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Effects of Heart Failure and its Pharmacological Management on Sleep

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Abstract

Heart failure (HF) patients have a high prevalence of disturbed sleep. Optimal pharmacological management of HF includes the use of angiotensin converting enzyme inhibitors and β-blockers, which have been associated with decreased severity of central sleep apnea, which is likely secondary to improvements in cardiac performance. There is also evidence, however, indicating that other pharmacological treatments for HF might adversely affect sleep. This brief review introduces the topic of disturbed sleep in HF and examines the extent to which its standard pharmacological management impacts sleep quality.

Keywords

Heart Failure; Sleep; Angiotensin Converting Enzyme Inhibitors; Aldosterone Inhibitors; β-blockers and Loop Diuretics

Heart failure (HF) is a major public health concern, especially in societies where a sizable proportion of the population is over 65 years of age. HF is often the last stage of cardiovascular disease, and its prognosis is grim - with high hospitalization and mortality rates.

HF patients have a disproportionately high prevalence of disturbed sleep. Moreover, those with more disturbed sleep have poorer quality of life and suffer worse cardiac outcomes. Standard treatment and management of HF requires polypharmacy. Currently, the degree to which standard pharmacological agents used to manage HF might mitigate or exacerbate disturbed sleep is unclear. The purpose of this brief review is to introduce the topic of disturbed sleep in HF, and to examine the extent to which standard pharmacological treatments for HF impact sleep.

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Heart Failure

In the United States, the prevalence of HF is 2.42%, with higher rates found in older adults [1]. Despite significant advances in treatment, the prognosis for patients remains grim: 20% to 30% of HF patients die within a year of diagnosis, and 45%-60% die within five years [2]. Among older adults, HF is the most common condition for hospitalization [3], with 990,000 per year in the US [1]. The estimated cost of HF for 2010 was $39.2 billion [4].

The American College of Cardiology (ACC) and American Heart Association (AHA) describe HF as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood [5]. The diagnosis of HF is based on the presence of specific symptoms in the patient's medical history and signs during physical examination (e.g., dyspnea and fatigue).

HF varies in its etiologies and clinical features. Broadly, it can be classified into two categories: 'HF with systolic dysfunction' [also known as 'HF with reduced ejection fraction' (HFrEF)], or 'HF with preserved ejection fraction' [(HFpEF); also known as 'HF with diastolic dysfunction']. In HF with systolic dysfunction, left ventricular ejection fraction (LVEF) is limited due to a reduction in the contractility of the left ventricle. HFpEF is a complex disorder, where LVEF is normal or mildly abnormal. However, the left ventricle can be characterized by other abnormalities, including concentric remodeling, LV hypertrophy, increased extracellular matrix, abnormal relaxation and filling, decreased diastolic distensibility, and abnormal calcium handling [6]. As shown in Table 1, HF is also classified by disease progression or stages, as well as by exercise intolerance or functional limitations.

Sleep Disorders in Heart Failure

HF is characterized by a disproportionately high prevalence of sleep disordered breathing (SDB), sleep deprivation, and fragmented sleep. Insufficient sleep can negatively affect quality of life [7] as well as cognitive processes and memory, which may in turn reduce HF treatment adherence. Given the importance of sound sleep on daily functioning and overall health, the high prevalence of sleep disorders in HF is concerning, and treating sleep disorders in the context of HF syndrome is becoming a clinical priority.

Sleep Disordered Breathing

Sleep Apnea Syndrome is perhaps the most clinically significant sleep disorder in HF, affecting approximately 50% of patients [8]. Traditionally, sleep apnea is defined as the absence of airflow of ≥90% for ≥10 seconds; a hypopnea is defined as a decrement in airflow of ≥50% but <90% for ≥10 seconds. Overall severity of sleep apnea is assessed via the Apnea-Hypopnea Index (AHI), which is a summation of the number of apneas and hypopneas per hour of sleep. Generally an AHI < 5 indicates normal, 5-15 mild apnea, >15-30 moderate apnea, and > 30 severe apnea.

Sleep apnea is classified according to two primary mechanisms: obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA is caused by a blockage of the airway, usually when the soft tissue in the rear of the throat collapses and closes during sleep. CSA is believed to result from the slower circulation of blood in HF and a consequent unmasking of the apneic threshold due to the decrease in the blood's partial pressure of carbon dioxide ($PaCO_2$), resulting in cessation of breathing.

OSA is a known risk factor for HF, whereas CSA is most often a consequence of HF. Approximately 35% of HF patients have OSA [9], compared to approximately 3% to 7% in

the general population [10]. Prevalence of CSA in HF patients is 35% to 66% [9], whereas prevalence of CSA in the general population is uncommon. Longitudinal studies indicate that untreated OSA and/or CSA in HF can increase risk of mortality. HF patients often have a combination of OSA and CSA.

Currently continuous positive airway pressure (CPAP) is the recommended treatment for OSA, including HF patients [11]. CPAP has been found to improve LVEF, and although limited, there is evidence to suggest that CPAP may reduce risk of mortality and hospitalization in HF [12]. Randomized control trials (RTCs) of therapy for CSA in HF have not established a significant benefit with respect to hospitalization or mortality, and thus, there is no consensus on an optimal treatment strategy [13]. Optimal treatment of HF, using angiotensin-converting enzyme inhibition and β-blockers, has been associated with alleviation of CSA [13]. In addition, theophylline, nocturnal oxygen supplemental, automatic positive airway pressure (APAP) with adaptive servo-ventilation have shown promise in reducing CSA.

Insomnia and Poor Sleep Architecture

Difficulty initiating or maintaining sleep, waking up too early, and non-restorative sleep are common complaints among HF patients, and are also subtypes of insomnia. Approximately 33% of HF patients suffer from insomnia, compared to 10-15% of the general population [14]. In addition to apnea, sleep deprivation may be exacerbated by elevation in sympathetic nervous system activity, which is common to HF. Onset or exacerbation of insomnia may also be related to mood disorders and psychological stress, which often accompany chronic disease. ACC/AHA guidelines have identified lack of or poor sleep as a barrier to self-care and treatment adherence in HF patients [15], providing yet another route to increased risk of morbidity and mortality.

Due to the lack of randomized controlled trials, assessing treatment of comorbid insomnia, it remains uncertain if treatments for primary insomnia are effective in HF. Precise treatment of co-morbid insomnia depends on the cause, but in the absence of a known cause, ramelteon has been used [16]. Pharmacological therapies for sleep should have minimal drug interactions because optimal management of HF already involves a complex medication regimen. Also, elimination times for medications may be prolonged in HF, which may result in increased risk for residual daytime effects for sleep agents with longer half-lives. Thus, non-pharmacologic therapy may be optimal for HF patients with co-morbid insomnia, including sleep hygiene education, cognitive therapy, relaxation therapy, stimulus control therapy, and sleep restriction therapy.

Standard Pharmacological Therapies for HF and Sleep

Although frequently overlooked, standard pharmacological therapies for treating HF may also contribute to sleep problems [15]. ACC/AHA guidelines state that most patients with HF with systolic dysfunction should be routinely managed with a combination of three classes of drugs: angiotensin converting enzyme inhibitors (ACEIs) or an angiotensin receptor blockers (ARBs), diuretics, and β-blockers [5]. Proper use of these medications has dramatically improved HF morbidity and mortality rates. ACEI, ARBs and β-blockers are often used in patients with HFpEF; however, there is less data to indicate that their use reduces morbidity and mortality due to HF. Much remains unknown about the extent to which these agents affect sleep in HF patients, who often already have existing sleep disorders. Medications and dosing commonly used to treat HF are listed in Table 2.

Angiotensin Converting Enzyme Inhibitors (ACEIs)

ACEIs have been shown to improve hemodynamics and cardiac functional capacity, as well as reduce hospitalizations and mortality in HF patients. The favorable effects of ACEIs cannot only be explained by the suppression of angiotensin II production, but also by enhancing the action of kinins and augmenting kinin-mediated prostaglandin production.

Effects of ACEIs on Sleep—Although limited, there is some evidence to suggest that ACEIs have favorable effects on sleep. Walsh et al [17] examined the effects of captopril on sleep in 8 HF patients and found that captopril reduced apneic episodes, desaturation effects, and number of arousals. Administration of captopril was also associated with reduced time spent in Stage 1 and 2 sleep, and more time spent in slow wave (SWS) and rapid eye movement (REM) sleep [17]. Gunderson et al [18] conducted a randomized, placebo-control trial on the effects of 12 weeks of ramipril (mean dose 8 mg) on quality of life in 223 HF patients. A trend towards improved sleep quality was observed, but there were no significant differences in quality of life scores. ACEIs can exacerbate or precipitate cough [5], which may interfere with sleep.

Angiotensin Receptor Blockers (ARBs)

While ACEIs are the first choice for inhibition of the renin-angiotensin system (RAS) in HF, ARBs are considered a reasonable alternative for patients who are unable to tolerate ACEIs due to cough or angioedema. ARBs block RAS activation through the direct inhibition of type I Angiotensin II receptors (AT_1 R), which play an important role in modulating the blood pressure response and other effects that contribute to the progression of cardiac dysfunction. ARBs are often used to treat HF patients with resistant hypertension.

Effects of ARBs on Sleep—There are few, if any, studies investigating the role of ARBs on sleep in HF. In a pilot study of prescription-event monitoring, researchers found that patients receiving losartan had more adverse effects, including insomnia, compared to controls who were taking ACE inhibitors or calcium channel blockers [19].

Aldosterone Antagonists

Aldosterone acts on the distal nephron resulting in conservation of sodium, secretion of potassium, increased water retention, and increased blood pressure. High levels of aldosterone have been associated with anatomical changes in cardiac myocytes, endothelial dysfunction, and cardiovascular fibrosis and remodeling. Given the deleterious effects of high levels of aldosterone, HF patients may require long-term suppression via aldosterone antagonists. Spironolactone is the most widely used, and in low doses, in addition to ACEI therapy, has been shown to reduce morality [5].

Effects of Aldosterone Antagonists on Sleep—Data suggests that aldosterone excess may contribute to OSA severity [20]. The proposed mechanism for this association is that chronic aldosterone-induced fluid retention causes peripharyngeal oedema, which obstructs the upper airway and may be exacerbated by supine position during sleep. A preliminary study assessing 12 resistant hypertensive patients with OSA showed that spironlactone treatment was associated with reductions in AHI (39.8±19.5 vs 22.0±6.8 events/h; $p<0.05$) and the hypoxic index (13.6±10.8 vs. 6.7±6.6 events/h; $p<0.05$) [21].

In our own laboratory, we utilized polysomnography to examine the potential effects of ACEIs, ARBs and aldosterone antagonists on sleep architecture and SDB in 67 NYHA classes II and III HF patients [mean age 55.6 years (±13.4)]. Seventy-seven percent (n=52) of patients were taking an ACEI, 16.4% (n=11) were taking an ARB, and 40.3% (n= 27) were taking an aldosterone antagonist. Using linear regression analysis, adjusting for age,

sex and BMI, we found that aldosterone antagonists were associated with patients having fewer awakenings following sleep onset (β=−.277, p≤.03) and spending less time in stage 1 sleep (β=−.240, p≤.05). Although not statistically significant, patients taking aldosterone antagonists also spent more time in Stage 2 sleep, SWS, and REM sleep.

Loop Diuretics

Loop diuretics are the primary method of treating fluid retention in HF, producing symptomatic benefits more rapidly than any other drug. Diuretics interfere with the sodium retention of HF by inhibiting the reabsorption of sodium or chloride at specific sites in the renal tubules. Loop diuretics are usually the preferred course of treatment because of their efficacy in increasing sodium excretion up to 20% to 25% of the filtered load of sodium, enhancing free water clearance and maintaining their efficacy even in cases of severe renal impairment [5].

***Effects of Loop Diuretics on Sleep*—**Research of the effects of loop diuretics on sleep is scarce; however, diuretic administration is often associated with nocturia, which may result in sleep fragmentation [15]. On the other hand, preliminary work indicates that administration of loop diuretics may improve OSA by reducing peripharyngeal oedema. Bucca et al. [22] examined if intensive unloading with IV administration of furosemide (20 mg bid for 3 days), co-administered with spironolactone (100 mg), improved OSA in 15 patients with severe OSA, systemic hypertension, and diastolic HF. Results indicated improvements in AHI, oropharyngeal junction (OPJ) area, and blood pressure, as well as a decrease in body weight.

β-blockers

HF is characterized by elevation in sympathetic nervous system activity, which over time can produce deleterious cardiac effects. β-blockers inhibit beta-adrenergic receptor activation by the sympathetic agonists norepinephrine and epinephrine. The role of β-blockers in slowing the progression of HF and improving survival has been extensively documented [5].

***Effect of β-blockers on Sleep*—**β-blockers may modulate ventilatory responses in HF [23]. Carvedilol [24] and metoprolol [25] have been associated with reduced apneic events in HF patients with CSA. Since CSA results from underlying cardiac dysfunction, the reduction of CSA conferred by these drugs may be due to their beneficial effects on the myocardium. However, prevalence studies indicate that the rate of CSA in HF patients remains unaltered despite increasing use of β-blockers to manage HF [13]. Conversely, β-blockers might negatively impact sleep architecture via decreases in nocturnal melatonin production [26], although this has not been examined in HF populations.

Discussion

Clinical and epidemiological observations demonstrate that HF patients have disproportionately high rates of SDB and insomnia, both of which are associated with poor prognoses. There is an open debate as to the degree to which standard pharmacotherapeutic agents used to manage HF syndrome exacerbate or mitigate disturbed sleep. Although the data is limited, aldosterone inhibitors appear to reduce the severity of OSA in HF patients, and data from our laboratory suggests that they may also have positive effects on sleep architecture. However, the literature is more challenging to navigate for the other drug classes. For example, loop diuretics have been associated with decreases in OSA severity; however, a side effect of diuretic administration is nocturia. Thus, benefits gained in reducing one sleep problem may be offset by causing or exacerbating another sleep problem.

In the case of CSA, where the disorder is thought to be a response to a decline in cardiac function, treating HF has resulted in a reduction of apnea severity.

Conclusion

There is still much work to be done with regard to understanding how pharmacological treatment of HF affects sleep. We know little about the synergistic effects of HF medication regimens on sleep. A major limitation in interpreting and applying the current body of evidence is that there are few studies conducted in HF populations, and many of these have small sample sizes. Preliminary findings suggest that ACEIs, aldosterone inhibitors, loop diuretics, and **β**-adrenergic receptor blockers may reduce sleep apnea severity; however, there is evidence to suggest that some of these same agents may also contribute to disturbed sleep. More studies are needed in order to assess the degree to which standard therapies used to manage HF attenuate or exacerbate sleep problems in this population.

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Table 1

Functional Classifications and Disease Progression Stages of Heart Failure

New York Heart Association Functional (NYHA) Classes

	Definition	Examples
NYHA Class I	No limitation of physical activity	Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
NYHA Class II	Slight limitation of physical activity	Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
NYHA Class III	Marked limitation of physical activity	Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
NYHA Class IV	Unable to carry out any physical activity without discomfort	Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

American College of Cardiology/American Heart Association Stages of Heart Failure

	Definition	Examples
Stage A	High risk for developing HF, but without structural heart disease or symptoms of HF	Hypertension, diabetes mellitus, CAD, family history of cardiomyopathy
Stage B	Structural heart disease, but asymptomatic	Previous myocardial infarction, left ventricular dysfunction, valvular heart disease
Stage C	Structural heart disease with previous or current symptoms, but managed with medical treatment	Structural heart disease, dyspnea and fatigue, impaired exercise tolerance
Stage D	Marked symptoms at rest despite maximal medical therapy	Advanced disease requiring hospital-based support, a heart transplant or palliative care

Table 2

Standard Drug Therapies and Dosing Ranges for Treating Heart Failure

Drug Class	Drug	Dosing Ranges
Angiotensin Converting Enzyme Inhibitors	Captopril	6.25 mg tid-50 mg tid
	Benazepril	10 mg qd-80 mg qd
	Enalapril	2.5 mg bid-20 mg bid
	Fosinopril	5 mg qd-40 mg qd
	Imidapril	2.5 mg qd-10 mg qd
	Lisinopril	2.5mg qd-40 mg qd
	Ramipril	2.5 mg qd-10 mg qd
	Trandolapril	1 mg qd-4 mg qd
	Quinapril	5 mg bid-20 mg bid
Angiotensin Receptor Blockers (ARBs)	Candesartan	4 mg qd- 32 mg qd
	Losartan	25 mg qd-100 mg qd
	Valsartan	40 mg bid-160 mg bid
Aldosterone Inhibitors	Spironolactone	12.5 mg to 100 mg in divided doses daily
	Eplerenone	25 mg to 100 mg daily in divided doses daily
Loop Diuretics	Bumetanide	0.5-8 mg in divided doses daily
	Furosemide	10-480 mg in divided doses daily
	Torsemide	10-100 mg in divided doses daily
β-Blockers	Bisoprolol	1.25 mg qd-10 mg qd
	Carvedilol	3.125 mg bid-25 mg bid (or 50 mg bid for patients >85 kg)
	Metoprolol succinate extended release (metoprolol CR/XL)	12.5 mg qd -200 mg qd

Table 3

Proposed and Hypothesized Sleep Effects of Standard Pharmaceutical Agents Used to Manage Heart Failure

Drug Class	Proposed or Hypothesized Negative Effects on Sleep	Proposed or Hypothesized Favorable Effects on Sleep
Angiotensin Converting Enzyme Inhibitors (ACEI)	Cough [5] Spirapril, although infrequently used in HF, associated with insomnia at doses of 6 mg when prescribed for hypertension [27]	Captoril reduced apneic episodes, desaturation effects and number of arousals in HF patients [17] Ramipril improved subjective sleep reports in HF patients [18]
Angiotensin Receptor Blockers (ARBs)	Losartan associated with insomnia [19]	
Aldosterone Inhibitors		Spironolactone reduced OSA episodes in hypertensives [21]
Loop Diuretics	Nocturia [15]	Furosemide improved OSA in patients with severe OSA, systemic hypertension, and diastolic HF [22]
β-blockers	Bisoprolol decreased the nocturnal melatonin production in healthy participants [28]	Carvedilol [24,29] and metoprolol [25] reduced apneic events in HF patients with CSA