

Sleep-Disordered Breathing—a Real Therapeutic Target for Hypertension, Pulmonary Hypertension, Ischemic Heart Disease, and Chronic Heart Failure?

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Sleep-disordered breathing (SDB) is a risk factor for cardiovascular disease including acute coronary syndrome and acute myocardial infarction, and treating SDB prevents their development and recurrence and improves a patient's prognosis. Therefore, SDB is considered a therapeutic target for cardiovascular disease. In 2010, the Japanese Circulation Society published guidelines for the diagnosis and treatment of SDB in patients with cardiovascular disease. However, therapeutic intervention for patients with SDB was recently reported not to suppress the development or deterioration of cardiovascular disease in three middle- to large-sized randomized clinical trials: the SERVE-HF trial, which examined the effects of adaptive servo-ventilation (ASV) on patients with chronic heart failure (CHF) and central sleep apnea; the CAT-HF trial, which examined the effects of ASV therapy on patients with CHF after acute deterioration; and the SAVE study, which examined the secondary preventive effect of continuous positive airway pressure (CPAP) on patients with ischemic heart disease who had mild to moderate obstructive sleep apnea. These studies caused hesitation among clinicians to proactively treat SDB by ASV or CPAP therapy. The present review is focused on hypertension, pulmonary hypertension, ischemic heart disease, and CHF to newly summarize the studies available to date from the viewpoints of epidemiology, pathogenesis, and treatment. I expect this review be informative and useful for physicians who treat patients with SDB by CPAP or ASV therapy in the clinical setting. (*J Nippon Med Sch* 2018; 85: 70–77)

Key words: sleep-disordered breathing, hypertension, pulmonary hypertension, ischemic heart disease, chronic heart failure

Introduction

Sleep-disordered breathing (SDB) is a risk factor for cardiovascular disease^{1–7}, and several clinical studies have shown that the treatment of SDB prevents its development and recurrence and improves the patient's prognosis^{7–9}. Therefore, the understanding that SDB is a therapeutic target for cardiovascular disease has grown rapidly since the year 2000. In 2010, the Japanese Circulation Society published guidelines for the diagnosis and treatment of SDB in patients with cardiovascular disease (*JCS* 2010)¹⁰. However, three middle- to large-sized randomized clinical trials^{11–13} have shown that therapeutic intervention for patients with SDB did not suppress the development or deterioration of cardiovascular disease. The first of the studies was the SERVE-HF trial, which examined the effects of adaptive servo-ventilation (ASV) on

patients with chronic heart failure (CHF) that was complicated by central sleep apnea (CSA); the study attracted much attention because of having suggested an increased cardiovascular mortality, though ASV therapy improved SDB compared with no provision of treatment¹¹. The second of the studies was the CAT-HF trial, which examined the effects of ASV therapy on patients with CHF after acute deterioration; the study was discontinued due to the reported outcomes from the SERVE-HF trial, and its results were analyzed under the situation that the target number of patients was not reached¹². Consequently, ASV therapy showed no significant effect on patients with CHF. The third of the studies was the SAVE study, which examined the secondary preventive effect of continuous positive airway pressure (CPAP) on patients with ischemic heart disease who had mild to moderate ob-

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structive sleep apnea (OSA); the study did not show any secondary preventive effect of usual care plus CPAP therapy compared with usual care alone¹³.

These studies caused hesitation among clinicians to proactively treat SDB by ASV or CPAP therapy. The present review is focused on hypertension, pulmonary hypertension, ischemic heart disease, and CHF to newly summarize the studies available to date from the viewpoints of epidemiology, pathogenesis, and treatment. I expect this review be informative and useful for physicians in the clinical setting.

The diagnostic criteria and severity classification of SDB are defined by the International Classification of Sleep Disorders (ICSD) published by the American Academy of Sleep Medicine (currently, the third edition)¹⁴, and both the JCS 2010¹⁰ and the guidelines published by the SDB Study Group are nearly in line with the ICSD.

Hypertension

Epidemiology

SDB of patients with hypertension mainly consists in OSA during which upper airway obstruction reduces or transiently halts airflow and respiratory efforts in the thoracoabdominal region. OSA is considered to coexist in 30% of patients with hypertension^{15,16}. Moreover, the prevalence of SDB is very high (80%) in patients with

drug-resistant hypertension¹⁷.

Pathogenesis

Upper airway obstruction, which causes OSA in many patients with hypertension, is determined by morphological factors (e.g., small cross-section of the airways) and functional factors that are balanced between the tension of the upper airway dilators and the negative pressure of the airway lumen¹⁰. OSA causes the hyperactivity of the sympathetic nervous system and increases the activity of the renin-angiotensin-aldosterone (RAA) system through the frequent provocation of arousal responses and the intermittent development of hypoxemia and hypercapnia^{18–21}; thus, OSA is known to be involved in the induction and deterioration of hypertension (Fig. 1). An association between sleep apnea syndrome assessed with apnea-hypopnea index (AHI) and the development of hypertension has been found³. In addition, OSA is associated with the development of nocturnal hypertension and nondipper hypertension²¹ and is known to precede nondipper hypertension²². Hence, the Guidelines for the Management of Hypertension in Japan²³ recognize the following: 1) OSA does not originate from hypertension but is a risk factor for the induction and deterioration of hypertension; and 2) it is essential to adequately diagnose and treat OSA in patients with hypertension. In particular, OSA is the most common factor for secondary hy-

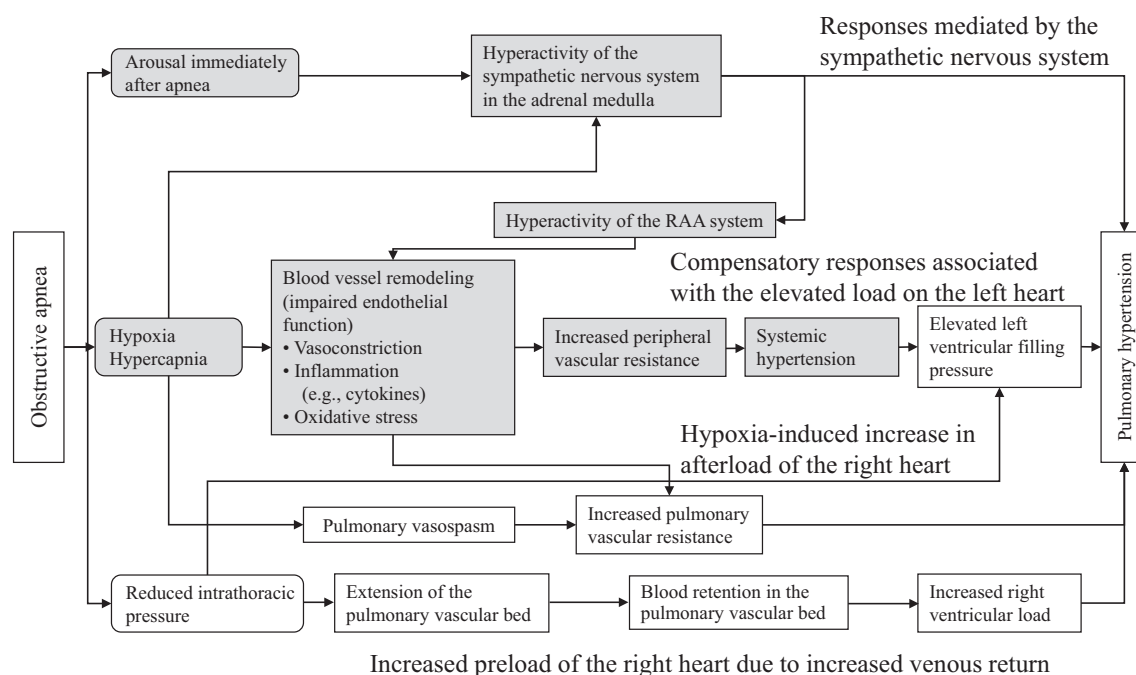


Fig. 1 Putative pathophysiologic mechanisms of obstructive sleep apnea in patients with hypertension or pulmonary hypertension

Gray shaded area: Occurs also in hypertension.

RAA, renin-angiotensin-aldosterone

pertension in patients with resistant hypertension²⁴. Therefore, physicians should actively suspect the presence of OSA and conduct a sleep test.

Treatment

The obesity-induced deposition of fat in upper airway soft tissue is considered to be the most important risk factor for OSA. Therefore, weight reduction should be attempted first in the treatment of OSA. However, obese patients are not necessarily predominant among Japanese patients with OSA. Hence, the morphology of the cranial and facial bones, especially the small size of the mandible, is considered to be an important factor. The treatment of choice for patients with moderate or severe OSA is CPAP therapy¹⁰. CPAP therapy delivers air via a nasal or oro-nasal mask to resolve the stenosis or obstruction of the upper airways by making their pressure positive. Several meta-analyses of randomized controlled clinical trials of CPAP therapy in patients with OSA have shown that the therapy can decrease systolic blood pressure and diastolic blood pressure by 2 to 2.5 mmHg and 1.5 to 2 mmHg, respectively, in patients with hypertension. CPAP therapy showed a more marked hypotensive effect on patients with refractory hypertension and recovered nocturnal blood pressures in patients with nondipper hypertension²⁵. A linear correlation between the duration of CPAP therapy and decreases in blood pressures was reported in patients with refractory hypertension (1.9- and 1.0-mmHg decreases in SBP and DBP, respectively, per 1 hour of CPAP therapy)²⁶. CPAP therapy was associated with a lower risk of hypertension^{27,28}. The minimum threshold duration of CPAP therapy per night to obtain the hypotensive effect is considered to be 4 hours^{25,29,30}, with the optimal duration being 5 to 6 hours²⁴. In clinical practice, many physicians consider that CPAP therapy is difficult to initiate or continue. In the clinical settings, for example, physicians would be concerned about how to adequately set the initial pressures for CPAP therapy and what should be done to motivate patients to continue with the therapy. In my experience, however, the initial setting of pressures for CPAP therapy is acceptable for many patients because the mode of automatic pressure change—which is provided in recently marketed respirators—varies pressures on an as-needed basis. The upper limit for pressures may be useful when patient adherence is poor. Fitting of the mask is more important than pressures for CPAP therapy. At the time of initiating CPAP therapy, it is critically important to select a mask that fits to the contours of the patient's face and to instruct the patient how to adequately wear the mask (i.e., to make

the patient realize the importance of not fastening the fixing band of the mask too tightly). For the objective of encouraging the patient to continue with CPAP therapy, furthermore, it is important that the attending physician verifies in the outpatient service whether the patient is using the device appropriately in an attempt to prevent a decline in the patient's motivation to continue with the therapy.

Pulmonary Hypertension

Epidemiology

A cross-sectional observational study of 220 patients with OSA who had an AHI >20 events/hour revealed the presence of pulmonary hypertension (average pulmonary arterial pressure: >20 mmHg) in 17% of patients²⁷. Thus, patients with OSA are known to be frequently affected with pulmonary hypertension. Secondary pulmonary hypertension due to SDB is listed in Group III of the clinical classifications of hypertension in the Guidelines for the Treatment of Pulmonary Hypertension in Japan (JCS 2012)²⁹.

Pathogenesis

OSA is one of the etiologies of pulmonary hypertension. Similar to hypertension, therefore, not only hypoxia and frequent arousal but also decreased intraperitoneal pressure is included in the putative pathophysiologic mechanisms (Fig. 1)^{10,31–33}.

Treatment

The treatment of first choice is CPAP therapy when OSA causes secondary pulmonary hypertension. The treatment of OSA by CPAP therapy is known to lower pulmonary arterial pressure at the time of arousal during the daytime^{34–36}. However, CPAP therapy is not indicated for events other than secondary pulmonary hypertension caused by hypoxia. Due to the possibility that positive airway pressure increases pulmonary blood vessel resistance, CPAP therapy cannot be recommended for patients with Group I pulmonary artery hypertension or Group IV chronic thromboembolic pulmonary hypertension that are defined in the Guidelines for the Treatment of Pulmonary Hypertension in Japan (appropriate pharmacotherapy and oxygenation therapy are selected in these patients). Since CPAP therapy cannot be sweepingly considered as a recommended choice for the treatment of pulmonary hypertension, it is therefore mandatory to precisely specify the cause(s) of pulmonary hypertension.

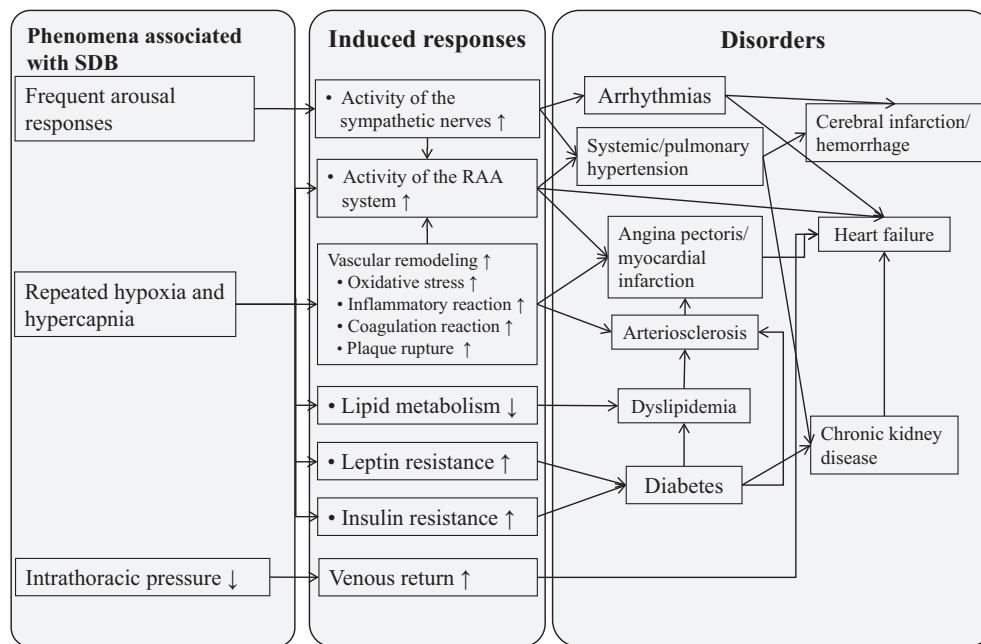


Fig. 2 Putative pathophysiologic mechanisms of sleep-disordered breathing in patients with cardiovascular disease including ischemic heart disease
SDB, sleep-disordered breathing; RAA, renin-angiotensin-aldosterone

Ischemic Heart Disease

Epidemiology

OSA frequently coexists in patients with coronary artery disease or acute coronary syndromes^{37,38}. The risk of developing ischemic heart disease is 1.2 to 6.9 times greater in patients with OSA than in healthy individuals⁶. Fatal and nonfatal cardiovascular events were 2.87 and 3.17 times more frequent, respectively, in patients with severe OSA who had an AHI of 30 events/hour than in healthy individuals⁷.

Pathogenesis

OSA is a risk factor for ischemic heart disease. SDB-induced intermittent hypoxia is known to be associated with glucose intolerance independent of age, sex, body mass index, and abdominal circumference³⁸. Similar to ischemia-reperfusion injury, moreover, intermittent hypoxia is considered to increase the risk of developing ischemic heart disease by decreasing the endothelial function of the coronary arteries through inflammation and free radicals (Fig. 2)³⁹.

Treatment

CPAP therapy is the treatment of choice for patients with severe OSA, as for patients with other cardiovascular disease. The incidence of cardiovascular events decreased to the level found in healthy individuals when CPAP therapy was conducted in patients with OSA who had an AHI >30 events/hour⁷, which led to the understanding that the treatment of patients with severe OSA

is effective for the primary prevention of cardiovascular disease¹⁰. As described in the first paragraph of this article, however, the SAVE study showed that CPAP therapy does not have any secondary preventive effect on cardiovascular disease and appears to indicate that CPAP therapy for the secondary prevention of cardiovascular disease is meaningless. However, attention should be paid to the facts that the SAVE study¹³ excluded patients with severe SDB who had an AHI >30 events/hour and patients whose SaO₂ was lowered by SDB, in addition to: 1) concern about the maintenance of treatment level among the study sites and 2) the issue that the average duration of CPAP therapy was less than 4 hours. The SAVE study excluded patients who should undergo CPAP therapy and examined patients with milder OSA. Furthermore, the patients in the RICCADSA randomized controlled trial in coronary artery disease who had no daytime sleepiness showed a cardiovascular risk reduction not in the study population but in a subgroup of patients who underwent ≥4-hour CPAP therapy⁴⁰. Therefore, I consider that CPAP therapy requires a minimum of 4 hours to exert a risk-reducing effect in patients with hypertension or cardiovascular disease. In light of my consideration, the SAVE study does not negate the conventional therapeutic strategy for patients with SDB. At my institution, we routinely conduct pulse oximetry as the first step before hospitalization to screen patients with ischemic heart disease for the presence or absence of intermittent hypoxia dur-

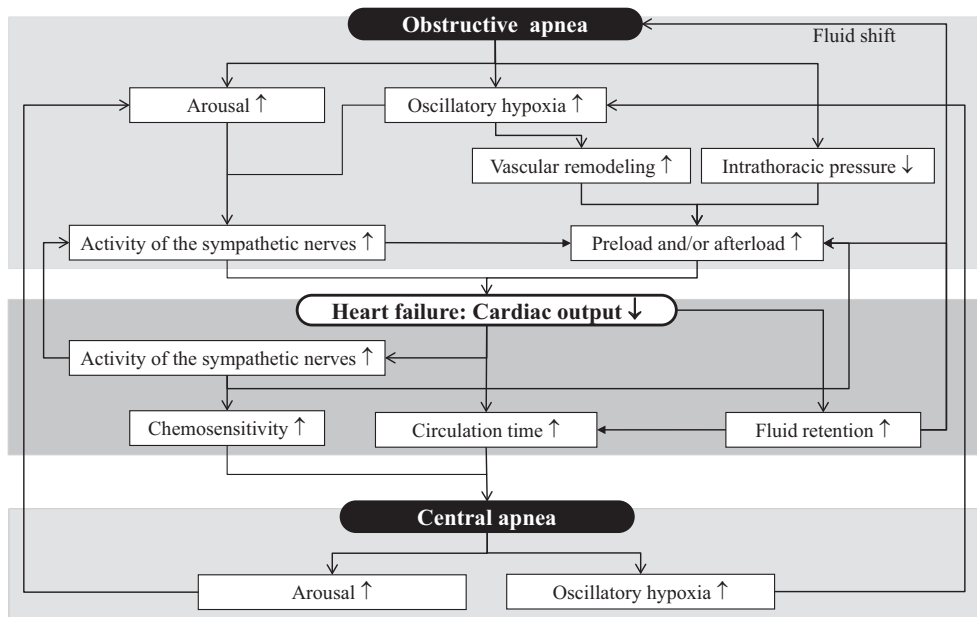


Fig. 3 Putative pathophysiologic mechanisms of sleep-disordered breathing and central apnea in patients with chronic heart failure

ing sleep; subsequently, we determine the further need to conduct a sleep test and begin treatment.

Chronic Heart Failure

Epidemiology

SDB of patients with CHF is featured by not only OSA, but also Cheyne-Stokes respiration (CSR-CSA), a type of CSA that is devoid of respiratory efforts in the thoracoabdominal region due to the suspension of respiratory stimuli from the central nervous system⁴¹. OSA and CSR-CSA were respectively found in 11 to 37% and 29 to 40% of patients who had heart failure with a reduced ejection fraction (HFrEF)^{4,42-45}. SDB was found in 55% of a small number of patients who had heart failure with a preserved ejection fraction (HFpEF)⁴⁵.

Pathogenesis

OSA is considered to be one of the etiologies of heart failure⁴⁶. In patients with heart failure, furthermore, so-called “fluid shift,” by which body fluids that are retained due to heart failure move to the craniocervical region, is provoked or aggravated by OSA⁴⁷. On the other hand, CSR-CSA occurs as a consequence of heart failure and when both of the following phenomena associated with heart failure progression—enhanced chemosensitivity and delayed circulation (i.e., low cardiac output)—appear (Fig. 3)⁴⁸. Overnight fluid shift to the craniocervical region may also contribute to the pathogenesis of CSA⁵⁰. Similar to OSA, furthermore, CSR-CSA is also considered as a prognosticator because of repeatedly causing hy-

poxia and arousal^{45,49}. Meanwhile, however, the SERVE-HF trial indicated that CSR-CSA might increase cardiac output in patients with chronic heart failure. Therefore, CSR-CSA is now under review as to its pathophysiologic role—“friend” or “foe”—in this patient population⁵¹.

Treatment

In patients with OSA, CPAP therapy improves not only SDB, but also sympathetic nerve activity⁵² and the left ventricular ejection fraction⁵³. The successful maintenance of CPAP compliance improved the prognosis of patients with heart failure⁵⁴.

In patients with CHF involving CSR-CSA, on the other hand, treatment with an artificial respirator that maintains the volume of ventilation constant in response to the volume of spontaneous respiration, that is ASV therapy, is being attempted, in addition to nocturnal oxygenation therapy and CPAP therapy. Randomized controlled clinical trials have been conducted for all of these therapeutic modalities. However, these modalities have not shown any definite effect on disease prognosis, although have shown a certain level of effect on improving cardiac function and symptoms^{11,12,55-57}. As described previously, the mortality rate increased significantly in patients with HFrEF who had CSR-CSA-dominant SDB in the ASV group of the SERVE-HF trial¹¹. In the CAT-HF trial as well, ASV showed no prognosis-improving effect on patients with HFrEF, although it did show a tendency to improve disease prognosis in patients with HFpEF¹². CPAP therapy and ASV therapy reduce the transmural

pressure of the left ventricle and venous return through positive airway pressure^{58,59}. However, low cardiac output frequently occurs in patients with CHF and CSR-CSA⁴⁴. CPAP therapy and ASV therapy reduce venous return through positive airway pressure in patients with preserved preload reserve, but they also reduce preload pressure and lower cardiac output. Excessive positive pressures were applied to treat some patients with SDB in both the SERVE-HF trial and the CAT-HF trial, which probably masked the patient prognosis- and cardiac function-improving effects of ASV therapy. Therefore, cardiologists should fully examine whether positive ventilation therapy adversely affects the hemodynamics of patients with CHF when conducting CPAP or ASV therapy and should then initiate and manage the therapy appropriately.

In Japan, the Japanese Circulation Society and the Japanese Heart Failure Society announced a joint statement for the proper use of ASV in patients with heart failure⁶⁰. Readers are invited to read the statement for reference.

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