randomizados, publicados nas bases de dados MEDLINE, PEDro, Cochrane Library, SciELO e PubMed, totalizando 165 participantes. O risco de viés foi avaliado através da escala PEDro. Nossos achados demonstraram que a CPAP no tratamento da AOS em pacientes com IC promove um aumento da fração de

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ejeção do ventrículo esquerdo e da saturação de oxigênio e uma redução da pressão arterial, dos índices de apneia/hipopneia e dos despertares durante a noite. Concluímos que o tratamento com CPAP promove uma melhora nos desfechos cardiorrespiratórios em pacientes com AOS e IC, beneficiando o prognóstico e reduzindo os riscos de morte súbita. Porém, os resultados devem ser interpretados com cautela, considerando o viés dos estudos e suas limitações.
Descritores | Pressão Positiva Contínua nas Vias Aéreas; Apneia Obstrutiva do Sono; Insuficiência Cardíaca; Revisão Sistemática.

RESUMEN | La apnea obstructiva del sueño (APS) es un problema de salud pública con gran impacto económico. Se estima que la prevalencia de portadores de AOS es del 4% al 6% en los hombres y del 2% al 4% en las mujeres en la población general. Existe una fuerte evidencia de que tanto los trastornos del sueño como la insuficiencia cardíaca (IC) tienen una asociación entre sí. La presión positiva continua en las vías respiratorias (CPAP) es el tratamiento no farmacológico estándar de oro para esta población. Sin embargo, aún existe un vacío en la literatura y sus efectos en pacientes con AOS e IC no están del todo claros. Ante esto, el objetivo de este estudio es evaluar, mediante ensayos clínicos aleatorizados, los efectos de la CPAP sobre la función cardiorrespiratoria en pacientes con AOS e IC. Se incluyeron seis ensayos clínicos aleatorizados, con publicación en las bases de datos MEDLINE, PEDro, Cochrane Library, SciELO y PubMed, con un total de 165 participantes. El riesgo de sesgo se evaluó mediante la escala PEDro. Nuestros hallazgos demuestran que la CPAP en el tratamiento de la AOS en pacientes con IC promueve un aumento de la fracción de eyección del ventrículo izquierdo y de la saturación de oxígeno, y una reducción de la presión arterial, de los índices de apnea/hipopnea y de los despertares nocturnos. Se concluye que el tratamiento con CPAP promueve una mejora en los resultados cardiorrespiratorios en pacientes con AOS e IC, mejorando el pronóstico y reduciendo el riesgo de muerte súbita. Sin embargo, sus datos deben interpretarse con cautela considerando el sesgo de los estudios y sus limitaciones.
Palabras clave | Presión Positiva Continua en la Vía Aérea; Apnea Obstructiva del Sueño; Insuficiencia Cardíaca; Revisión Sistemática.

INTRODUCTION

Obstructive sleep apnea (OSA) is a public health problem with significant economic impact[1]. Apnea is defined as the absence of airflow in the upper airways for a period of at least 10 seconds (complete airway occlusion), while hypopnea occurs when there is a reduction (0.50%) in airflow also for at least 10 seconds (partial airway narrowing)[2]. OSA is caused by a collapse of the pharynx and may occur at different levels, being more frequent in the retropalatal area and rarely at the level of the epiglottis or glottis[3]. This is the most common sleep disorder and is characterized by repeated episodes of upper airway partial obstruction (obstructive hypopnea) or complete obstruction (obstructive apnea) during sleep[1].

The prevalence of OSA is estimated at 4–6% among men and 2–4% among women in the general population, with an increased incidence in the age group above 70 years[4]. Studies have concluded that obesity and the male sex are the risk factors most strongly associated with OSA and that the prevalence of this syndrome is higher in men than in women[3].

The occurrence of repetitive apnea exposes the cardiovascular system to hypoxia and awakenings from sleep[5]. The clinical manifestations of this condition: loud and frequent snoring, pauses in the respiratory cycle, intermittent nocturnal awakenings, daytime fatigue and sleepiness, difficulty concentrating, and mood changes[1]. OSA, when not properly diagnosed and treated, can have serious hemodynamic consequences, and even lead to death. Some of the complications that may occur are systemic and pulmonary arterial hypertension, cardiac arrhythmias, ischemic heart disease, congestive heart failure, and Cheyne-Stokes respiration[3]. There is strong evidence that sleep disorders and heart failure may be related[2,6-8].

Heart failure (HF) has been identified as an important public health problem, being considered an emerging epidemic with high mortality and morbidity. As one of the main diseases that affect the heart, HF is the most important clinical problem today. Fatigue, dyspnea and water retention are the three classic clinical manifestations of this disease[4]. OSA, chronic lung disease and diabetes are common conditions in patients with HF, being negative factors for the clinical prognosis[9]. Among patients with reduced left ventricular ejection fraction (LVEF), 45% have sleep apnea[10].

OSA is diagnosed through polysomnography in a sleep laboratory, which quantifies the apnea-hypopnea index (AHI) per hour of sleep and assesses the severity of the disease[1]. Qualified professionals are responsible for interpreting the data provided by the exam and defining the best treatment options, which can be measures aimed at patient education, body weight reduction, use of mandibular advancement devices, surgical treatment, or use of continuous positive airway pressure (CPAP)[3].

CPAP is the most widely used resource for cases of OSA, as it is the gold standard treatment for sleep disorders and is also recommended for OSA in patients with chronic HF[11]. Its use can contribute to improve cardiac function even when there are anatomical changes at the pharyngeal level[11]. Positive air pressure is used, which keeps upper airways unobstructed during sleep in order to avoid collapse[3]. The effect is obtained through the use of a device with different nasal, oronasal or facial interfaces (masks)[1]. It is known that CPAP is one of the most effective therapies in the treatment of OSA[12]; however, its effects in patients with OSA and HF are still not fully established. Only one systematic review evaluated the effects of the treatment on the airways in patients with OSA associated with HF. However, it included studies with patients affected by different types of apnea (for example, central sleep apnea, obesity hypoventilation syndrome, and Cheyne-Stokes respiration)[4], in addition to not having been registered in the International Prospective Register of Systematic Reviews (PROSPERO). Thus, our systematic review aims to evaluate through randomized clinical trials the effects of CPAP on cardiorespiratory function in patients with OSA and HF.

METHODOLOGY

This systematic review was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13] and was previously registered in PROSPERO (under No.: CRD42023400304). The population, intervention, comparison, outcome, and time (PICOT) question model was followed, being: (P) patients with HF and OSA; (I) use of nocturnal CPAP; (C) any other intervention or control group; (O) cardiorespiratory effects, quality of life, and daytime sleepiness scale; and (T) medium-term intervention time (one to six months).

The search was performed in the PubMed, SciELO, Cochrane, PEDro and MEDLINE databases from the beginning of the publications in the databases until March 2023, using the following combinations of descriptors: (1) continuous positive airway pressure OR CPAP, and (2) obstructive sleep apnoea OR apnoea OR sleep wake disorders, and (3) heart failure, and (4) controlled clinical trial.

The studies were selected based on the following inclusion criteria: (1) randomized clinical trials; (2) with humans diagnosed with HF and OSA; (3) who have undergone treatment with CPAP; and (4) with cardiorespiratory alterations present (for example, HF, acute myocardial infarction, denaturation, ischemic heart diseases, among others). The studies were selected by two independent reviewers through the reading of titles, identification of duplicates, reading of abstracts and reading of full text. In cases of disagreement, a third reviewer was consulted.

Two independent reviewers extracted from the studies the following information: author and year of publication; sample characteristics (number of participants, mean age); diagnosis (according to study description); prescription (time of use of CPAP in hours/night); intervention (intervention group and control group); time of intervention; outcomes; main results; and PEDro scale score.

Each study was assessed as to risk of bias using the PEDro scale[14], which has high levels of reliability and validity. The score ranges from 1 to 10: studies with a score equal to or greater than 7 were considered to have a low risk of bias, while studies with a score equal to or less than 6, a high risk of bias[15,16].

Data analysis used a descriptive approach. We conducted a general comparison of the effects of CPAP in patients with OSA and HF on cardiovascular and respiratory outcomes, quality of life, exercise capacity, and Epworth sleepiness score.

RESULTS

The search in the different databases resulted in 105 articles. After removal of duplicate studies, 100 studies remained. Through the reading of titles and abstracts, 88 studies were excluded, leaving 12 studies for reading. After full reading, we removed six more studies (two for evaluating other results, two for evaluating only one group, and two for evaluating another type of positive pressure or treatment); thus, six articles were included in this systematic review, totaling 165 patients (Figure 1)[17-22].

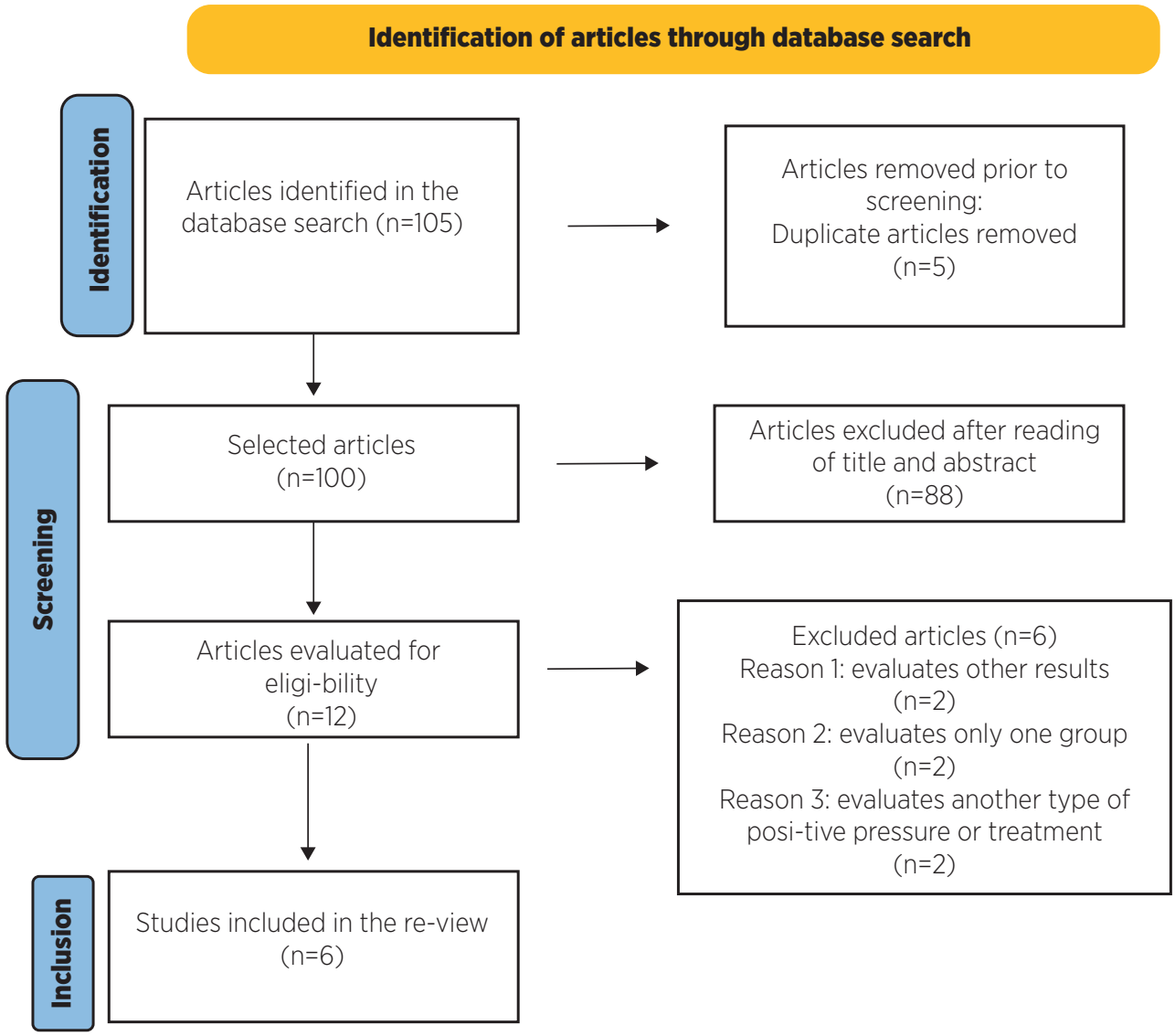

Figure 1. Study selection flowchart

The included studies were published between 2003 and 2008 (Table 1). Four studies used as intervention CPAP associated with optimal drug treatment for HF[17-20]; one study adopted CPAP in the intervention group, while the control group was neither treated nor received any intervention[16]; and one study employed auto-titrating CPAP in the intervention group and simulated CPAP with 1 cmH_2O pressure in the control group[22]. The CPAP parameters used in the studies were titrated at an average of 7–8.8 cmH_2O of nocturnal CPAP. Patients were instructed, for a period of one to six months, to use CPAP for as long as possible per night, with an average adherence of four to six hours per night[17-22].

In our findings, of the six studies included, five showed a statistically significant difference for the outcome of increased LVEF[17-22]; three showed an improvement in blood pressure (BP)[17,18,20,21]; four studies showed an increase in minimum saturation[17-19,21]; one observed a decrease in heart rate (HR)[17,18]; five studies had a decrease in AHI[17,18,20,21]; three showed a reduction in the number of awakenings from sleep/hour (AFSH)[17-20]; two studies had a decrease in urinary norepinephrine (UNE) or other catecholamines[17,21]; one study showed an improvement in the quality of life scale (SF-36)[21]; three studies showed a decrease in the Epworth sleepiness score (ESS)[21,22]; and one study showed a decrease in ventricular premature beat (VPB)[17]. One study evaluated exercise capacity, but there was no significant change for this outcome[22].

Table 1. Characteristics of selected articles

Author (year)	Sample (N; NFem; Mean age)	Prescription (hours) nocturnal CPAP and Intervention time	Design (intervention group × control group)	Outcomes	Results IG × CG
Ryan et al. (2005)[17]	10; 8; IG: 57,6 (2,2); CG: 60,3 (4,1)	6 hours 1 month	**IG:** Ideal drug treatment for HF+nocturnal CPAP (average of 8.0±0.5 cmH_2O) **CG:** Drug treatment for HF (digoxin, diuretic, ACE inhibitors, β-blockers)	Cardiac Effects+Respiratory Effects	VPB: IG<CG UNE: IG<CG LVEF: IG>CG HR: IG<CG SBP: IG<CG DBP: IG<CG AHI: IG<CG AFSH: IG<CG
Kaneko et al. (2003)[18]	12; 12; IG: 55.9 (2.5); CG: 55.2 (3.6)	6 hours 1 month	**IG:** Ideal drug treatment for HF+nocturnal CPAP (an average of 8.9±0.7 cmH_2O) **CG:** Drug treatment for HF (digoxin, diuretics, ACE inhibitors, hydralazine, nitrates, β-blockers)	Cardiac Effects + Respiratory Effects + AFSH	LVEF: IG>CG HR: IG>CG SBP: IG<CG DBP: IG<CG AHI: IG<CG SaO_2: IG>CG AFSH: IG<CG
Gilman et al. (2008)[19]	12; 7; IG: 56.7 (8.0) CG: 58.1 (7.1)	>6 hours 1 month	**IG:** Ideal drug treatment for HF+nocturnal CPAP (average pressure of 8.8±2.4 cmH_2O) **CG:** Drug treatment for HF (digoxin, diuretics, ACE inhibitors, hydralazine, nitrates, β-blockers)	Cardiac Effects + Respiratory Effects + AFSH	HF-HRV: IG>CG LVEF: IG>CG AHI: IG<CG SaO_2: IG>CG AFSH: IG<CG
Ferrier et al. (2008)[20]	19; 7; IG: 58.5 (11.2) CG: 60.3 (4.3)	Participants were instructed to use every night for as long as possible. Average adherence was 4.2 hours per night (range of 0–7.9 hours per night) 6 months	**IG:** Ideal drug treatment for HF+CPAP that was manually titrated with polysomnography. Participants received an educational video and were contacted by phone after one night. After two and four weeks, the results were reviewed by a sleep technician to assess the side effects of CPAP, mask adjustment, and the need for humidification **CG:** Drug treatment for HF (β-blocker, ACE or AT II inhibitor, spironolactone, loop diuretics, digoxin, calcium antagonist, nitrate)	Cardiac effects + Respiratory effects + AFSH + Catecholamines + Quality of life (SF-36) + Exercise capacity + ESS	LVEF: IG>CG* SBP: IG<CG CG* AHI: IG<CG* ESS: IG<CG*
Mansfield et al. (2004)[21]	28; 27; IG: 57.2 (1.7) CG: 57.5 (1.6)	Average time from 5.6 to 0.4 hours 3 months	**IG:** nocturnal nasal CPAP (average pressure of 8.8 to 1.4 mmHg) **CG:** No intervention	Cardiac effects + Respiratory effects + AFSH + ESS + Quality of life (SF-36)	UNE: IG<CG LVEF: IG>CG AHI: IG<CG SaO_2(%): IG>CG ESS: IG<CG Quality of life (SF-36): IG>CG
Smith et al. (2007)[22]	12; 11; 61±8	6 hours 6 weeks	**IG:** auto-titrated nocturnal CPAP (adjusts pressure according to upper airway obstruction). The average CPAP pressure applied was 7±2 cmH_2O) **CG:** simulated CPAP (1 cmH_2O)	Cardiac effects + Quality of life (SF-36) + Exercise capacity	ESS: IG<CG

CPAP: continuous positive airway pressure; CG: control group; IG: intervention group; HF: heart failure; ACE: angiotensin-converting enzyme; VPB: ventricular premature beat; UNE: urinary norepinephrine; LVEF: left ventricular ejection fraction; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; AHI: apnea/hypopnea index; AFSH: awakenings from sleep/hour; SaO_2: oxygen saturation; AT II: angiotensin type 2 receptor; SF-36: quality of life scale; ESS: Epworth sleepiness score; HF: high frequency; HRV: HR variability; * intragroup results only.

In our findings, of the six studies included, five showed a statistically significant difference for the outcome of increased LVEF[17-22]; three showed an improvement in blood pressure (BP)[17,18,20,21]; four studies showed an increase in minimum saturation[17-19,21]; one observed a decrease in heart rate (HR)[17,18]; five studies had a decrease in AHI[17,18,20,21]; three showed a reduction in the number of awakenings from sleep/hour (AFSH)[17-20]; two studies had a decrease in urinary norepinephrine (UNE) or other catecholamines[17,21]; one study showed an improvement in the quality of life scale (SF-36)[21]; three studies showed a decrease in the Epworth sleepiness score (ESS)[21,22]; and one study showed a decrease in ventricular premature beat (VPB)[17]. One study evaluated exercise capacity, but there was no significant change for this outcome[22].

Of the six studies included, only one reached a score equal to 7[22], that is, it presents a low risk of bias; while the other studies obtained scores between 4 and 6[17,18,20-22] on the PEDro scale (Table 2). Considering the items of the PEDro scale, no study blinded therapists; all studies presented measures of accuracy and variability; only one study blinded patients[22]; and only one study analyzed by intention to treat[20].

Table 2. PEDro Scale

Author (Year)	Random-ization	Allocation secrecy	Baseline Comparability	Blinding of participants	Blinding of therapists	Blinding of evaluators	Adequate **follow-up**	intention to treat	Comparison between groups	Measures of accuracy and variability	Total score
Ryan et al. (2005)[17]	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	6/10
Kaneko et al. (2003)[18]	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Gilman et al. (2008)[19]	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	6/10
Ferrier et al. (2008)[20]	No	No	Yes	No	No	Yes	No	Yes	No	Yes	4/10
Mansfield et al. (2004)[21]	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Smith et al. (2007)[22]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	7/10

DISCUSSION

This study aimed to systematically review the literature on the effects of CPAP on cardiorespiratory outcomes in patients with OSA and HF. Of the six randomized clinical trials included in this review, four used CPAP associated with optimal drug treatment for HF in the intervention group and only drug treatment in the control group[17-20]; one applied CPAP in the intervention group, while the control group received no treatment[21]; and one employed auto-titrated CPAP in the intervention group and simulated CPAP with pressure of 1 cmH_2O in the control group[22]. According to the data obtained, we observed that in the group treated with CPAP there was an increase in LVEF, improvement in BP and oxyhemoglobin saturation and a decrease in AHI and AFSH, compared to the control group.

This review was conducted in accordance with the PRISMA[13] recommendations, ensuring consistency and uniformity in the research description. A comprehensive search was conducted in several databases, such as MEDLINE, PubMed, PEDro, Cochrane and SciELO. However, this review also has some limitations: for example, all studies had a small sample of participants and most of them have a high risk of bias. In addition, only English language studies were included. The heterogeneity between time/dose of intervention with CPAP and characteristics of the comparison groups prevented meta-analysis. Thus, the results should be analyzed with caution, taking these limitations into consideration.

To the best of our knowledge, this is the second systematic review that sought to evaluate the effects of CPAP in patients with OSA and HF. However, the previous review, by Thomas et al.[4], included studies with patients with different types of OSA, in addition to not having been registered in PROSPERO. Despite similar criteria, only one study was included in this and in the previous review[20]. Our findings corroborate those of the previous review. Both reviews observed that CPAP treatment promoted an increase in LVEF and oxygen saturation, in addition to a reduction in apnea and hypopnea indices in patients with OSA and HF. Therefore, our review updates the knowledge on this topic by including different studies with higher methodological rigor.

Five of the six studies included had scores equal to or below 6 on the PEDro scale[17-21]. It is noted, however, that blinding of physiotherapists is a complex item to be achieved in randomized clinical trials of physiotherapeutic interventions, due to the nature of the interventions. However, future studies on the topic should have higher methodological rigor, for example, by adequately conducting randomization, maintaining allocation secrecy and blinding patients and evaluators, avoiding losses greater than 15% and using an analysis by intention to treat — items that were not adequately complied with in the studies included in this review. It is also important that they present more clearly the parameters addressed and the significant time for the result of the therapeutic use of CPAP, since the clinical relevance of the treatment for this niche of patients is due exactly to its possible long-term effects, with this being a limitation in the studies included in this review.

We observed through the six studies that CPAP can promote improvement of LVEF and important reduction in AHI and nocturnal hypoxia. These data make it possible to provide a better quality of life and a reduction in sleep disruption in the population addressed, in addition to a considerable decrease in the risks of sudden death, especially when the treatment is combined with drug treatment. The reduction of OSA mortality in HF, as well as the improvement of sleep quality are key points to analyze CPAP as an appropriate therapeutic tool. However, it is necessary that future studies compare different ventilatory modes, that there is a standardization of the time of use per night and of the titration of the continuous positive pressure to be recommended, as well as a verification of the long-term effects.

CONCLUSION

This systematic review suggests that the use of CPAP in patients with OSA and HF is a safe form of non-pharmacological treatment, and confirms that the technique improves LVEF and apnea/hypopnea indices and promotes an increase in oxygen saturation, reducing the risks of sudden death and benefiting the prognosis of patients with this clinical condition. However, there is a limitation as to information on ventilatory mode, recommended use time, most appropriate positive pressure parameters, and monitoring of medium and long-term effects after the intervention period.

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