



Heart failure and sleep disordered breathing

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[Review]

Heart failure and sleep disordered breathing

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Abstract

Sleep-disordered breathing (SDB) is frequently observed in patients with heart failure (HF), and complex pathologic conditions exist between both conditions. In this review article, we describe the characteristics of SDB complicated with HF, the prognostic impact of SDB in HF patients, and the favorable effects of positive airway pressure in HF patients with SDB.

Key words : Sleep-disordered breathing (SDB), heart failure, continuous positive airway pressure (CPAP), adaptive servo-ventilation (ASV)

Introduction

Heart failure (HF) is a systemic disease with a devastating prognosis, and affects many of the organ systems. In HF patients, sleep-disordered breathing (SDB) is a frequent co-morbidity and its prevalence is related to the severity of the clinical status¹⁻⁴. Over 50% of patients with HF (with either preserved or reduced ejection fraction [EF]) have SDB, which is around 10 times the rate in the general population². In current clinical practice, SDB remains undiagnosed in many HF patients. Older age, male gender, increased body mass index, lower EF, and the presence of atrial fibrillation are independent predictors for the presence of SDB³. Referring to recent articles¹⁻⁴, and adding our findings, we describe the characteristics of SDB complicated with HF, the prognostic impact of SDB in HF patients, and the favorable effects of positive airway pressure in HF patients with SDB.

Definition and classification of SDB

Polysomnography including the assessment of the electroencephalogram, electrooculogram, electrocardiogram, electromyogram, nasal and oral airflows, respiratory movement (thoracic and abdominal respiratory effort), snoring oxygen saturation, body position, and sleep stage, has long been considered the gold standard test for SDB (Figure 1). An

apnea is the absence of inspiratory airflow for at least 10 sec. A hypopnea is a lesser decrease in airflow, lasting 10 sec or longer, and associated with a drop in arterial oxygen saturation and/or an electroencephalographic arousal¹⁻⁴. Apnea and hypopnea are classified as obstructive or central, but in either case, they result from an absence or reduction of breathing command of brainstem to upper airway muscles (e.g., genioglossus) and/or lower thoracic inspiratory pump muscles (diaphragm and intercostal muscles)^{1,5}. SDB includes obstructive sleep apnea (OSA), central sleep apnea (CSA) with Cheyne-Stokes respiration (CSR), or a combination of both. The pattern of neural output determines the phenotype. OSA is characterized by cessation or marked reduction of the airflow in the presence of respiratory effort (Figure 1). OSA occurs when complete upper airway occlusion occurs (absent airflow, tongue falling back, regardless of activity of the inspiratory thoracic pump muscles. In OSA, there is collapse of the pharynx during sleep with consequent upper airway obstruction, often with snoring. Predisposing factors include obesity, a short neck, and retrognathism. In contrast, CSA is characterized by cessation of both airflow and respiratory effort during sleep (Figure 2). CSA occurs when there is a transient reduction by the pontomedullary pacemaker in the generation of breathing rhythm, usually reflecting changes in the partial pressure of CO₂, which can fall below the apnea threshold¹.

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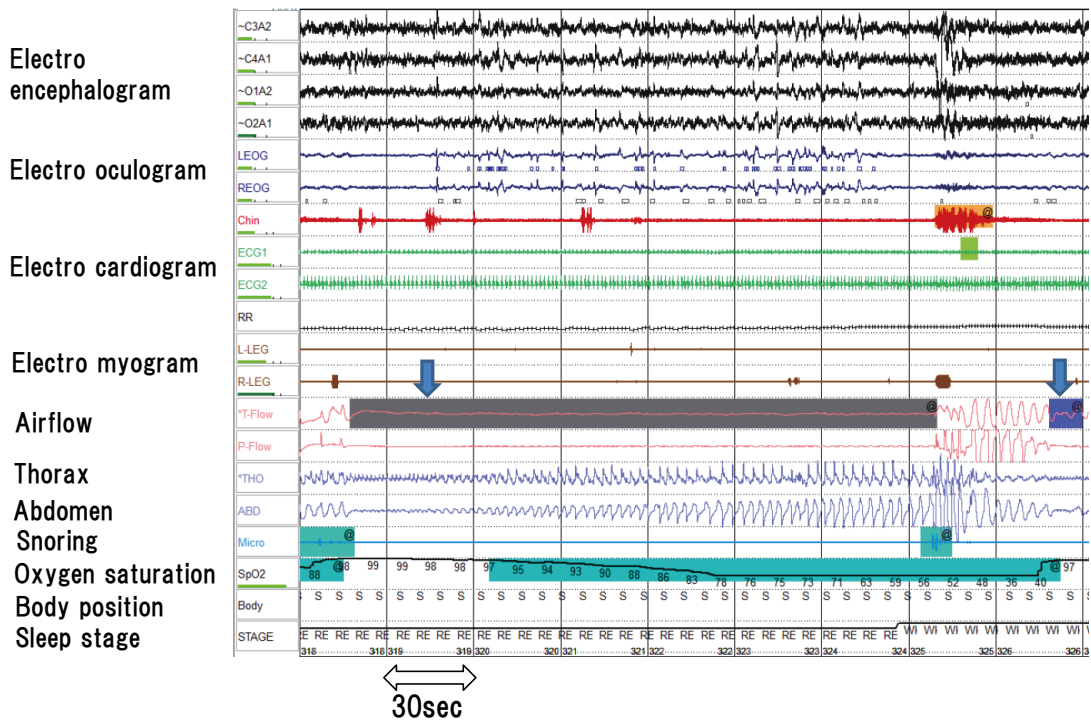


Fig. 1. Obstructive sleep apnea
 Obstructive sleep apnea (downward arrow) is characterized by cessation or marked reduction of the airflow (airflow band) in the presence of respiratory effort (thorax and abdomen band).

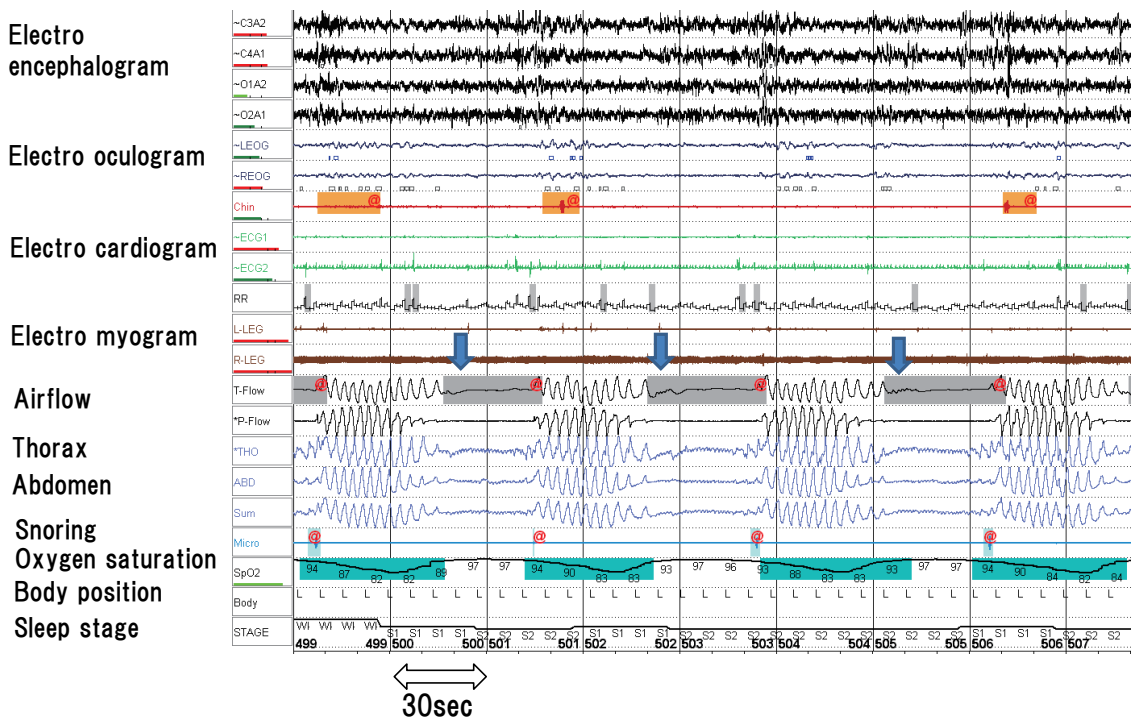


Fig. 2. Central sleep apnea
 Central sleep apnea (downward arrow) is characterized by cessation of both airflow (airflow band) and respiratory effort (thorax and abdomen band) during sleep. Cheyne-Stokes respiration is recognized as increasing and decreasing gradually repeated respiratory pattern.

CSR is one type of CSA, and is recognized as a repeated respiratory pattern of gradually increasing and decreasing ventilatory volume.

In HF, rostral fluid shift during sleep leads to pharyngeal edema, which may exacerbate the tendency to obstruct⁶. 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 brain stem and carotid bodies, which trigger an increase in respiratory drive in response to a rise in arterial carbon dioxide (PaCO₂), thus maintaining PaCO₂ within a narrow range^{2,6}. Patients with HF and CSA tend to have an exaggerated respiratory response to carbon dioxide associated with excess sympathetic nervous activity, and so that a modest rise in PaCO₂ that may occur during sleep results in inappropriate hyperventilation^{2,7,8}. This drives the PaCO₂ below the 'apneic threshold', at which point the neural drive to respire is too low to stimulate effective inspiration, and an apnea or hypopnea ensues.

Whilst polysomnography provides comprehensive data, it is expensive, laborious, and not available in all centers. A more limited, multichannel sleep polygraphy (with oxygen saturation, nasal airflow, and chest and abdominal movement recording capability) is more widely available and can 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^{2,9,10}. Because of the lack of subjects' and physicians' awareness of SDB, especially in subjects with HF, and limited access to a portable sleep monitor or overnight polysomnography, the majority of SDB subjects remain undiagnosed. SDB is associated with an altered sympathovagal balance determined by the nocturnal cyclic alternating of apneas and hyperventilation-bradycardia during apnea, followed by abrupt tachycardia¹¹. This phenomenon causes cyclic variation in heart rate¹¹. Not only OSA but also CSA-CSA demonstrated heart rate oscillations¹². Both types of SDB present cyclic lengthening/shortening in the R-R interval, during apnea-post apneic hyperventilation¹³. We previously reported that cyclic variation of heart rate score (CVHRS) determined by Holter electrocardiogram is a useful screening index for severe SDB in HF subjects¹⁴. In that study, there was a significant positive correlation between CVHRS and apnea hypopnea index, which is a primary index of SDB ($R=0.60$, $P<0.001$)¹⁴. In addition, the receiver operating curve analysis revealed that CVHRS (a

cut off value of 30/h) identified severe SDB with a sensitivity of 82%, specificity of 77%, and area under the curve of 0.83 (95% confidence interval 0.72–0.93)¹⁴. Pacemaker algorithms were recently developed to detect and quantify SDB accurately¹⁵. It is now 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 thoracic impedance, with the inverse occurring on expiration, with consequent proportional changes in detected potential difference. It has been recently reported that intrathoracic impedance has a sensitivity of 88.9% and specificity of 84.6% for the diagnosis of moderate to severe SDB¹⁵.

Impact of SDB in HF patients

Inspiratory efforts in OSA against the occluded upper airway are associated with intrathoracic pressure oscillations that result in increased sympathetic activity^{4,16}. The hypoxia, hypercapnia, and arousal from sleep that occur at the end of the OSA further increase sympathetic activity. The post-apneic period is when a patient recovers upper airway patency and is often characterized by marked increases in blood pressure and heart rate^{4,17}. Importantly, the adverse cardiovascular consequences of OSA are not confined to sleep. Indeed, increased daytime sympathetic nervous activity and arterial hypertension are also reported to occur in OSA patients. OSA may accelerate the progression of HF in several ways. The negative intrathoracic pressure generated by the respiratory muscles trying to inspire against the closed airway increases venous return to the right heart; thus, increasing pre-load and causing the septum to shift to the left, which may compromise left ventricular (LV) function²⁻⁴. The ability of the failing left ventricle to cope with enhanced preload is further impaired by the increased transmural pressure during episodes of negative intrathoracic pressure, which in turn increases the afterload. Apnea and hypopnea activate the sympathetic nervous system, and levels of circulating catecholamines and muscle sympathetic nervous activity are higher in those with SDB and HF than HF without SDB^{2,8,18}. These factors accompanied with inflammatory mediators cause hypertension, arrhythmia, coronary arterial disease, myocardial dysfunction and HF⁴. We have previously reported that 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 levels¹⁹). 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^{20,21}. It still remains unclear whether CSA-CSR is merely a marker of the severity of HF, or an important risk factor that independently worsens the prognosis of HF patients, and whether treatment of CSA-CSR is useful in HF patients. When multivariate analyses were performed to control for potential confounders involved in determining outcome in patients with HF, CSA was an independent factor for death or cardiac transplantation in these patients^{4,22,23}. Some large-scale studies have demonstrated that SDB is associated with occurrence of ventricular arrhythmias^{20,24} and adverse prognosis in HF patients^{25,26}.

Treatment of OSA in HF patients

Continuous positive airway pressure (CPAP) is widely established in clinical guidelines for the treatment of symptomatic OSA in the non-HF population⁵. CPAP provides continuous pressure throughout the respiratory cycle. The resultant positive pressure prevents the pharynx from collapsing and thus improves apnea and hypopnea (Figure

3). It may have additional benefits in HF, as positive end-expiratory pressure prevents alveoli collapsing secondary to pulmonary edema and maintains alveoli at a greater diameter, thus reducing the work of breathing (Figure 3). It also increases alveolar recruitment, improves gas exchange, and reduces right to left intrapulmonary shunting of blood^{1,2}. The positive intrathoracic pressure reduces venous return (preload) and LV transmural pressure (afterload), and may therefore benefit cardiac function in some patients². In the current study, CPAP caused abolition of negative intrathoracic pressure swings and reductions in nocturnal blood pressure, which caused a dramatic reduction in LV afterload that was accompanied by a decrease in heart rate. We reported that CPAP improves right ventricular systolic function, pulmonary function and exercise capacity, resulting in reduction in all-cause mortality in HF patients with preserved EF²⁷.

Treatment of CSA in HF patients

The optimal management of CSA in HF is less well determined than that of OSA. Standard therapy of HF such as diuretics²⁸, beta-blockers²⁹, and cardiac resynchronization therapy³⁰ improves CSA

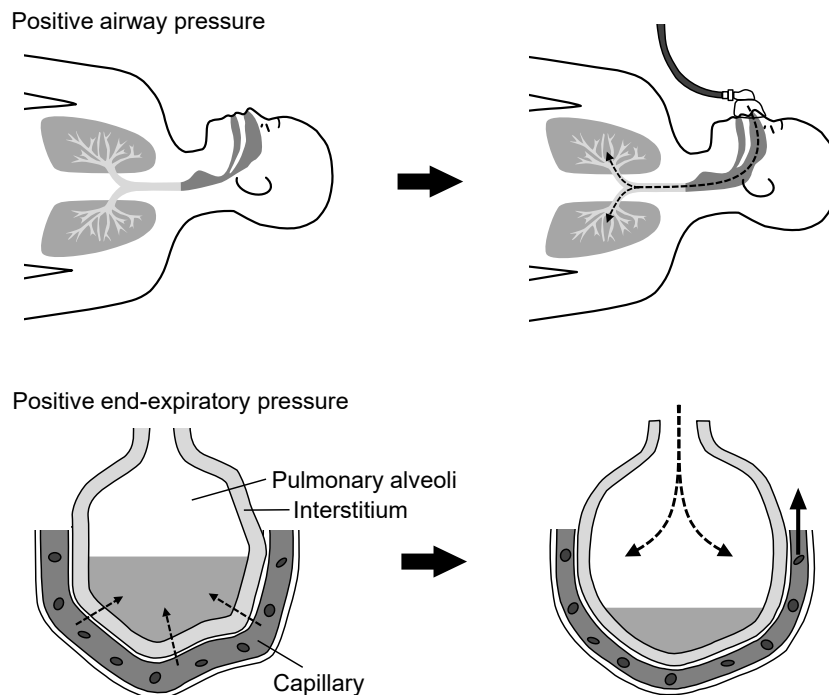


Fig. 3. Effect of positive airway pressure

Upper panels : Positive airway pressure widens an upper airway and pulmonary alveoli.

Lower panels : Positive end-expiratory pressure expands pulmonary alveoli, decreases pulmonary fluid and improves congestion and gas exchange in patients with heart failure.

in HF patients. Therefore, standard HF therapy is performed prior to specific CSA therapy in HF. Nocturnal oxygen therapy has been shown to reduce sympathetic drive and increase nocturnal oxygen saturation in HF patients with CSA³¹. Oxygen therapy improves not only CSA, but also attenuates sympathetic nervous activity and ongoing myocardial damage³², and improve LVEF at least up to 12 weeks³³. Nasal CPAP treatment showed an improvement in the CSA, an increase in LVEF and nocturnal oxygen saturation, a reduction in the plasma levels of norepinephrine, and an improved 6-min walking distance compared with the placebo group³⁴. Unfortunately, no improvement was found in the overall death and heart transplantation rates between the two groups. However, a post-hoc analysis showed a decrease in mortality in patients in whom CPAP therapy resulted in improvement of CSA³⁵. Interestingly, the responder group (CPAP-CSA-suppressed) had a significant increase in LVEF at 3 months, and had a higher transplantation-free survival than the control subjects³⁵. No differences in any of these variables were found in the non-responder group (CPAP-CSA-unsuppressed)³⁵. Therefore, suppression of CSA has been focused upon. Technological progress has led to the development of devices for adaptive servo ventilation (ASV), which provide varying amounts of ventilatory pressure support against a background of low-level CPAP³⁶. Several studies suggest that ASV is more effective than CPAP, bi-level pressure support ventilation, or increased dead space in alleviating CSA³⁶⁻³⁹. We demonstrated that ASV improves not only left ventricular systolic⁴⁰⁻⁴² and diastolic function⁴³, but also pulmonary function²⁷, renal function⁴⁴, vascular function⁴³, as well as prognosis in HF patients with reduced or preserved EF^{27,40-44}. Recent meta-analyses on ASV in HF patients with CSA suggested an overall improvement in CSA, as well as improvements in LVEF, diastolic dimensions and function, 6-min walk test distance, plasma natriuretic peptide concentration, and sympathetic activity^{2,45}. However, a recent randomized trial failed to demonstrate that ASV improves prognosis of HF patients with CSA⁴⁶. Further studies are needed to determine whether managing SDB improves prognosis of HF patients.

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