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Review

Review

Association between obstructive sleep apnea and cardiovascular diseases

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Abstract

Obstructive sleep apnea (OSA) is a common respiratory disorder characterized by partial obstruction of upper respiratory tract and repetitive cessation of breathing during sleep. The etiology behind OSA is associated with the occurrence of intermittent hypoxemia, recurrent arousals and intrathoracic pressure swings. These contributing factors may turn on various signaling mechanisms including elevated sympathetic tone, oxidative stress, inflammation, endothelial dysfunction, cardiovascular variability, abnormal coagulation and metabolic defect (*e.g.*, insulin resistance, leptin resistance and altered hepatic metabolism). Given its close tie with major cardiovascular risk factors, OSA is commonly linked to the pathogenesis of a wide array of cardiovascular diseases (CVDs) including hypertension, heart failure, arrhythmias, coronary artery disease, stroke, cerebrovascular disease and pulmonary hypertension (PH). The current standard treatment for OSA using adequate nasal continuous positive airway pressure (CPAP) confers a significant reduction in cardiovascular morbidity. Nonetheless, despite the availability of effective therapy, patients with CVDs are still deemed highly vulnerable to OSA and related adverse clinical outcomes. A better understanding of the etiology of OSA along with early diagnosis should be essential for this undertreated disorder in the clinical setting.

Key words obstructive sleep apnea, cardiovascular disease, pathophysiology, continuous positive airway pressure therapy

Introduction

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing (SDB), affecting approximately 34% in men and 17% in women between the age of 30 and 70 [1,2]. OSA is characterized by partial obstruction of upper respiratory tract and reduced airflow or repetitive breathing cessation in sleep [3], resulting in unfavorable outcomes including sleep deprivation, intermittent hypoxemia (IH), intrathoracic pressure changes and surges in sympathetic tone [4]. These periodical episodes of respiratory disruption cause both acute and chronic pathophysiological stress, *en route* to onset of cardiovascular disease (CVD) including systemic hypertension, congestive heart failure (HF), arrhythmias, atherosclerosis, stroke and pulmonary hypertension (PH) [2,5–8]. As such, all OSA patients should receive intensive therapy, including weight loss and behavioral changes. Standard treatment modality for OSA includes continuous positive airway pressure (CPAP) which may greatly reduce non-fatal and fatal cardiovascular sequelae [9]. Alternative treatments for more severe OSA patients with CPAP intolerance or mild symptoms include oral appliances and surgical interventions, although less information is available for their efficacies [10].

In this review, we will focus on the epidemiology and diagnosis of OSA, to provide insights on pathophysiological mechanisms and complications of OSA. A better understanding of these aspects of OSA should help to optimize clinical treatment and outcomes for OSA.

Overview of OSA

Epidemiology and risk factors

OSA is a common pathological condition and approximately 24 million American remain undiagnosed for OSA [10,11]. The prevalence for OSA is much higher in the elderly, ethnic minorities, male gender, and overweight/obese populations. Of note, in patients with prominent CVDs such as atrial fibrillation (AF), HF, hypertension and stroke, the prevalence of OSA is drastically elevated with a rate up to 40% to 80% [12,13].

Uncorrected obesity is perhaps the most important independent risk factor for the onset of OSA with a bidirectional correlation between OSA and obesity. For example, a 10% increase in body weight is linked to a 32% rise in apnea hypopnea index (AHI), while modest weight control is effective in reducing the incidence of SDB [14,15]. Indeed, increased adipose tissue mass in the tongue and pharynx may easily reduce the luminal diameter of upper respiratory tract, making it more prone to collapse during sleep. Notably, male gender is another identified risk factor for OSA. It is shown that higher androgen levels such as those observed in patients with polycystic ovary disease or androgen supplement therapy worsen OSA due to elevated tongue muscular mass [16]. On the other side of the coin, higher level of progesterone leads to lower prevalence of OSA in premenopausal women compared with older women, as progesterone stimulates ventilation in upper tract muscles [17]. Furthermore, hypothyroidism and acromegaly also confer a tendency to the occurrence of OSA [18,19]. In addition, craniofacial abnormalities such as maxillary insufficiency and retrognathia represent as important independent OSA risk factors and may explain the prevalence of severe OSA in Asian males in the absence of obesity [20]. Other less well-established risk factors encompass family history, race and ethnicity, advanced age and cigarette smoking. Moreover, use of alcohol or illicit drugs (*e.g.*, opiates and benzodiazepines) can deteriorate pre-existing OSA incidences.

Pathophysiology of OSA

The pathophysiological mechanisms of OSA are multifactorial and complicated with many unrecognized contributing factors. For example, abnormal respiratory tract anatomical structure and sleep-related factors in respiratory system are believed to be heavily involved in the pathogenesis of OSA [10]. Ample evidence has indicated that medullary inspiratory neurons innervating upper and lower respiratory muscles display lower electrical activity during sleep, resulting in lower tone in upper tract dilatory muscles and diaphragm [20]. Other physiological conditions also contribute to respiratory changes in sleep such as elevated airway resistance in upper respiratory tract, damaged respiratory load compensation and decreased pharyngeal diameter. Furthermore, a number of anatomical and morphological abnormalities may also compromise upper respiratory airway conductance including edema of upper respiratory tract, hypertrophied tonsils, reduced lung volume and obesity. Other contributing factors involve changes in chemosensitivity, loop gain, arousal threshold and airway critical closure pressure [21,22]. Interestingly, personalized therapy may be a feasible approach for a better amenable treatment in OSA. For example, stimulation of hypoglossal nerve should ameliorate upper airway dilatory muscle anomalies, whereas an increased chemosensitivity may respond to drugs downregulating nighttime hypoxic response, and high arousal threshold may be compliant with hypnotics [23].

Clinical manifestation and diagnosis

OSA is often estimated according to signs and symptoms as specified below: daytime sleepiness, irregular or loud snoring, gasping and choking during sleep, nocturia, non-refreshing sleep, memory impairment, dry mouth and headache on awakening, body mass index (BMI) > 30 and increased neck circumference [24]. OSA is often linked to poor life quality, increasing venture for job-associated and car accidents, more frequent health-related sick day. However, OSA is widely underdiagnosed. Population surveys demonstrate that 86% to 95% individuals with obviously clinical OSA exhibit little previous diagnosis of OSA [25]. As for the diagnosis of SDB, polysomnography (PSG) requiring an all-night stay in a sleep laboratory is considered as the gold standard diagnostic criterion. Using measurement of electroencephalography (EEG), electrocardiographic (ECG), and electromyographic (EMG) activities, nasal airflow and thoracoabdominal movement, PSG would allow identification of SDB subtype and severity. In addition, apnea-hypopnea index (AHI; the number of apneic and hypopneic events per hour of sleep) is the most widely employed parameter for OSA quantification, with 5–15/h being mild, 15–30/h being moderate and > 30/h being severe in the disease progression [26]. Nevertheless, AHI is only a modest predictor for the consequences of OSA, highlighting the requirement for more sensitive indicators of disease severity and metrics of OSA complications [27]. Recently, home sleep apnea testing (HSAT) using a portable detecting device becomes available as an alternative OSA testing strategy. Compared with PSG, HSAT is cost-effective and less resource-intensive despite limited sensitivity and possible outcomes of false-negative results [28].

Pathophysiological Mechanism Linking OSA with Cardiovascular Risk

Intermittent hypoxia

Intermittent hypoxia (IH) is a distinguished character of OSA featured by repeated short desaturation cycles following quick reoxygenation. Notably, IH is considered as a "double-edged sword" in cardiometabolic processes [29]. There is increasing evidence indicating that mild OSA patients exposed to short period of mild IH may trigger an adaptive response through a cardioprotective preconditioning process. However, patients with moderate to severe OSA who frequently experience short cycles of IH with extended desaturations suffer from multiple deleterious reactions (Figure 1) [30]. In support of a unique role for IH in the cardiometabolic processes, ample evidence has denoted that IH participates in the progression of CVD in OSA by activating inflammatory signaling pathways which involve the hypoxia-sensitive transcription factors hypoxia-inducible factor-1 (HIF-1) and NF-κB [31]. Moreover, IH likely contributes to vascular dysfunction ranging from initial changes in atherosclerosis to full plaque formation, and this atherosclerotic process could be further amplified in conjunction with other risk factors (such as diet rich in cholesterol) [32]. In line with clinical data, ample evidence revealed that changes in vascular function evoked by IH (*e.g.*, impaired endothelium-dependent vasodilation and increased vasoconstrictive reaction) occur prior to onset of atherogenic process [33]. In addition, IH is related to an increased susceptibility of HF in OSA patients including ventricular hypertrophy, cardiac dilatation, myocardial interstitial fibrosis and dropped stroke volume [34,35]. Other than these unfavorable clinical sequelae, IH may also instigate higher incidences of hypertension and myocardial infarction (MI) in OSA patients [36–38]. These data have offered an overwhelming support for a detrimental role for IH in cardiovascular pathogenesis in OSA patients.

OSA is characterized by repetitive episodes of apnea and hypopnea, resulting in unfavorable outcomes including intrathoracic pressure changes, hypercapnia, IH, coagulation disorder, and metabolic dysfunction. These periodical episodes of respiratory disruption cause both acute and chronic pathophysiological stress, *en route* to onset of CVDs including systemic hypertension, congestive

HF, arrhythmias, atherosclerosis, stroke and PH.

Recurrent arousals

Recurrent arousal is a hallmark of OSA resulting in sleep fragmentation and the next day drowsiness during daytime. The emergence of recurrent arousal relies on individual arousal threshold but usually reflects a consequence of interrupted ventilation with the subsequent hypercapnia, hypoxia and enhanced respiratory effort to resume ventilation. Arousal is linked to repeated blood pressure elevation by up to 80 mmHg [39]. However, whether these blood pressure fluctuations lead to systemic hypertension or vascular disease remains controversial. In canine or rat models, hypertension was not provoked by acoustic stimuli which induce recurrent arousals [40]. Furthermore, Launois and colleagues noted that only respiratory arousals resulted in blood pressure surges compared with non-respiratory cases in a porcine model, offering a rational explanation to the inconsistency among various research groups [41]. Therefore, recurrent arousals should play an additional role in the onset and development of CVD in OSA, although further translational studies are needed to elucidate its specific function.

Intrathoracic pressure changes

In OSA, the upper respiratory tract is completely or partially obstructed during sleep, causing repetitive episodes of apnea and hypopnea. The intrathoracic negative pressure rapidly elevates to resist airway occlusion, resulting in further intensified respiration effort. On one hand, pressure changes lead to the increased pressure difference between inside and outside of cardiac lumen to stimulate sympathetic nerve. Indeed, elevated transmural pressure of left ventricle and aorta compromise hemodynamics, ventricular function and stability of autonomic nerve [21]. On the other hand, rapid elevation of intrathoracic negative pressure may decrease left atrial volume, increase left ventricular afterload and end-systolic volume of left ventricle, resulting in decreased left ventricular ejection fraction and cardiac output (Figure 1). As a result, reduced coronary blood flow ensues, leading to myocardial ischemia [42]. In addition, repeated changes of thoracic pressure and fluctuation in the returned blood volume may irritate baroreceptors on aortic body and carotid sinus, as well as stimulate sympathetic excitability. Long-term repetitive sympathetic excitation and myocardial ischemia can cause HF, whereas pulmonary vasoconstriction evoked by hypoxia contributes to PH, resulting in aggravated right ventricular afterload and the development of HF [43]. In addition to elevated intrathoracic pressure, sympathetic overactivity has also been reported to play a vital role in the CVD progression of OSA patients.

Sympathetic overactivity

The episodes of IH during sleep are characteristic of OSA and may trigger surges in blood pressure (BP) and sympathetic nervous system overactivity via carotid chemoreceptors (Figure 1) [44]. Notably, with the exception of nighttime BP fluctuation, OSA patients often demonstrate a constant BP augmentation during the awakening period because of elevated sympathetic drive manifested as increased catecholamine levels in urine and plasma [45]. Even normotensive OSA patients in the absence of obesity experience increased sympathetic tone in peripheral vessels during the

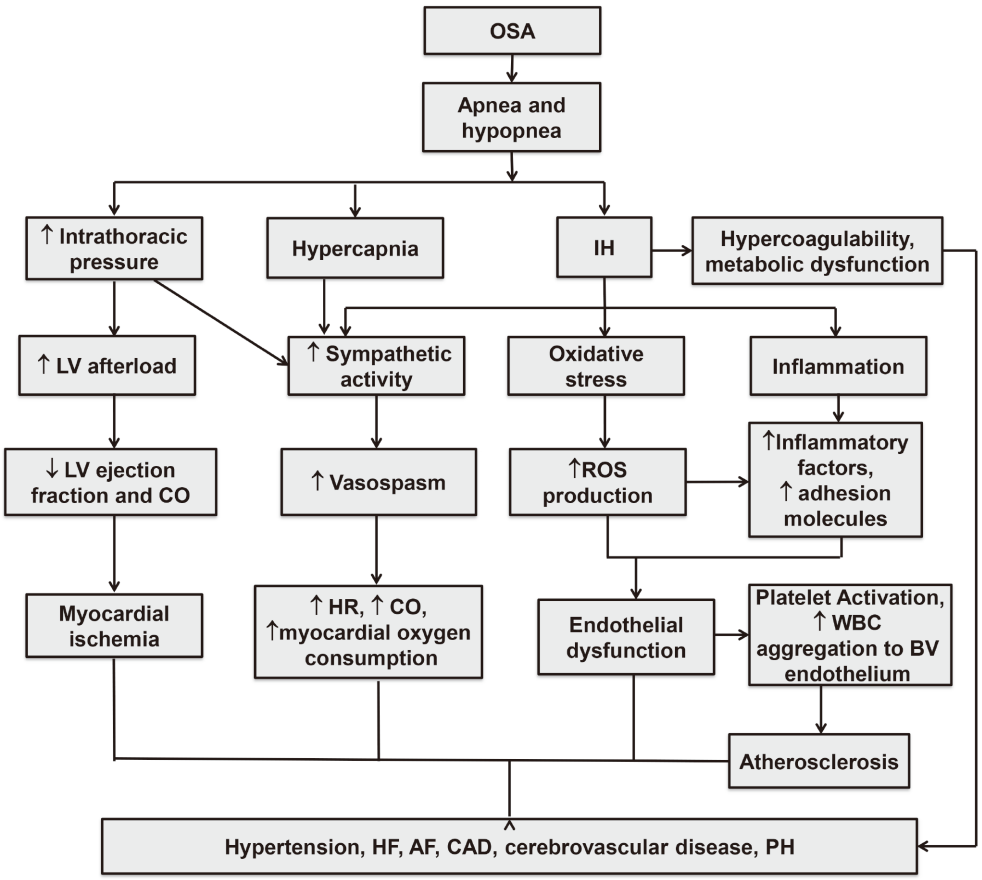

Figure 1. Schematic diagram showing the pathophysiological mechanisms involved in OSA-related cardiovascular complications

awakening hours. Furthermore, it has been reported that the sensitivity of peripheral chemoreflex shows a selective potentiation in OSA patients versus normotensive controls [46], while the autonomous baroreflex sensitivity of the heart reduces in OSA patients during diurnal and nocturnal periods [47]. Using the microneurography, muscle sympathetic nervous activity (MSNA) was found to increase during wakefulness in OSA compared with fatty controls [48]. Moreover, experimental studies have offered compelling support for a role of sympathetic hyperactivity in the pathogenesis of CVD in OSA patients. In animal models of OSA such as rats and dogs, BP elevation was declined once the airway obstruction was relieved, favoring the effect of sympathetic hyperactivity on hypertension progression in OSA [49]. In addition, this increased sympathetic trafficking is assumed to play a vital role in OSA patients afflicted with arrhythmia. Based on these opinions, CPAP treatment may provide beneficial effects on attenuating sympathetic overactivation [50].

Obstructive stress, inflammation and endothelial dysfunction

Loss of balance between reactive oxygen species (ROS) and cellular antioxidant capacity leads to oxidative stress, and serves as a possible trigger for chronic intermittent hypoxemia-re-oxygenation (CIH) associated with recurring apnea in OSA. Specifically, CIH can selectively activate the proinflammatory transcriptional regulator NF-κB, a necessary messenger connecting OSA and cardiovascular pathology, and its function may be normalized by adequate CPAP treatment. Not surprisingly, NF-κB is known to upregulate adhesion molecules including VCAM-1, E-selectin and ICAM-1 to participate in the recruitment and migration of leucocytes to inflammatory site, leading to worsened endothelial defect [45,51].

ROS accumulation is a common manifestation of OSA which can result in oxidative stress and subsequently cell injury. On one hand, ROS promotes proinflammatory factors (*e.g.*, TNF-α, IL-6, CRP, *etc.*) and adhesion molecules by initiating inflammatory reaction cascades, producing abundant proinflammatory cytokines and inflammatory responses [52]. On the other hand, pronounced endothelial dysfunction develops in response to ROS-evoked risk factors such as activation of transcription factors, inflammatory cell growth and migration and endothelial cell damage [53]. Moreover, ROS overproduction triggers membrane peroxidation, protein degeneration and DNA mutation, leading to abnormal cell function and ultimately irreversible cell damage or death [54,55]. Furthermore, impaired endothelial cells stimulate the release of inflammatory factors and induce the aggregation of inflammatory cell to the vascular endothelium, triggering atherogenesis and higher incidence of acute coronary syndrome (Figure 1) [56].

It is noteworthy that sleep deprivation evoked by sleep apnea and disturbed circadian rhythm is associated with increased CVD morbidity and mortality, with a significant contribution from endothelial dysfunction. Fluctuation in sleep duration causes endothelial cell damage partially by vascular inflammation, oxidative stress within vasculature and loss of the bioavailability for nitric oxide. Upregulation of systemic inflammation and alteration in oxidative environment leads to microcirculation dysfunction and vascular remodeling including angiogenesis, vessel stiffening and atherogenesis [52,57]. Moreover, sleep deprivation may also provoke endothelial dysfunction through autonomic disorder, manifested as sympathetic nervous system (SNS) hyperactivity. Once hyperactivated, SNS can enhance vascular smooth muscle tension and promote vascular contraction pathways, predisposing to endothelial dysfunction [58,59].

Blood coagulation abnormalities

Increased cardiovascular risk in OSA patients may be associated with blood coagulation abnormalities and platelet activation (Figure 1) [60]. Blood viscosity and plasma fibrinogen elevation as well as decreased fibrinolysis are noted in patients with OSA. Meanwhile, OSA is also associated with elevated levels of thrombin-antithrombin complex, clotting factors XIIa and VIIa [61]. Additionally, platelet activation and aggregability, platelet coagulation and other potential thrombosis markers are all increased in OSA patients. Notably, although the precise mechanism of action remains elusive for platelet activation in OSA, sympathetic hyperactivity seems to play a role. It is known that IH episodes during sleep can provoke sympathetic nervous system, resulting in high levels of epinephrine and norepinephrine, while these catecholamines evoke platelet activation in a dose-dependent manner [62]. Not surprisingly, risks of coagulability and thrombosis are reported to be decreased following CPAP intervention, although further studies are needed to offer a more definitive evaluation of CPAP treatment on the hypercoagulable state in OSA [63].

Insulin resistance

Insulin resistance (IR), as characterized by an impaired biological response to insulin and thus a reduced insulin-mediated glucose processing, has been implicated in the pathogenesis of coronary artery disease (CAD) in OSA [64–67]. Despite controlling obesity and other important cofounding factors of insulin level, OSA severity markers (minimum oxygen saturation and apnea hyponea index) are predominant contributing factors of IR [68]. Several studies concerning the linkage between IR and hypertension demonstrated IR as an independent determinant of hypertension. Furthermore, ample evidence favors the notion that OSA worsens glucose metabolism. Several studies revealed that such glucose metabolism change is reversible with CPAP, whereas others noted the opposite outcome [69,70]. Indeed, CPAP treatment is more profitable to glycemic normal in non-obese individuals, while CPAP is less likely to evoke improvement on IR symptom in obese patients without weight loss [71].

Other than IR, OSA is related to more confounding metabolic defects including hyperleptinemia, non-alcoholic fatty liver disease (NAFLD), obesity and diabetes mellitus (Figure 1) [72,73]. Taken together, the main hallmarks of OSA, including IH, recurrent arousals, intrathoracic pressure swing, sympathetic hyperactivity, oxidative stress and coagulation abnormalities may participate in CVD pathogenesis. Although these clinical manifestations may be delineated separately, they occur in concert and are intertwined. In consequence, these culprit factors provoke various cardiovascular complications (to be described in later sections).

Cardiovascular Complications of OSA

Cardiovascular mortality

OSA has constantly been related to decreased survival rate in epidemiology. Xie and coworkers elucidated that elevated mortality of all-cause and CVD were linked to severe OSA, rather, no connection between mild or moderate OSA (AHI < 30) was found [74]. Moreover, in observational work examining several PAP patterns, an

obvious reduction in mortality was identified with PAP, and HF patients were observed to have a greater risk reduction. Nevertheless, large randomized controlled trials (RCTs) have not shown the impact of PAP on overall survival. Explanations on this incongruity may include low mortality with comparatively short follow-up duration in clinical trials, preclusion of severe hypoxemia patients during nighttime, and possible confounding bias in given observational studies [75]. In an analysis from the Sleep Heart Healthy Study (SHHS), a 42% reduction in mortality was noted by PAP procedure in severe OSA patients following a 6–7 year follow-up period [76]. The precise contribution of PAP treatment requires more RCTs with much longer follow-up to focus on patients with more severe OSA.

Hypertension

Hypertension is a prevalent character in OSA patients. It is estimated that 30% to 50% hypertensive patients possess comorbid OSA, and particularly, up to 80% may have OSA in patients with resistant hypertension. On the other hand, around 50% OSA patients are hypertensive [6]. Despite the fact that hypertension and OSA are common diseases with multiple etiological factors and coexist in cardiovascular comorbidities (*e.g.* obesity and metabolic syndrome), an independent relationship between these two seems to exist [77]. The most compelling piece of epidemiological evidence for the causality between hypertension and OSA is supplied by the Wisconsin Sleep Cohort Study with a four-year follow-up. The odds ratio of developing hypertension during follow-up period elevated linearly with aggrandizing apnea hyponea index (AHI) independent of other comorbidities [78]. Early aberration resulting in persistent hypertension in OSA might be the sympathetic-mediated hypertensive response exposing to nighttime desaturation [79], which was demonstrated by IH experiments in individuals without OSA or CAD (Table 1). In addition, the close relationship between noradrenaline level and AHI may advocate the potential effect of increased sympathetic tone on the onset and pathogenesis of hypertension in OSA patients. The causal connection between hypertension and OSA is also indicated by hyperactivation of sympathetic system persisting to wakefulness [45]. Moreover, circulating pro-inflammatory markers are found to be elevated in hypertensive patients with OSA, with the exception of a significant rise in sympathetic activity. These proinflammatory markers include IL-6, TNF-α, high-sensitivity C-reactive protein (hs-CRP) and asymmetric dimethylarginine [80]. Among them, TNF-α serves as an independent inflammatory factor closely tied with hypertension or OSA [81]. Indeed, elevation in these inflammatory cytokines in OSA and hypertensive patients prompts a deeper comprehension in the potential mechanism in OSA-related health risks.

Substantial evidence has indicated that CPAP reduces blood pressure in patients with OSA. Compared with the conventional therapy, CPAP treatment is associated with a 2 to 2.5 mmHg fall in systolic blood pressure (SBP) and a 1.5 to 2 mmHg drop in diastolic blood pressure (DBP) with a 24-hour blood pressure monitor, with a more pronounced response in resistant hypertensive patients [85]. Although the reduction range is relatively moderate, it was demonstrated that even a subtle reduction in blood pressure may be associated with overtly drop in cardiovascular risk. Moreover, CPAP may lower blood pressure more significantly in patients with more severe OSA, good CPAP adherence and no hypertension drug therapeutic history [86]. Further work is needed to confirm the possible mechanisms underlying the antihypertensive effect of CPAP intervention.

Heart failure

HF is usually a cardiac end point of OSA. Given that independent connections have been established between OSA and CVD, it is not surprising that OSA is associated with adverse outcome in patients with HF, and the impairment degree may be dependent upon the severity of OSA [87]. It was reported that the overall prevalence of OSA among HF patients fluctuates from 15% to 50%, and is more common in men compared with women with HF [88]. Meanwhile, the morbidity rate is high in patients with co-existing systolic and diastolic HF. Moreover, the result of SHHS cohort displayed that patients without HF but diagnosed with OSA are at higher risk of subsequent HF. Indeed, male patients with severe OSA are prone to HF at a higher risk of 58% compared with those without OSA [89]. Notably, several mechanisms have been proposed regarding the pathophysiological effects of OSA associated with HF (Table 1). The repeated and acute swings in intrathoracic pressure induced by apneic events during sleep cause increase in venous return and left ventricular afterload, accompanied by stroke volume (SV) decrease, whereas activation of sympathetic nervous system secondary to hypoxia and arousal leads to tachycardia, peripheral vasoconstriction and higher myocardial oxygen consumption. To this end, an imbalance between myocardial demand and supply results in impaired cardiac contractility and higher risk of myocardial infarction [90]. Furthermore, sleep apnea associated hypoxia is an independent predictor of damaged ventricular diastole and myocardial contractility. It can also contribute to oxidative stress and myocardial impairment, *en route* to myocardial dysfunction manifested as lower left ventricular ejection fraction (LVEF) and systolic/diastolic dysfunction [82]. In addition, hypoxia-induced PH aggravates right ventricular afterload and promotes HF development [43]. Further studies are needed to better elucidate the association between OSA and HF.

To ameliorate sleep quality and daytime sleepiness in patients with OSA and CVD, CPAP is recommended as a possible therapeutic strategy. Several studies have shown the benefit of CPAP in HF patients, encompassing decreased sympathetic activity and blood pressure, reduced myocardial oxygen consumption, increased cardiac function and lower HF hospitalization rate [91]. However, CPAP failed to improve LVEF following a 3-month therapy in OSA patients with stable systolic dysfunction [92]. Long-term advantage of CPAP treatment in HF patients would require further investigation. With the exception of sleep apnea, HF patients suffering from other sleep disorders may also benefit from therapeutic approaches. For example, nonbenzodiazepines (Zolpidem, Zaleplon and Eszopiclone) may lower rehospitalization risk for HF and cardiac death in HF patients with co-existing insomnia compared with the classical benzodiazepines [93]. Furthermore, the melatonin receptor MT1/MT2 agonists (agomelatine, tasimelteon and ramelteon) also offer cardiovascular benefit [83].

Atrial fibrillation

OSA is an independent risk factor for AF in patients without other cardiac comorbidities. This received support from a 4-fold increase in the prevalence of AF in patients with severe OSA (AHI ≥ 30) compared with those without OSA [84]. Not surprisingly, AF and OSA have similar risk factors containing obesity, male sex, old age,

HF and hypertension, and are related to adverse effects. However, no clear evidence indicates that OSA causes AF. Indeed, the reduction in nighttime oxygen saturation has been regarded as a predictor of incident AF, and the decreasing level as well as the duration may be used to predict AF severity in patients with OSA [94]. There are several conceivable mechanisms to evoke the onset of AF in OSA patients. Repetitive episodes of apnea and hypopnea during sleep result in abrupt intrathoracic negative pressure alterations and chronic recurrence, which may cause structural and functional remodeling in atrium and result in atrial fibrosis accompanied with electrophysiological change [95]. In addition, sympathetic hyperactivity induced by apnea during OSA can evoke myocardial excitability, causing the beginning of AF (Table 1).

Numerous observational studies have indicated that CPAP intervention is linked to a low AF recurrence rate following ablation or electrical cardioversion, in particularly, a lower risk for the development of more permanent AF and occurrence of paroxysmal AF [96,97]. Notably, young, male gender and obese patients may benefit most from CPAP therapy. Based on this finding, AF-connected OSA presents a higher AF recurrence rate following cardioversion and a higher risk of catheter ablation failure [98]. Although the reproducibility of these results from observational reports is convincing, prospective clinical trials are needed to clarify the effect of OSA on AF burden and prognosis.

Coronary artery disease

Ample evidence has demonstrated an elevated risk of CAD in patients with OSA in spite of other co-existing CVD comorbidities [99]. In particular, the prevalence of SDB in CAD patients is doubled compared with the general population and more than 70% patients for acute coronary heart disease are afflicted with undiagnosed OSA. Moreover, coronary artery calcification, a subclinical coronary disease indicator, is identified in 67% patients with OSA versus in 31% patients without OSA. Plaque instability and vulnerability are deemed much severer in patients with OSA than in patients without OSA [100]. Furthermore, OSA has been associated with a higher risk of nocturnal ischemic events and appears to trigger the incidence of sudden death at nighttime. It was reported that 32% OSA patients would suffer from MI attack between 12 AM and 6 PM compared with 7% in non-OSA patients [101]. Moreover, OSA is an independent indicator for worsened outcome following percutaneous coronary intervention (PCI) in acute coronary heart disease patients.

Several potential mechanisms have been postulated to explain the relationship between OSA and CAD. Oxidative stress elicited by repetitive hypoxia and reperfusion during OSA may play a role in CAD and MI development (Table 1). The hypoxemia-re-oxygenation cycles related to OSA result in higher ROS production, the effect of which may be reinforced by changes in vascular reactivity. Two weeks of CIH exposure enhanced vasoconstriction in mice, and an imbalance between vasoconstriction and vasodilation may likely contribute to myocardial ischemic damage evoked by OSA [102]. Moreover, myocardial ischemia is commonly mediated by inflammation with a key contribution from endothelin and HIF-1α. It was also reported that the incongruity between increased oxygen demand and decreased oxygen supply at night can aggregate myocardial ischemia in OSA patients [103]. Furthermore, as a dynamic progression evolved from the subclinical state of endothelial dysfunction, atherosclerosis presents early signs in OSA patients without any other CAD comorbidities. Chronic outcomes of OSA, such as sympathetic overactivation, oxidative stress, systemic inflammation, IR, elevated lipid levels, and endothelial dysfunction, may promote the onset and progression of atherosclerosis. Thereafter, acute effects of OSA, including IH, acidosis, and increased blood pressure, join the culprit team to combine with coinstantaneous intrathoracic pressure triggering plaque rupture [4].

Reminiscent of its beneficial roles in hypertension, HF and arrhythmia, CPAP treatment might be a benchmark for favorable prognosis in CAD. It can reduce the occurrence of new cardiovascular events and cardiovascular mortality in OSA patients with CAD comorbidity compared to CPAP-intolerant ones [104]. In addition, 4-month CPAP treatment may relive early atherosclerotic signs including thicknesses of artery and carotid intima-media as well as levels of catecholamine and hs-CRP [105]. However, further RCTs evaluating the efficacy of CPAP treatment are still warranted in large-scale populations.

Cerebrovascular disease

OSA triggers the development of stroke and associated unfavorable clinical outcome in patients with established stroke [106]. The prevalence of OSA is higher among patients with stroke ranging from 50% to 80% compared with normal controls. Recurrent stroke patients suffer from a higher OSA morbidity compared with those with first-time stroke (74% to 57%) [107]. An association is also

Table 1. List of clinical phenotypes and possible mechanisms of CVDs in OSA patients

Disease identity	OSA-related mechanisms in pathogenesis of CVD
Hypertension [62,64]	Sympathetic hyperactivity-induced vasospasm, tachycardia and elevated CO; increased circulating pro-inflammatory markers, involving TNF-α
Heart failure [30,39,69]	Ventricular hypertrophy, cardiac dilation, heart fibrosis and decreased SV; sympathetic overactivation disturbed myocardial demand and impaired cardiac contractility due to IH and oxidative stress
Atrial fibrillation [75]	Intrathoracic pressure swings and chronic recurrence-caused atrium structural and functional remodeling; myocardial excitability elicitation as a result of apnea-induced sympathetic nerve system overactivity
Coronary artery disease [48,81]	Vasoconstriction-vasodilation disequilibrium and myocardial ischemic damage provoked by CIH; inflammatory factors release and WBC aggregation in BV wall stimulated by ROS impaired endothelial cells
Cerebrovascular disease [3,82]	Stroke deterioration due to inflammation, oxidative stress, hypercoagulability, altered cerebral perfusion, atrial arrhythmias with thrombosis and mechanical stress on carotid atherosclerosis during OSA
Pulmonary hypertension [83,84]	Sudden, reversible elevation in pulmonary artery pressures triggered by IH-induced pulmonary arteriolar constriction; pulmonary vascular remodeling and irreversible pulmonary vascular resistance increase because of inflammatory pathways

CVD, cardiovascular disease; OSA, obstructive sleep apnea; HR, heart rate; CO, cardiac output; TNF-α, tumor necrosis factor-α; IH, intermittent hypoxemia; SV, stroke volume; CIH, chronic intermittent hypoxia; ROS, reactive oxygen species; WBC, white blood cell; BV, blood vessel.

deciphered between deteriorative OSA severity and higher risk of stroke and death. For example, every 10-unit rise in AHI is associated with a 36% increase in the odds ratio in cerebrovascular event [108]. Various mechanisms have been postulated for OSA-exacerbated stroke including hypertension, inflammation, oxidative stress, hypercoagulability, altered cerebral perfusion, cerebral autoregulation, atrial rhythm with thrombogenesis, resulting in embolism and mechanical stress on carotid atherosclerosis during periodic apnea snoring (Table 1) [4,109]. Observational studies have provided compelling evidence to support a favorable outcome of CPAP on cerebrovascular events and stroke recovery in patients with OSA [110]. However, the adherence and tolerability of CPAP treatment are unsatisfactory in patients recovering from stroke compared with those without stroke. Better compliance for therapy and early intervention following stroke onset are considered crucial components for clinical outcome [111]. Further work is warranted to delineate the mechanism of arrhythmia in OSA patients in order to develop optimal therapeutic regimens.

Pulmonary hypertension

OSA is closely associated with PH, with a 70%–80% prevalence of OSA in patients diagnosed with PH using right heart catheterization [112]. PH associated with OSA is usually mild in the absence of other cardiopulmonary diseases, with an average pulmonary artery pressure between 25 and 30 mmHg. Nonetheless, OSA aggravates PH disease development and increases mortality in severe PH ascribed to other underlying cardiopulmonary causes [113]. The main culprit for pathogenesis of PH in the OSA condition is thought to be nocturnal episodic hypoxia, which reflexively triggers pulmonary arteriolar constriction resulting in sudden, reversible increase in pulmonary artery pressures, involving changes in endothelin, nitric oxide, angiopoietin-1, serotonin and NADPH-oxidase signaling cascades [113]. In addition, chronic hypoxia provokes proinflammatory pathways leading to pulmonary vascular remodeling and irreversible increases in pulmonary vascular resistance (Table 1) [114]. More in-depth examination revealed the involvement of ROS generation, increased pulmonary vascular reactivity to hypoxia and right-sided preload from negative transthoracic pressure following airway obstruction in PH pathogenesis associated with OSA [115]. Moreover, OSA indirectly deteriorates PH through post-capillary PH in patients with refractory hypertension. Multiple observational studies indicated that management of OSA with CPAP offers potential benefit to PH. Following CPAP treatment, PH patients exhibit moderate decreases in pulmonary artery pressure, pulmonary vascular resistance as well as pulmonary vascular reactivity to hypoxia [116]. However, the current available studies are somewhat restricted by sample size and study duration, longer randomized studies in larger cohorts are required to consolidate the efficacy of CPAP therapy on PH in OSA patients.

OSA and cardiovascular consequences in special populations: women and the elderly

Differences exist with regards to prevalence, clinical manifestations, pathogenesis and severity of OSA between women and men. Despite these disparities, the pathophysiology of OSA has not been fully understood in women, while most studies have focused on obese men in their middle ages. In premenopausal women, hormonal factors usually protect them from upper respiratory tract collapsibility, contributing to a lower prevalence and severity of OSA in premenopausal women compared with BMI-matched men [116]. However, SDB typically attacks during the third trimester and evokes onset of preeclampsia through enhancing cardiovascular reactions to nocturnal respiratory or endothelial events [117]. Moreover, endothelial injury markers are more closely correlated with the SDB severity in both genders, whereas association between OSA and hypertension may be weaker in women compared with men [118]. Little information is available with regards to gender differences in the clinical manifestations and prognosis of OSA, although preliminary evidence has noted that women are more prone to cardiovascular consequences of OSA. OSA-related mortality seems to be much higher in women than in men with comparable airway obstructive manifestation. Notably, timely CPAP treatment may protect against such anomalies [119] and reconcile such gender disparity.

In elderly patients, obstructive apneic events during sleep are more prevalent compared with young to middle-aged subjects. Nevertheless, it still remains controversial whether OSA aggravates adverse outcomes of cardiovascular disease in the elderly. Analysis of the SHHS cohort reported a connection between death-rate and other incident cardiovascular events and severe OSA, but only limited to patients under 70 years of age [89]. Moreover, several reports have demonstrated increased mortality and risk of stroke and HF in untreated elderly patients with severe OSA, with a relatively weak association with CAD [120,121]. The relationship between OSA severity and CVD in elderly patients needs to be scrutinized further.

Future Directions and Conclusion

Ample clinical and experimental data have consolidated deleterious effects of OSA on cardiovascular health. The pathophysiological mechanisms underscoring OSA-evoked CVD include IH, recurrent arousals, intrathoracic pressure swing, sympathetic overactivation, oxidative stress, coagulation abnormalities, hypertension, HF, AF, CAD, cerebrovascular disease and PH. Though numerous complications have been identified concerning OSA, there are still major gaps in scientific and clinical knowledge, including exact mechanisms through which OSA causes unfavorable cardiovascular events and proper therapeutic medication for OSA. A better understanding of the mechanisms underlying OSA-related CVDs should assist better recognition and intervention of OSA anomalies. There is an urgent demand for translational studies along with large RCTs to decrease cardiovascular risks attributed to OSA.

To-date, CPAP therapy has been proven to improve cardiovascular anomalies of OSA. Nonetheless, the exact mechanisms of this amelioration require further investigations. Follow-up sleep tests should be implemented to evaluate the effectiveness of CPAP treatment due to its limited adherence. Moreover, innovative and valid options for therapy (*e.g.*, mandibular devices and neural stimulation methods) as well as evidence of risk reduction are critical following steps in relieving medical and financial burdens of OSA. Despite the proven tight relationship between OSA and cardiovascular complications, OSA is always underrecognized and undertreated in particular in relevance to cardiovascular field. Given the significance of early OSA identification, it is recommended that CVD patients should be screened for OSA, while all patients with OSA should be subject to immediate and intense treatment.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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