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Obstructive Sleep Apnea in Heart Failure:

Review of Prevalence, Treatment with Continuous Positive Airway Pressure, and Prognosis

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Obstructive sleep apnea is a sleep-related breathing disorder that has a major impact on cardiovascular function. It has been associated with hypertension, coronary artery disease, cardiac arrhythmias, sudden cardiac death, and heart failure. This review focuses on the relationship between obstructive sleep apnea and heart failure with either reduced or preserved ejection fraction. We discuss the pathophysiology of obstructive sleep apnea, as well as its prevalence, treatment outcomes with continuous positive airway pressure, and prognosis in these 2 distinct types of heart failure. We also identify areas in which further work is needed to improve our understanding of this association in heart failure patients. (Tex Heart Inst J 2018;45(3):151-61)

Key words: Continuous positive airway pressure/methods; heart diseases/epidemiology/etiology; heart failure/complications/therapy; prevalence; risk factors; sleep apnea syndromes/classification/physiopathology; sleep apnea, obstructive/complications/prevention & control/therapy; treatment outcome; ventricular function

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Hart failure (HF), which affects approximately 23 million people worldwide¹ and 5.8 million in the United States, has created a substantial healthcare burden.² The incidence and prevalence of HF are increasing in the U.S., mainly because of an aging population and the ability to prolong cardiac patients' lives by means of innovative therapies.² Many factors contribute to the development and progression of HF; one of these is obstructive sleep apnea (OSA). The prevalence of OSA is substantially higher in patients who have HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) than in the general population. In this literature review, we explore the relationship between OSA and these 2 types of HF and provide perspective on the pathophysiologic and clinical significance of these associations.

Sleep Apnea

Sleep apnea is characterized by partial or complete cessation of breathing during nighttime sleep, resulting in repeated arousal from sleep, oxyhemoglobin desaturation, and daytime sleepiness. Apnea is defined as complete cessation of airflow for >10 s (Table 1).³ Hypopnea, a partial cessation of airflow, is defined as a 50% to 90% reduction in airflow for >10 s, accompanied by a >3% decrease in oxyhemoglobin saturation (SaO₂) and terminated by electroencephalographic arousal.⁴ The 3 types of apnea are central, obstructive, and mixed. Central sleep apnea (CSA) is characterized by a complete withdrawal of central respiratory drive to the inspiratory muscles, including the diaphragm, and results in the simultaneous absence of naso-oral airflow and thoracoabdominal excursions. In OSA, the thoracic inspiratory muscles, including the diaphragm, are active, so thoracoabdominal excursions are seen. Absence of airflow results from upper-airway occlusion caused by lost pharyngeal dilator muscle tone, with consequent pharyngeal collapse. Mixed apnea has an initial central component followed by an obstructive component. Like apnea, hypopnea can also be obstructive or central. We focus here on obstructive causes.

Although OSA is also called obstructive sleep apnea-hypopnea syndrome,⁵ we use the term OSA as defined by the American Academy of Sleep Medicine Task Force, in which 5 or more episodes of apnea or hypopnea occur per hour of sleep (apnea-hypopnea index [AHI]). Clinically, OSA can present as daytime sleepiness or loud snoring, witnessed apneas, arousal due to gasping or choking, impaired concentration or memory, morning headaches, mood disorders, or insomnia.⁴ Obstructive sleep apnea is classified as mild (AHI, 5–14), moderate (AHI, 15–30), or severe (AHI, >30). Attended overnight polysomnography in a sleep laboratory is accepted as the best diagnostic test for measuring AHI. Portable cardiorespiratory monitoring devices have

TABLE I. Terminology Used in Sleep-Disordered Breathing³

Apnea

Cessation of airflow for >10 s

Hypopnea

A reduction in but not complete cessation of airflow to <50% of normal, usually in association with a >3% reduction in oxyhemoglobin saturation, lasting >10 s

Apnea-Hypopnea Index (AHI)

The frequency of apnea and hypopnea events per hour of sleep; a measure of the severity of sleep apnea

Arousal

Transient awakening from sleep, lasting <10 s

Epworth Sleepiness Scale (ESS)

Subjectively measures sleepiness during routine daily activities and is often used as a screening test for detecting excessive sleepiness

NREM (non-rapid eye movement) sleep

Quiet sleep

REM (rapid eye movement) sleep

Active sleep; associated with skeletal muscle atonia and dreaming

Oxygen desaturation

Reduction in oxyhemoglobin saturation, usually consequent to apnea or hypopnea

Polysomnography

Multiparametric electrophysiologic recording of electroencephalographic, electroculographic, electromyographic, electrocardiographic, and respiratory activity to identify sleep-related breathing disturbances

Thoracoabdominal excursions

Measured qualitatively by respiratory inductance plethysmography or by pneumatic respiration transducers placed over the ribcage and abdomen

Adapted with permission from Chowdhury M, et al., *J Card Fail* 2010;16(2):164-74.³

also been developed for in-home screening and diagnosis of OSA. However, despite the advantages of convenience, lower cost, and patient acceptance, they measure fewer physiologic variables than does polysomnography. In-home polysomnographic results have not been meticulously validated and are not considered adequate to guide therapy, particularly in the HF population.

Obstructive Sleep Apnea in the General Population

In the general population, OSA affects approximately 4% of middle-aged men and 2% of middle-aged women.⁶ The lower prevalence of OSA in women is not well understood, although female hormones may play a role.^{7,8} In the Wisconsin Sleep Cohort Study,⁶ a population-based prospective study of cardiopulmonary disorders of sleep in 3,513 participants, the estimated prevalence of undiagnosed sleep apnea was 9% in women and 24% in men. In other studies,⁸⁻¹⁴

population-prevalence estimates for mild and moderate OSA range from 3% to 28% and 1% to 14%, respectively. On the basis of average prevalence, an estimated 1 in 5 adults has at least mild OSA and 1 in 15 has at least moderate OSA.⁷ Data from the Sleep Heart Health Study,¹⁵ in which investigators examined cross-sectional relationships between sleep-related breathing disorders and self-reported cardiovascular disease in 6,424 adults, showed that OSA is associated with a 2.38 relative odds of having HF. The results of several studies in HF populations show a diverse overall prevalence of obstructive and central sleep-related breathing disorders (range, 47%–81%), probably attributable to different demographic criteria (age, sex, ethnicity, and race), risk factors (obesity and comorbid conditions), AHI cutoff, and severity of HF in the different populations.

Pathophysiologic Consequences of Obstructive Sleep Apnea and Heart Failure

Obstructive sleep apnea is characterized by recurrent pharyngeal collapse during sleep. Patients generally have a narrow, highly compliant pharynx that is prone to collapse upon normal withdrawal of pharyngeal dilator muscle tone during sleep, thus enabling airway narrowing (hypopnea) or occlusion (apnea). Many patients are obese, and fat deposition around the pharynx may be partly responsible for pharyngeal narrowing.¹⁶ Evidence suggests that rostral displacement of fluid that has accumulated in the legs during the day causes edema of the peripharyngeal structures when lying asleep, predisposing the individual to OSA.¹⁷⁻²⁰

Obstructive sleep apnea is deleterious to the cardiovascular system through mechanical, chemical, neuro-humoral, and inflammatory mechanisms (Fig. 1).²¹ The immediate effects of an attempted inspiratory effort during an episode of mechanical obstruction to airflow include an exaggerated drop in intrathoracic pressure, hypoxia, and arousal. The drop in intrathoracic pressure increases left ventricular (LV) transmural pressure, which increases afterload; this drop in pressure increases venous return, causing right ventricular distention and a leftward shift of the interventricular septum and consequent decreased LV filling.²² The net result of decreased LV filling and increased afterload is reduced stroke volume. Obstructive sleep apnea also causes marked and repeated elevations in systemic blood pressure (BP) secondary to hypoxia, arousals from sleep, and increased sympathetic nervous system activity (SNA). The SNA is furthered by the decreased stroke volume, by suppression of the sympathetic inhibitory effects of lung stretch receptors by apnea, or both. The combination of increased LV afterload and faster heart rate secondary to augmented SNA leads to myocardial oxygen supply/demand mismatch, acutely predisposing the patient to cardiac ischemia and arrhythmias, and chronically to LV hypertrophy, LV enlargement, and HF.

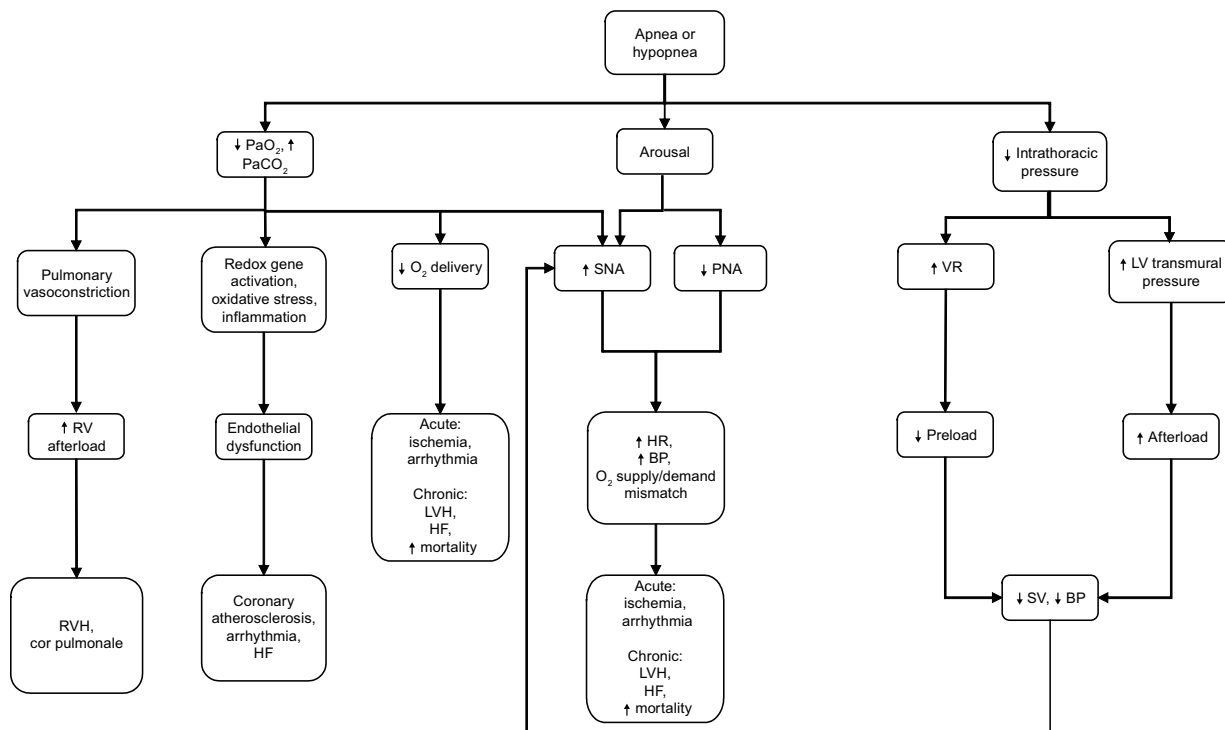


Fig. 1 Diagram shows pathophysiologic mechanisms by which obstructive sleep apnea affects cardiovascular function and heart failure. Modified with permission from Mann DL. *Heart failure: a companion to Braunwald's heart disease*. Philadelphia: Elsevier; 2011. p. 484.²¹

BP = blood pressure; HF = heart failure; HR = heart rate; LV = left ventricular; LVH = left ventricular hypertrophy; PNA = parasympathetic nervous system activity; RV = right ventricular; RVH = right ventricular hypertrophy; SNA = sympathetic nervous system activity; SV = stroke volume; VR = venous return

Except for rapid-eye-movement (REM) sleep, which generally constitutes 20% to 25% of sleep and is associated with short surges of sympathetic activity, sleep generally is a period of increased vagal activity that results in slower heart rates and lower BPs. Conversely, arousals after disordered breathing events in OSA increase SNA and most likely the risk of HF development or progression.²³

Hypoxemia with resultant systolic²⁴⁻²⁸ or diastolic²⁹ dysfunction may also diminish oxygen delivery to the myocardium. Risks include myocardial ischemia, arrhythmias, and sudden cardiac death during sleep from the generation of free oxygen radicals and inflammation. Patients with OSA have low plasma nitrite concentrations and diminished endothelial-mediated vasodilation.³⁰ Reactive oxygen species selectively activate inflammatory pathways by activating nuclear factor-kappa B (NFκB) rather than hypoxia-inducible factor-1 (HIF-1), the transcriptional regulator of the adaptive pathway.³¹ Activation of NFκB leads to increased production of tumor necrosis factor-α, interleukin-6, interleukin-8, and C-reactive protein, as well as adhesion molecules such as intracellular and vascular cell adhesion molecules, E selectin, and CD15,³² that can lead to endothelial damage, atherogenesis, and HF. Infiltrating

inflammatory cells activate profibrotic transforming growth factor-β, which leads to increased deposition of extracellular matrix and consequent myocardial fibrosis,³³ and to worsening LV diastolic function.

Prevalence of Obstructive Sleep Apnea in Heart Failure with Reduced Ejection Fraction

Polysomnographic³⁴⁻³⁹ and polygraphic study results⁴⁰⁻⁴² have shown a higher prevalence of sleep-disordered breathing (SDB) (47%–81%) and OSA (12%–53%) in HFrEF patients than in the general population (Fig. 2).⁴³ Table II³⁴⁻⁴² summarizes prevalence studies of OSA in HFrEF patients³; most patients were male, and mean ages were similar. Mean body mass index (BMI) was below 30 in all studies. The inclusion criteria varied from AHI ≥5 to ≥15, and did or did not include patients with CSA. The relative proportion of patients with OSA or CSA tended to be highest in the studies that categorized patients as having OSA at AHI ≥5; regardless, significant OSA is prevalent in HFrEF patients.

Older age,^{34,35,39-42} male sex,³⁴ higher BMI,^{34,36-38} and habitual snoring^{36,38} are major risk factors for OSA in patients with HFrEF, just as in the general population.⁶ However, OSA patients with HFrEF have less subjective daytime sleepiness despite shorter sleep times, and the

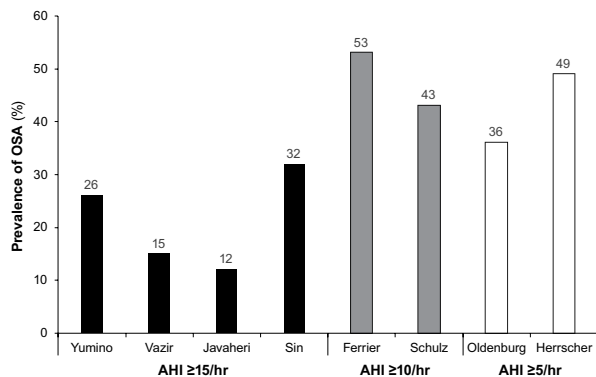


Fig. 2 Graph shows prevalence of obstructive sleep apnea (OSA) in studies of patients with heart failure and reduced ejection fraction. Authors used Apnea-Hypopnea Index (AHI) cutoffs of ≥ 15 events/hr (Yumino D, et al.³⁴; Vazir A, et al.³⁵; Javaheri S, et al.³⁶; and Sin DD, et al.³⁷), ≥ 10 events/hr (Ferrier K, et al.⁴⁰; and Schulz R, et al.³⁹), and ≥ 5 events/hr (Herrscher T, et al.⁴¹; and Oldenburg O, et al.⁴²). Unattended overnight cardiorespiratory polygraphy was used in hospital^{39,42} and home⁴¹ sleep studies; otherwise, overnight-attended polysomnography was used. One study was retrospective³⁷; the others were prospective. Because of patient overlap between 2 studies,^{36,38} one³⁸ is not included here.

Figure adapted with permission from Kasai T, Bradley TD. *J Am Coll Cardiol* 2011;57(2):119-27.⁴³

*Vazir A, et al.³⁵ inconsistently refer to >15 and ≥ 15 AHI cutoffs.

Epworth Sleepiness Scale (ESS) is not helpful in identifying OSA in this population.^{34,39,44} Moreover, atrial fibrillation,^{34,36-40,42} ventricular arrhythmias,^{36,38} lower LV ejection fraction (LVEF),^{36,38,39,42} and higher levels of serum brain natriuretic peptide (BNP),^{35,41} endothelin-1,³⁵ and urinary norepinephrine³⁹ have been reported as predictors of risk for SDB and particularly CSA in HFrEF.

Prevalence of Obstructive Sleep Apnea in Heart Failure with Preserved Ejection Fraction

The prevalence of diastolic dysfunction has been studied echocardiographically in OSA patients who have no history of HF (Table III).⁴⁵⁻⁴⁷ Fung and colleagues⁴⁵ used transmitral valve pulsed-wave Doppler echocardiography to find diastolic dysfunction (grade I) in 37% of patients with newly diagnosed OSA. When comparing patients with an AHI >40 versus <40 , the authors reported an association between severe SDB and a higher degree of diastolic dysfunction evidenced by prolonged isovolumetric relaxation time (IVRT), although, of note, this AHI cutpoint of 40 identified severely affected patients. Other authors reported abnormal diastolic function (with use of tissue-Doppler echocardiography) and an increased left atrial volume index in obese but otherwise healthy patients with OSA in comparison with similarly obese patients without OSA.⁴⁶ Finally,

TABLE II. Prevalence Studies of Sleep-Disordered Breathing in Patients with Heart Failure and Reduced Ejection Fraction³

Reference	Pts (n)	Male (%)	Mean Age (yr)	Mean BMI (kg/m ²)	LVEF	ICM (%)	AHI Cutoff*	NYHA Class	AHI in SDB Pts*	OSA (%)	CSA (%)
Javaheri S, et al. ³⁸ (1998) ^a	81	100	63	28	0.25	75	>15	I-III	44 ^b	11	40
Sin DD, et al. ³⁷ (1999)	450	85	60 ^b	29 ^b	0.27 ^b	66	>15	II-IV	37.6 ^b	32	29
Ferrier K, et al. ⁴⁰ (2005)	53	77	60.1	28	0.34	NR	>10	I-IV	31 ^b	53	15
Javaheri S, et al. ³⁶ (2006) ^a	100	100	65	NR	0.24 ^b	69	>15	I-III	44 ^b	12	37
Oldenburg O, et al. ⁴² (2007)	700	80	64.5 ^b	27	0.283	46	>5	II-IV	24.7 ^b	36	40
Schulz R, et al. ³⁹ (2007)	203	75	65.3	27.6	0.28	57	>10	II-III	34 ^b	43	28
Vazir A, et al. ³⁵ (2007)	55	100	61	29.4	0.306	53	$> \text{or } \geq 15$ ^c	II	27 ^b	15	38
Yumino D, et al. ³⁴ (2009)	218	77	55.6	29.2	0.25 ^d	40	>15	II-IV	NR	26	21
Herrscher T, et al. ⁴¹ (2011) ^e	71	85	61.4	28.4	0.296	73	>5	II-IV	NR	49	32

AHI = Apnea-Hypopnea Index; BMI = body mass index; CSA = central sleep apnea; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NR = not reported; OSA = obstructive sleep apnea; Pts = patients; SDB = sleep-disordered breathing

*Events/hr

^a Significant difference between patients with and without SDB.

^b Overlap of patients between 2 trials.

^c Source article variably states >15 and ≥ 15 .

^d Data exclude CSA patients.

^e Data exclude patients with heart failure with preserved ejection fraction.

All studies were prospective except Sin DD, et al.³⁷ (retrospective).

Table adapted from Chowdhury M, et al. *J Card Fail* 2010;16(2):164-74.³ Used with permission.

diastolic dysfunction was more prevalent in moderate-to-severe OSA than in mild or no OSA.⁴⁷

Data on the prevalence of SDB in patients with HFpEF are sparse (Table IV).^{41,48,49} Chan and colleagues⁴⁸ found significant SDB in 11 of 20 patients and used prolonged deceleration time to show that those with SDB had worse diastolic dysfunction. In a study of 244 patients with HFpEF, Bitter and associates⁴⁹ estimated that 69% had SDB (40% had OSA and 29% CSA). The proportion of patients with SDB, particularly CSA, increased as did diastolic dysfunction, suggesting that CSA acts as a marker of HFpEF severity, as in HFrEF.⁴² In addition, older age, worse New York Heart Association (NYHA) functional class, obesity, and higher levels of N-terminal pro-BNP were associated with both types of SDB. Diabetes mellitus and

higher BMI were predictors of OSA. When Herrscher and colleagues⁴¹ studied a population similar to that of Bitter and associates in terms of age, sex, NYHA class, and the use of HF medications, the prevalence of OSA was 64%. Higher BMI was significantly associated with OSA. However, in these studies,^{41,49} SDB was evaluated by using unattended overnight cardiorespiratory polygraphy; only Chan and colleagues' patients underwent overnight-attended polysomnography.⁴⁸

CPAP in Patients with Heart Failure and Reduced Ejection Fraction

In a study of the effects of continuous positive airway pressure (CPAP) in 8 patients with OSA and HFrEF,⁵⁰ oxygen desaturation, systolic BP, heart rate, and intrathoracic pressure decreased during stage 2 non-REM

TABLE III. Prevalence Studies* of Diastolic Dysfunction in Patients with OSA and No History of Heart Failure

Reference	Pts (n)	Male (%)	Mean Age (yr)	Characteristics	BMI (kg/m ²)	AHI**	Findings
Fung JW, et al. ⁴⁵ (2002)	68	90	48.1	Newly diagnosed OSA	28.5	≥5	DD in 37% pts; more severe OSA associated with worse DD (longer IVRT)
Sidana J, et al. ⁴⁷ (2005)	20	30	45	Obese, pregastric bypass; 12 pts with and 8 without OSA	49 vs 48	<5 >5–14 ≥15	Moderate-to-severe OSA associated with higher prevalence of moderate-to-severe DD
Otto ME, et al. ⁴⁶ (2007)	41	100	45	Obese; 23 pts with and 18 without OSA	33.7 vs 32.3	≥15 vs <5	Increased left atrial volume index and DD in OSA pts vs non-OSA pts

AHI = Apnea-Hypopnea Index; BMI = body mass index; DD = diastolic dysfunction; IVRT = isovolumetric relaxation time; OSA = obstructive sleep apnea; Pts = patients

*With use of echocardiography

**Events/hr

TABLE IV. Prevalence Studies of Sleep-Disordered Breathing in Patients with Heart Failure and Preserved Ejection Fraction

Reference	Pts (n)	Male (%)	Mean Age (yr)	BMI (kg/m ²)			LVEF	AHI Cutoff*	NYHA Functional Class	OSA (%)	CSA (%)
				Mean	OSA	No SDB					
Chan J, et al. ⁴⁸ (1997)	20	65	65	28	29.1 ^a	27.6	>0.50	>10	II–III	35	20
Bitter T, et al. ⁴⁹ (2009)	244	64	65	NR	29.3 ^b	26.4	>0.55	≥5	II–IV	40	29
Herrscher T, et al. ⁴¹ (2011) ^c	44	71	62.8	30.4	32 ^b	27.9	0.517	>5	II–IV	64	18

AHI = Apnea-Hypopnea Index; BMI = body mass index; CSA = central sleep apnea; LVEF = left ventricular ejection fraction; NR = not reported; NYHA = New York Heart Association; OSA = obstructive sleep apnea; Pts = patients; SDB = sleep-disordered breathing

*Events/hr

^a Patients with SDB (includes OSA and CSA)

^b OSA versus no SDB, *P* < 0.05

^c Data exclude patients with systolic heart failure.

sleep. Nocturnal CPAP has also been shown to reduce central sympathetic vasoconstrictor outflow⁵¹ and improve vagal modulation of the heart by increasing high-frequency heart rate variability.⁵²

Investigators have conducted randomized clinical investigations (Table V)^{43,53-56} into the effects of nocturnal CPAP in patients with HFrEF and OSA. In a monthlong study of 24 patients, Kaneko and colleagues⁵³ found significant reductions in AHI, number of arousals per night, and daytime systolic BP and heart rate in conjunction with a decrease in LV end-systolic diameter and an 8.8% absolute increase in LVEF on 2-dimensional echocardiograms. This study had no placebo group; however, the same measurement in the untreated control group did not improve, which suggests that a sustained reduction in LV afterload secondary to CPAP therapy was the reason for improved LVEF in the treated group. This study included equal numbers of patients with ischemic and nonischemic cardiomyopathy.

Previously, the same group of authors,⁵⁷ in an uncontrolled study of 8 patients with OSA and nonischemic dilated cardiomyopathy, reported a 12% increase in LVEF after one month of CPAP therapy. Upon withdrawal of CPAP for one week, LVEF worsened, strongly suggesting that CPAP had reversed OSA. Mansfield and co-authors,⁵⁴ in a randomized trial of 40 patients, reported that 3 months of CPAP treatment resulted in a significant absolute increase of 5% in LVEF. However, no decrease in BP was reported; the authors at-

tributed this result to optimal vasodilator therapy that may have diminished the beneficial effects of CPAP on BP. The improved LVEF was related to a decrease in SNA, as evidenced by a 42% decrease in overnight urinary norepinephrine levels.⁵⁴ The modestly improved LVEF, as compared with that reported by Kaneko and colleagues,⁵³ can be attributed to less severe OSA (AHI, 26 vs 42) and higher baseline LVEF (0.35 vs 0.28). There were also significant reductions in AHI and improvement in subjective sleepiness measured by the ESS. Smith and associates,⁵⁵ in a placebo-controlled crossover trial of autotitrating CPAP in 23 patients with HFrEF and OSA, reported modest improvement in subjective sleepiness, but none in other subjective or objective criteria of HF severity, including LVEF. This was notable, because these patients had baseline LVEF and OSA severity similar to Kaneko and colleagues' patients.⁵³ Autotitrating CPAP has reduced AHI and ESS scores as has fixed CPAP; however, the relative efficacy of auto-CPAP versus clinically titrated CPAP remains unclear.^{58,59} Compliance with CPAP was poorer⁵⁵ (3.5 hr/night) than that reported by Kaneko⁵³ (6.2 hr/night) and Mansfield⁵⁴ (5.6 hr/night), and its efficacy was not tested by using follow-up polysomnography. Therefore, lower compliance with CPAP and thus its poorer efficacy might explain the absence of cardiovascular benefits.

In a randomized, multicenter, placebo-controlled trial of CPAP therapy in 45 OSA patients with HFrEF,⁵⁶

TABLE V. Clinical Trials of Effects of CPAP Treatment in Patients with OSA and Heart Failure with Reduced Ejection Fraction⁴³

Reference	Study Groups	Pts (n)	Mean Age (yr)	Male (n)	Mean BMI (kg/m ²)	Duration (mo)	CPAP (avg. hr)	Baseline			Changes with CPAP Use			
								AHI*	LVEF	ESS	AHI*	LVEF	ESS	SBP (mmHg)
Kaneko Y, et al. ⁵³ (2003)	Control	12	55.2	10	32.3	—	—	45.2	0.285	5.7	-0.5	0.15	NA	6
	CPAP	12	55.9	11	30.4	1	6.2	37.1	0.25	6.8	-28.8 ^a	0.88 ^a	NA	-10 ^a
Mansfield DR, et al. ⁵⁴ (2004)	Control	21	57.5	18	34.6	—	—	26	0.336	8.8	-8.4	0.15	11	-6
	CPAP	19	57.2	19	33.5	3	5.6	25	0.376	9.5	-21.1 ^a	0.50 ^a	-3.1 ^a	1
Smith LA, et al. ⁵⁵ (2007)	Sham ACPAP	23	61	20	31	—	—	36	0.29	10	NA	0.10	-2	NA
	ACPAP	—	—	—	—	1.5	3.5	—	—	—	—	0.10	-3 ^b	NA
Egea CJ, et al. ⁵⁶ (2008) ^c	Sham CPAP	25	64	23	30.5	—	—	35	0.272	6.9	-7.3	-0.05	-1.7	-1.6
	CPAP	20	63	19	31.7	3	NR	44	0.288	8.6	-32.9 ^a	0.22 ^a	-3.6	0

ACPAP = auto-titrating continuous positive airway pressure; AHI = Apnea-Hypopnea Index; avg = average; BMI = body mass index; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; LVEF = left ventricular ejection fraction; NA = not available; NR = not reported; OSA = obstructive sleep apnea; Pts = patients; SBP = systolic blood pressure; SDB = sleep-disordered breathing

*Events/hr

^aP < 0.01 for comparison between groups

^bP < 0.05 for comparison between groups

^cInvestigators studied patients with SDB, including both OSA and CSA; data shown here, except for AHI, are for patients with OSA.

Studies were randomized clinical trials; one⁵⁵ included double-crossover.

Adapted with permission from Kasai T, Bradley TD. *J Am Coll Cardiol* 2011;57(2):119-27.⁴³

LVEF improved by an absolute 2.2% in the treatment group. Even greater improvement in patients with baseline LVEF >0.30 suggests that myocardial contractile reserve is a marker of LVEF improvement. Follow-up polysomnography proved the efficacy of CPAP by revealing significantly reduced AHI in patients who had CSA and OSA.

Investigators in a nonrandomized trial of patients with HFrEF⁶⁰ compared the effects of acute and chronic CPAP therapy on LV systolic and diastolic functions in 7 patients with OSA and 5 without OSA. Stroke volume and LVEF were reduced in acute CPAP administration, whereas 7 weeks of chronic CPAP resulted in improved stroke volume and an absolute increase of 5% in LVEF. Neither therapy affected diastolic function or LV filling pressures. The improved stroke volume and LVEF from chronic CPAP therapy was directly related to the systemic vascular resistance index. Similarly, in an observational study to evaluate the effects of 6 months of CPAP therapy on HFrEF and OSA, Ferrier and associates⁶¹ compared 19 patients treated with CPAP and 7 untreated patients. With CPAP therapy, improvement occurred in LVEF (4.7% absolute increase), systolic BP, and sleepiness, but not in exercise levels, BNP, or sympathetic activity as measured by urinary norepinephrine levels and heart rate. The modest increase in LVEF as compared with that found by Kaneko and colleagues⁵³ was attributed to lower compliance with CPAP (4.2 vs 6.2 hr/night) and less severe baseline systolic dysfunction (mean LVEF, 0.35 vs 0.28).

On the basis of the observations in the randomized (Table V)^{43,53-56} and nonrandomized clinical trials of CPAP treatment in OSA and HFrEF, we concur with the conclusions of Kasai and co-authors⁵² that fixed-pressure CPAP reduces sympathetic activity,^{50,53,54} BP,^{50,52,60} and ESS scores,^{54,55,61} and improves LVEF.^{53,54,56,60,61} Improved quality of life was noted in patients with baseline ESS scores >10,⁵⁴ but not in those with scores <10.^{56,61} Autotitrating CPAP failed to improve LVEF.⁵²

CPAP in Patients with Heart Failure with Preserved Ejection Fraction

Investigators have examined the effects of CPAP therapy on LV diastolic function in patients with OSA but without HFpEF. In a randomized, placebo-controlled, double-blinded crossover study,⁶² diastolic function improved in these patients after 12 weeks of CPAP therapy. Conventional echocardiography showed improved function through significantly reduced IVRT and deceleration time as well as an increase in the ratio of peak early filling velocity (E) to peak late filling velocity (A) of diastolic transmitral flow (E/A). Other authors⁶³ compared 15 patients who had moderate-to-severe OSA and no comorbidities with normal obese persons and reported significantly decreased diastolic

BP and improved diastolic dysfunction (increased E/A ratio, decreased IVRT) after 3 months of CPAP therapy. Cloward and colleagues⁶⁴ reported regression of LV hypertrophy in 25 patients with severe OSA after 6 months of nasal CPAP therapy. In another study,⁶⁵ although LVEF was conserved, the authors reported significantly reduced LV wall thickness (interventricular septum and LV posterior wall) and improved global function after 6 months of CPAP therapy in patients with severe OSA. Shivalkar and associates⁶⁶ studied patients with OSA and no concomitant cardiopulmonary disease who had 6 months of CPAP therapy and found that their symptoms, hemodynamic status, and ventricular structure and function significantly improved. Diastolic velocities improved significantly in younger patients and variably in older patients.⁶⁶ In another study,⁶⁷ tissue-Doppler images showed improved systolic and diastolic function after 6 months of CPAP therapy in patients with newly diagnosed OSA.

We are unaware of randomized or nonrandomized clinical trials of the effects of chronic CPAP therapy in patients with OSA and HFpEF. The only report of diastolic function in patients with OSA and HFpEF after CPAP therapy noted no changes in relevant echocardiographic indices.⁶⁰ However, this study lasted only 7 weeks, so longer therapy may be necessary to determine whether CPAP has beneficial effects on diastolic function, as reported in the studies of patients with OSA and no history of HFpEF (3–6 mo).⁶²⁻⁶⁷

Effects of CPAP on Morbidity and Mortality Rates in Heart Failure with Reduced Ejection Fraction

In a study of HF patients undergoing evaluation for heart transplantation, Roebuck and colleagues⁶⁸ monitored 22 patients with OSA and 23 patients without OSA for a median duration of 52 months. Results of CPAP's efficacy were inconclusive, because no distinction was made between treated and untreated OSA. Few investigators have researched the effects of CPAP on mortality rates in OSA patients with HFrEF (Table VI).^{69,70} Wang and associates⁶⁹ prospectively recruited 164 patients with HFrEF, categorized them into 3 groups (mild to no sleep apnea, untreated OSA, and OSA treated with CPAP), and monitored them for a median duration of >7 years. After control for confounding variables, the mortality rate was significantly higher among the group of 37 patients with untreated moderate-to-severe OSA than in the group with mild to no sleep apnea. The 14 patients treated with CPAP had slightly better survival prospects than did the untreated patients ($P=0.07$). The study was limited by small sample size, nonrandomization, higher baseline AHI in the treatment group, and unavailable data on CPAP compliance; a large-scale, randomized trial might confirm better survival rates in HFrEF patients whose OSA is treated.

TABLE VI. Observational Studies of Effects of CPAP Treatment on Long-Term Outcomes in Patients with OSA and Heart Failure with Reduced Ejection Fraction⁴³

Reference	Design	Pts (n)	Male (%)	Age (yr)	BMI (kg/m ²)	LVEF	AHI (events/hr)	CPAP (avg. hr/night)	Follow-Up Mean/Max. (yr)	Findings
Wang H, et al. ⁶⁹ (2007)	M-NSA	113	66	53.5	29	0.255	6.9	—	2.9/7.3	Higher mortality rate in untreated group vs M-NSA group; tendency toward decreased mortality rate in treated vs untreated group ($P=0.07$)
	Untreated	37	87	58.5	30.1	0.259	32.8	—		
	Treated	14	100	53.2	32.3*	0.239	38.8	NR		
Kasai T, et al. ⁷⁰ (2008)	Untreated	23	83	59.8	24.9	0.35	38.2	—	2.1/4.8	Increased risk of death and hospitalization in untreated group ($P=0.03$) and less compliant CPAP-treated group ($P=0.01$)
	Treated	65	95	59.6	27.5**	0.362	45.1	4.9		

AHI = Apnea-Hypopnea Index; avg = average; BMI = body mass index; CPAP = continuous positive airway pressure; LVEF = left ventricular ejection fraction; Max. = maximum; M-NSA = mild to no sleep apnea; NR = not reported; OSA = obstructive sleep apnea; Pts = patients

* $P < 0.05$ for comparison with M-NSA

** $P < 0.05$ for comparison between groups

Adapted with permission from Kasai T, Bradley TD. *J Am Coll Cardiol* 2011;57(2):119-27.⁴³

Kasai and colleagues⁷⁰ classified 88 patients with moderate-to-severe OSA into a CPAP-treated group (n=65) and an untreated group (n=23). The CPAP group was subdivided into 2 groups: more compliant (n=32; average nightly CPAP use, 6 hr) and less compliant (n=33; average nightly CPAP use, 3.5 hr). After a mean duration of 2.1 years, increased risk of death and hospitalization was found in the untreated ($P=0.03$) and less compliant ($P=0.01$) groups. Because of the small sample size and the 39% first-month dropout rate among untreated patients, these findings need to be confirmed by results from a larger study.

Jilek and co-authors,⁷¹ in an observational study of 273 patients with HFrEF, concluded that SDB was associated with higher mortality rates and positive airway pressure was associated with improved prognosis. The study compared mortality rates in patients with severe SDB versus none to moderate SDB; however, only 22% of patients in the severe-SDB group had predominant OSA, so the results did not confirm that CPAP would lower mortality rates in patients with HFrEF.

In an observational study of 384 patients with HFrEF (62% had OSA), Damy and coworkers⁷² reported a poor prognosis after a mean follow-up period of 47 ± 25 months in patients whose OSA had improved with use of nocturnal ventilation therapy (CPAP with bilevel positive airway pressure and adaptive servoventilation). Because of the nonrandomized nature of this study, the cutoff of 20 events/hr for treatment, and the different ventilation modes, we think that these findings need confirmation by a larger and randomized trial in which patients receive treatment on the basis of the most recent recommendations. Khayat and colleagues, who had suggested a role for OSA in acute decompensation of

HF,⁷³ later found that severe OSA (AHI, >30) independently predicted 6-month cardiac hospital readmissions in patients with HFrEF. However, this does not show that CPAP treatment would necessarily be effective.⁷⁴

Remaining Questions and Challenges

We found no studies in which the effects of CPAP on mortality rates in patients with OSA and HFpEF were examined. Further research is needed.

Obstructive sleep apnea contributes substantially to the development and progression of HF. In patients with HFrEF and HFpEF, OSA is more prevalent than in the general population. However, the effects of CPAP on HF progression and mortality rates have been studied only in OSA patients who have HFrEF. Promising echocardiographic studies have been conducted into the effect of CPAP on diastolic dysfunction in patients with OSA. In addition, despite considerable advances in managing OSA in HFrEF, minimal progress has been made in managing OSA in HFpEF. Therefore, randomized clinical trials are certainly needed to evaluate the effects of CPAP on HF progression and survival prospects in HFpEF patients with OSA.

Furthermore, excessive daytime sleepiness caused by repeated arousals at night is characteristic of OSA in patients without HF. Patients with OSA and HF have less subjective daytime sleepiness despite less sleep time, and the ESS is unhelpful in predicting OSA in this population.^{34,39,41,44} Although fixed-pressure CPAP reduces ESS scores in HFrEF patients,^{54,55,61} it improves quality of life only when baseline ESS scores are >10.⁵⁴

These observations illuminate 3 important questions regarding the relationship between OSA and HF. First, which HF patients need a screening sleep study

when the ESS is unreliable for screening? Schulz and colleagues⁴⁰ recommended sleep studies in all HFrEF patients with LVEF <0.40; however, this idea has not been generally accepted, because of uncertainty about whether and how to treat OSA in this population and the need for treatment goals.⁷⁵ Currently, because of no guidelines, the indications for sleep studies to evaluate OSA in patients without HF apply equally to patients with HF: obesity, habitual snoring, witnessed apnea, unrefreshing sleep, excessive daytime sleepiness, and hypertension.

Second, subjective excessive daytime sleepiness may be absent in patients with OSA and HF, so do they need CPAP treatment? This question applies even to patients with OSA and no evidence of HF. The observations by Wang⁶⁹ and Kasai⁷⁰ support CPAP in patients with HF, regardless of daytime symptoms. However, the need for large-scale, highly powered clinical trials is apparent.

Third, the ESS is unreliable in HF patients, so there is a need for a new sleepiness scale that can better predict the risk of OSA in these patients. Poor quality of life in HF might be why sleepiness is not perceived as a predominant symptom; the new sleepiness scale should take quality of life into consideration.

Because patients with HFpEF and OSA share clinical profiles, it may not be surprising if a large study were to show that OSA is more prevalent in HFpEF than in HFrEF, a finding noted in the only small-scale study that included both HFpEF and HFrEF patients.⁴¹ For these reasons, we think that further elucidation of the role of OSA and OSA treatment in patients with HFpEF is needed.

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