Sleep Disordered Breathing and Cardiovascular Diseases

Akiomi Yoshihisa[1, 2] and Yasuchika Takeishi[1]

[1]Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan
[2]Department of Advanced Cardiac Therapeutics, Fukushima Medical University, Fukushima, Japan

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 lowered 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 sleep[1-4], 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 prevalent[10-14] and is associated with an elevated risk of serious vascular outcomes[2, 3, 15], as well as multiple risk factors, including hypertension[5, 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 pressure[14], improve insulin resistance, enhance endothelial function, and increase insulin sensitivity, although improvements in glycemic control and body mass index have not been demonstrated[20-23]. 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 CVD[18, 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, $5 \le$ AHI <15/h; moderate, $15 \le$ 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-
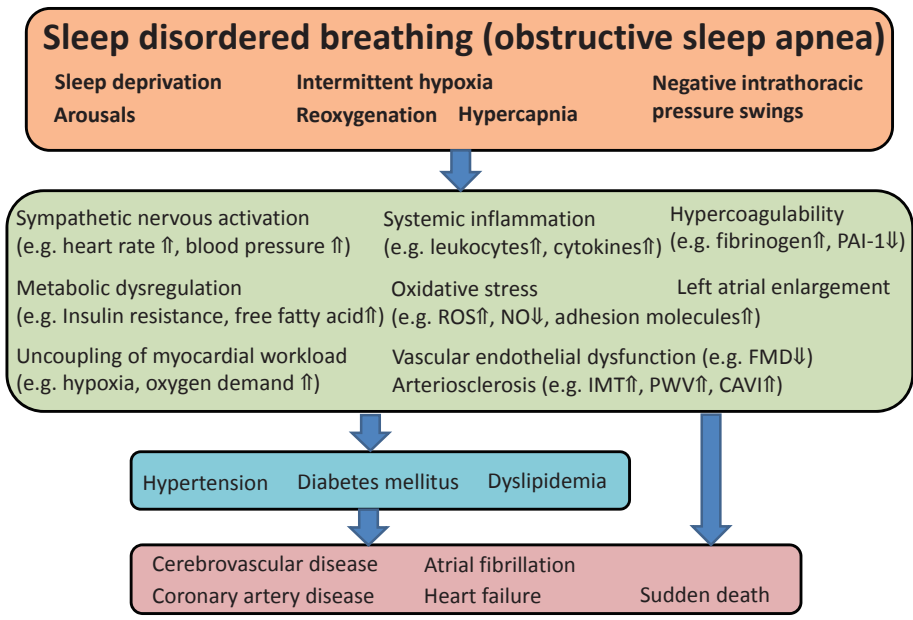
Fig. 1. Pathophysiology of the impact of sleep disordered breathing, OSA, on cardiovascular disease

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.
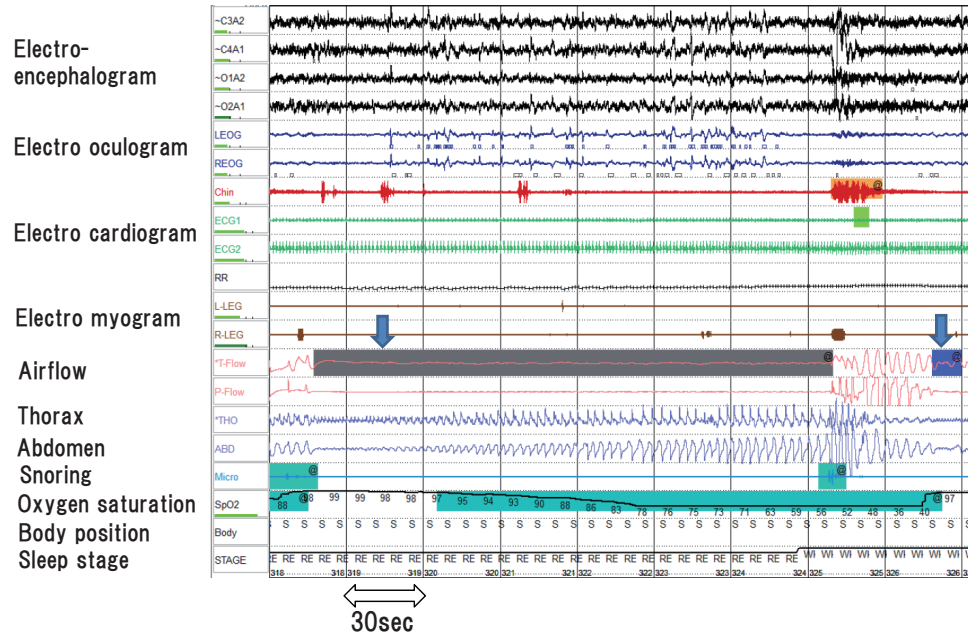

Fig. 2. OSA

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.
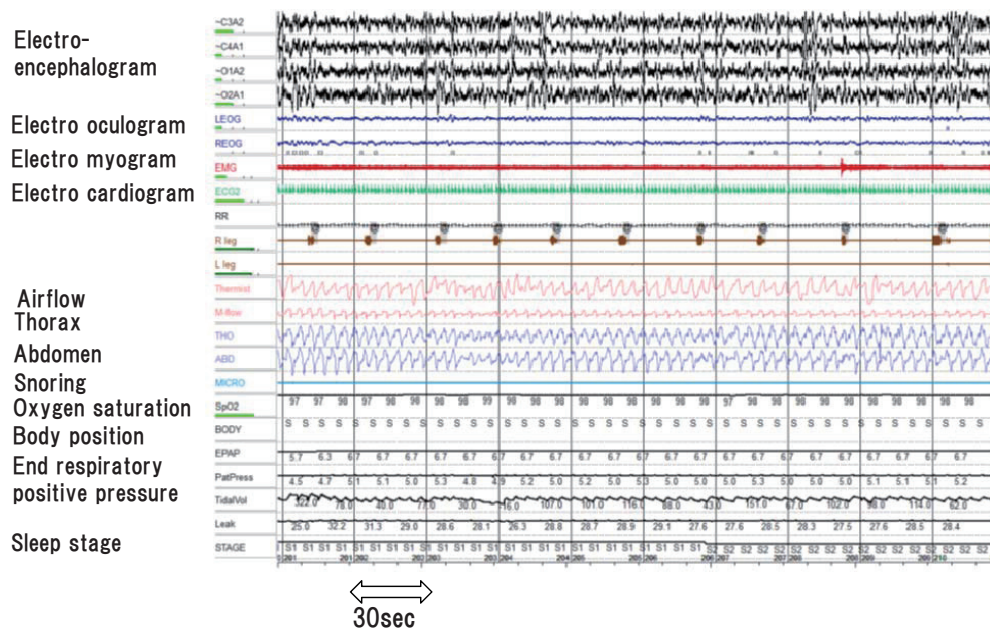
Electro-encephalogram
Electro oculogram
Electro myogram
Electro cardiogram

Airflow
Thorax
Abdomen
Snoring
Oxygen saturation
Body position
End respiratory
positive pressure

Sleep stage

30sec

Fig. 3. OSA on treatment with positive airway pressure.

CPAP provides continuous pressure throughout the respiratory cycle, preventing the pharynx from collapsing and thus suppresses cessation or reduction of airflow and desaturation.

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, 29]. In HF, rostral fluid shift during sleep leads to pharyngeal edema, which may exacerbate obstructive tendencies[29, 30]. 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 ($PaCO_2$), thus maintaining PaCO2 within a narrow range[4, 30]. 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, 31]. 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
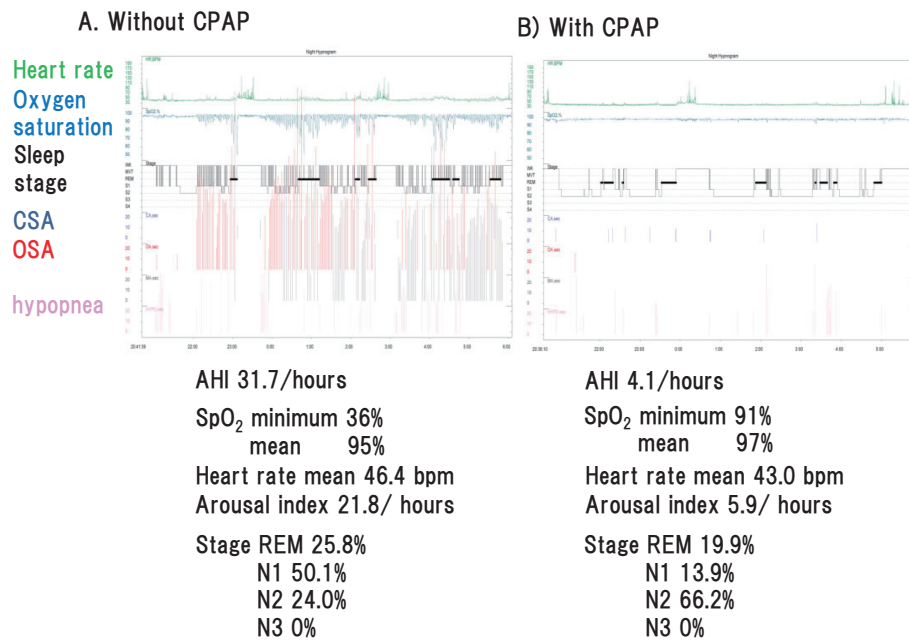
A. Without CPAP

B) With CPAP

Heart rate
Oxygen saturation
Sleep stage
CSA
OSA

hypopnea

AHI 31.7/hours

SpO₂ minimum 36%
     mean   95%
Heart rate mean 46.4 bpm
Arousal index 21.8/ hours

Stage REM 25.8%
    N1 50.1%
    N2 24.0%
    N3 0%

AHI 4.1/hours

SpO₂ minimum 91%
     mean   97%
Heart rate mean 43.0 bpm
Arousal index 5.9/ hours

Stage REM 19.9%
    N1 13.9%
    N2 66.2%
    N3 0%

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.
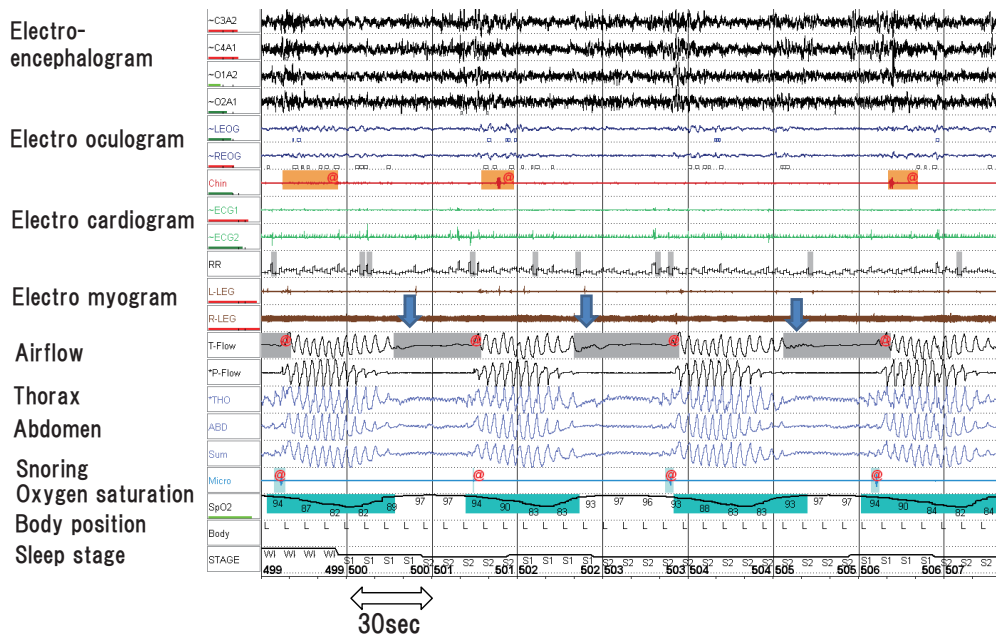
Electro-encephalogram
Electro oculogram
Electro cardiogram
Electro myogram
Airflow
Thorax
Abdomen
Snoring
Oxygen saturation
Body position
Sleep stage

30sec

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[4, 32]. 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 sympatho-vagal balance determined by the nocturnal cyclic alternating of apneas and hyperventilation-bradycardia during apnea, followed by abrupt tachycardia[33]. This phenomenon causes cyclic variations in heart rate[33]. 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[34]. In that study, there was a significant positive correlation between CVHRS and AHI (R=0.60, $P<$ 0.001)[34]. 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)[34]. Recently, pacemaker algorithms have been developed to detect and quantify SDB accurately[35]. 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[35].

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 (**Fig. 1**), such as intermittent hypoxia, sleep deprivation, and arousals[36]. Inflammatory pathways triggered by intermittent hypoxia in OSA might also contribute to the development and progression of atherosclerosis. SDB severity is reportedly associated with endothelial dysfunction determined by flow-mediated dilatation[37] or arterial stiffness determined by cardio-ankle vascular index[38]. With regard to cerebral artery, SDB-related oxidative stress and systemic inflammation promote increased intima-media thickness[20, 39]. Markers of oxidative stress and inflammation are associated

with SDB-related hypoxia and intima-media thickness[40]. Patients with OSA without other known risk factors for arteriosclerosis have increased intima-media thickness compared with those without OSA[41], and intima-media thickness is related to nocturnal hypoxia severity[42]. In a small RCT, effective CPAP therapy was associated with a significant reduction in intima-media thickness over a period of <6 months[43]. With regard to the coronary arteries, OSA is associated with an increased burden of noncalcified and calcified coronary plaques, determined by coronary computed tomography angiography[44, 45]. Doubling of the AHI was associated with a 19% increase in coronary artery calcium in men aged <65 years, and a 17% increase of the same parameter in women of all ages[44]. It has been reported that SDB severity is significantly associated with coronary atherosclerotic burden severity (Gensini score), and reflected elevated troponin T as silent myocardial ischemia and minute myocardial injury, even in patients with stable CAD[46].

In a large observational cohort study, Marin *et al.* reported that untreated severe OSA was associated with a 3-fold increase in the relative risk of fatal CVD (stroke and myocardial infarction [MI]) and nonfatal CVD (MI, stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography), compared with patients without SDB[47]. CPAP 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[48].

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[2]. Inspiratory efforts in OSA against the occluded upper airway are associated with intrathoracic pressure oscillations that result in increased sympathetic activity[49]. 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[49]. 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[51], 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 bioresorbable 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 affecting 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 anti-hypertensive 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[71, 73]. 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, $P=0.026$)[71, 73].

With regard to patients with AF, CPAP is associated with a significantly decreased recurrence rate of AF, even after electrical cardioversion or catheter ablation[74-77]. 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[74-77]. A recent meta-analysis has revealed that OSA treated with CPAP after AF intervention has a reduced AF risk[78]. 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[79, 80]. Parra *et al.*[81] 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[2, 4, 29]. The positive intrathoracic pressure reduces venous return (preload) and LV transmural pressure (afterload), and may therefore benefit cardiac function in some patients[4]. 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[82]. Taken together, it seems that CPAP for OSA in patients with HF ameliorates LVEF, and possibly improves cardiovascular prognosis[83]. On the contrary, treatment of CSA or CSA-CSR in HF improves not only LV systolic[84-87] and diastolic function[88] but also pulmonary[82], renal[89, 90], and vascular functions[88, 91]; thus, it also potentially improves prognosis in patients with HF having reduced or preserved EF[4, 29, 82, 84-89, 92-94, 95] However, a recent RCT failed to demonstrate that treatment of CSA improves the prognosis of patients with HF having CSA[96].

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[24-26] 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 use[24-26]. Second, other treatments, including oral appliances[97] or upper airway stimulation devices[98], 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[99], and the meta-regression identified no association between follow-up time
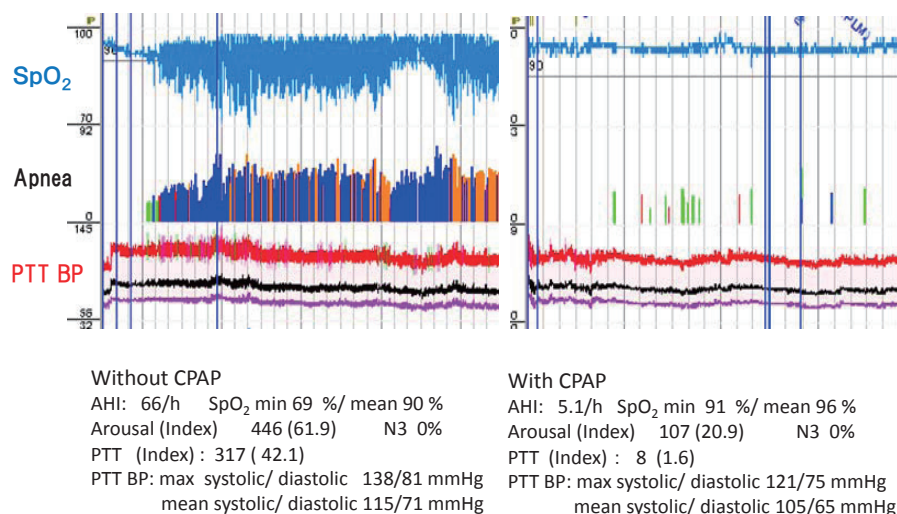
Fig. 6. Effect of CPAP on SDB and arterial blood pressure measured by the PTT method

Improvement of SDB by CPAP leads to decreased PTT-based blood pressure and PTT index. AHI, apnea hypopnea index; SpO2, oxygen saturation; REM, rapid eye movement.

and the HR of CPAP versus control in the contributing trials[24-26]. 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[100-103]. In addition, the use of continuous blood pressure measurement by using pulse transit time (PTT) has recently been reported[104, 105]. Arterial PTT was measured between the R-spike of the electrocardiogram and the plethysmographic curve of finger pulse-oximetry[104, 105]. 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[104, 105]. Comparing blood pressure measured using the PTT-based method and that measured using a cuff resulted in a significant correlation[104, 105]. 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[106] or HF[107, 108] 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.

References

1) Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K and Harrod CG: Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med, 2017; 13: 479-504
2) Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, Malhotra A, Martinez-Garcia MA, Mehra R, Pack AI, Polotsky VY, Redline S and Somers VK: Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardiol, 2017; 69: 841-858
3) Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T, American Heart Association Council for High Blood Pressure Research Professional Education Committee CoCC, American Heart Association Stroke C, American Heart Association Council on Cardiovascular N and American

College of Cardiology F: Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation, 2008; 118: 1080-1111

4) Pearse SG and Cowie MR: Sleep-disordered breathing in heart failure. Eur J Heart Fail, 2016; 18: 353-361

5) Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, Barbe F, Vicente E, Wei Y, Nieto FJ and Jelic S: Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA, 2012; 307: 2169-2176

6) Lavie L: Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited--the bad ugly and good: implications to the heart and brain. Sleep Med Rev, 2015; 20: 27-45

7) Phillips CL, McEwen BJ, Morel-Kopp MC, Yee BJ, Sullivan DR, Ward CM, Tofler GH and Grunstein RR: Effects of continuous positive airway pressure on coagulability in obstructive sleep apnoea: a randomised, placebo-controlled crossover study. Thorax, 2012; 67: 639-644

8) Maruyama K, Morishita E, Sekiya A, Omote M, Kadono T, Asakura H, Hashimoto M, Kobayashi M, Nakatsumi Y, Takada S and Ohtake S: Plasma levels of platelet-derived microparticles in patients with obstructive sleep apnea syndrome. J Atheroscler Thromb, 2012; 19: 98-104

9) Oga T, Chin K, Tabuchi A, Kawato M, Morimoto T, Takahashi K, Handa T, Takahashi K, Taniguchi R, Kondo H, Mishima M, Kita T and Horiuchi H: Effects of obstructive sleep apnea with intermittent hypoxia on platelet aggregability. J Atheroscler Thromb, 2009; 16: 862-869

10) Young T, Palta M, Dempsey J, Skatrud J, Weber S and Badr S: The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med, 1993; 328: 1230-1235

11) Peppard PE, Young T, Barnet JH, Palta M, Hagen EW and Hla KM: Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol, 2013; 177: 1006-1014

12) Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM and Wahl PW: The Sleep Heart Health Study: design, rationale, and methods. Sleep, 1997; 20: 1077-1085

13) Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A and Kales A: Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med, 2001; 163: 608-613

14) Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M and Haba-Rubio J: Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med, 2015; 3: 310-318

15) Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M and Young T: Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol, 2008; 52: 686-717

16) Pataka A and Riha RL: Continuous positive airway pressure and cardiovascular events in patients with obstructive sleep apnea. Curr Cardiol Rep, 2013; 15: 385

17) Pack AI and Gislason T: Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. Prog Cardiovasc Dis, 2009; 51: 434-451

18) Sundstrom J, Arima H, Jackson R, Turnbull F, Rahimi K, Chalmers J, Woodward M, Neal B and Blood Pressure Lowering Treatment Trialists C: Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann Intern Med, 2015; 162: 184-191

19) Aziz M, Ali SS, Das S, Younus A, Malik R, Latif MA, Humayun C, Anugula D, Abbas G, Salami J, Elizondo JV, Veledar E and Nasir K: Association of Subjective and Objective Sleep Duration as well as Sleep Quality with Non-Invasive Markers of Sub-Clinical Cardiovascular Disease (CVD): A Systematic Review. J Atheroscler Thromb, 2017; 24: 208-226

20) Arzt M, Hetzenecker A, Steiner S and Buchner S: Sleep-Disordered Breathing and Coronary Artery Disease. Can J Cardiol, 2015; 31: 909-917

21) Schwarz EI, Puhan MA, Schlatzer C, Stradling JR and Kohler M: Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis. Respirology, 2015; 20: 889-895

22) Feng Y, Zhang Z and Dong ZZ: Effects of continuous positive airway pressure therapy on glycaemic control, insulin sensitivity and body mass index in patients with obstructive sleep apnoea and type 2 diabetes: a systematic review and meta-analysis. NPJ Prim Care Respir Med, 2015; 25: 15005

23) Quan SF, Budhiraja R, Clarke DP, Goodwin JL, Gottlieb DJ, Nichols DA, Simon RD, Smith TW, Walsh JK and Kushida CA: Impact of treatment with continuous positive airway pressure (CPAP) on weight in obstructive sleep apnea. J Clin Sleep Med, 2013; 9: 989-993

24) Yu J, Zhou Z, McEvoy RD, Anderson CS, Rodgers A, Perkovic V and Neal B: Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis. JAMA, 2017; 318: 156-166

25) Khan SU, Duran CA, Rahman H, Lekkala M, Saleem MA and Kaluski E: A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea. Eur Heart J, 2018; 39: 2291-2297

26) Abuzaid AS, Al Ashry HS, Elbadawi A, Ld H, Saad M, Elgendy IY, Elgendy A, Mahmoud AN, Mentias A, Barakat A and Lal C: Meta-Analysis of Cardiovascular

Outcomes With Continuous Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea. Am J Cardiol, 2017; 120: 693-699

27) Blood Pressure Lowering Treatment Trialists C: Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet, 2014; 384: 591-598

28) Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM and American Academy of Sleep M: Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med, 2012; 8: 597-619

29) Yoshihisa A and Takeishi Y: Heart failure and sleep disordered breathing. Fukushima J Med Sci, 2017; 63: 32-38

30) Yumino D, Redolfi S, Ruttanaumpawan P, Su MC, Smith S, Newton GE, Mak S and Bradley TD: Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. Circulation, 2010; 121: 1598-1605

31) Javaheri S: A mechanism of central sleep apnea in patients with heart failure. N Engl J Med, 1999; 341: 949-954

32) Pinna GD, Robbi E, Pizza F, Taurino AE, Pronzato C, La Rovere MT and Maestri R: Can cardiorespiratory polygraphy replace portable polysomnography in the assessment of sleep-disordered breathing in heart failure patients? Sleep Breath, 2014; 18: 475-482

33) Guilleminault C, Connolly S, Winkle R, Melvin K and Tilkian A: Cyclical variation of the heart rate in sleep apnoea syndrome. Mechanisms, and usefulness of 24 h electrocardiography as a screening technique. Lancet, 1984; 1: 126-131

34) Shimizu T, Yoshihisa A, Iwaya S, Abe S, Sato T, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Cyclic variation in heart rate score by holter electrocardiogram as screening for sleep-disordered breathing in subjects with heart failure. Respir Care, 2015; 60: 72-80

35) Defaye P, de la Cruz I, Marti-Almor J, Villuendas R, Bru P, Senechal J, Tamisier R and Pepin JL: A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: the DREAM European study. Heart Rhythm, 2014; 11: 842-848

36) Budweiser S, Enderlein S, Jorres RA, Hitzl AP, Wieland WF, Pfeifer M and Arzt M: Sleep apnea is an independent correlate of erectile and sexual dysfunction. J Sex Med, 2009; 6: 3147-3157

37) Yoshihisa A, Owada T, Hoshino Y, Miyata M, Misaka T, Sato T, Suzuki S, Sakamoto N, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S, Ishibashi T and Takeishi Y: Flow-mediated dilatation identifies impaired endothelial function in patients with sleep apnea syndrome. Fukushima J Med Sci, 2010; 56: 115-120

38) Iguchi A, Yamakage H, Tochiya M, Muranaka K, Sasaki Y, Kono S, Shimatsu A and Satoh-Asahara N: Effects of weight reduction therapy on obstructive sleep apnea syndrome and arterial stiffness in patients with obesity and metabolic syndrome. J Atheroscler Thromb, 2013; 20: 807-820

39) Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH and Le Jemtel TH: Vascular inflammation in obesity and sleep apnea. Circulation, 2010; 121: 1014-1021

40) Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, Oda N, Okada S, Ohta S, Naito H and Adachi M: Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med, 2005; 172: 625-630

41) Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM and Lorenzi-Filho G: Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med, 2005; 172: 613-618

42) Ayas NT, Patel SR, Malhotra A, Schulzer M, Malhotra M, Jung D, Fleetham J and White DP: Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. Sleep, 2004; 27: 249-253

43) Hui DS, Shang Q, Ko FW, Ng SS, Szeto CC, Ngai J, Tung AH, To KW, Chan TO and Yu CM: A prospective cohort study of the long-term effects of CPAP on carotid artery intima-media thickness in obstructive sleep apnea syndrome. Respir Res, 2012; 13: 22

44) Weinreich G, Wessendorf TE, Erdmann T, Moebus S, Dragano N, Lehmann N, Stang A, Roggenbuck U, Bauer M, Jockel KH, Erbel R, Teschler H, Mohlenkamp S and Heinz Nixdorf Recall study g: Association of obstructive sleep apnoea with subclinical coronary atherosclerosis. Atherosclerosis, 2013; 231: 191-197

45) Kent BD, Garvey JF, Ryan S, Nolan G, Dodd JD and McNicholas WT: Severity of obstructive sleep apnoea predicts coronary artery plaque burden: a coronary computed tomographic angiography study. Eur Respir J, 2013; 42: 1263-1270

46) Inami T, Seino Y, Otsuka T, Yamamoto M, Kimata N, Murakami D, Takano M, Ohba T, Ibuki C and Mizuno K: Links between sleep disordered breathing, coronary atherosclerotic burden, and cardiac biomarkers in patients with stable coronary artery disease. J Cardiol, 2012; 60: 180-186

47) Marin JM, Carrizo SJ, Vicente E and Agusti AG: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet, 2005; 365: 1046-1053

48) Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M and Shahar E: Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation, 2010; 122: 352-360

49) Parati G, Lombardi C, Castagna F, Mattaliano P, Filardi PP, Agostoni P and Italian Society of Cardiology Working Group on Heart Failure m: Heart failure and sleep disorders. Nature reviews Cardiology, 2016; 13: 389-403

50) Hamilton GS, Meredith IT, Walker AM and Solin P: Obstructive sleep apnea leads to transient uncoupling of coronary blood flow and myocardial work in humans. Sleep, 2009; 32: 263-270

51) Hetzenecker A, Buchner S, Greimel T, Satzl A, Luchner A, Debl K, Husser O, Hamer OW, Fellner C, Riegger GAJ, Pfeifer M and Arzt M: Cardiac workload in patients with sleep-disordered breathing early after acute myocardial infarction. Chest, 2013; 143: 1294-1301

52) Buchner S, Satzl A, Debl K, Hetzenecker A, Luchner A, Husser O, Hamer OW, Poschenrieder F, Fellner C, Zeman F, Riegger GA, Pfeifer M and Arzt M: Impact of sleep-disordered breathing on myocardial salvage and infarct size in patients with acute myocardial infarction. Eur Heart J, 2014; 35: 192-199

53) Mazaki T, Kasai T, Yokoi H, Kuramitsu S, Yamaji K, Morinaga T, Masuda H, Shirai S and Ando K: Impact of Sleep-Disordered Breathing on Long-Term Outcomes in Patients With Acute Coronary Syndrome Who Have Undergone Primary Percutaneous Coronary Intervention. Journal of the American Heart Association, 2016; 5:

54) Lee CH, Sethi R, Li R, Ho HH, Hein T, Jim MH, Loo G, Koo CY, Gao XF, Chandra S, Yang XX, Furlan SF, Ge Z, Mundhekar A, Zhang WW, Uchoa CH, Kharwar RB, Chan PF, Chen SL, Chan MY, Richards AM, Tan HC, Ong TH, Roldan G, Tai BC, Drager LF and Zhang JJ: Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. Circulation, 2016; 133: 2008-2017

55) Ludka O, Stepanova R, Sert-Kuniyoshi F, Spinar J, Somers VK and Kara T: Differential likelihood of NSTEMI vs STEMI in patients with sleep apnea. Int J Cardiol, 2017; 248: 64-68

56) Kanno Y, Yoshihisa A, Watanabe S, Takiguchi M, Yokokawa T, Sato A, Miura S, Shimizu T, Nakamura Y, Abe S, Sato T, Suzuki S, Oikawa M, Saitoh S and Takeishi Y: Prognostic Significance of Insomnia in Heart Failure. Circ J, 2016; 80: 1571-1577

57) Yoshihisa A, Suzuki S, Kanno Y, Takiguchi M, Sato A, Miura S, Masuda A, Yokokawa T, Shimizu T, Nakamura Y, Yamauchi H, Owada T, Abe S, Sato T, Oikawa M, Saitoh S and Takeishi Y: Prognostic significance of periodic leg movements during sleep in failure patients. Int J Cardiol, 2016; 212: 11-13

58) Arzt M, Woehrle H, Oldenburg O, Graml A, Suling A, Erdmann E, Teschler H, Wegscheider K and Schla HFI: Prevalence and Predictors of Sleep-Disordered Breathing in Patients With Stable Chronic Heart Failure: The SchlaHF Registry. JACC Heart failure, 2016; 4:116-125

59) Spaak J, Egri ZJ, Kubo T, Yu E, Ando S, Kaneko Y, Usui K, Bradley TD and Floras JS: Muscle sympathetic nerve activity during wakefulness in heart failure patients with and without sleep apnea. Hypertension, 2005; 46: 1327-1332

60) Miyata M, Yoshihisa A, Yamauchi H, Owada T, Sato T, Suzuki S, Sugimoto K, Yamaki T, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Impact of sleep-disordered breathing on myocardial damage and metabolism in patients with chronic heart failure. Heart Vessels, 2015; 30: 318-324

61) Nakamura Y, Yoshihisa A, Takiguchi M, Shimizu T, Yamauchi H, Iwaya S, Owada T, Miyata M, Abe S, Sato T, Suzuki S, Oikawa M, Kobayashi A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and

Takeishi Y: High-sensitivity cardiac troponin T predicts non-cardiac mortality in heart failure. Circ J, 2014; 78: 890-895

62) Aimo A, Januzzi JL, Jr., Vergaro G, Ripoli A, Latini R, Masson S, Magnoli M, Anand IS, Cohn JN, Tavazzi L, Tognoni G, Gravning J, Ueland T, Nymo SH, Brunner-La Rocca HP, Bayes-Genis A, Lupon J, de Boer RA, Yoshihisa A, Takeishi Y, Egstrup M, Gustafsson I, Gaggin HK, Eggers KM, Huber K, Tentzeris I, Tang WHW, Grodin J, Passino C and Emdin M: Prognostic Value of High-Sensitivity Troponin T in Chronic Heart Failure: An Individual Patient Data Meta-Analysis. Circulation, 2018; 137: 286-297

63) Aimo A, Januzzi JL, Jr., Vergaro G, Ripoli A, Latini R, Masson S, Magnoli M, Anand IS, Cohn JN, Tavazzi L, Tognoni G, Gravning J, Ueland T, Nymo SH, Rocca HB, Bayes-Genis A, Lupon J, de Boer RA, Yoshihisa A, Takeishi Y, Egstrup M, Gustafsson I, Gaggin HK, Eggers KM, Huber K, Tentzeris I, Wilson Tang WH, Grodin JL, Passino C and Emdin M: High-sensitivity troponin T, NT-proBNP and glomerular filtration rate: A multimarker strategy for risk stratification in chronic heart failure. Int J Cardiol, 2019; 277: 166-172

64) Yamada S, Suzuki H, Kamioka M, Suzuki S, Kamiyama Y, Yoshihisa A, Saitoh S and Takeishi Y: Sleep-disordered breathing increases risk for fatal ventricular arrhythmias in patients with chronic heart failure. Circ J, 2013; 77: 1466-1473

65) Yoshihisa A, Suzuki S, Takiguchi M, Shimizu T, Abe S, Sato T, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Impact of sleep-disordered breathing on heart rate turbulence in heart failure patients. PLoS One, 2014; 9: e101307

66) Yamada S, Yoshihisa A, Sato Y, Sato T, Kamioka M, Kaneshiro T, Oikawa M, Kobayashi A, Suzuki H, Ishida T and Takeishi Y: Utility of heart rate turbulence and T-wave alternans to assess risk for readmission and cardiac death in hospitalized heart failure patients. J Cardiovasc Electrophysiol, 2018; 29: 1257-1264

67) Sin DD, Logan AG, Fitzgerald FS, Liu PP and Bradley TD: Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation, 2000; 102: 61-66

68) Bitter T, Westerheide N, Prinz C, Hossain MS, Vogt J, Langer C, Horstkotte D and Oldenburg O: Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. Eur Heart J, 2011; 32: 61-74

69) Javaheri S, Shukla R, Zeigler H and Wexler L: Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol, 2007; 49: 2028-2034

70) Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, Ruttanaumpawan P, Tomlinson G and Bradley TD: Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol, 2007; 49: 1625-1631

71) Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, Martinez-Alonso M, Carmona C, Barcelo A, Chiner E, Masa JF, Gonzalez M, Marin JM, Garcia-Rio F, Diaz de Atauri J, Teran J, Mayos M, de la Pena M, Monasterio C, del Campo F, Montserrat JM, Spanish S and Breathing N: Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in non-sleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA, 2012; 307: 2161-2168

72) McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS, Investigators S and Coordinators: CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med, 2016; 375: 919-931

73) Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J and Thunstrom E: Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. Am J Respir Crit Care Med, 2016; 194: 613-620

74) Neilan TG, Farhad H, Dodson JA, Shah RV, Abbasi SA, Bakker JP, Michaud GF, van der Geest R, Blankstein R, Steigner M, John RM, Jerosch-Herold M, Malhotra A and Kwong RY: Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. Journal of the American Heart Association, 2013; 2: e000421

75) Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, Kramer DB, Zimetbaum PJ, Buxton AE, Josephson ME and Anter E: Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol, 2013; 62: 300-305

76) Naruse Y, Tada H, Satoh M, Yanagihara M, Tsuneoka H, Hirata Y, Ito Y, Kuroki K, Machino T, Yamasaki H, Igarashi M, Sekiguchi Y, Sato A and Aonuma K: Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm, 2013; 10: 331-337

77) Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, Hylek EM, Mahaffey KW, Freeman JV, Chang P, Holmes DN, Peterson ED, Piccini JP, Gersh BJ and Investigators O-A: Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J, 2015; 169: 647-654 e642

78) Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, Soliman EZ and Al-Mallah MH: Meta-Analysis of Continuous Positive Airway Pressure as a Therapy of Atrial Fibrillation in Obstructive Sleep Apnea. Am J Cardiol, 2015; 116: 1767-1773

79) Lyons OD and Ryan CM: Sleep Apnea and Stroke. Can J Cardiol, 2015; 31: 918-927

80) Kim Y, Koo YS, Lee HY and Lee SY: Can Continuous Positive Airway Pressure Reduce the Risk of Stroke in Obstructive Sleep Apnea Patients? A Systematic Review and Meta-Analysis. PLoS One, 2016; 11: e0146317

81) Parra O, Sanchez-Armengol A, Bonnin M, Arboix A, Campos-Rodriguez F, Perez-Ronchel J, Duran-Cantolla J, de la Torre G, Gonzalez Marcos JR, de la Pena M, Carmen Jimenez M, Masa F, Casado I, Luz Alonso M and Macarron JL: Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. Eur Respir J, 2011; 37: 1128-1136

82) Yoshihisa A, Suzuki S, Yamauchi H, Sato T, Oikawa M, Kobayashi A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Beneficial Effects of Positive Airway Pressure Therapy for Sleep-Disordered Breathing in Heart Failure Patients With Preserved Left Ventricular Ejection Fraction. Clin Cardiol, 2015; 38: 413-421

83) Kasai T: Sleep apnea and heart failure. J Cardiol, 2012; 60: 78-85

84) Bradley TD, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS and Investigators C: Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med, 2005; 353: 2025-2033

85) Suzuki S, Yoshihisa A, Miyata M, Sato T, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Adaptive servo-ventilation therapy improves long-term prognosis in heart failure patients with anemia and sleep-disordered breathing. Int Heart J, 2014; 55: 342-349

86) Yoshihisa A, Shimizu T, Owada T, Nakamura Y, Iwaya S, Yamauchi H, Miyata M, Hoshino Y, Sato T, Suzuki S, Sugimoto K, Yamaki T, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Adaptive servo ventilation improves cardiac dysfunction and prognosis in chronic heart failure patients with Cheyne-Stokes respiration. Int Heart J, 2011; 52: 218-223

87) Miyata M, Yoshihisa A, Suzuki S, Yamada S, Kamioka M, Kamiyama Y, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Adaptive servo ventilation improves Cheyne-Stokes respiration, cardiac function, and prognosis in chronic heart failure patients with cardiac resynchronization therapy. J Cardiol, 2012; 60: 222-227

88) Yoshihisa A, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. Eur J Heart Fail, 2013; 15: 543-550

89) Owada T, Yoshihisa A, Yamauchi H, Iwaya S, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Adaptive servoventilation improves cardiorenal function and prognosis in heart failure patients with chronic kidney disease and sleep-disordered breathing. J Card Fail, 2013; 19: 225-232

90) Yoshihisa A, Suzuki S, Owada T, Iwaya S, Yamauchi H, Miyata M, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Short-term use of adaptive servo ventilation improves renal function in heart failure patients with sleep-disordered breathing.

Heart Vessels, 2013; 28: 728-734

91) Suzuki S, Yoshihisa A, Sato Y, Watanabe S, Yokokawa T, Sato T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Nakazato K, Suzuki H, Saitoh SI, Ishida T and Takeishi Y: Association between sleep-disordered breathing and arterial stiffness in heart failure patients with reduced or preserved ejection fraction. ESC Heart Fail, 2018; 5: 284-291

92) Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Ryan C, Tomlinson G, Bradley TD and Investigators C: Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation, 2007; 115: 3173-3180

93) Sharma BK, Bakker JP, McSharry DG, Desai AS, Javaheri S and Malhotra A: Adaptive servoventilation for treatment of sleep-disordered breathing in heart failure: a systematic review and meta-analysis. Chest, 2012; 142: 1211-1221

94) Iwaya S, Yoshihisa A, Nodera M, Owada T, Yamada S, Sato T, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Suppressive effects of adaptive servo-ventilation on ventricular premature complexes with attenuation of sympathetic nervous activity in heart failure patients with sleep-disordered breathing. Heart Vessels, 2014; 29: 470-477

95) Yoshida M, Ando SI, Kodama K, Ebihara K, Tanaka K, Hayashi A, Taguchi E, Kadokami T, Nakao K and Sakamoto T: Adaptive servo-ventilation therapy reduces hospitalization rate in patients with severe heart failure. Int J Cardiol, 2017; 238: 173-176

96) Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F and Teschler H: Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med, 2015; 373: 1095-1105

97) Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM and Chervin RD: Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med, 2015; 11: 773-827

98) Strollo PJ, Jr., Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP and Group ST: Upper-airway stimulation for obstructive sleep apnea. N Engl J Med, 2014; 370: 139-149

99) Parra O, Sanchez-Armengol A, Capote F, Bonnin M, Arboix A, Campos-Rodriguez F, Perez-Ronchel J, Duran-Cantolla J, Martinez-Null C, de la Pena M, Jimenez MC, Masa F, Casadon I, Alonso ML and Macarron JL: Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. J Sleep Res, 2015; 24: 47-53

100) Sawatari H, Chishaki A, Nishizaka M, Tokunou T, Adachi S, Yoshimura C, Ohkusa T and Ando S: Cumulative Hypoxemia During Sleep Predicts Vascular Endothelial Dysfunction in Patients With Sleep-Disordered Breathing. Am J Hypertens, 2016; 29: 458-463

101) Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, Ancoli-Israel S, Ensrud K, Purcell S, White DP, Redline S and Wellman A: The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. Eur Heart J, 2018;

102) Oldenburg O, Wellmann B, Buchholz A, Bitter T, Fox H, Thiem U, Horstkotte D and Wegscheider K: Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. Eur Heart J, 2016; 37: 1695-1703

103) Yamaguchi T, Takata Y, Usui Y, Asanuma R, Nishihata Y, Kato K, Shiina K and Yamashina A: Nocturnal Intermittent Hypoxia Is Associated With Left Ventricular Hypertrophy in Middle-Aged Men With Hypertension and Obstructive Sleep Apnea. Am J Hypertens, 2016; 29: 372-378

104) Gehring J, Gesche H, Drewniok G, Kuchler G and Patzak A: Nocturnal blood pressure fluctuations measured by using pulse transit time in patients with severe obstructive sleep apnea syndrome. Sleep Breath, 2018; 22: 337-343

105) Gesche H, Grosskurth D, Kuchler G and Patzak A: Continuous blood pressure measurement by using the pulse transit time: comparison to a cuff-based method. Eur J Appl Physiol, 2012; 112: 309-315

106) Esquinas C, Sanchez-de-la Torre M, Aldoma A, Flores M, Martinez M, Barcelo A, Barbe F and Spanish Sleep N: Rationale and methodology of the impact of continuous positive airway pressure on patients with ACS and nonsleepy OSA: the ISAACC Trial. Clin Cardiol, 2013; 36: 495-501

107) Lyons OD, Floras JS, Logan AG, Beanlands R, Cantolla JD, Fitzpatrick M, Fleetham J, John Kimoff R, Leung RS, Lorenzi Filho G, Mayer P, Mielniczuk L, Morrison DL, Ryan CM, Series F, Tomlinson GA, Woo A, Arzt M, Parthasarathy S, Redolfi S, Kasai T, Parati G, Delgado DH, Bradley TD and Investigators A-H: Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. Eur J Heart Fail, 2017; 19: 579-587

108) Haruki N and Floras JS: Sleep-Disordered Breathing in Heart Failure- A Therapeutic Dilemma. Circ J, 2017; 81: 903-912