1. Cardiovascular diseases: Heart failure, coronary artery disease, arrhythmias, and hypertension

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Summary

There is a bidirectional relationship between cardiovascular diseases (CVD), sleep-disordered breathing and quality of sleep. The repeated exposure to biological consequences of obstructive sleep apnea (OSA) including altered blood gas chemistry, arousals and large negative swings in intrathoracic/juxta-cardiac pressure will in the long run lead to a variety of cardiovascular disorders including hypertension, heart failure, arrhythmias, coronary artery disease, and stroke. Randomized controlled trials (RCTs) have consistently shown that the treatment of OSA lowers blood pressure, particularly those with resistant hypertension and most adherent to therapy with continuous positive airway pressure (CPAP) devices. However, to date, RCTs have failed to show that therapy with CPAP improves downstream cardiovascular consequences. Notably, the Achilles tendon of these trials has been the lack of adequate adherence to CPAP. Central sleep apnea (CSA) frequently occurs in subjects with left ventricular dysfunction, particularly those with heart failure and reduced ejection fraction. The acute consequences of CSA are qualitatively similar to OSA, although less severe. Multiple observational trials have shown the effectiveness of adaptive servoventilation in suppressing CSA. Yet, unlike OSA, a large RCT on cardiovascular outcomes was neutral or even detrimental, showing a lack of effectiveness of treatment with adaptive servoventilation when compared to usual care. Another trial using an adaptive servoventilation device with an updated algorithm is in progress. This chapter intends to provide a comprehensive overview of the major cardiovascular consequences of sleep disturbances also pointing to research gaps and perspectives. Several observational studies have shown associations between sleep duration or quality and CVD. Yet, prospective data are not available and the observed relationships may be due to confounders.

KEYWORDS

cardiac transplantation, cardiovascular disease (CVD), continuous positive airway pressure (CPAP), oxygen therapy, sleep apnea, sleep duration

1 | INTRODUCTION

1.1 | The burden of cardiovascular disease

Cardiovascular diseases (CVD) have a high prevalence and are associated with excessive morbidity and mortality, and huge economic costs. Annually, the American Heart Association and other government agencies, update statistics on the impact of CVD. According to the 2020 update (Virani et al., 2020), the prevalence of CVD in adults aged ≥20 years is 48% (122 million in 2016) and increases with age in both males and females. With exclusion of hypertension, the prevalence of CVD (coronary heart disease [CHD], heart failure [HF], and stroke only) is 9% (24 million in 2016). In 2017, the estimated mortality of cardiovascular death was 859,125 individuals. There is a huge associated economic impact of $351 billion.

The global burden of CVD is also staggering; in 2016, ~18 million deaths were attributed to CVD globally, which amounted to an increase of 15% from 2006. CVD is the leading global cause of death and is expected to account for >24 million deaths by 2030 (Virani et al., 2020). In parallel to the traditional risk factors associated with CVD, growing interest has been devoted to exploring the impact of poor quality and quantity of sleep, and a variety of sleep disorders could contribute to the burden of CVD. In this chapter, we will summarize this evidence, also discussing the potential gaps in the literature.

1.2 | Normal sleep and cardiovascular haemodynamics

Sleep–wake related 24-hr changes in central nervous system autonomic sympathetic and parasympathetic output undergo circadian and sleep-related alterations with both beneficial and adverse consequences on the cardiovascular system (Somers, Dyken, Mark, & Abboud, 1993). Sleep, itself, is not a homogeneous state, consisting of both non-rapid eye movement (NREM) and REM sleep. NREM sleep consists of three stages, N1–N3 and with orchestrated changes in autonomic nervous system activity, such that the state of NREM sleep is characterized by autonomic stability due to a simultaneous decrease in sympathetic nervous system activity and elevated parasympathetic neural tone (Somers et al., 1993). Consequently, arterial blood pressure (BP) and heart rate decrease progressively throughout NREM sleep, decreasing cardiac workload. Based on these autonomic alterations and haemodynamic changes, NREM sleep is generally considered "peaceful" for the cardiovascular system (Floras, 2015).

Although sleep is generally beneficial for the cardiovascular system, a number of cardiovascular events including asymptomatic myocardial ischaemia, nocturnal angina, myocardial infarction, acute cardiogenic pulmonary oedema, arrhythmias and sudden death also occur during sleep (Gami, Howard, Olson, & Somers, 2005; Uchôa et al., 2017). These events occur both in NREM and REM sleep for differing physiological reasons dictated by each stage of sleep and the associated haemodynamic changes. Specifically, two peaks of sudden cardiac death have been observed, one occurring between midnight and 02:00 hours, when NREM sleep is predominant, and the other between 05:00 and 06:00 hours, when REM sleep predominates (Lavery, Mittleman, Cohen, Muller, & Verrier, 1997). The pathophysiological reasons are discussed below.

In NREM sleep, particularly in N3 when sympathetic activity is at its nadir (Somers et al., 1993), the normal physiological drop in diastolic BP, one of the main determinants of coronary blood flow, could precipitate myocardial ischaemia. Another determinant of coronary blood flow, coronary artery resistance, is increased in the presence of coronary artery disease (CAD). Because of the combined drop in diastolic BP and presence of coronary artery stenosis, ischaemia becomes more likely even though the heart rate is low. For the latter reason, this is referred to as non-demand myocardial ischaemia, in contrast to demand ischaemia when cardiac oxygen consumption is elevated. In this regard, it is well known that low BP,

KEY POINTS

- Obstructive sleep apnea (OSA) is quite common in patients with hypertension, arrhythmias, coronary heart disease, and heart failure (HF).
- Randomized controlled trials (RCTs) using ambulatory blood pressure (BP) monitoring have consistently demonstrated that treatment of OSA with continuous positive airway pressure (CPAP) lowers BP.
- The drop in BP is most pronounced in those with resistant hypertension and those who are most adherent to therapy.
- However, RCTs have failed to show that therapy with CPAP improves cardiovascular outcomes, perhaps in part due to poor adherence with CPAP.
- Central sleep apnea (CSA), a rare polysomnographic finding in the general population, is highly prevalent in patients with HF. A large RCT using an adaptive servoventilation device with improved algorithm is in progress.
- Altered sleep duration or quality may be associated with an increased risk of cardiovascular disease.

LEARNING OBJECTIVES

- To discuss the cardiovascular consequences of OSA.
- To review RCTs showing efficacy of treatment of OSA on hypertension.
- To discuss why RCTs have failed to show any efficacy of CPAP in improving cardiovascular outcomes.
- To discuss the prevalence and consequences of CSA in HF and treatment options.
- To review current knowledge on the relation between sleep quality/duration and cardiovascular disease.

both in the senior population (Floras, 1988) and in patients with HF and sleep apnea (Javaheri, Shukla, Zeigler, & Wexler, 2007), is associated with increased mortality, which is at least in part based on the same pathophysiology.

In contrast to NREM sleep, in phasic REM sleep heart rate and BP increase intermittently in association with increased sympathetic activity. This is most pronounced during intense ocular movements of REM sleep, analogous to ponto-geniculo-occipital waves observed in sleeping cats. The increase in BP increases left ventricle (LV) afterload and myocardial oxygen consumption, which is further augmented by an increase in heart rate, another determinant of myocardial oxygen consumption. These changes could result in an imbalance between demand and supply, precipitated by the increased demand (Lavery et al., 1997). Also, REM sleep could impose an additional respiratory burden due to decreased activity of both upper airway dilator and intercostal muscles, further contributing to hypoxaemia and adverse cardiovascular consequences (Mokhlesi et al., 2014). The overall increase in metabolic demand potentially combined with diminished oxygen delivery could precipitate myocardial ischaemia in the vulnerable heart (Floras, 1988; Lavery et al., 1997; Nowlin et al., 1965).

1.3 | Sleep quantity and quality and cardiovascular diseases

The prevalence of chronic behaviourally induced sleep restriction and insomnia is quite high with ~20% of USA adults sleeping <7 hr/night (Virani et al., 2020), a major public health problem. If sleep is restorative for the cardiovascular system, it should be of no surprise that short sleep duration is associated with a number of cardiovascular and metabolic health outcomes, including increased prevalence and incidence of obesity, incident diabetes mellitus (DM), CHD, stroke, atrial fibrillation (AF) and a greater risk of all-cause mortality (Genuardi et al., 2019; Javaheri & Redline, 2017; Virani et al., 2020). Moreover, an irregular sleep routine may be a risk factor for CVD independent of average sleep duration, insomnia, or obstructive sleep apnea (OSA; Huang, Mariani, & Redline, 2020).

The bio-pathophysiological mechanisms mediating the adverse cardio-cerebrovascular and metabolic consequences of short sleep, sleep fragmentation, and insomnia relate to alterations in sympathetic/parasympathetic activity and upregulation of the inflammatory cascade (Javaheri & Redline, 2017).

Similar to short sleep, prolonged sleep (defined by time in bed of ≥8 or ≥9 hr/night) is also associated with cardio-cerebrovascular events and mortality (Jike, Itani, Watanabe, Buysse, & Kaneita, 2018). The reasons remain to be elucidated, and disorders causing prolonged sleep could be in part the mechanisms. We emphasize that the vast majority of the aforementioned studies are based on subjective sleep data, and that the links are correlational, not necessarily causal. Although observational studies show relationships between sleep duration or quality and CVD, these relationships may be due to residual confounding factors.

2 | SLEEP AND HEART FAILURE

For a variety of reasons related to HF itself, or other associated disorders, patients with HF have poor sleep architecture characterized by excessive light sleep, insomnia, and excessive arousals. In a 2-night sleep laboratory study, the first night for habituation with electrode placement, and second night for polysomnographic recording, sleep architecture was abnormal even in those without sleep-disordered breathing (SDB). In this group (n = 32), stage N1 accounted for 34% of total sleep time, and N3 was virtually absent (Javaheri, 2006; Javaheri et al., 1995, 1998). The apnea–hypopnea index (AHI) was normal (mean AHI of 2 events/hr). Subjects suffered from insomnia with a sleep efficiency of ~72% (Javaheri, 2006). There were excessive arousals (15 events/hr). Importantly, upon awakening after the second night, when asked, the patients noted that their sleep quantity and quality in the laboratory was the same as they experienced at home. Symptoms of HF such as cough, paroxysmal nocturnal dyspnea, orthopnea, and nocturia, as well as medications used for treatment of HF, and associated comorbidities could account for poor sleep. Depression, a common cause of insomnia, is frequently comorbid with HF and carries a poor prognosis if left untreated (Kato et al., 2012). The synthesis and secretion of melatonin are primarily regulated through the β-adrenergic signal transduction system and could be impaired by administration of some β-blockers used for the treatment of HF (Arendt, Bojkowski, Franey, Wright, & Marks, 1985).

2.1 | Heart failure and sleep-disordered breathing

There is a bidirectional relationship between SDB and HF. The results from the Sleep Heart Health Study (SHHS), a large cohort of subjects from the general population, suggest that OSA is linked to incident HF, and that this association is stronger in men than women (Gottlieb et al., 2010). On the other hand, OSA and central sleep apnea (CSA) are common in subjects with systolic or diastolic HF, patients hospitalized for HF, and even asymptomatic subjects with LV systolic and diastolic dysfunction. The phenotype of SDB, OSA and CSA varies according to the phenotype of LV dysfunction (systolic vs. diastolic) and stability of HF (Arendt et al., 1985; Bitter, Faber, et al., 2009; Javaheri, 2006; Kato et al., 2012; Uchôa et al., 2017).

2.2 | Clinical presentation of sleep-disordered breathing in patients with heart failure

For various reasons SDB is underdiagnosed in patients with HF (Bitter, Faber, et al., 2009), particularly in those with CSA (Javaheri, 2006), as they are commonly not obese and do not snore as much as those with OSA (Kato et al., 2012). Another reason is that most patients with HF do not complain of subjective excessive daytime sleepiness. This is the case for both CSA and OSA, and is the main reason that the disorder was referred

to as "occult" (Javaheri, 2006). Yet, when a multiple sleep latency test (MSLT) is performed, sleepiness is unmasked. In one study of patients with HF and reduced ejection fraction (HFrEF) and OSA, many subjects exhibited pathological objective sleepiness, despite of an Epworth Sleepiness Score (ESS) of <10 (Mehra et al., 2017). Other investigators have shown the same dissociation in patients with HFrEF and CSA (Hanly & Zuberi-Khokhar, 1995; Pepperell et al., 2003). That the objectively measured sleep latency is diminished is inconsistent with the notion that the lack of subjective daytime sleepiness would be due to increased sympathetic activity (Taranto Montemurro et al., 2012). If that would be the case, the MSLT should also be normal, not pathologically decreased. The presence of daytime sleepiness may be underrated or go unnoticed in the broader symptomatic picture of HF and SDB, two lasting comorbid conditions. This is consistent with the observation from a randomized controlled trial (RCT) that when CSA was treated, objective daytime sleepiness improved, but the patients did not observe improvement in subjective daytime sleepiness (Pepperell et al., 2003). In any case, the lack of subjective sleepiness remains the main reason for underdiagnosis of SDB, particularly in patients with HF and CSA, who are commonly leaner than and do not snore as much as those with OSA.

2.3 | Heart failure and obstructive sleep apnea

The prevalence of OSA is on the rise, as obesity remains a major risk factor for OSA, although multiple other factors play a role in its pathogenesis (Javaheri et al., 2017; Javaheri, Brown, Abraham, & Khayat, 2020). The adverse biological signatures of OSA and its downstream consequences are depicted in Figure 1.

The pathogenesis of OSA in HF is not basically different from OSA in general. However, in the presence of cardiac dysfunction, OSA imposes additional adverse consequences. For example, in the presence of LV systolic dysfunction, the large negative swings in juxta-cardiac pressure could impair LV stroke volume by at least two mechanisms, the combined increase in venous return to the heart leading to right ventricular septal deviation to the left and increasing LV afterload. Furthermore, in subjects with HF, OSA frequently co-exists with CSA, and for both OSA and CSA, the cycle length is prolonged due to increased circulation time.

Sleep apnea is quite common in patients admitted to the hospital with acute decompensated HF. Both OSA and CSA have been reported (Khayat et al., 2015; Uchôa et al., 2017), although OSA is most prevalent (Uchôa et al., 2017). In an observational longitudinal study, OSA was independently associated with higher rates of recurrence of acute cardiogenic pulmonary oedema and both fatal and nonfatal cardiovascular events (Uchôa et al., 2017). Amongst patients recovering from acute decompensated HF, hypoxaemia has a greater poor prognostic value than the severity of sleep apnea, as measured by the AHI (Huang, Wang, et al., 2020).

Observational studies suggest that OSA is associated with increased hospital readmission (Javaheri, Caref, Chen, Tong, & Abraham, 2011; Khayat et al., 2015; Uchôa et al., 2017) and treatment with continuous positive airway pressure (CPAP) reduces readmission and hospital costs (Javaheri et al., 2011). Also, observational studies show that OSA is independently associated with excess

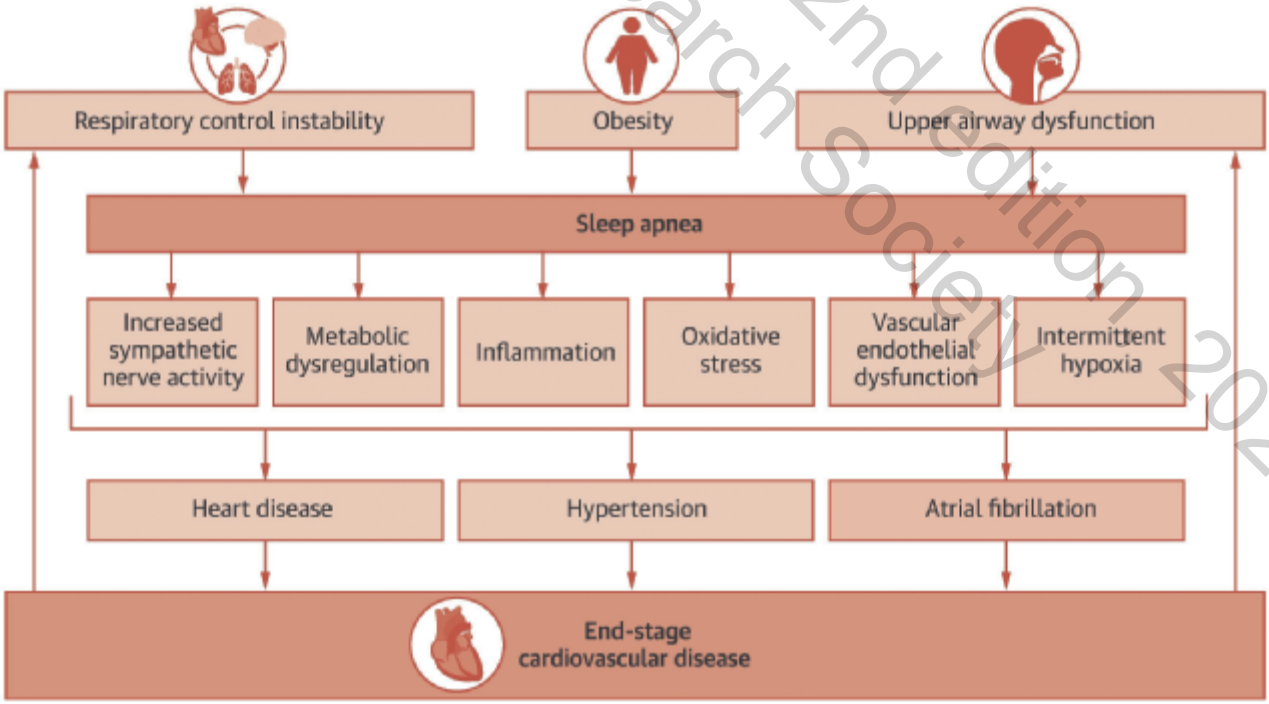

FIGURE 1 Multi-aetiological risk factors of obstructive sleep apnea and its downstream consequences. Modified from Javaheri et al. (2017)

mortality in patients with HF (Javaheri et al., 2011; Kasai et al., 2008; Khayat et al., 2015; Uchôa et al., 2017; Wang et al., 2007) and mortality is lower in patients treated with CPAP (Javaheri et al., 2011; Kasai et al., 2008), particularly in those who are adherent to CPAP (Wang et al., 2007). RCTs are not available and are badly needed.

2.4 | Heart failure and central sleep apnea

In the population at large, CSA is a rare polysomnographic finding. HF and use of opioids are probably the two most common causes of CSA. CSA has been most extensively studied in patients with HFrEF. In this subgroup of patients with HF, CSA occurs in the context of periodic breathing characterized by a repetitive pattern of crescendo-decrescendo ventilation interposed by central apnea, or hypopnea. The naming for this pattern of breathing should be Hunter–Cheyne–Stokes breathing (HCSB), as it was first described by Hunter, almost 37 years before Cheyne's description (Javaheri, 2017). This unique pattern with periodic breathing in HF is a manifestation of respiratory instability during NREM sleep (Javaheri, Brown, & Khayat, 2020a).

Patients with HFrEF frequently have both OSA and CSA as shown on polysomnography. Similar to OSA, CSA is associated with intermittent arousals, hypoxaemia, and negative swings in intrathoracic/juxta-cardiac pressure. The latter two consequences are less severe than those in OSA. In CSA, the negative swings occur at the peak of hyperventilation, and these swings are relatively large, proportional to the severity of congestion of the respiratory system. Like OSA, CSA leads to sustained sympathetic overactivity, which has been shown to carry a poor prognosis in HFrEF.

Based on observational studies of patients with HF, CSA (like OSA) is associated with excess hospital readmissions (Khayat et al., 2015) and premature mortality (Javaheri et al., 2007; Oldenburg et al., 2016). In an observational long-term Veterans Affairs study (Javaheri et al., 2007), in patients with HFrEF, the presence of CSA increased the chance of premature death by 150% compared to those without CSA. Furthermore, there was a higher rate of mortality in each category of the AHI, when the lower threshold was compared to the higher one. In this study, amongst 24 variables in a multivariate analysis, three variables (i.e., AHI, low diastolic BP, and impaired right ventricular function) were associated with premature mortality. In the largest study, in which >900 patients with HFrEF were followed for up to 10 years, amongst a few variables, oxyhaemoglobin desaturation was independently associated with premature death (Oldenburg et al., 2016). Time with oxygen saturation at <90% (T90) predicted the risk of death in a dose-dependent manner, namely an increase of 16% per hour of T90.

Regarding HF with preserved ejection fraction (HFpEF) and SDB, two studies involving 263 consecutive patients showed that 47% had sleep apnea (AHI of ≥15 events/hr): 24% OSA, and 23% CSA (Bitter, Faber, et al., 2009; Herrscher, Akre, Overland, Sandvik, & Westheim, 2011). There are no large systematic studies on HFpEF in the USA population, and in our experience, OSA, rather than CSA is most common.

2.5 | Sleep in cardiac transplant recipients

Annually, a limited number of patients with HF receive cardiac transplantation. There are limited studies regarding sleep architecture of these patients when in stable condition. In the largest prospective and most systematic study reported to date (Javaheri et al., 2004), 45 of 60 consecutive patients underwent polysomnography, at ≥5 months after transplantation. Subjects were receiving prednisone at a maintenance dose of 5–10 mg daily, as well as anti-rejection medications including cyclosporine. The important findings included persistence of disturbed sleep architecture even in the group without prior sleep disorders, and development of OSA, restless legs syndrome (RLS) and periodic limb movements (PLMs). There were individuals without OSA and PLM. This group continued to have altered sleep structure with reduced sleep efficiency of ~72% and a large amount of N1 (~28% of total sleep time). REM sleep was normal at 22% of total sleep time, but N3 was absent. After transplantation, a large number of patients developed OSA. In all, 53% had an obstructive AHI of ≥5 events/hr, and 36% had an obstructive AHI of ≥15 events/hr (Javaheri et al., 2004). OSA occurred in patients who had gained the most weight after transplantation. These patients also had other features of OSA including habitual snoring, excessive daytime sleepiness, unrefreshing sleep, systemic hypertension, and an impaired physical component on the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) questionnaire. One patient with OSA developed LV systolic dysfunction, potentially related to rejection and the impact of SDB. This hypothesis is supported by the results of a retrospective study involving 146 consecutive cardiac transplant recipients (Afzal et al., 2019), in which 29 patients (20%) with untreated OSA had a three-times higher risk of developing late graft dysfunction than those with treated or no OSA. However, subjects with untreated OSA were significantly older, heavier, and not surprisingly, had a higher prevalence of hypertension. Therefore, the results should be interpreted with caution (Afzal et al., 2019).

Another interesting feature of the study by Javaheri et al. (2004) was the observation that 45% of the patients met the international criteria for RLS, which was relatively severe, 31% of the cohort had severe PLM during sleep with an index of 55/hr of which 5/hr were associated with arousals. The mechanisms of development of RLS and PLM are unclear. It should be noted that these patients had normal renal function, thyroid-stimulating hormone, haemoglobin, and haematocrit levels. Overall, it seems important to monitor patients who receive cardiac transplantation for the development sleep disorders, so that appropriate therapy can be instituted.

3 | SLEEP AND CARDIAC RHYTHM DISORDERS

The cerebro-cardiac neuroanatomy describes the neuronal pathways between the brain stem and other brain structures to the heart (Hanna et al., 2017; Shen & Zipes, 2014). Accordingly, sympathetic

signals descend via the spinal cord to the cervico-thoracic stellate ganglion synapsing with the terminals of the cardiac nerves, whereas parasympathetic fibres travel via the vagal nerve into the pericardial sack. This neuro-cardiac axis of the autonomic nervous system plays an important role in controlling the heart rhythm, and the imbalance in sympatho-vagal activity underlies cardiac arrhythmogenesis (Waldron, Fudim, Mathew, & Piccini, 2019). In concert with favourable changes in autonomic nervous system activity during NREM sleep (Somers et al., 1993), incident ventricular arrhythmias are usually suppressed (Verrier & Josephson, 2009), evidence which is supported by reduced discharges of implantable cardioverter–defibrillators in ischaemic heart disease (Bitter, Fox, Gaddam, Horstkotte, & Oldenburg, 2015). However, surges in cardiac sympathetic nerve activity during REM sleep could cause nocturnal myocardial ischaemia and arrhythmias, even in the absence of coronary heart disease (Uchôa et al., 2017). Similarly, arousals, which are associated with increased sympathetic activity, have been implicated in promoting ventricular arrhythmias during sleep in patients with HF and CSA (Javaheri, Shukla, & Wexler, 2012).

Atrial fibrillation is the most common chronic cardiac rhythm disorder, affecting millions of individuals worldwide. It is associated with an increased risk of cardiovascular complications, including cerebral and systemic embolization, HF, hospitalization, excess mortality, and increased healthcare costs. Although OSA could be a major cause (Mehra et al., 2006), there are at least two peaks in the onset of AF during sleep, unrelated to OSA. A midnight to 02:00 hours peak, presumably vagally mediated (Rostagno et al., 1993), and a 04:00–05:00 hours peak, presumably triggered by REM sleep-related surges in sympathetic nerve activity (Gillis et al., 2001).

The presence of OSA significantly increases the risk of AF and other arrhythmias during sleep (Mehra et al., 2006; Monahan et al., 2009). In the SHHS cohort (Mehra et al., 2006), there was a strong association between nocturnal cardiac arrhythmias and SDB, with point estimates in the two–four-fold increased risk range, after confounding factors such as obesity and self-reported cardiac disease were accounted for. There are multiple features of OSA that collectively contribute to inducing AF (May, Van Wagoner, & Mehra, 2017). These include negative swings in intrathoracic and juxta-cardiac pressure, which distend the compliant thin wall atria, and at the same time cause volume overload of the right atrium, stimulating stretch-mechanoreceptors. In addition, other apnea-associated effects may play a role (i.e., hypoxaemia, hypercapnia/acidosis, exaggerated sympathetic activity, and upregulation of the inflammatory cascade). These pathogenetic mechanisms could have a more deleterious effect in the presence of cardiac disorders such as HF.

Despite overwhelming pathophysiological evidence linking OSA to AF, to date, no systematic RCT has been performed to determine if treatment of OSA has any impact in eliminating or reducing the incidence rates of recurrent AF. However, in two meta-analyses of observational studies (Qureshi et al., 2015; Shukla et al., 2015) the use of CPAP was associated with reduced recurrence of AF even in those with pulmonary vein isolation. In one meta-analysis (Qureshi et al., 2015) comparing 698 CPAP users with 549 non-CPAP users, those with OSA treated with CPAP after AF intervention had a 44% reduced risk of relapse; younger, more obese, and male patients benefited the most. For all the aforementioned reasons, expert consensus supports the presence of OSA as a risk factor for AF recurrence after surgical and catheter ablation, and recommends its treatment (Calkins et al., 2012).

As discussed above, OSA is considered a cause of AF. However, AF, in turn could cause CSA, which is prevalent in subjects with AF (Bitter, Langer, et al., 2009; Leung et al., 2005). In addition, the presence of CSA appears to herald incident AF, and age could be a confounding variable. In an epidemiological study involving older men, a differential relationship was observed such that OSA and hypoxia exhibited stronger associations with ventricular arrhythmias, whereas HCSB showed stronger associations with AF (Mehra et al., 2009). Furthermore, the presence of CSA is associated with future development of both AF and HF (Javaheri, Blackwell, et al., 2016; Javaheri, Brown, Randerath, & Khayat, 2016; May et al., 2016). In these individuals, CSA presumably reflects early structural heart disease, which is asymptomatic at first. The association between CSA and AF has been best documented in subjects with HFrEF (Arendt et al., 1985). In this study, 80% of those with AF had CSA. In another study of 150 patients with AF and normal LVEF, CSA was observed in 31% of the patients (Bitter, Faber, et al., 2009). Interestingly, in a very small study in a subset of participants of the SERVE-HF RCT (ClinicalTrials.gov Identifier: NCT00733343), the change in the AF burden from baseline to follow-up was −16% with adaptive servoventilation (ASV) devices versus +24% with usual care ($p = .0340$; Piccini et al., 2019), suggesting that treatment of sleep apnea could improve the AF burden.

The mechanism underlying AF causing CSA is probably related to increased left atrial pressure and pulmonary capillary BP somehow increasing the propensity to periodic breathing. This premise is based on experiments in naturally sleeping dogs in which an elevated atrial pressure (via a balloon in the left atrium) resulted in narrowing the partial pressure of carbon dioxide (PCO_2) reserve thus facilitating periodic breathing (Chenuel, Smith, Skatrud, Henderson, & Dempsey, 2006).

A particular form of cardiac arrhythmia is the Brugada syndrome. This is an autosomal-dominant disorder with mutation of a sodium current gene, sodium voltage-gated channel alpha subunit 5 (*SCN5A*). It may account for 20% of sudden cardiac deaths whilst asleep or at rest. It occurs in young men with structurally normal hearts. Presence of ST-segment elevation in the right precordial electrocardiogram leads is characteristic of the syndrome (Priori et al., 2013). It is conceivable that slowing of the heart rate at rest or during sleep predisposes to arrhythmias and sudden death. The recommended therapy is an implantable cardioverter defibrillator.

4 | SLEEP AND SYSTEMIC HYPERTENSION

It is well known that OSA is a cause of hypertension (Peppard, Young, Palta, & Skatrud, 2000), and hypertension is a major risk factor for

CVD and stroke (Virani et al., 2020). Based on the mechanisms of autonomic changes during sleep, systemic BP decreases ≥10% during sleep. Importantly, non-dippers, subjects whose night-time arterial BP declines <10% from day to night are at increased risk of cardiovascular endpoints, LV hypertrophy (Verdecchia et al., 1990), myocardial (Pierdomenico et al., 1998) and cerebral ischaemia (Schwartz et al., 2007).

Administration of melatonin at night has been shown to lower nocturnal BP in at least three RCTs (Arangino et al., 1999; Cagnacci et al., 2005; Scheer, Van Montfrans, van Someren, Mairuhu, & Buijs, 2004). Utilizing ambulatory BP monitoring, two randomized, placebo-controlled crossover trials with administration of melatonin an hour before sleep (Scheer et al., 2004) showed that prolonged administration of this substance significantly reduced nocturnal BP. The mechanisms are unclear and could be related to improved sleep quality resulting in a favourable autonomic nervous system balance, as well as the potential effects of melatonin on vascular system including vasodilatation (Arangino et al., 1999).

Of note, sleep in subjects with hypertension could be disturbed by β-blockers, as synthesis of melatonin in the pineal gland is under the control of a β_1-adrenoreceptor signal transduction system. Multiple studies have shown that some β-blockers inhibit synthesis of melatonin (see the above section on HF). Therefore, it may be speculated that concomitant administration of melatonin with β-blockers not only may improve sleep, but also be more effective than β-blockers alone for treatment of hypertension. To test this hypothesis, systematic studies need to be performed using polysomnography and appropriate protocols.

Finally, it should be emphasized that a major reason for non-dipping of BP, diurnal hypertension, and resistant hypertension could be OSA, particularly in lean individuals, as obesity per se is a well-known cause of hypertension. In the prospective SHHS, amongst leaner subjects (body mass index of <27.3 kg/m^2), but not amongst more obese subjects, a baseline AHI of >30 events/hr was associated with a significantly increased risk of hypertension (odds ratio 2.71, 95% confidence interval [CI] 1.24–5.93; O'Connor et al., 2009).

As will be reviewed below under treatment of OSA, multiple RCTs have shown that treatment of OSA lowers BP, which is most pronounced in those with resistant hypertension.

5 | SLEEP IN CORONARY HEART DISEASE AND MYOCARDIAL INFARCTION

Sleep-disordered breathing is common in subjects with CHD and myocardial infarction. Moderate-to-severe OSA is highly prevalent in subjects with either established CAD or acute coronary syndrome (McEvoy et al., 2016; Peker et al., 2016; Sanchez-de-la-Torre et al., 2020). In a Swedish study, amongst 662 revascularized patients with CAD (Peker et al., 2016), 64% had an AHI of ≥15 events/hr and most did not report daytime hypersomnolence. In a Spanish study, amongst 2,551 patients with acute coronary syndrome, based on polygraphy (hypopnea with 4% desaturation), 1,264 (almost 50%) patients had an AHI of >15 events/hr and 1,287 (50%) had an AHI of <15 events/hr (Sanchez-de-la-Torre et al., 2020).

Large-scale epidemiological studies suggest that OSA, particularly when severe, is associated with excess cardiovascular mortality (Marshall et al., 2008; Punjabi et al., 2009; Young et al., 2008). Observational therapeutic studies suggest that treatment of OSA with CPAP improves cardiovascular mortality (Javaheri et al., 2017). Therapeutic results are reviewed below.

6 | TREATMENT OF OBSTRUCTIVE SLEEP APNEA IN HYPERTENSION AND CORONARY ARTERY DISEASE

The multidimensional approach to the treatment of SDB is covered in the Chapter D. 5. Treatment. Here we review RCTs using CPAP to treat OSA in cardiovascular disorders, specifically hypertension and CAD.

6.1 | Systemic hypertension

Multiple RCTs using 24-hr BP monitoring (Javaheri et al., 2017) consistently report drops of 2–2.5 mmHg in systolic BP and 1.5–2 mmHg in diastolic BP compared with subtherapeutic or conservative treatment (Figure 2). Of note, these previous studies have mixed data from normotensive patients, as well as patients with controlled hypertension (Fatureto-Borges, Lorenzi-Filho, & Drager, 2016). The reduction in BP is most pronounced in resistant hypertension (between 4.7–7.2 mmHg in systolic BP and 2.9–4.9 mmHg in diastolic BP; Figure 3).

Because long-term reductions in BP, although small, have been shown to significantly reduce incidence of stroke and CHD, long-term treatment of OSA in hypertensive patients could eventually reduce the incident cardiovascular burden. Notably, the drop in BP depends on OSA severity, baseline hypertension, and hours of CPAP use (Javaheri et al., 2017). Depending on these characteristics, some patients might experience great antihypertensive benefits from CPAP as demonstrated in the spread of the antihypertensive effect of CPAP (Figures 2 and 3). The level of adherence is a major issue and greater CPAP adherence is associated with improved BP control, insulin sensitivity, and other cardiovascular outcomes (Javaheri et al., 2017). A recent meta-analysis confirmed that severe desaturation, uncontrolled hypertension and age <60 years predict the best reduction in BP with therapy (Pengo et al., 2020). Despite the fact that CPAP treatment may significantly lower BP in patients with OSA, a RCT reported that valsartan induced a four-fold higher decrease in mean 24-hr BP than CPAP in untreated hypertensive patients with OSA (Pepin et al., 2010). Thus, regular treatment with conventional antihypertensives should not be withheld in patients with OSA with elevated BP.

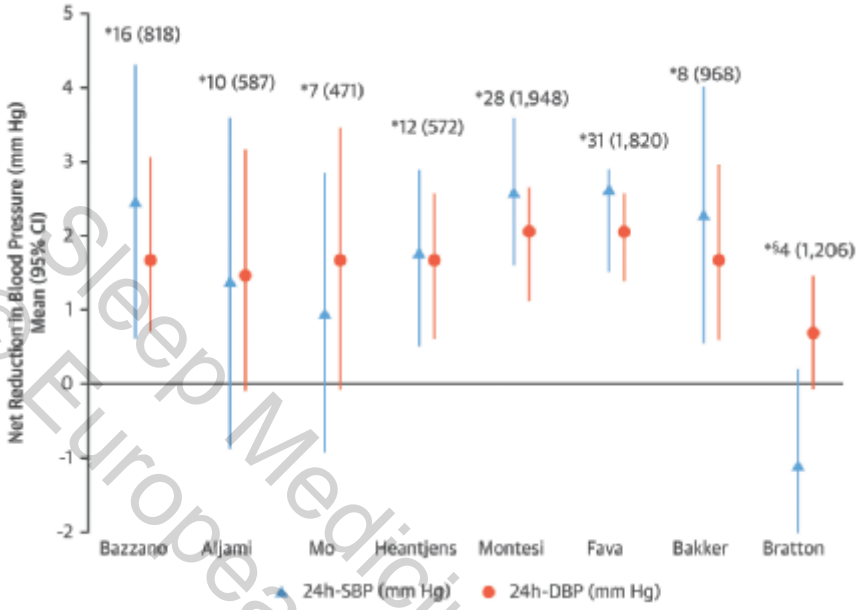

FIGURE 2 Effect of CPAP therapy on BP in patients with hypertension. Summary of different meta-analyses of RCTs. Positive figures mean improvement in BP level with CPAP (net changes). *Number of studies included (number of patients included). §Patients without daytime hypersomnia. BP, blood pressure; CI, confidence interval; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; RCT, randomized controlled trial; SBP, systolic blood pressure. Reproduced with permission from Javaheri et al. (2017)

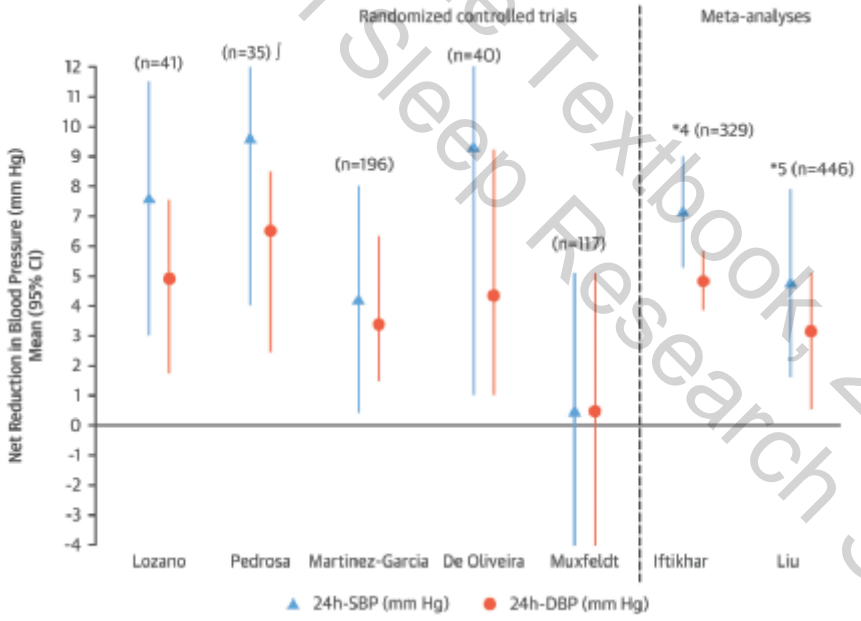

FIGURE 3 Effect of CPAP therapy on BP in patients with resistant hypertension. The figure shows five RCTs and two meta-analyses. The differences between the two meta-analyses depend on the most updated references included in the 2015 meta-analysis. Positive figures mean improvement in BP level with CPAP (net changes). *Number of studies included (number of patients included). Daytime BP values. BP, blood pressure; CI, confidence interval; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; RCT, randomized controlled trial; SBP, systolic blood pressure. Reproduced with permission from Javaheri et al. (2017)

6.2 | Myocardial infarction, coronary artery disease and sleep-disordered breathing

Whilst observational therapeutic studies suggest that treatment of OSA with CPAP improves cardiovascular mortality (Javaheri et al., 2017), results of three RCTs did not confirm a beneficial effect (McEvoy et al., 2016; Peker et al., 2016; Sanchez-de-la-Torre et al., 2020).

In the Swedish RICCADSA trial (ClinicalTrials.gov Identifier: NCT00519597) (Peker et al., 2016), 244 consecutive non-sleepy (ESS of <10) subjects with revascularized CAD and at least moderate OSA (AHI of ≥15 events/hr) were allocated to auto-titrating PAP or no auto-titrating PAP. The incidence of the primary composite cardiovascular endpoint, which included new revascularization, myocardial infarction, stroke or cardiovascular mortality, did not differ between the two groups (adjusted hazard ratio [HR] for CPAP 0.62, 95% CI 0 0.34–1.13). The median follow-up period was 57 months. Importantly, on-treatment analysis defined as PAP use of ≥4 hr/night showed a significant risk reduction (adjusted HR 0.29, 95% CI 0.10–0.86).

In the Spanish ISAACC trial (ClinicalTrials.gov Identifier: NCT01335087) (Sanchez-de-la-Torre et al., 2020), 1,868 patients with acute coronary syndrome and moderate to severe OSA (AHI of ≥15 events/hr), a threshold similar to RICADSSA trial, were randomized to CPAP or usual care. The rate of the composite of cardiovascular endpoint, which included cardiovascular death or nonfatal events acute myocardial infarction, nonfatal stroke, hospital admission for HF, and new hospitalizations for unstable angina or transient ischaemic attack, did not differ significantly between the two groups. The follow-up period was 3.4 years and the average PAP adherence

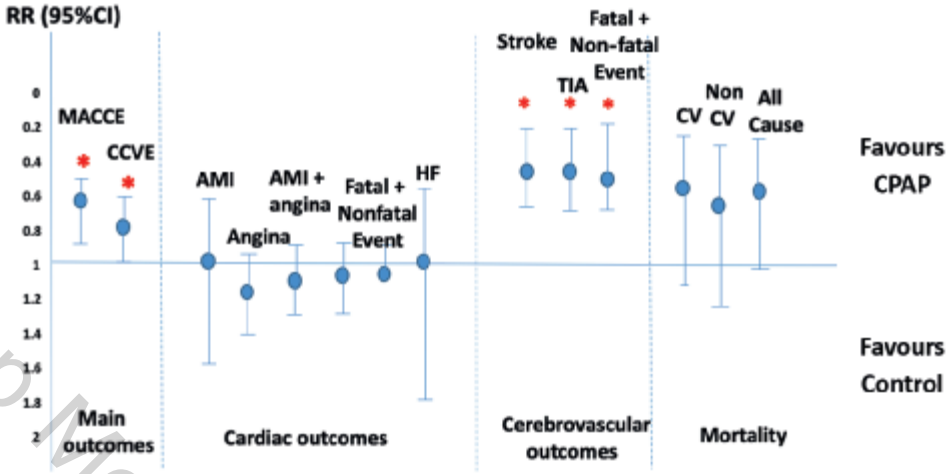

FIGURE 4 Relative risk for single and composite outcomes regarding fatal and non-fatal CV events in patients using CPAP vs. controls. $N = 943$ in the CPAP group vs. 1,141 in the control group. AMI, acute myocardial infarction; CCVE, cerebro-cardiovascular events; CPAP, continuous positive airway pressure; CV, cardiovascular; HF, heart failure; MACCE, major adverse cerebrovascular and cardiovascular events; RR, relative risk; TIA, transient ischaemic attack; $^{*}p < .05$. Modified from Javaheri et al. (2020)

was 2.8 hr/night for the whole group. In contrast to RICADSSA trial, the investigators observed no association between PAP adherence and outcomes.

Amongst the three trials, the Sleep Apnea cardioVascular Endpoints (SAVE) study (ClinicalTrials.gov Identifier: NCT00738179) is the largest reported to date (McEvoy et al., 2016). In this multicentre trial, 2,717 non-sleepy or mildly sleepy (ESS of <15) adults with a history of hypertension, various cardiac diseases (HF or CAD) or cerebrovascular disease were randomized to PAP therapy or usual care. The investigators assessed SDB using a device for home recording consisting of a pressure probe and oximetry. The minimum oxygen desaturation index (ODI) was 12/hr. The composite primary endpoint included cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina, HF, or transient ischaemic attack. In the intention-to-treat analysis, there was no significant difference in the outcomes between the two groups. The average follow up was 3.7 years. Similar to the other two RCTs, the average use of PAP was low, 3.3 hr/night. However, 42% of the subjects used the device for ≥4 hr/night assessed at the 2-year follow up. In a propensity-score matching, the investigators were able to match 561 of the CPAP users with 561 subjects from the usual care group (McEvoy et al., 2016). In this analysis, the composite endpoint of cerebral events was significantly lower in the CPAP group than in the usual care group (HR 0.52, 95% CI 0.30–0.90).

Lessons learned from these RCTs provide clues for designing future trials (Drager et al., 2017; Javaheri, Martinez-Garcia, & Campos-Rodriguez, 2019; Martinez-Garcia, Campos-Rodriguez, & Gozal, 2020; Peker, 2020). Two aspects of these trials are of prime importance. First, the relatively poor adherence to CPAP, and second the use of combining multiple endpoints as outcome. The latter has the disadvantage that OSA may have different adverse consequences on different organs, with consequent different CPAP outcomes. In an analysis of several RCTs (Javaheri, Martinez-Garcia, Campos-Rodriguez, Muriel, & Peker, 2020), which included the aforementioned trials, subjects with adequate CPAP use, defined as ≥4 hr/night, were selected and were compared to the control group. The only beneficial effect of CPAP was reflected in the cerebrovascular, not cardiac outcomes (Javaheri et al., 2020; Figure 4).

This finding is consistent with both epidemiological and physiological data suggesting that OSA has its most adverse consequences on the brain. There are both epidemiological and physiological reasons for our finding, strongly suggesting that the main downstream consequence of OSA is stroke (Catalan-Serra et al., 2019; Redline et al., 2010; Shahar et al., 2001). Pathophysiologically, repetitive cycles of OSA and recurring nocturnal fluctuations in arterial systolic and diastolic BP must exert shear force on the cerebrovascular bed as autoregulation is impaired, under dynamic conditions of apnea-recovery cycles. However, myocardial blood flow occurs only in diastole, protecting the heart from the ups and downs of BP. It is also well known that OSA could be a cause of atherosclerosis (Drager, Bortolotto, Figueiredo, Krieger, & Lorenzi, 2007), and BP fluctuations in carotid and vertebral arteries noted above, along with transmission of snoring-related vibration could be contributing factors. Further, as noted earlier, OSA can be a cause of AF, including paroxysmal AF during sleep, resulting in cardio-embolic stroke, which could also occur during sleep (wake-up stroke).

6.3 | Phenotypic aspects of obstructive sleep apnea therapy

The personalized approach to therapy includes clinical considerations, for example, presence or absence of insomnia, excessive daytime sleepiness, or oedema, polysomnographic findings (Zinchuk et al., 2018), and evaluating physiological traits (Figure 5;

Bitter, Faber, et al., 2009; Eckert, 2018; Eckert, White, Jordan, Malhotra, & Wellman, 2013; Javaheri et al., 2017; Lebkuchen, Freitas, Cardozo, & Drager, 2020). It is anticipated that clinical and pathophysiological subtyping may hold promise for targeted therapy with better adherence and improved outcomes. Other chapters in this textbook cover these traits. Below, we will emphasize only some of these issues.

6.3.1 | The role of oedema

Patients with OSA, obesity and hypertension, and those with HF frequently have salt retention, and lower extremity oedema. In the supine position, fluid from the lower extremities moves intravascularly cephalad causing vascular congestion and pharyngeal narrowing facilitating upper airway occlusion. This was first shown by Shepard, Pevernagie, Stanson, Daniels, and Sheedy (1996) many years ago in patients with OSA and surprisingly remained unnoticed. In patients with HF and biventricular dysfunction, elevated right atrial and central venous pressure additionally contributes to pharyngeal vascular congestion and oedema (Lyons & Bradley, 2015). In those patients, mixed apneas are frequently observed on polysomnography (Dowdell, Javaheri, & McGinnis, 1990). Therefore, an appropriate therapeutic approach to decrease the lower extremity oedema and venous congestion is advisable, although care must be taken to avoid volume depletion, hypotension, and renal failure. Also, treatment of HF aimed at decreasing pulmonary oedema and pleural effusion could increase lung volumes and, as a beneficial side effect, the lung volume-dependent upper airway size.

6.3.2 | Physiological traits

Currently, treatment based on pathophysiological phenotypes considers four traits. These include high loop gain (LG; Eckert, 2018; Eckert et al., 2013; Gottlieb et al., 2010; Javaheri, Brown, & Khayat, 2020b), a low respiratory arousal threshold (Eckert, Malhotra, Wellman, & White, 2014), an anatomically narrow airway (Kuhn, Schwarz, Bratton, Rossi, & Kohler, 2017; Op de Beeck et al., 2019; Phillips et al., 2013), and reduced pharyngeal dilator muscle activity (Lee, Seay, Walters, Scalzitti, & Dedhia, 2019; Strollo et al., 2014). All or some of these factors can contribute to SDB, thus accounting for the known phenotypic variations (Figure 5). However, the phenotypically targeted therapy is a concept in its infancy, awaiting large RCTs.

6.3.3 | Body weight and physical health

Continuous positive airway pressure remains the most effective therapy, particularly in subjects with established CVD. We note, however, that even though CPAP is quite effective in eliminating consequences of OSA, long-term adherence is low in some patients and its metabolic effects (on DM and hyperlipidaemia) remain limited. Adequate application of CPAP therapy does not necessarily entail

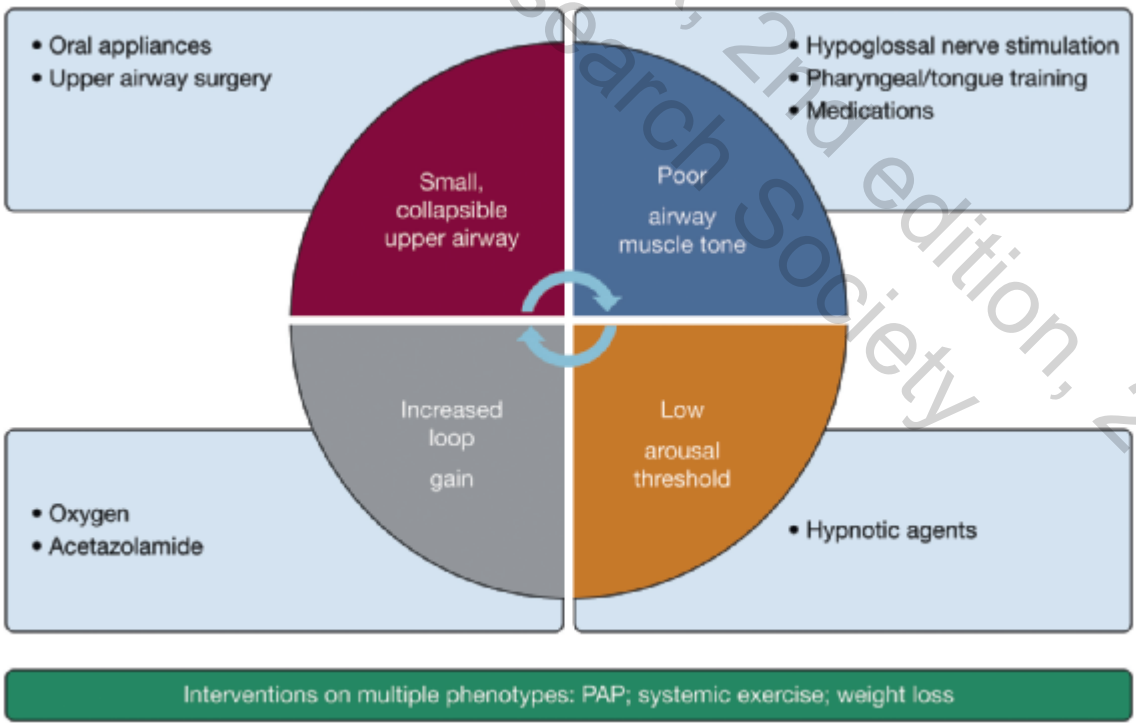

FIGURE 5 Treatment interventions for obstructive sleep apnea in patients with heart failure guided by different phenotypic pathways. PAP, positive airway pressure. Reproduced with permission from Javaheri, Brown, Abraham, et al. (2020)

weight loss and, contrary to expectation, many OSA patients actually gain weight when using CPAP (Drager et al., 2015; Tachikawa et al., 2016). Combination therapy including weight loss and/or exercise with CPAP has shown additional health benefits (Iftikhar, Kline, & Youngstedt, 2014; Ueno et al., 2009). In a long-term RCT, Chirinos et al. have shown that weight loss adds incremental BP reduction in CPAP-adherent patients with OSA (Chirinos et al., 2014). In a four-arm RCT involving patients with OSA and comorbid HF, comparing baseline versus 3 months, the AHI did not change much in the control group, but decreased significantly in the exercise group from an average of 28 to 18 events/hr of sleep ($p < .03$; Servantes et al., 2018). Weight change was minimal. Furthermore, compared with the control group, improvements in the quality of life scores were significant only in the exercise and exercise with CPAP groups ($p < .05$). The postulated mechanisms of the therapeutic effects of exercise include decreased rostral fluid redistribution, stabilization of chemoreceptor sensitivity, improved nasal resistance and strength of pharyngeal dilator muscles, weight loss, and improved sleep quality (Javaheri et al., 2017). Obviously, multimodal therapeutic regimens may have advantages over single point targeted treatment, and, therefore, such combined interventions should be routinely recommended to subjects with OSA.

7 | TREATMENT OF CENTRAL SLEEP APNEA IN HEART FAILURE

Heart failure is the most common cause of CSA, and CSA is frequently observed on polysomnography of subjects with symptomatic or asymptomatic LV dysfunction. General and specific approaches to CSA in the context of HF have been addressed in Chapter D. 5. Treatment. Below we discuss briefly some particular approaches to therapy, although the state of knowledge is limited and much more research is needed in this area (Javaheri et al., 2020b).

7.1 | Treatment options to reduce high loop gain

High LG is the major mechanism underlying HCSB, a phenomenon that predominates in NREM sleep and subsides or is virtually absent in REM sleep. The three major components of LG underlying HCSB are increased chemical drive, increased plant gain and increased mixing gain due to a prolonged circulation time (Javaheri & Dempsey, 2013; see also Chapter D. 2. Pathophysiology). Furthermore, there is a decreased PCO_2 reserve bringing eupneic partial pressure of carbon dioxide, arterial close to the apneic threshold, facilitating central apnea when ventilatory overshoots occur during sleep. Drugs that could attenuate LG, and thus improve CSA, include oxygen that downregulates chemosensitivity, and acetazolamide and theophylline that act mainly by decreasing plant gain. The latter two have been discussed previously and will not be further addressed in this chapter. As discussed in Chapter D. 5. Treatment, positive results on HCSB have been documented with nocturnal supplemental low-flow oxygen therapy in RCTs of limited duration. However, the long-term effects of this treatment are unknown. A phase III long-term RCT with oxygen therapy has been funded by the National Institutes of Health of the USA (NIH: LOFT-HF trial.Gov). The composite endpoint of the study is rehospitalization and mortality. The study is ongoing and results of this 5-year trial will become available in the next few years.

7.2 | Treatment options to stabilize the upper airway

Narrowing and closure of the upper airway may occur in the terminal phase of CSA (Badr, Toiber, Skatrud, & Dempsey, 1995) and mixed sleep apneas are frequently observed during sleep in patients with HF. That could be the reason why oral appliance or CPAP therapy may be helpful in some subjects with HFrEF and upper airway obstruction. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial has demonstrated beneficial effects of CPAP treatment on clinical outcomes in a subset of patients with HCSB (Bradley et al., 2005). Whilst CPAP therapy was not effective in 53% of the patients, and hence no positive effects on survival were observed, a post hoc analysis of the data showed significant improvement in survival in patients whose AHI was suppressed by CPAP and who were adherent treatment (Arzt et al., 2007).

Oral appliances are indicated to treat OSA, as discussed earlier. The data from Eskafi, Cline, Nilner, and Israelsson (2006) showed improvement of the AHI in patients with HF, but it is not clear how many had CSA. The lack of evidence prompts additional research based on well-designed RCTs, along with appropriate physiological investigations.

7.3 | Ventilatory support and pacing

Adaptive servoventilation devices have been discussed in Chapter D. 5. Treatment. These devices are controlled by a dedicated electronic algorithm to provide varying inspiratory pressure support, anti-cyclic (i.e., out of phase) to the periodic breathing seen in patients with HF. Current ASV devices have two other virtues, an automatic expiratory PAP algorithm capable of stabilizing the upper airway to eliminate obstructive events, and a mandatory timed back-up mode to abort impending central apneas (Javaheri, Brown, & Randerath, 2014). Surprisingly, in the SERVE-HF study, the largest RCT trial to date (Cowie et al., 2015), not only did ASV fail to show efficacy across the board, but it also significantly increased cardiovascular mortality. Whilst arguably CSA might have a protective role in the disease progress of HF, and ASV by treating CSA could have provoked adverse effects (Javaheri, Brown, & Khayat, 2018), a potential contributor to the excess cardiovascular mortality seen in the SERVE-HF study was inappropriate pressure delivery, and possibly also an outdated algorithm of the ASV apparatus (Javaheri, Brown, et al., 2016; Knitter et al., 2019). There is an

ongoing study (the ADVENT-HF trial; ClinicalTrials.gov Identifier: NCT01128816) using an ASV device with an improved algorithm (Lyons et al., 2017). The results of this study will be published in the next few years. To date, no signs of premature mortality have become apparent with this device.

Unilateral phrenic nerve stimulation has been approved by the United States Food and Drug Administration (FDA) for physiological treatment of CSA (Ponikowski et al., 2012). In an RCT (Costanzo et al., 2016), 151 patients with CSA were implanted and randomized to stimulation or no stimulation for 6 months. With stimulation, multiple measures of sleep apnea severity (AHI, Central Apnea Index, Arousal Index, and Oxygen Desaturation Index), quality of life, and daytime sleepiness, improved significantly. The most common side effect was therapy-related discomfort that was resolved with reprogramming in most. Local side effects, such as infection and dislodgment occurred in 13 of 151 implanted patients. Sustained effects have been observed up to 36 months (Fox et al., 2019). However, long-term trials with mortality as an endpoint are not available as yet.

8 | PERIODIC LIMB MOVEMENT DISORDER AND CARDIOVASCULAR DISEASE

Periodic limb movement disorder (PLMD) is a common polysomnographic finding and generally needs no treatment unless accompanied by RLS. However, it has been suggested that PLM could also be associated with CVD including hypertension, arrhythmia, and also mortality (Kendzerska, Kamra, Murray, & Boulos, 2017; Koo et al., 2014; Nannapaneni & Ramar, 2014; Pennestri et al., 2013; Siddiqui et al., 2007). During sleep, PLMs are associated with parallel surges in BP and in heart rate, particularly when followed by arousals (Pennestri et al., 2013; Siddiqui et al., 2007). In a study of unselected patients with OSA (Lombardi et al., 2019), PLMs were associated with a rise in systolic BP regardless of AHI and independent of clinical and sociodemographic confounders. Based on the aforementioned studies, presence of PLMs could thus carry an increased risk of CVD. Furthermore, if PLMs are associated with insomnia, particularly if RLS is comorbid, insomnia could also contribute to autonomic dysfunction and CVD.

It is emphasized that all aforementioned studies are observational leaving questions as to causality. Furthermore, limb movements could frequently co-occur with respiratory effort-related arousals that appear in the context of the so-called upper airway resistance syndrome popularized by the late Dr Christian Guilleminault (Javaheri & Gay, 2019). In this case, it is the respiratory disorder and the related arousal rather than the movement that would contribute to autonomic dysfunction and hypertension (Budhiraja, Javaheri, Parthasarathy, Berry, & Quan, 2019). It is not clear from the literature, if and how polysomnograms were scored such that PLMs could be discerned from alterations in upper airway resistance.

9 | CONCLUSIONS

Sleep has profound effects on the cardiovascular system. Normally, as sleep deepens from N1 to N3, both systolic and diastolic BP, along with heart rate decrease. The reduction in this double effect decreases cardiac workload allowing restoration of myocytes whilst asleep. The phasic REM sleep, however, could cause haemodynamic instability and non-demand myocardial ischaemia.

Sleep in CVD could be disrupted for various reasons. OSA is a common cause of CVD including hypertension, HF, CAD, arrhythmias, and stroke. Whereas OSA can be a cause of HF, HF by itself, particularly HFrEF causes CSA. Expectedly, cardiac transplantation virtually eliminates CSA, but recipients are prone to gain weight and develop OSA.

Central sleep apnea is quite common in LV dysfunction, particularly in HFrEF. Treatment of CSA remains a challenge. Multiple therapeutic options including use of oxygen, acetazolamide, theophylline, CPAP, adaptive servoventilation and the phrenic nerve stimulation have demonstrated that none can completely eliminate CSA. This is in contrast with OSA where CPAP proves quite effective. Currently, ASV is contraindicated for use in HFrEF-associated CSA, but no other causes of CSA including HFpEF. The ASV used in the SERVE-HF trial had deficiencies, which may have contributed to premature death. An RCT with an improved ASV is ongoing.

Phrenic nerve stimulation is a promising treatment option that has been approved by the FDA for treatment of CSA. Also, renewed interest in oxygen therapy for the treatment of CSA has materialized into a long-term, FDA-approved RCT, the results of which will be available within the next few years.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

SJ, LFD, DAP, and GL-F authors made substantial contributions to the content and writing of this chapter.

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