Sleep Disordered Breathing and Cardiovascular Diseases

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Sleep disordered breathing (SDB), which causes sleep deprivation, intermittent hypoxia, and negative intrathoracic pressure swings, can be accompanied by other harmful pathophysiologies relating to cardiovascular diseases (CVD), including sudden death, atrial fibrillation, stroke, and coronary artery disease leading to heart failure. Continuous positive airway pressure (CPAP) therapy for SDB has been reported to provide favorable effects such as lower systemic blood pressure and improved endothelial function. However, in recent randomized controlled trials, CPAP has failed to demonstrate its beneficial prognostic impact on the primary or secondary setting of CVD. In this review article, we describe the characteristics of SDB complicated with CVD, the prognostic impacts of SDB in CVD, and the beneficial effects of CPAP on CVD.

Key words: Sleep apnea syndrome, Cerebrovascular disease, Coronary artery disease, Atrial fibrillation, Heart failure

Introduction

Sleep disordered breathing (SDB) is characterized by repetitive episodes of shallow breathing or apnea during sleep¹⁴), and can result in intermittent hypoxemia. It is typically associated with elevated blood pressure, oxidative stress, inflammation, and hypercoagulation (Fig. 1)², ³, ⁵-⁹). SDB is highly prevalent¹⁰-¹⁴) and is associated with an elevated risk of serious vascular outcomes², ³, ¹⁵), as well as multiple risk factors, including hypertension⁵, ¹⁶-¹⁸), obesity, insulin resistance, and dyslipidemia. Observational studies have indicated that SDB is associated with a high risk of serious cardiovascular disease (CVD), including sudden death, atrial fibrillation (AF), stroke, and coronary artery disease (CAD), leading to heart failure (HF)²-⁴, ¹⁵, ¹⁹, ²⁰). Continuous positive airway pressure (CPAP) therapy for SDB has been reported to lower blood pressure¹⁴), improve insulin resistance, enhance endothelial function, and increase insulin sensitivity, although improvements in glycemic control and body mass index have not been demonstrated²⁰-²³). Thus, patients with SDB are at a significant risk of CVD, and recent randomized controlled trials (RCTs) focusing on treatment using CPAP have failed to demonstrate its beneficial prognostic impact on the primary or secondary setting of CVD¹⁸, ²³-²⁷). In this review article, we describe the characteristics of SDB complicated with CVD, prognostic impacts of SDB in CVD, and beneficial effects of CPAP on CVD.

Diagnosis, Definition and Classification of SDB

Overnight polysomnography, which includes assessments of electroencephalogram, electrooculogram, electrocardiogram, and electromyogram, as well as the nasal and oral airflows, respiratory movement (thorax and abdominal respiratory effort), snore, oxygen saturation, body position, and sleep stage, is the gold standard test for SDB (Fig. 2)¹, ²⁸). Apnea is the absence of inspiratory airflow for at least 10 s. Hypopnea, a decrease in airflow lasting 10 s or longer, is associated with a drop in arterial oxygen saturation and/or an electroencephalographic arousal.¹, ²⁸ The total counts of apnea or hypopnea per hour are defined as the apnea hypopnea index (AHI), and is used to determine SDB: normal, AHI < 5/h; mild, 5 ≤ AHI < 15/h; moderate, 15 ≤ AHI < 30/h; severe, AHI ≥ 30/h. Apnea and hypopnea are classified as obstructive or central, but they both result from an absence or reduc-
Sleep disordered breathing (obstructive sleep apnea)

Sympathetic nervous activation (e.g. heart rate †, blood pressure †)
Metabolic dysregulation (e.g. insulin resistance, free fatty acid†)
Uncoupling of myocardial workload (e.g. hypoxia, oxygen demand †)

Systemic inflammation (e.g. leukocytes†, cytokines†)
Oxidative stress (e.g. ROS†, NO†, adhesion molecules†)
Vascular endothelial dysfunction (e.g. FMD†)
Arteriosclerosis (e.g. IMT†, PWV†, CAVI†)

Hypertension
Diabetes mellitus
Dyslipidemia
Cerebrovascular disease
Coronary artery disease
Atrial fibrillation
Heart failure
Sudden death

**Fig. 1.** Pathophysiology of the impact of sleep disordered breathing, OSA, on cardiovascular disease

PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; NO, nitric oxide; FMD, flow-mediated dilatation; IMT, intima-media thickness; PWV, pulse wave velocity; CAVI, cardio-ankle vascular index.

**Fig. 2.** OSA

OSA (downward arrow) is characterized by cessation or marked reduction of the airflow (airflow band) in the presence of respiratory effort (thorax and abdomen band), followed by arousal with breathing resumption.
tion of brainstem neural output to upper airway muscles (e.g., genioglossus) and/or lower thoracic inspiratory pump muscles (diaphragm and intercostal muscles)\(^1\)\(^-\)\(^3\). SDB includes obstructive sleep apnea (OSA), central sleep apnea (CSA) with Cheyne–Stokes respiration (CSR), or a combination of both\(^1\)\(^-\)\(^3\). The pattern of neural output determines the phenotype. OSA is characterized by cessation or marked reduction of airflow in the presence of respiratory effort (Fig. 2). OSA occurs when complete upper airway occlusion occurs (absent airflow, tongue falling backward) in the face of continued activity of inspiratory thoracic pump muscles. In OSA, there is a collapse of the pharynx during sleep with consequent upper airway obstruction, often with snoring. Predisposing factors include obesity, a short neck, and retrognathism. CPAP is well established in clinical guidelines for the treatment of symptomatic OSA (e.g., sleepy) in the non-HF population\(^3\), and provides continuous pressure throughout the respiratory cycle, prevents the pharynx from collapsing, and thus suppresses cessation or reduction of airflow and desaturation (Fig. 3). The overnight hypnogram shows an overview of the night’s sleep including SDB event, sleep stage, heart rate, and oxygen saturation (Fig. 4). In the present case, CPAP attenuates SDB, and improves sleep quality and heart rate variation (Fig. 4).

On the other contrary, CSA is characterized by cessation of both airflow and respiratory effort during sleep (Fig. 5). CSR is recognized as increasing and decreasing gradually repeated respiratory pattern (Fig. 5). CSA occurs when there is a transient reduction of the generation of breathing rhythm by the pontomedullary pacemaker, usually reflecting changes in the partial pressure of CO\(_2\)\(^2\),\(^2\),\(^9\). In HF, rostral fluid shift during sleep leads to pharyngeal edema, which may exacerbate obstructive tendencies\(^2\),\(^9\),\(^3\). In CSA, the underlying abnormality is in the regulation of breathing in the respiratory centers of the brainstem. In normal physiology, minute ventilation during sleep is primarily regulated by chemoreceptors in the brainstem and carotid bodies, which trigger an increase in respiratory drive in response to a rise in arterial carbon dioxide (PaCO\(_2\))\(^4\),\(^3\)\(^0\). Patients with HF and CSA tend to have an exaggerated respiratory response to carbon dioxide associated with excess sympathetic nervous activity, such that the modest rise in PaCO\(_2\) that may occur during sleep results in appropriate hyperventilation\(^4\),\(^3\)\(^1\). This drives the PaCO\(_2\) below the “apneic threshold,” at which point the neural drive to respire is too low to stimulate effective inspiration, and apnea or hypopnea ensues.

Although polysomnography provides comprehensive data, it is expensive, laborious, and unavailable in many centers. Moreover, multichannel sleep polygraphs (with oxygen saturation, nasal airflow, and chest and abdominal movement record) is more
**Fig. 4.** Hypnogram shows an overview of the night's sleep, including SDB, sleep stage, heart rate, and oxygen saturation.

In the hypnogram of representative case, CPAP attenuates SDB, and improves both sleep quality and heart rate variation. CSA, central sleep apnea; OSA, obstructive sleep apnea; SpO2, oxygen saturation; AHI, apnea hypopnea index; REM, rapid eye movement.

**Fig. 5.** CSA

CSA (downward arrow) is characterized by cessation of both airflow (airflow band) and respiratory effort (thorax and abdomen band) during sleep. Cheyne–Stokes respiration is recognized as increasing and decreasing gradually repeated respiratory pattern.
widely available and can even be set up by the patient at home. Studies comparing the diagnostic accuracy of home polygraphy have shown that it has a sensitivity and specificity of 90%–100% for the diagnosis of significant SDB. Because of limited access to portable sleep monitors or overnight polysomnography, the majority of subjects with SDB remain undiagnosed. SDB is associated with an altered sympato-vagal balance determined by the nocturnal cyclic alternating of apneas and hyperventilation-bradycardia during apnea, followed by abrupt tachycardia. This phenomenon causes cyclic variations in heart rate. Not only OSA but also CSA-CSR demonstrates heart rate oscillations. Both types of SDB present cyclic lengthening/shortening in the R-R interval during apnea and post-apneic hyperventilation. We have reported that cyclic variation of heart rate score (CVHRS) determined by Holter electrocardiogram is a useful screening index for severe SDB in patients with CVD. In that study, there was a significant positive correlation between CVHRS and AHI (R = 0.60, P < 0.001). In addition, the receiver operating curve analysis revealed that CVHRS (with a cut-off value of 30/h) identified severe SDB with a sensitivity of 82%, a specificity of 77%, and an area under the curve of 0.83 (95% confidence interval [CI]: 0.72–0.93). Recently, pacemaker algorithms have been developed to detect and quantify SDB accurately. It is possible to measure thoracic impedance continually between the right ventricular lead tip and the generator. On inspiration, the increased volume of air in the chest increases the thoracic impedance, with the inverse occurring on expiration, with consequent proportional changes in detected potential differences. It has recently been reported that intrathoracic impedance revealed a sensitivity of 88.9% and a specificity of 84.6% for the diagnosis of moderate to severe SDB.

**Associations between SDB and CVD**

Endothelial dysfunction can be caused by oxidative stress, systemic inflammation, and sympathetic nervous activation. These factors are affected by SDB, such as intermittent hypoxia, sleep deprivation, and arousals. Inflammatory pathways triggered by intermittent hypoxia in OSA might also contribute to the development and progression of atherosclerosis. SDB severity is reportedly associated with coronary atherosclerotic burden severity. In a small RCT, effective CPAP therapy attenuated these CVD risks. Gottlieb et al. reported that OSA was a significant predictor of incident CAD (MI, revascularization procedure, or cardiac death) after adjustment for multiple risk factors in men aged <70 years, but not in older men or women of any age. Among men aged 40–70 years, those with severe OSA were 68% more likely to develop CAD than those without SDB.

Pathophysiological and Prognostic Impact of SDB in Patients with CVD

OSA is observed in 30%–83% of patients with hypertension, 38%–65% of those with CAD, 57%–75% of those who had a stroke, 12%–55% of those with HF, and 20%–50% of those with arrhythmias. Inspiratory efforts in OSA against the occluded upper airway are associated with intrathoracic pressure oscillations that result in increased sympathetic activity. As shown in Figs. 1 and 2, the hypoxia, hypercapnia, and arousal from sleep that occur at the end of the OSA further increase sympathetic activity. The post-apneic period, when a patient recovers upper airway patency, is often characterized by marked increases in blood pressure and heart rate. During apneic phases, increased cardiac oxygen demand is paralleled by reduced oxygen supply because of excessive desatura-
tion during apnea. Uncoupling of myocardial workload and coronary blood flow have been demonstrated\(^{20, 50}\). Hypoxia-induced vasodilation is reduced in the presence of endothelial dysfunction and arteriosclerosis. In patients with acute MI, SDB was associated with higher work load\(^{13}\), less myocardial salvage, and a smaller reduction in infarct size\(^{52}\). The presence of SDB among Japanese patients with acute coronary syndrome following primary percutaneous coronary intervention has been reported to be associated with a higher incidence of major adverse CVD events during long-term follow-up\(^{53}\). Among 241 patients with acute coronary syndrome, SDB was found in 126 (52.3\%)\(^{53}\). The cumulative incidence of major adverse cardiocerebrovascular events (MACCEs) was significantly higher in patients with SDB than in those without (21.4\% vs. 7.8\%, \(P = 0.006\), hazard ratio [HR]: 2.28, 95\% CI: 1.06–4.92, \(P = 0.035\))\(^{53}\). In patients with CAD, OSA is independently associated with subsequent MACCEs in patients undergoing percutaneous coronary intervention (drug-eluting stents were used in 80.1\% and biodegradable vascular scaffolds in 6.3\% of these patients)\(^{54}\). Although target lesion revascularization is not associated with the presence of SDB, the crude incidence of MACCEs was higher in the OSA group than in the non-OSA group (3-year estimate, 18.9\% vs. 14.0\%, \(P = 0.001\)). Multivariate Cox regression analysis indicated that OSA was a predictor of MACCEs (adjusted HR: 1.57, 95\% CI: 1.10–2.24, \(P = 0.013\))\(^{54}\).

Thus, SDB seems to negatively affect CVD; however, intermittent hypoxia caused by SDB may lead to ischemic preconditioning in the myocardium in patients with CAD. In a study by Ludka et al., SDB was present in 65.7\% (\(n = 399\)) of their study population, and non-ST-elevation MI (NSTEMI) was present in 30\% (\(n = 182\))\(^{55}\). In that study, the degree of SDB severity was associated with an increasing likelihood of NSTEMI, and with a decreasing likelihood of STEMI (\(P < 0.001\))\(^{55}\). The relative frequency of NSTEMI in the moderate to severe SDB group of that study was 40.6\% versus 29.9\% for STEMI (\(P = 0.01\))\(^{55}\). NSTEMI prevalence increases with increasing SDB severity. This finding may suggest a cardioprotective role of SDB, which may attenuate the development of STEMI, perhaps through ischemic preconditioning\(^{55}\).

In patients with HF, presence of sleep disturbance including OSA is associated with adverse prognosis\(^{3, 56, 57}\). OSA may accelerate the progression of HF in several ways. The negative intrathoracic pressure generated by the respiratory muscles trying to inspire against closed airways increases venous return to the right heart, increasing preload and causing the septum shift to the left, which may compromise left ventricular ejection fraction (LVEF)\(^{4, 49, 58}\). The ability of the failing left ventricle to cope with enhanced preload is further impaired by increased transmural pressure during episodes of negative intrathoracic pressure, thereby increasing the afterload. Apnea and hypopnea activate the sympathetic nervous system; levels of circulating catecholamines and muscle sympathetic nerve activity are higher in those with HF and SDB than those with HF without SDB\(^{4, 59}\). SDB is associated with latent myocardial damage and alteration of myocardial carnitine metabolism in patients with HF, presented by higher circulation troponin T and carnitine levels\(^{60, 63}\). In addition, SDB induces impairment of vagal activity, cardiac electrical instability, and ventricular arrhythmias across a 24-hour period accessed by heart rate variability and heart rate turbulence using Holter electrocardiogram\(^{64-66}\).

The incidence of CSA-CSR has been increasing in the past two decades, and whether it is merely a marker of the severity of underlying diseases or an important risk factor that independently worsens the prognosis of patients with HF, and therefore requires treatment, is still widely debated. Indeed, when multivariate analyses were performed to control for potential confounders involved in determining the outcome in patients with HF, CSA was found to be an independent factor for death or cardiac transplantation in these patients\(^{49, 67}\). Some large-scale studies have demonstrated that SDB is associated with occurrence of ventricular arrhythmias\(^{64, 68}\) and adverse prognosis in subjects with HF\(^{69, 70}\).

**Effects of CPAP Therapy for OSA on CVD Outcome in Patients with CVD or AF**

Although CPAP is the gold standard therapy for OSA, the effects of CPAP on the morbidity and mortality of CVD remain unproven. In a study that included patients with moderate to severe OSA without daytime sleepiness, the prescription of CPAP compared with usual care did not result in a statistically significant reduction in the incidence of hypertension or cardiovascular events (HR: 0.83, 95\% CI: 0.63–1.1, \(P = 0.20\))\(^{71}\). However, in an adherence analysis, patients who used CPAP for at least 4 h/night showed a lower risk of CVD (HR: 0.72, 95\% CI: 0.52–0.98, \(P = 0.04\))\(^{71}\).

With regard to patients with CAD, the Continuous Positive Airway Pressure Treatment of OSA to Prevent Cardiovascular Disease (SAVE) trial randomized 2,602 patients with a prior history of CVD and without moderate sleepiness who received either CPAP or usual care\(^{72}\). After a mean follow-up of 3.7
years, there was no benefit regarding any cause-specific CVD outcome (CPAP vs. usual care, HR: 1.10, 95% CI: 0.91–1.32, P=0.34), despite improved sleepiness scores and quality-of-life measures. After propensity-score matching, the group of patients who used CPAP for at least 4 h/night showed a lower risk of CVD (HR: 0.52, 95% CI: 0.30–0.90, P=0.02). Possible explanations for the lacking benefit for CVD were assumed to be because of the exclusion of study subjects with sleepy or severe SDB, a relatively short mean follow-up period, poor CPAP compliance (mean usage, 3.3 h/night), diagnosis determined by portable sleep monitor, and study subjects with more than 84% of the patients being nonsmokers, being of Asian descent (63.7%), and those with a prescription of effective medication including aspirin (75%) or antihypertensive agents (77%). In addition, a similar favorable trend with adequate nightly CPAP time (>4 h/night) was noticed in the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea (RICCADSA) study, which involved patients with newly revascularized CAD and moderate to severe OSA. In this study, although the use of a CPAP compared with usual care did not result in a significant reduction in the incidence of CVD, including the incidence of MI, repeat revascularization, stroke, or cardiovascular mortality (95% CI: 0.63–1.1, P=0.20), CPAP with better adherence (>4 h/night) may reduce the CVD (HR: 0.29; 95% CI: 0.10–0.86, P=0.026).

With regard to patients with AF, CPAP is associated with a significantly decreased recurrence rate of AF, even after electrical cardioversion or catheter ablation. In addition, patients are less likely to progress to more permanent forms of AF and have significantly reduced occurrence of paroxysmal AF compared with untreated patients. A recent meta-analysis has revealed that OSA treated with CPAP after AF intervention has a reduced AF risk. With regard to patients with stroke, there is some evidence that CPAP improves long-term survival in patients with ischemic stroke having moderate to severe OSA. Parra et al. followed up patients with stroke for 24 months, and found that, compared with nonusers, CPAP users had notable interval delay until the occurrence of the first CVD event after initial stroke (14.9 vs. 7.9 months, P=0.044). Although CPAP users had lower cardiovascular mortality (0% vs. 4.3%, P=0.161) and lower MACE (including cardiac ischemic events, stroke recurrence, and cardiovascular death; 12.3% vs. 11.6%, P=0.560) compared with nonusers, the differences did not reach statistical significance.

### Effects of SDB Therapy on CVD Outcome in Patients with HF

Regarding HF, positive end-expiratory pressure prevents alveoli collapsing secondary to pulmonary edema and maintains alveoli at a greater diameter, and reducing breathing workload. It also increases alveolar recruitment, improves gas exchange, and reduces right to left intrapulmonary shunting of blood. The positive intrathoracic pressure reduces venous return (preload) and LV transmural pressure (afterload), and may therefore benefit cardiac function in some patients. CPAP caused abolition of negative intrathoracic pressure swings and reductions in nocturnal blood pressure, which resulted in a dramatic reduction in LV afterload that was accompanied by a decrease in heart rate. We have previously reported that CPAP improves right ventricular systolic function, pulmonary function, and exercise capacity, resulting in reduction of all-cause mortality in patients with HF having preserved EF. Taken together, it seems that CPAP for OSA in patients with HF ameliorates LVEF, and possibly improves cardiovascular prognosis. On the contrary, treatment of CSA or CSA-CSR in HF improves not only LV systolic and diastolic function but also pulmonary, renal, and vascular functions; thus, it also potentially improves prognosis in patients with HF having reduced or preserved EF. However, a recent RCT failed to demonstrate that treatment of CSA improves the prognosis of patients with HF having CSA.

### Interpretation of Recent Randomized Clinical Trials and Future Perspectives

We propose the possible explanations for the lacking benefit for CVD as follows: 1) CPAP adherence, 2) the method of SDB treatment, 3) a relatively short follow-up period, 4) the selection of study subjects, and 5) diagnosis or risk stratification of SDB. First, recent meta-analysis suggests that CPAP compliance is key in reducing the risk of adverse cardiovascular outcomes in patients with OSA, with decreased incidence of MACE having been observed in patients using CPAP ≥ 4 h compared with those not on CPAP. Thus, patients with OSA should be extensively counseled on the importance of compliance with CPAP. Second, other treatments, including oral appliances or upper airway stimulation devices, may lead to the improvement of CVD outcome. Third, the short follow-up duration of most trials may have given insufficient time for CPAP to have affected CVD outcomes, and the meta-regression identified no association between follow-up time...
and the HR of CPAP versus control in the contributing trials. Fourth, recent RCTs do not include severe SDB or sleepy subjects, who are generally recommended CPAP therapy. Fifth, with regard to the risk stratification or therapeutic targets, parameters of hypoxia (time with oxygen saturation), rather than classic AHI, seems to be an appropriate therapeutic target. In addition, the use of continuous blood pressure measurement by using pulse transit time (PTT) has recently been reported. Arterial PTT was measured between the R-spike of the electrocardiogram and the plethysmographic curve of finger pulse-oximetry. Both PTT and pulse wave velocity were shown to have a correlation with blood pressure, and have been reported to be suitable for indirect blood pressure measurements. In a representative case (Fig.6), CPAP improved not only SDB but also both PTT index and mean or maximum blood pressure. Thus, arterial PTT is useful for detecting night-time blood pressure, which may be a useful risk stratification or therapeutic target in patients with SDB.

Further studies are needed to determine whether managing SDB improves the prognosis of patients with SDB. Several studies in patients with CAD or HF are ongoing and their results are expected.

**Conclusion**

SDB causes sleep deprivation, intermittent hypoxia, and negative intrathoracic pressure swings, accompanied by other harmful pathophysiology that leads to CVD. Further studies are needed to determine whether appropriately managing SDB improves the prognosis of patients with SDB and cardiovascular diseases.

**Conflict of Interest**

Akiomi Yoshihisa belongs to the Department of Advanced Cardiac Therapeutics, supported by Fukuda-denshi Co, Ltd.

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