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JACC STATE-OF-THE-ART REVIEW

Interactions of Obstructive Sleep Apnea With the Pathophysiology of Cardiovascular Disease, Part 1

JACC State-of-the-Art Review

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ABSTRACT

The American Heart Association considers sleep health an essential component of cardiovascular health, and sleep is generally a time of cardiovascular quiescence, such that any deviation from normal sleep may be associated with adverse cardiovascular consequences. Many studies have shown that both impaired quantity and quality of sleep, particularly with obstructive sleep apnea (OSA) and comorbid sleep disorders, are associated with incident cardiometabolic consequences. OSA is associated with repetitive episodes of altered blood gases, arousals, large negative swings in intrathoracic pressures, and increased sympathetic activity. Recent studies show that OSA is also associated with altered gut microbiota, which could contribute to increased risk of cardiovascular disease. OSA has been associated with hypertension, atrial fibrillation, heart failure, coronary artery disease, stroke, and excess cardiovascular mortality. Association of OSA with chronic obstructive lung disease (overlap syndrome) and morbid obesity (obesity hypoventilation syndrome) increases the odds of mortality. (JACC. 2024;84:1208–1223) © 2024 by the American College of Cardiology Foundation.

Cardiovascular disease (CVD) is highly prevalent and remains the leading global cause of death. It is expected to account for >24 million deaths by 2030.[1] In this context, there is growing interest regarding the impact of poor quality and quantity of sleep and sleep disordered breathing (SDB) as contributors to the burden of CVD.[1,2] The American Heart Association recently added sleep as 1 component of Life's Essential 8 for optimal cardiovascular (CV) health.[2] In this paper, we focus on unhealthy sleep and obstructive sleep apnea (OSA) and discuss their association with CVD. In part 1 of this State-of-the-Art Review, novel additions include highlighting the implications of OSA comorbid with chronic obstructive pulmonary disease (COPD; ie, the overlap syndrome), with obesity hypoventilation syndrome (OHS), and with insomnia and short sleep and their relation to CVD. We also review the biological mechanisms linking OSA to CVD, including association with altered gut microbiota that may further contribute to CVD and OSA in children. Central sleep apnea is beyond the scope of this review and has been extensively covered elsewhere.[3] In part 2 of this State-of-the-Art Review, we examine the landscape

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HIGHLIGHTS

- OSA is associated with increased cardiovascular risk, amplified by OHS and overlap syndromes.
- The presentation and cardiovascular implications of OSA differ between men and women.
- Potential mechanism linking sleep apnea to incident CVD may involve alterations in the gut microbiome.

of therapeutic options with an emphasis on OSA. Past and ongoing interventional studies are discussed, and designs for future trials are suggested.

NORMAL SLEEP AND CARDIOVASCULAR HEMODYNAMICS

Sleep is not a homogeneous state and comprises different stages. During nonrapid eye movement (NREM) sleep, which consists of 3 stages (N1-N3), there is autonomic and hemodynamic stability with a progressive decrease in central sympathetic outflow, increase in parasympathetic neural tone, and decrease in heart rate and blood pressure (BP). NREM sleep is considered "restful" for the CV system with reduced arterial BP, heart rate, metabolic rate, and subsequently reduced cardiac workload.[4] Sleep architecture also plays a role in BP regulation. The SHHS (Sleep Heart Health Study) has shown an association between reduced slow-wave sleep or N3 sleep and incident hypertension.[5] Studies are needed to evaluate the possibility of increased stage N3 sleep as a therapeutic target in hypertension.

In contrast to NREM sleep, in phasic REM, sleep heart rate and BP increase intermittently, and often abruptly, in association with increased sympathetic activity. The rise in BP increases left ventricular (LV) afterload and myocardial oxygen consumption, which is further augmented by an increase in heart rate, another determinant of myocardial oxygen consumption. On the other hand, during REM sleep, brief episodes of augmented vagal cardiac drive may rarely manifest as bradycardia or even asystole.[6] Furthermore, because of muscle hypotonia during REM sleep, OSA events are often more prevalent and severe, and are associated with pronounced hypoxemia compared with NREM sleep. These findings have important implications both for understanding downstream CV consequences of OSA and the effects of poor continuous positive airway pressure (CPAP) adherence, particularly when using CPAP the first few hours of sleep as REM predominates during the latter half of the night. In the following section, we discuss deviations from normal sleep followed by adverse cardiometabolic consequences of OSA.

SLEEP QUANTITY AND QUALITY AND CARDIOCEREBROVASCULAR CONSEQUENCES

As noted, the writing group of the American Heart Association endorses the systematic assessment and inclusion of sleep duration as an important component of CV health.[2] Importantly, disruption of normal sleep patterns (generally considered 7-9 hours per night), including short sleep duration, sleep fragmentation, and mistimed sleep, is associated with increased cardiometabolic disease risk.[7] Multiple studies have shown a U-shaped association between sleep duration and hypertension, coronary artery disease (CAD), and stroke, as well as increased CV mortality.[8,9] In a large prospective study involving 403,187 participants from the UK Biobank, a healthy sleep pattern was associated with lower risks of atrial fibrillation (AF) and bradyarrhythmia, independent of traditional risk factors.[10-12]

Chronic insomnia, the most prevalent sleep disorder in the United States, is characterized by difficulty falling asleep and/or maintaining sleep (despite adequate opportunity for sleep) coupled with some sort of daytime impairment such as fatigue, mood disturbances, impaired cognitive function, and/or poor job performance. Biologically, insomnia is closely associated with high levels of psychological and physiological arousal as evidenced by elevated sympathetic nervous system activity and increased brain metabolic activity during sleep.[13] Consequently, chronic insomnia disorder has been shown to be accompanied by less nocturnal blood pressure dipping, systemic endothelial dysfunction, impaired glucose homeostasis, and insulin sensitivity.[7,8,11,13]

Similar to insomnia, short sleep is also associated with incident CVD, and insomnia coupled with objective short sleep may actually represent a distinct phenotype associated with increased risk of CVD compared with either condition alone.[7] A meta-analysis of short sleep duration and health outcomes examined data from prospective studies

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
AF = atrial fibrillation
AHI = apnea-hypopnea index
BP = blood pressure
CAD = coronary artery disease
CO_2 = carbon dioxide
COPD = chronic obstructive pulmonary disease
CPAP = continuous positive airway pressure
CV = cardiovascular
CVD = cardiovascular disease
EDS = excessive daytime sleepiness
LV = left ventricular
NREM = non-rapid eye movement
OHS = obesity hypoventilation syndrome
OSA = obstructive sleep apnea
PCO_2 = partial pressure of carbon dioxide
PFO = patent foramen ovale
PH = pulmonary hypertension
REM = rapid eye movement
SDB = sleep disordered breathing
TNF = tumor necrosis factor

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of at least 1 year duration (n = 5,172,710 participants from 153 studies) and found that short sleep (<6 hours) was significantly associated with mortality, diabetes mellitus, hypertension, CVD, coronary heart disease, and obesity.[14] In addition, multiple studies have reported additive risk of incident CVD with insomnia coupled with short sleep compared with either condition alone.[7] Mechanisms underlying these associations may include hypothalamic-pituitary axis dysregulation, increased sympathetic nervous system activity, and increased inflammation systemically. Experimental human models of sleep restriction show subsequent increases in BP, C-reactive protein, soluble tumor necrosis factor (TNF)-α receptor, and interleukin-6.[7] The extent to which insomnia vs short sleep confer increased risk of CVD is unclear, but, as already mentioned, the evidence suggests that the combination of the 2 confers additional risk compared with either condition alone.

CIRCADIAN RHYTHM DISRUPTION AND CVD

Risk for CV events such as myocardial infarction,[15] cardiac arrhythmias,[16] and cerebrovascular accident[17] is higher in the morning hours. Although alterations in sleep physiology and behaviors may contribute, circadian regulation of CV function and coagulation factors plays a prominent role in the morning timing of CVD events.[18,19] The molecular circadian clock is found in nearly all cells and consists of a set of core genes that maintain self-sustaining circadian rhythms via autoregulatory loops.[20] Circadian disruption, which can occur at multiple organizational domains, negatively affects the normal rhythmic regulation of CV function at the molecular, cellular, and organ levels. In humans, circadian disruption, most commonly circadian misalignment such as shift work and delayed sleep phase, has been associated with increased risk of CVD risk factors, including hypertension, nocturnal nondipping of BP, resting heart rate, and inflammation.

Multiple studies have concluded that individuals with an evening chronotype (ie, "night owls") are at increased risk of CV and metabolic disorders. In a large cross-sectional study involving 2,471 participants from the EpiHealth cohort, circulating proteins were analyzed using a multiplexed proximity extension technique.[21] Seventeen proteins were identified as being associated with chronotype, and the evening chronotype was positively associated with proteins previously linked to insulin resistance and CV risk, namely retinoic acid receptor protein 2, adipocyte fatty acid-binding protein, tissue-type plasminogen activator, and plasminogen activator inhibitor 1. Circadian-based approaches aiming to improve alignment between the environment, behaviors, and endogenous circadian rhythms may have the potential to improve CVD outcomes.

Sleep irregularities, particularly sleep duration variability, have been independently associated with several measures of subclinical atherosclerosis such as high coronary artery calcium burden.[22]

A topic that has garnered recent attention is a circadian approach to timing of medications. Approximately 1,000 drugs are metabolized, transported, or act on a clock-regulated gene product,[23] suggesting that timing of drug administration may affect treatment efficacy in hypertension given the prominent diurnal rhythm of BP. A recent large prospective study included patients with hypertension who were allocated to morning or bedtime dosing of BP-lowering medication and followed up for 6 years; a decreased risk of CV events (stroke, MI, heart failure) was reported in the group dosed at bedtime.[24] However, a more recent large, prospective study did not find any difference in major CV events after 5 years of follow-up.[25]

Although these findings have been controversial,[26] a systematic review of smaller trials seems to support the notion that evening dosing of certain BP therapy may be beneficial for some patients.[27] Use of 24-hour ambulatory BP monitoring might be helpful in identifying such patients. Additional multicenter prospective studies are needed to evaluate the potential benefits and disadvantages of chronotherapy for CVD.

SDB AND CVD. OSA is characterized by the relaxation of the dilator muscles of the upper airway, principally the genioglossus muscle, allowing the tongue to fall backward, completely closing (apnea) or partially narrowing (hypopnea) the pharyngeal airway. An apnea is defined as cessation of breathing for ≥10 seconds, roughly equivalent to 2 breaths, and a hypopnea is defined as a reduction in breathing for ≥10 seconds coupled with either a 3% or 4% oxygen desaturation or an arousal from sleep. Gottlieb and Punjabi[28] recently reviewed OSA-associated diurnal symptomatology in depth, including intermittent snoring, unrefreshing sleep, excessive daytime sleepiness, fatigue, tiredness, or lack of energy, waking up with or without gasping and choking, and witnessed apneas. Nocturia is also a common symptom and may in part result from the release of atrial natriuretic peptide due to dilatation of atria mediated by increased negative intrathoracic pressure swings. Morning headaches, likely due to cerebral hypoxia

and hypercapnia, are another potential consequence of OSA and usually resolve shortly after awakening with resumption of normal breathing.[29]

Excessive daytime sleepiness (EDS) is the most common symptom for which patients seek medical advice. Several factors may contribute to EDS, including the microarousals following apneas, alterations in microbiome, and up-regulation of somnogenic inflammatory cytokines such as TNF-α.[30] Notably, although the prevalence of OSA is much higher in subjects with CVD than in the general population, many patients with CVD do not report EDS or other symptoms experienced by the general population, thereby contributing to the underdiagnosis of OSA and lower adherence to therapy.[30]

BIOLOGICAL PATHWAYS MEDIATING CV CONSEQUENCES OF OSA. While asleep, repeated cycles of obstructive apneas and hypopneas are associated with 3 major acute adverse CV consequences: 1) intermittent hypoxemia-reoxygenation and fluctuations in partial pressure of carbon dioxide (PCO_2); 2) repeated arousals, predominantly after apneas and hypopneas, resulting in increased sympathetic activity; and 3) large negative intrathoracic pressure swings while breathing against an occluded airway, most pronounced in OSA (**Central Illustration**, **Figure 1**). Upon repeated exposure, sustained increases in tonic and reactive sympathetic activity and up-regulation of inflammatory cascades occur, ultimately contributing to incident CVD.[31] Further research studies additionally suggest that OSA is associated with an altered gut microbiome that could also contribute to the pathogenesis of CVD.[32,33] These important factors are discussed below. Additional mechanisms underlying OSA, including anatomical and functional features (low arousal threshold and alterations of neuromuscular excitability), as well as unstable ventilatory control will be detailed in part 2 of this State-of-the-Art Review with related therapeutic options (**Central Illustration**).

OSA AND ITS MOLECULAR SIGNATURES LEADING TO CVD

Systemic inflammation and oxidative stress are widely accepted factors in the pathogenesis of CVD, and adipose tissue-associated inflammation in the setting of obesity contributes to this pro-inflammatory state.[34] Cumulative evidence also provides strong support that OSA is a chronic low-grade inflammatory disease associated with up-regulation of inflammatory cascades and oxidative stress,[35] which have important implications for the development of CV comorbidities. Intermittent hypoxia seems to be a key factor in the development of this inflammatory response, and a cell culture model has shown a brisk up-regulation of the pro-inflammatory transcription factor nuclear factor κB in response to intermittent hypoxia. In contrast, the adaptive transcription factor hypoxia-inducible factor-1α was not up-regulated.[36]

Furthermore, downstream expression of inflammatory cytokines in response to nuclear factor κB (eg, TNF-α) and interleukin-8 promote leukocyte migration into the vascular endothelium and adhesion molecules such as inter-cellular adhesion molecule 1, which further contribute to vascular inflammation. Notably, these biomarkers decrease with CPAP therapy.[36]

Intermittent hypoxia also results in oxidative stress with increased production of reactive oxygen species and plasma lipid peroxidation.[37] This oxidative stress represents an important factor in vascular endothelial injury and subsequent inflammation, which in turn is a major factor in the development of atherosclerosis and consequent CVD. Leukocyte migration into the vascular endothelium is promoted by inflammatory cytokines such as interleukin-8 and adhesion molecules such as inter-cellular adhesion molecule 1, which further contribute to vascular inflammation.

One study investigating serum proteomic biomarkers profiling 1,300 proteins in serum samples of 713 individuals undergoing polysomnography reported that the severity of SDB was associated with up-regulation of 65 proteins.[38] The up-regulated proteins were predominantly involved in complement, coagulation, cytokine signaling, and hemostasis pathways, all of which are biologically plausibly associated with downstream effects of OSA-related CVD and hypercoagulability. Furthermore, another study reported that BP response to CPAP in patients with OSA and resistant hypertension can be predicted by measuring the plasma levels of 3 specific microribonucleic acids,[39] which may help to personalize this treatment in the future.

OSA-RELATED SYMPATHETIC AND PARASYMPATHETIC ACTIVITY

OSA induces intermittent and often profound hypoxemia and hypercapnia, which act through the peripheral and central chemoreceptors to increase central sympathetic outflow. This neural response is normally blunted by the inspiratory stretch of the thoracic afferents, but this does not occur in OSA because the airway obstruction prevents lung inflation.[40] Hence, the combination of apnea, hypoxemia,

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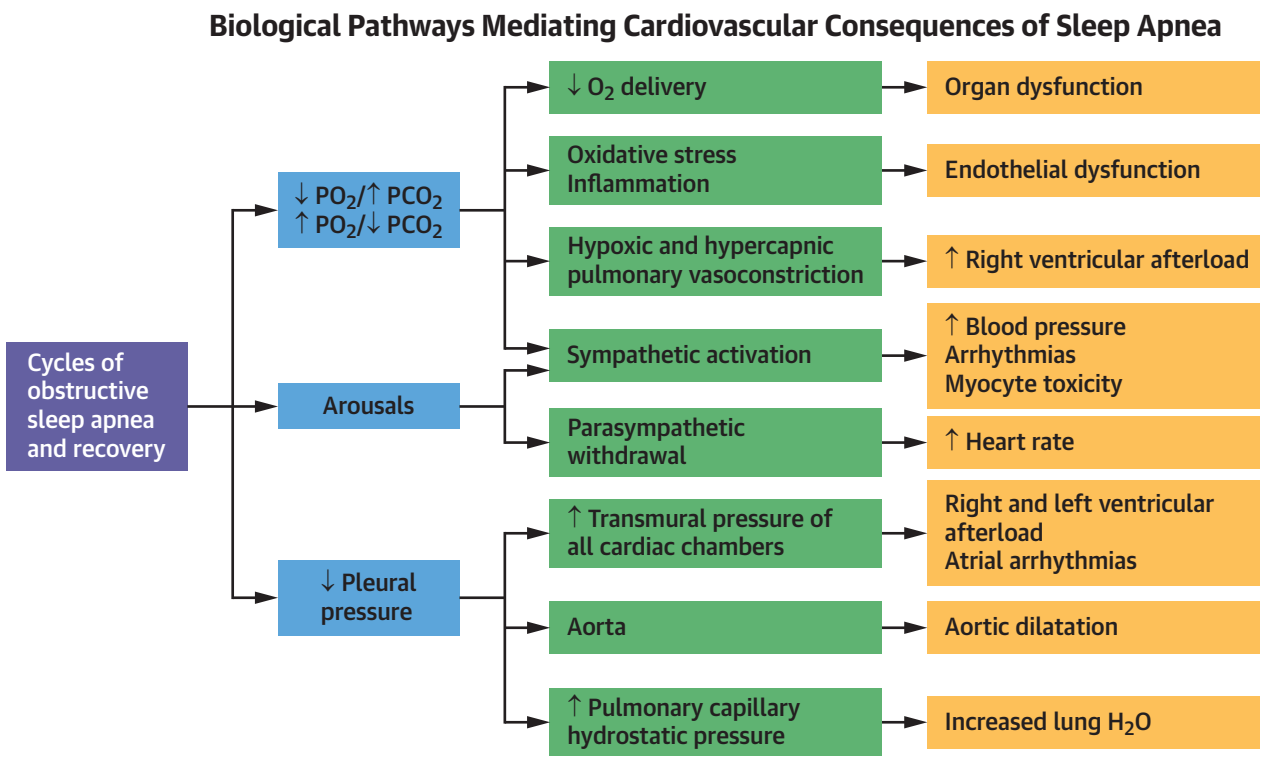
CENTRAL ILLUSTRATION **Pathophysiological Consequences of Sleep Apnea and Hypopnea**



Javaheri S, et al. JACC. 2024;84(13):1208–1223.

Pleural pressure (Ppl) is a surrogate of the pressure surrounding the heart and other vascular structures. Reproduced from Javaheri et al.[1]

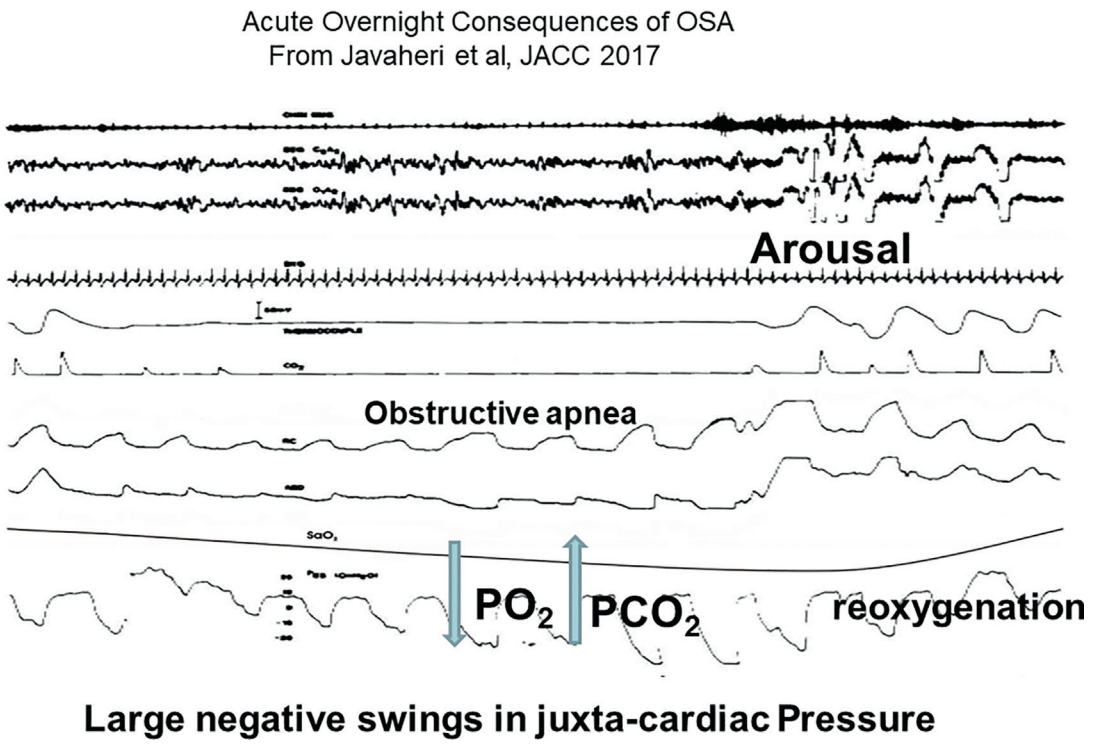
and hypercapnia elicits marked increases in sympathetic outflow with peripheral vasoconstriction and increases in BP.[41]

Parasympathetic or vagal cardiac control is also important during apneas. The combination of apnea and hypoxemia, while increasing sympathetic outflow to peripheral blood vessels, also elicits increases in cardiac vagal activation (ie, the diving reflex). Thus, peripheral sympathetic vasoconstriction may be accompanied by simultaneous vagal bradycardia, which may even present as repetitive prolonged periods of nocturnal asystole, usually terminated by inspiration at the end of the apnea.[42] These autonomic responses to apnea have important implications for OSA-related CVD. Sympathetic activation at night with consequent BP surges in the setting of hypoxemia and hypercapnia likely contribute to the adverse cardiocerebrovascular consequences of OSA, including nocturnal non-dipping, cardiac ischemia, myocardial infarction, and arrhythmias such as AF.[31] Nondipping of nocturnal BP can itself carry significant risk for CV events, independent of BP. Notably, nocturnal sympathetic activation appears to carry over into daytime normoxic wakefulness, possibly due to tonic chemoreflex activation, with implications for daytime hypertension.[42] Emerging evidence suggests that ganglia situated in the epicardial fat pads serve as important regulatory centers for cardiac autonomic control,[43] and they may be potential targets for therapeutic modulation of autonomic responses to apnea, especially when the apnea itself is not easily treatable.

OSA AND GUT MICROBIOTA: IMPLICATIONS FOR CVD

The episodic nature of hypoxemic events that is associated with OSA is reflected by fluctuating levels in the arterial partial pressure of oxygen of the gut lumen contents across a centrifugal gradient.[32,44-46] The nocturnal changes in luminal arterial partial pressure of oxygen promote substantial alterations in the gut microbiome that are further compounded by changes imposed by the repetitive arousals that characterize OSA. Furthermore, the changes in gut

FIGURE 1 30-Second Epoch of Obstructive Sleep Apnea



These tracings show that during an obstructive apnea, airflow is absent while breathing effort continues. Breathing resumes with the onset of arousal. The first tracing is a chin electromyogram, the second and third tracings are an electroencephalogram, fourth is electrocardiogram, fifth and sixth are airflow measured by thermocouple (fifth) and carbon dioxide (CO_2) (sixth), seventh and eighth are rib cage (seventh) and abdominal (eighth), ninth is oxyhemoglobin saturation measured by pulse oximetry, and tenth is esophageal pressure. Reproduced with permission from Javaheri et al.[1] PCO_2 = partial pressure of carbon dioxide; PO_2 = partial pressure of oxygen.

microbiota induced by the presence of intermittent hypoxia, hypercapnia, or sleep fragmentation have in turn been implicated in the disruption of intestinal epithelial permeability and promotion of local and systemic inflammatory responses; these ultimately translate into exacerbation of the typical cardiometabolic morbidities associated with OSA.

Indeed, it has been suggested that disruption of gut microbial ecosystems as induced by nocturnal intermittent hypoxia underlies the emergence of OSA-related systemic hypertension. Increased abundance of the genus *Lachnospiraceae* and reduced detection of the genus *Coprococcus* in rats exposed to intermittent hypoxia-simulating features of OSA induced significant increases in T helper 1, T helper 17, and TNF-α^+ cells in the gut, spleen, and aorta, along with neuroinflammatory responses, all of which were further causally implicated in systemic hypertension.[33] It is further postulated that interventions with specific modulators of gut microbiota (ie, prebiotics, probiotics) may palliate or abrogate the cardiometabolic and other morbidities induced by OSA.

Sleep fragmentation, another prototypic manifestation of OSA, also induces significant changes in gut microbiota as illustrated by increased abundance of *Lachnospiraceae* and several other bacterial species, all of which are mechanistically and cooperatively implicated in metabolic dysfunction.[47] In a murine model, chronic prolonged intermittent hypoxia induced hypertension as well as coronary artery dysfunction.[48] These exposures not only prompted predictable changes in the gut microbiome, but fecal microbiota transfer of these altered microbial contents to naive mice also induced excessive daytime sleepiness, hypertension, and coronary artery flow responses.[32,49] Although all findings were derived from studies in animal models, recent preliminary data in patients with OSA confirm the presence of divergences in gut microbiota, and they offer a

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unique opportunity for interventional trials using restoration of the abnormal gut microbiome as an adjuvant therapeutic strategy aimed at improved reversibility or prevention of OSA-induced morbidities. Indeed, in a Mendelian randomization study, the family of Peptostreptococcaceae and genus Coprococcus were associated with increased risk of OSA, whereas changes in the abundance of the family of Acidaminococcaceae and genus *Blautia* may reduce such risk.[50]

In another study of patients with OSA, the ratio of *Firmicutes* to *Bacteroidetes* was significantly higher in patients with more severe OSA while the relative abundance of short-chain fatty acid-producing bacteria such as *Bacteroides* and *Prevotella* was reduced.[45] In a population-based cohort of 3,570 individuals aged 50 to 64 years in Sweden who underwent home-based sleep studies, OSA parameters were associated with lower diversity of species in the gut, along with increased relative abundance of 128 gut bacterial species such as *Blautia obeum* and *Collinsella aerofaciens*, the latter being associated with the presence of systemic BP.[46] Taken together, these preliminary studies suggest that OSA not only induces substantive modification in gut microbiome but that such changes underlie some of the end-organ morbidities of OSA. It remains unclear and unexplored whether therapeutic interventions aimed at restoring the gut microbiome will mitigate the magnitude of CV morbidities or enhance the reversibility of such morbidities when CPAP treatment in instituted.

OSA AND SYSTEMIC HYPERTENSION

Systemic hypertension is the most common CV consequence of OSA and may itself be a potential mediator of incident cardio-cerebrovascular disease, including AF, heart failure, and stroke, all of which are increased in patients with OSA.[51-53] High-quality longitudinal cohort studies show that OSA is an independent risk factor for incident hypertension (about a 2-fold higher risk compared with non-OSA subjects).[54] There is a high prevalence of OSA (30%) among individuals with hypertension and conversely a high prevalence of hypertension (50%) among individuals with OSA. Remarkably, the prevalence of OSA increases to 60% to 90% in subjects with resistant hypertension, and this association is even stronger for refractory hypertension, with 95% of these patients having moderate to severe OSA. OSA has also been identified as the most common condition associated with resistant hypertension.[53]

In addition to the mechanisms already described, sleep stage-specific nocturnal sympathetic activation may lead to non-dipping and high nocturnal BP pattern. Phasic REM sleep is associated with higher sympathetic activity and CV instability in patients with OSA, and studies report an association between REM OSA (mostly defined as REM apnea-hypopnea index [AHI] ≥15 events per hour) and incident hypertension and nondipping BP pattern.[55] Based on the evidence, international guidelines acknowledge OSA as an important contributing factor to hypertension and resistant hypertension.[56]

OSA AND PULMONARY HYPERTENSION

OSA is classified as World Health Organization group 3 for causes of pulmonary hypertension (PH) due to chronic hypoxemia with or without hypercapnia. However, OSA may also cause PH through LV diastolic dysfunction (World Health Organization group 2). Based on the current criteria, prevalence of precapillary PH was 28% among 105 patients with OSA who simultaneously underwent polysomnography and right heart catheterization. In most cases, PH is mild, but severity increases in the presence of obesity, particularly in those with OHS, COPD, and left heart disease. The Pickwick Study showed that nearly 50% of patients with OHS and concomitant OSA have echocardiographic evidence of PH. Treatment of OSA with PAP devices in patients with OHS and PH reduced pulmonary artery systolic pressure by nearly 9 to 10 mm Hg. This beneficial effect was present at 1 year and sustained at 3 years.[57] The exact mechanisms by which long-term PAP therapy improves PH remains unclear but is likely related to a combination of improving sleep architecture, wake hypoxemia and hypercapnia, reduced nocturnal BP, and subsequent improvement in LV diastolic dysfunction.

The American College of Cardiology and the American Heart Association expert consensus document recommends polysomnography to rule out OSA for all patients with PH.[58] This recommendation is based on the notion that targeted therapy of OSA may either improve or prevent further deterioration in pulmonary hemodynamics.

OSA AND CARDIAC ARRHYTHMIAS

Imbalances in sympathovagal activity underlie cardiac arrhythmogenesis. In concert with favorable changes in autonomic nervous system activity during NREM sleep, ventricular arrhythmia burden is usually suppressed,[59] supported by reduced discharges of

implantable cardioverter-defibrillators during NREM in ischemic heart disease.[60] However, in the presence of SDB, with consequent hypoxemia, hypercapnia, negative intrathoracic pressure swings, and hemodynamic stress, repetitive intermittent sympathetic and vagal activation occurs, providing a potent synergy of triggers for cardiac arrhythmias, especially in patients with OSA with a vulnerable cardiac substrate. These arrhythmic responses include bradyarrhythmias, AF, and ventricular arrhythmias. Bradyarrhythmia can include prolonged and repetitive episodes of asystole, lasting for up to 1 minute or more. These are due to the diving reflex described earlier and are often captured on Holter or other continuous electrocardiogram monitoring. If these events occur exclusively during sleep, they are then likely apnea induced, and treatment should focus on addressing the apnea, although management remains controversial.[6] Bradyarrhythmia, together with high levels of circulating catecholamines, may also predispose to AF (ie, the so-called cholinergic AF).[61]

Patients with OSA are at a substantially higher risk of incident AF, with severity of nocturnal hypoxemia serving as an independent predictor of future AF.[62] This may be particularly important in patients with CV substrates such as heart failure dependent on rate control and atrial kick, in which development of AF may be prognostically problematic. Both heart failure and AF have a high likelihood of comorbid OSA, and there is increasing evidence that comorbid OSA is linked to a heightened risk of incident AF. OSA is important even in patients with established AF, who have a high prevalence of often undiagnosed OSA.[63] Diagnosis and treatment of OSA may be important in treating AF, and observational studies consistently show that treatment of OSA after interventions focused on restoration of sinus rhythm helps reduce recurrence of AF.[64,65] This notion is true whether the AF is treated by electrical cardioversion or by catheter-based pulmonary venous isolation. However, despite the consistency of a large number of observational studies showing that patients with OSA have a high risk of incident AF, that patients with AF have a high prevalence of OSA, and that treatment of OSA increases the likelihood of maintaining sinus rhythm after cardioversion or pulmonary vein isolation,[63] small randomized trials of treating OSA to prevent AF recurrence have shown no evidence of benefit.[65,66] There are several possible explanations for the discordance in findings. These include low observed burden of AF, which may have compromised power to detect treatment effect, short duration of treatment (excluding those individuals most likely to benefit), and recognition that the patterning of PAP usage may have important treatment implications. Lastly, it is also possible that treatment of OSA does not have any effect on incident or recurrent AF.

OSA has also been linked to ventricular tachyarrhythmias and chronologically tied to the obstructive apneic event,[6] and patients with OSA are more likely to die suddenly at night.[67] Studies in patients with implanted cardiac defibrillators show that appropriate discharges from these devices are more likely to occur at night in those with SDB,[68] suggesting that SDB may be triggering life-threatening ventricular tachyarrhythmias. Epidemiologic studies identify 2-fold higher odds of nonsustained ventricular tachycardia and a 50% increase in complex ventricular ectopy in OSA as well as a dose-response monotonic increase in complex ventricular ectopy burden paralleling increases in degree of OSA.[69] Nocturnal hypoxia is an important independent driver of sudden nocturnal cardiac death, with immediacy of respiratory events linked to discrete ventricular arrhythmic events.[6] Small interventional studies support the benefit of PAP treatment to reduce ventricular tachyarrhythmia burden, particularly in heart failure,[70] but larger confirmatory clinical trials are needed.

OSA AND PATENT FORAMEN OVALE

Multiple studies show a higher prevalence of patent foramen ovale (PFO) among subjects with OSA compared with those without OSA,[71] likely due to the well-known hemodynamic mechanisms of OSA resulting in increased right relative to left atrial pressure. With OSA, the negative swings in intrathoracic pressure increase venous return to the right atrium, and OSA-related hypoxemia and hypercapnia cause PH and right ventricular dysfunction.[72] Increased flow to the right atrium together with elevated right ventricular pressure raises right atrial pressure, and subsequently blood follows the path of least resistance to the left atrium via the PFO. Potential consequences include hypoxemia (right to left shunt) and paradoxical embolism. The latter is perhaps more apt to occur at night as OSA-related hypoxemia/hypercapnia and long obstructive apneas further increase pulmonary vascular resistance,[73] elevating right-sided cardiac pressures considerably.

OSA AND CORONARY ARTERY DISEASE

The risk of experiencing an acute coronary syndrome (ACS) such as unstable angina, acute myocardial infarction, or sudden cardiac death increases during

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the late hours of sleep or in the early morning hours soon after awakening, potentially due to OSA.[74] In addition, ACS events occur more frequently during REM sleep, which consolidates just before awakening and when apneas are often more prevalent with prolonged severe hypoxemia. These data are consistent with the SHHS, which showed that OSA could also lead to incident CAD in middle-aged men.[75] However, the association was not significant in the elderly or in women. Meanwhile, OSA is also highly prevalent in patients with CAD as shown in randomized controlled trials, which enrolled consecutive eligible nonsleepy subjects with established CAD. In the RICCADSA (Randomized Intervention with CPAP in Coronary Artery Disease and Obstructive Sleep Apnoea) trial from Sweden, among 662 revascularized CAD patients, 64% had moderate to severe OSA with an AHI ≥15 events per hour.[76] In a study from Spain, among 2,551 consecutive nonsleepy patients with ACS, 1,264 (almost 50%) had moderate to severe OSA.[77] Similar results were observed in the SAVE (Sleep Apnea and CardioVascular Endpoints) trial.[78] The high prevalence of OSA in these aforementioned studies was most probably underestimated because, for ethical reasons, subjects with clinically significant EDS (the cardinal symptom of OSA) as well as those with severe hypoxia were excluded.

OSA AND HEART FAILURE

OSA and LV systolic and diastolic dysfunction are commonly comorbid (**Figure 2**). OSA is common in both symptomatic and asymptomatic LV dysfunction, with the highest prevalence rates cited in hospitalized patients with acute decompensated heart failure.[79]

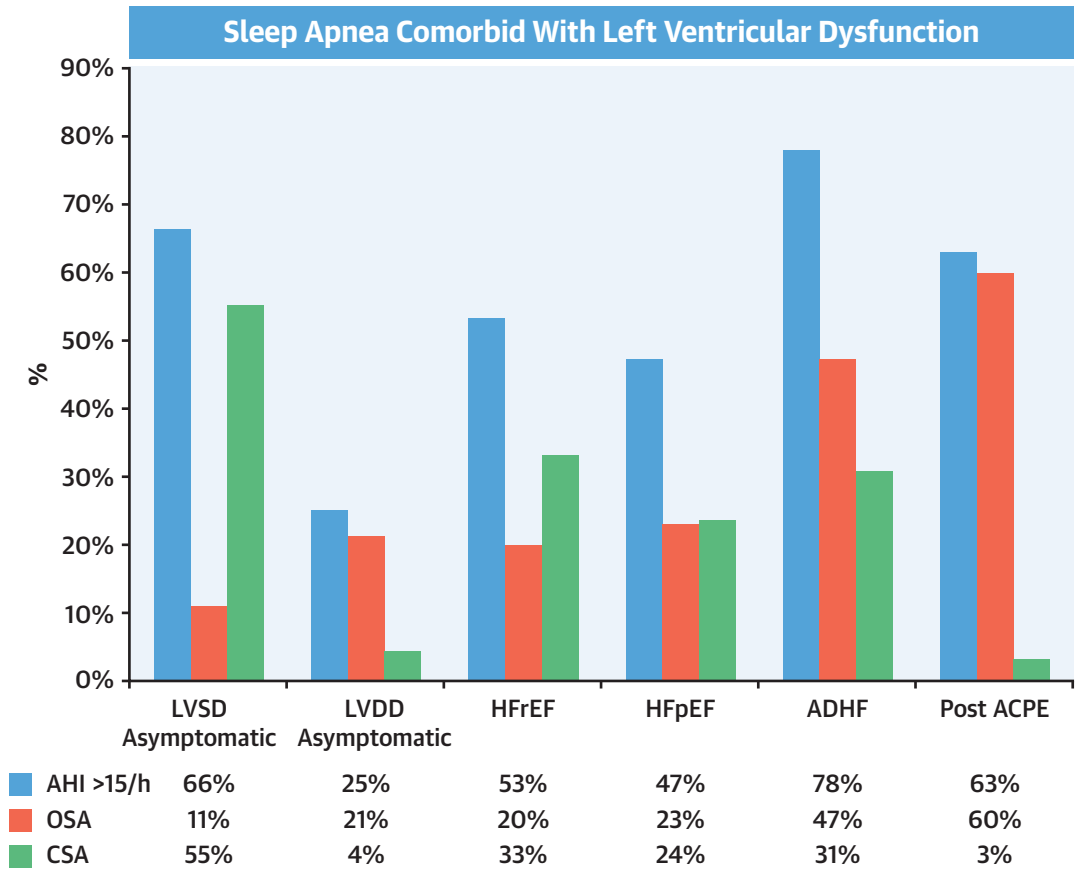
The high prevalence is most likely related to volume overload associated with decompensation[80] due to cephalad movement of fluid from the lower extremities to the neck in the supine position, narrowing the pharyngeal area and promoting OSA. However, obesity remains an important risk factor for OSA in heart failure, as it is in the general population. This is related to the mechanical factors of obesity with accumulation of upper body fat in the abdomen, tongue, and throat, all contributing to the narrowing of the upper airway. OSA is associated with hypoxemia/hypercapnia, arousals, increased sympathetic activity, and large negative swings in intrathoracic pressure (**Figure 1**), collectively imposing adverse chemical (blood gases) and hemodynamic consequences on the failing heart.[79] Hemodynamically, during inspiration, the large negative swings in juxtacardiac pressures created by diaphragmatic contraction against a closed upper airway could decrease LV stroke volume; this occurs by combination of an increase in venous return to the right heart shifting the septum to the left and increasing LV transmural pressure and its afterload. A third mechanism is apnea-related alveolar hypoxia and hypercapnia causing pulmonary vasoconstriction, further impeding right ventricular stroke volume and the return to the left heart. Chemically, hypoxemia and hypercapnia result in diminished myocardial oxygen delivery and acidosis, respectively. The diminished oxygen delivery, combined with increased myocardial oxygen demand, due to increased wall tension, increased BP, and heart rate, could cause considerable cardiomyocyte hypoxia. In the long run, chronic untreated OSA could adversely affect the already impaired cardiac structure and function. In this regard, OSA has been shown to be independently associated with daytime increased sympathetic activity, excess hospital readmissions, acute and recurrent cardiogenic pulmonary edema, and mortality.[81] Sleep hypoxemia seems to have a poor prognostic value, as is the case for central sleep apnea in heart failure.[81-85]

OSA AND CEREBROVASCULAR DISEASE

According to the 2023 American Heart Association update, it is estimated that 7.0 million Americans ≥20 years of age have had a stroke and 5 million had had a transient ischemic attack.[86] Stroke is an important downstream consequence of OSA, and OSA is highly prevalent in patients with stroke or transient ischemic attack. OSA can be a cause of stroke via multiple possible intermediary mechanisms, including simple snoring, AF, carotid artery stenosis, paradoxical embolism via PFO, and hypertension.[87] The INTERSTROKE study, an international case-control study incorporating 4,496 participants, reported that after extensive adjustments for many cofounders, OSA-related symptoms of snoring, snorting, and breath cessation were associated with statistically increased odds for acute stroke.[88] Individual estimates were highest in the night-time and wake-up subgroups.

Based on the available data, the American Heart Association/American Stroke Association[89] has made the following statements: “A sleep study might be considered for patients with an ischemic stroke or transient ischemic attack on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population.”

FIGURE 2 Prevalence of Sleep Disordered Breathing Types



The bar graph details the prevalence of specific types of sleep disordered breathing among patients with a range of left ventricular dysfunction to overt heart failure. Adapted from Javaheri et al.[1] ACPE = acute cardiogenic pulmonary edema; ADHF = acute diastolic heart failure; AHI = apnea hypopnea index; CSA = central sleep apnea; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVDD = left ventricular diastolic dysfunction; LVSD = left ventricular systolic dysfunction; OSA = obstructive sleep apnea.

OHS AND CVD

OHS is defined by obesity, SDB, and daytime hypercapnia (partial pressure of arterial carbon dioxide [CO_2] ≥45 mm Hg), in the absence of other known causes of hypoventilation.[90] Nearly 70% of patients with OHS have concomitant severe OSA.[91]

The prevalence of OHS in obese patients referred to clinical sleep laboratories for suspicion of OSA is 10% to 20%. Although the prevalence of OHS in the community has not been ascertained, it has been estimated that nearly 0.5% to 1% of the adult population in the United States is afflicted with OHS.[90] With the obesity epidemic, there are disproportionately higher rates of severe obesity, defined as body mass index ≥40 kg/m^2. Indeed, the Centers for Disease Control and Prevention reported that from 2005 to 2017, the prevalence of people with severe obesity increased from 3.1% to 6.9% in men and from 6.2% to 11.5% in women.[92] With such a high prevalence of severe obesity, the prevalence of OHS is bound to increase further.

The underlying mechanisms of OHS are complex. Chronic steady-state hypercapnia occurs when the normal compensatory ventilatory mechanisms fail to maintain arterial PCO_2 within the normal range. In the presence of OSA and reduced ventilation, CO_2 accumulates during sleep, particularly when apneas are repetitive, reducing interapneic time and impairing CO_2 clearance. In addition, CO_2 production is increased due to excess adipose tissue.[93] Following apneas, when breathing resumes and ventilation increases, so does the work of breathing with additional CO_2 production. With time, nocturnal hypercapnia

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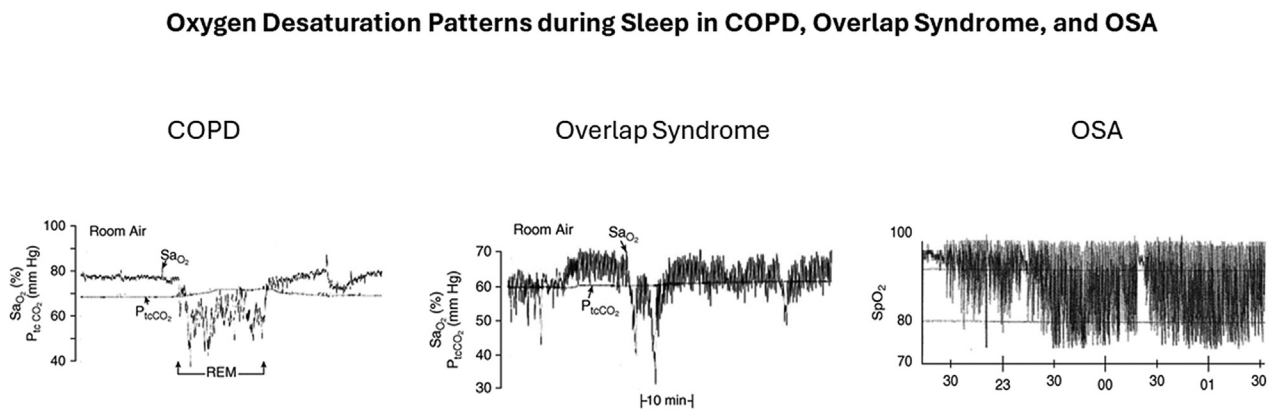
FIGURE 3 Patterns of Oxygen Desaturation During Sleep



Depiction of oxygen desaturation patterns during sleep in individual patients with chronic obstructive pulmonary disease (COPD) alone, overlap syndrome of COPD and obstructive sleep apnea (OSA), and OSA alone. The COPD example shows stable desaturation during nonrapid eye movement sleep that is more pronounced during rapid eye movement. The OSA example shows intermittent desaturations during apnea with resaturation to normal levels in between events. The overlap example shows more pronounced baseline desaturation with superimposed intermittent further desaturations during apnea.

persists as serum bicarbonate concentration increases and compensatory mechanisms fail to normalize PCO_2. A physiological study in humans has shown that excessive CO_2 production, which is related to body mass, significantly contributes to elevated partial pressure of arterial CO_2, suggesting the importance of weight loss.[94]

In contrast to the garden-variety OSA, which is characterized by intermittent hypoxemia during sleep, patients with OHS are exposed to much more profound intermittent hypoxemia as well as severe sustained hypoxemia and hypercapnia, both during sleep and wakefulness. Not surprisingly, when compared with eucapnic OSA, patients with OHS have a higher pro-atherosclerotic RANTES chemokine, a more prominent decrease in the anti-inflammatory adipokine adiponectin, and increasingly impaired endothelial function, conditions known to be strongly associated with increased CV risk.[95] In this context, in the Pickwick Study, participants with OHS had a significant burden of CV and metabolic morbidity, including systemic hypertension, impaired LV diastolic dysfunction and type 2 diabetes mellitus. Meanwhile, OSA has been associated with diabetes mellitus type II and elevated hemoglobin A1C and randomized trials have shown that adequate use of CPAP improves hemoglobin A1C.[96-98] With echocardiographic assessment, 52% had PH defined as pulmonary artery systolic pressures >40 mm Hg.[57] As discussed in the management section, with treatment, these parameters improved.

OSA AND COPD (OVERLAP SYNDROME) AND CVD

OSA and COPD are both highly prevalent, with general population-based studies indicating a prevalence of at least 10% for each disorder alone. Thus, the overlap of OSA and COPD is likely to be present in at least 1% of the population based on chance association alone. However, there are factors relating to COPD that may increase or decrease the likelihood of OSA. Promoting factors include rostral fluid shift in the setting of right heart failure and skeletal muscle wasting, whereas protective factors include lung hyperinflation and low body mass index.[99] Nocturnal oxygen desaturation patterns differ between OSA, COPD, and the OSA-COPD overlap (Figure 3). Overlap syndrome has the most profound desaturation, with a pattern of intermittent desaturation from a low baseline saturation because of the underlying COPD. In contrast, isolated OSA is typically associated with intermittent desaturation during apnea with a relatively normal baseline saturation.

OSA and COPD are each associated with an increased prevalence of CVD, but notably, a number of CVD are more prevalent in the overlap syndrome compared with either disorder alone.[100] These include the following: 1) PH, which is the consequence of more severe hypoxemia in patients with the overlap syndrome, especially during sleep; 2) right ventricular hypertrophy because of PH, which may progress to right heart failure; and 3) AF.[101] The latter is due to increased cardiac sympathetic

activity, assessed by heart rate variability, which is more elevated in OSA-COPD overlap compared with each disorder alone.[102]

To this end, a large sleep clinic population study found that CV morbidity and all-cause mortality was greater in patients with OSA-COPD overlap compared with each disorder alone.[103] Some data support treatment of patients with hypercapnic COPD as well as patients with overlap syndrome.[104,105]

OSA IN WOMEN AND DIFFERENCES WITH MEN

Comparing OSA in men vs women, there are differences in prevalence, clinical manifestations, and treatment responsiveness. Notably, reports from community-based studies relay a markedly lower male to female OSA prevalence than that of clinic-based studies, underscoring the importance of clinical underdiagnosis of OSA in women.[106,107] Although the overall prevalence of SDB is lower in women compared with men, there are periods of increased vulnerability for SDB in women, including pregnancy[108] and postmenopause, and the degree of SDB may be mitigated with hormone replacement therapy.

Consistent with sex-specific differences in clinical cardiac symptom presentation, SDB clinical expression and symptom profiles also differ in men vs women. Women often have more pervasive symptoms of fatigue, insomnia, and depression attributable to untreated SDB than severe sleepiness and snoring as reported in men; this has implications for screening and prevention strategies aimed at mitigation of CV and metabolic risks resulting from untreated SDB. The physiological phenotype of SDB in women also seems to differ compared with men: women typically have an overall lower AHI, although higher REM-related apnea, shorter duration apnea and hypopnea, less pronounced oxygen desaturation, positional differences, and a higher degree of airflow limitation accompanied by microarousals during sleep,[91] which affects sex-specific differential SDB drivers of CV outcomes.

Multicenter epidemiologic data from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort identified that as the cohort aged, women manifested greater SDB-related CV risk not observed in men, including increased incident heart failure and LV mass, and increasing high-sensitivity troponin levels, perhaps due to aging-related alterations in female hormone levels.[109] Women may have more endothelial dysfunction associated with SDB than men,[110] consistent with experimental models identifying enhanced sensitivity of the female vascular endothelium to intermittent hypoxia. Notably, higher prevalence of REM-related OSA in women relative to men is known to be associated with higher cardiometabolic morbidity.[111] Moreover, in the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients; n = 3,141; 67% women) study, women with high-risk OSA were more likely to have worse health status, depression, and quality of life than high-risk men at 1 and 12 months after acute myocardial infarction. This finding suggests that women are a higher risk of poorer health outcomes after myocardial infarction and potentially focused OSA screening.[112]

PEDIATRIC OSA AND BIOMARKERS OF POTENTIAL CVD

The prevalence of OSA in children, albeit lower than in adults, constitutes 2% to 5% of all children and may reach up to 35% in the context of concurrent obesity.[113-115] As with adults, there is clear evidence that pediatric OSA can induce endothelial dysfunction, and it increases the risk of both systemic hypertension and LV dysfunction.[115] The consensus points to several pathophysiological components that jointly contribute to the emergence of markers of CVD in children with OSA, namely autonomic dysregulation, increased platelet aggregability, systemic inflammation, and likely a large set of gene targets and mediators that are perturbed in the context of the disease. Taken together, the current evidence identifies the presence of increased risk for markers of CVD in children affected by OSA, particularly when obesity is present.[35,116,117]

However, substantial uncertainty remains as to the major determinants of CVD risk and phenotype in specific children and why divergence of CVD phenotype exists among children with similar severity of OSA. Although it is likely that genetic and environmental factors underlie the CVD phenotypic heterogeneity of pediatric OSA, exploration of early life events (ie, periconceptional, gestational or immediate postnatal) and associated epigenetic modifications has not been systematically pursued, nor have multi-omics analyses been undertaken to address this important issue. Furthermore, considering the potential for long-term CV consequences of pediatric OSA, even after treatment, it is imperative to identify with greater precision those children at risk and to develop interventions aimed at curtailing CVD risk both in the short term and long term.

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OSA AND CV MORTALITY

Multiple observational studies, including the WSC (Wisconsin Sleep Cohort) study[118] and the SHHS,[119] have consistently shown that OSA is independently associated with excess CV mortality. Although there seems to be a dose-dependent relationship between AHI severity and mortality, only severe OSA displays a statistically significant association.[118] Aside from the severity of AHI, recent studies suggest that other variables associated with incident CVD and mortality should be considered in the design of future trials, as discussed in part 2 of this State-of-the-Art Review.

CONCLUSIONS

Considerable progress has been made regarding our understanding of sleep health and its impact on the CV system. Although the mechanisms linking poor quality and quantity of sleep and OSA to cardiometabolic risk are well known, definitive randomized trials showing improvements in hard outcomes with interventions are still lacking, raising the question of whether OSA is truly an independent CVD risk factor. Such studies are needed in children and adults, as well as in those with OHS, overlap syndrome, and OSA comorbid with type 2 diabetes mellitus and heart failure with preserved ejection fraction. Studies in women, particularly during pregnancy, are also lacking. In part 2, we discuss various treatment options, potential reasons for null results of randomized controlled trials treating OSA to reduce CVD mortality, and suggested approaches for future trials.

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