Review

Treatment of Cheyne–Stokes respiration—central sleep apnea in patients with heart failure

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Central sleep apnea; Cheyne–Stokes respiration; Oxygen therapy; Continuous positive airway pressure; Adaptive servo-ventilation

Summary  Sleep disordered breathing including obstructive sleep apnea (OSA) and central sleep apnea (CSA) with Cheyne–Stokes respiration (CSR) is often accompanied by heart failure. Treatment of OSA centered on continuous positive airway pressure (CPAP) is established. However, treatment of CSR-CSA is still controversial. Since CSR-CSA occurs as a consequence of heart failure, optimization of heart failure is essential to treat CSR-CSA. For treatment directed at CSR-CSA itself, a variety of treatment approaches including night oxygen therapy and non-invasive positive pressure ventilation have been applied. Among them, night oxygen therapy improves patients’ symptoms, quality of life (QOL), and left ventricular function, but had yet been shown to improve clinical outcome. For CPAP, there are responders and non-responders and for responders CPAP can also improve survival. Adaptive servo-ventilation (ASV), which most effectively treats CSR-CSA, improves exercise capacity, QOL, and cardiac function. Recent reports suggested ASV may also prevent cardiac events in patients with heart failure. However, further studies are needed to conclude that this treatment improves patient survival.

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Introduction

Recent advances in management of heart failure have greatly improved prognosis of patients with this syndrome. However, the mortality rate of heart failure is still not low. Among Japanese patients with heart failure, the annual mortality rate is 7–8% [1,2]. It is known that sleep disordered breathing is often complicated with heart failure.

There are two types of sleep apnea, obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA is a common disease and its prevalence is high in the normal population. OSA occurs due to obstruction of upper airway and closely related life style such as overweight, smoking, and alcohol drinking. OSA is associated with many cardiovascular diseases including hypertension, coronary heart disease, arrhythmia, aortic dissection pulmonary hypertension, and heart failure.

On the other hand CSA is due to loss of respiratory drive from the respiratory center and is rare among the general population. While on the other hand, among a variety of cardiovascular diseases, heart failure is the only one which often accompanies CSA. CSA in the cardiovascular field, shares a common mechanism with Cheyne-Stoke respiration, a weaning and waxing periodical breathing which is observed also during waking in patients with heart failure. Therefore, CSA and CSR are usually combined as CSR-CSA. CSR-CSA occurs as a consequence of heart failure. Either type of sleep disordered breathing worsens the prognosis of patients with heart failure [3,4]. However, the relationship to heart failure is different between OSA and CSA. OSA locates upstream of heart failure, and is important as a risk factor for cardiovascular disease. On the other hand, CSR-CSA locates downstream of heart failure and it plays an important role in the progression of heart failure. Yumino et al. compared background of OSA and CSR-CSA, and reported that patients with CSA are older, thinner, had lower EF, and more severe New York Heart Association (NYHA) class [5]. Bitter et al. reported that in patients with diastolic dysfunction with an increasing impairment of diastolic function the proportion of sleep disordered breathing, and CSA in particular, increased [6]. Thus CSA is accompanied with more severe heart failure. This coincides with the fact that CSA occurs as a consequence of heart failure, while OSA can impair myocardial contractility and cause development and progression of heart failure [7]. Treatment of OSA centering on continuous positive airway pressure (CPAP) is established. However, treatment of CSR-CSA has not been established yet.

In this article, treatment of CSR-CSA will be the focus.

Mechanism of CSR-CSA in heart failure

In patients with heart failure, pulmonary congestion occurs. Pulmonary congestion leads to hyperventilation through pulmonary vagal reflex. Hypoxemia with pulmonary congestion or pulmonary edema also exacerbates hyperventilation. As a result of hyperventilation, hypocapnea is induced. Chemoreceptors detect hypocapnea and suppress neuronal drive from the respiratory center. In normal subjects, this feedback mechanism normalizes hypocapnea and respiration is stabilized. However, in patients with heart failure, the chemoreceptor response is enhanced because of elevated sympathetic tone and excessive respiratory suppression due to over correction by the chemoreceptor, which brings about apnea. Once respiration ceases, blood carbon dioxide is increased and hyperventilation occurs again, thus hyperventilation and apnea/hypopnea are repeated.

Prolonged circulation time due to low cardiac output in heart failure also contributes to the development of CSR-CSA. Delivery of information of blood gases such as blood CO₂ and O₂ to the chemoreceptor is delayed due to prolonged circulation time and this in turn delays feedback input to the respiratory center.

Recently, Yumino et al. demonstrated that nocturnal rostral fluid shift is also contributing to the pathogenesis of CSA as well as OSA in patients with heart failure [8]. This fluid shift is also important as a trigger and maintaining factor of CSR-CSA.

Treatment of CSA

There are reported to be many treatment approaches to CSR-CSA, including optimization of heart failure treatment, night oxygen therapy, positive pressure ventilation, etc. (Table 1, Fig. 1).

Treatment of heart failure seems to be most important in the treatment of CSR-CSA. Since CSR-CSA occurs as a result of heart failure, it is essential to optimize treatment of heart failure itself first of all. Especially, beta-blockers improve CSR-CSA as well as heart failure itself. Tamura et al. reported induction of beta-blocker, carvedilol, improves

| Table 1 | Treatment of Cheyne–Stokes respiration—central sleep apnea with heart failure. |
|-----------------------------------------------|
| 1. Evidence based treatment of heart failure  |
| 2. Continuous positive airway pressure        |
| 3. Non-invasive positive pressure ventilation (adaptive servo-ventilation, bi-level-positive airway pressure) |
| 4. Night oxygen inhalation                     |
| 5. Carbon dioxide inhalation                   |
| 6. Theophylline                               |
| 7. Acetazolamide                              |
| 8. Phrenic nerve stimulation                   |
| 9. Atrial overdrive pacing                     |
Figure 1  Algorithm for the treatment of sleep disordered breathing in patients with heart failure. HF, heart failure; SDB, sleep disordered breathing; OSA, obstructive sleep apnea; CSR-CSA, Cheyne—Stokes respiration—central sleep apnea; PSG, polysomnography; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; ASV, adaptive servo-ventilation; PAP, positive airway pressure; HOT, home oxygen therapy.

CSR-CSA but not OSA in patients with heart failure due to left ventricular (LV) systolic dysfunction.

Diuretics could also improve CSR-CSA by alleviating pulmonary congestion which is the initial event of the sequence from heart failure to CSR-CSA. Acetazolamide, is reported to improve CSR-CSA in patients with CSR-CSA. The mechanism of the effect of acetazolamide is firstly its respiratory stimulating effect and secondly its diuretic effect. However acetazolamide is not a first-line diuretic for the treatment of heart failure. Furosemide is the most widely used diuretic for the treatment of heart failure. However, so far there is no report which demonstrated that furosemide improves CSR-CSA, although it improved OSA [9]. In patients with heart failure, body fluid shifts to upper body while patient is sleeping at night. This fluid shift may contribute to the development of CSA by enhancing pulmonary congestion, a trigger of the sequence of CSR-CSA as well as OSA by increasing airway edema (nocturnal rostral fluid shift is a unifying concept for the pathogenesis of OSA and CSA in men with heart failure) [8]. Therefore normalization of fluid status with diuretics in patients with heart failure is essential.

Theophylline

Theophylline stimulates respiration by competing with adenosine, a respiratory depressant and improves sleep disordered breathing, although the entire mechanism through which this drug improves sleep apnea is not fully understood.

Many years ago, Javaheri reported the short-term effect of theophylline on CSR-CSA [10]. This effect of theophylline was attested by Hu et al. in an Asian population with heart failure [11]. Theophylline also has a positive inotropic effect through phosphodiesterase III inhibitory action. However, every drug which has positive inotropic effects including phosphodiesterase inhibitors has a negative impact on mortality in patients with chronic heart failure due to depressed LV dysfunction. Thus theophylline is not recommended for patients with heart failure especially due to LV systolic dysfunction.

Non-pharmacological treatment of heart failure

Non-pharmacological treatment of heart failure also improves CSR-CSA. In 2004, Sinha et al. reported that resynchronization brought a significant decrease in apnea-hypopnea index (AHI) and sleep quality index (10.4 ± 1.6 to 3.9 ± 2.4, p < 0.001) without CSR and a significant increase in SaO2 min (84 ± 5% to 89 ± 2%, p < 0.001) in 14 patients with CSR-CSA, while there was no significant change in AHI, and
SaO2 min in patients without CSA [12]. This finding is supported by a recent meta-analysis [13]. In this meta-analysis, 170 patients from six manuscripts and three abstracts were included. After treatment with cardiac resynchronization therapy, a significant reduction in AHI was found in patients with CSA with a mean reduction of $-13.05 (CI -16.74 to -9.36; p < 0.00001)$ but not in patients with OSA.

**Atrial overdrive pacing**

In 2002, Garrigue reported that atrial pacing improves CSR-CSA as well as OSA [14] in patients with pacemaker implantation because of the treatment of bradycardia. Meta-analysis also showed that overdrive atrial pacing reduces AHI in patients with predominantly CSA [15]. However, the additional effect of atrial overdrive pacing on CSR-CSA in patients with heart failure was only small [16]. Thus atrial overdrive pacing should not be applied simply to treat CSR-CSA.

**Home oxygen therapy**

Originally in 1989, Hanly et al. reported that the acute effect of nocturnal oxygen therapy on CSR corrects hypoxemia, and consolidates sleep by reducing arousals caused by the hypopneic phase of CSR [17]. A decade after the first report by Hanly, Javaheri also reported that oxygen inhalation acutely improved CSR in patients with heart failure and this effect of oxygen, however, may be modulated by the level of arterial PCO2 [18]. However in these studies the effects of oxygen inhalation to indexes of heart failure, including ejection fraction and NYHA class were not evaluated. In 1996, Andreas et al. demonstrated that successful treatment of CSR with nocturnal nasal oxygen improves not only sleep, but also exercise tolerance and cognitive function in patients with congestive heart failure [19]. More recently, three randomized studies were presented from Japan [20,21]. In the short-term study by Sasayama et al., night oxygen inhalation improved CSR-CSA as well as LV function and quality of life assessed by specific activity scale. In the 1-year study, home oxygen therapy (HOT) was well tolerated and the benefit on LV function and quality of life observed in the 12-week trial was maintained over a prolonged period although this study failed to show benefit on the primary composite cardiac endpoints of combined rate of cardiac death, hospitalization because of worsening heart failure, and a decrease in the Specific Activity Scale by $>1$ Mets, because of the small sample size. Another randomized study reported by Japanese researchers demonstrated that HOT improves exercise capacity, cardiac function, and cardiac sympathetic nerve activity in patients with congestive heart failure and CSA [22]. Thus, in Japan, HOT is approved for reimbursement by public health insurance in patients with NYHA class III or IV, with optimal medical therapy for heart failure and AHI higher than 20 by polysomnography.

The mechanism of night oxygen therapy is not fully understood, but by maintaining PO2 level with night oxygen therapy sympathetic hyperactivity is alleviated [23] and may normalize VE/PCO2 relationship in CSR.

**Continuous positive airway pressure**

CPAP was originally a standard treatment for OSA by supplying pressure higher than the obstructive pressure of the airway and not specifically designed to treat CSR-CSA. However, CPAP may also reduce CSR-CSA in patients with heart failure through its unloading effect. CPAP reduces LV preload by supplying positive pressure to thoracic cage and improves pulmonary congestion. This may attenuate hyperventilation through pulmonary vagal irritant receptors and subsequent CSR. In fact in 2000, Sin et al. reported the results of a randomized study. In this study CPAP improved survival in patients with heart failure and CSR-CSA [24]. This has led to the CANPAP, a large-scale randomized study to evaluate the effect of CPAP on survival in patients with heart failure complicated with CSR-CSA [25]. As is well known, although CPAP did not improve survival it attenuated CSA, improved nocturnal oxygenation, increased the ejection fraction, lowered norepinephrine levels, and increased exercise capacity evaluated by 6 min walk distance. Sub-analysis of CANPAP by Arzt et al. had some positive impact [26]. In 57 patients out of 110 in the CPAP group, AHI was improved to below 15. In this group, CPAP treatment resulted in a greater increase in LV ejection fraction at 3 months and significantly better transplant-free survival than control subjects, whereas in the rest of the patients, whose AHI remained above 15, neither LV ejection fraction or survival was improved. Thus there are “responders” and “non-responders” to CPAP in heart failure patients with CSR-CSA. “Non-responders” are older, had more severe sleep disordered breathing, and a larger fraction of central component compared with “responders”. Five years before the results of CANPAP were published, Javaheri reported that there are responsive and non-responsive patients whose CSA was acutely treated by CPAP [27]. Moreover non-responsive patients had higher AHI and more pure CSA. Thus, CPAP has a limited effect on the treatment of patients with heart failure and CSR-CSA.

**Non-invasive positive pressure ventilation**

Bi-level positive airway pressure (PAP) was originally used to treat patients’ respiratory failure and supply oblong pressure support to forcibly ventilate these patients. On the assumption that bi-level PAP may also treat CSR-CSA, clinical studies were performed in heart failure patients with CSR-CSA. Dohi et al. treated 20 heart failure patients with CSR-CSA first with CPAP for one night and then with bi-level PAP in 11 patients in whom AHI remained >15 with CPAP. Those who were unresponsive to CPAP had significantly lower PCO2, higher plasma brain natriuretic peptide (BNP), longer mean duration of CSR and fewer obstructive episodes than CPAP responders. Among these 11 patients, 7 were chronically treated with bi-level PAP for 6 months with improved LV ejection fraction [28]. Thus they concluded bi-level PAP could be an effective alternative for patients with heart failure and pure CSR-CSA who are unresponsive to CPAP. Kasai treated 7 heart failure patients complicated with CSR-CSA with bi-level PAP and compared with the same number of patients with conventional therapy. Bi-level PAP significantly improved LV ejection fraction, mitral regurgitation, BNP, and NYHA class [29]. Similarly, Noda et al. treated 52 dilated
cardiomyopathy patients with coexisting CSR-CSA with bi-level PAP and found that bi-level PAP improves LV function as well as CSR-CSA [30]. Thus bi-level PAP is more effective than CPAP in treating CSR-CSA and improves LV function. However the problem of bi-level PAP was its low compliance, and it could not be taken over CPAP.

Adaptive servo-ventilation

To date, the most effective treatment for CSR-CSA is adaptive servo-ventilation (ASV). Teschler et al. compared the effect of one night of ASV on sleep and breathing with the effect of other treatment modalities including nasal oxygen (2 L/min), CPAP (mean 9.25 cm H₂O), bi-level PAP (mean 13.5/5.2 cm H₂O), or ASV largely at the default settings (mean pressure 7—9 cm H₂O) during polysomnography in 14 subjects with stable cardiac failure and receiving optimal medical treatment. These four treatment modalities were tested on four treatment nights in random order. They found that one night ASV more strongly suppresses CSA and/or CSR (CSA/CSR) in heart failure and improves sleep quality better than any other treatment modalities [31]. Since then, an increasing number of reports on ASV effects in patients with heart failure and sleep disordered breathing have been published [32–38].

Pepperell demonstrated significant falls in plasma BNP and urinary metadrenaline excretion with 1 month active treatment compared with subtherapeutic patients [32]. Oldenburg demonstrated that ASV improved indexes of exercise capacity including anaerobic threshold (AT), peak oxygen uptake, and peak workload as well as improvement in LV ejection fraction and blood N terminal pro-BNP level in patients with heart failure due to LV systolic dysfunction [39].

The effect of ASV is not limited to heart failure patients with reduced LV ejection fraction but extended to those with preserved LV ejection fraction. Bitter et al. reported ASV effectively attenuates CSR in 39 patients with heart failure and normal LV ejection fraction and improves heart failure symptoms and cardiac function, especially echo-Doppler indexes of diastolic function [40]. Superiority of ASV to other treatments has also been reported. Phillipe et al. randomized patients to ASV and CPAP [33]. They found that both ASV and CPAP decreased the AHI but, noticeably, only ASV completely corrected CSA—CSR, with AHI below 10 h⁻¹. At 3 months, compliance was comparable between ASV and CPAP; however, at 6 months compliance with CPAP was significantly less than with ASV. At 6 months, improvement in quality of life was higher with ASV and only ASV induced a significant increase in LV ejection fraction. Campbell et al. compared two treatments for CSA—CSR, night oxygen therapy and ASV in patients with chronic heart failure using a cross over design [41]. They found that CSA—CSR is reduced to a greater extent by ASV than oxygen therapy over 8 weeks but was not accepted long term. However, neither treatment improved prognostic indices of heart failure or symptoms in the short term. Eight weeks was probably too short to show improvement in LV function for both treatment modalities.

Another type of ASV (auto servo-ventilation) also effectively treats CSR-CSA [42]. Kasai et al. reported the results of randomized study, J-ASV, of this device in comparison with CPAP in patients with chronic heart failure and coexisting CSR-CSA and OSA [43]. In this study, 31 patients with chronic heart failure, defined as LV ejection fraction ≤30% and NYHA class ≥II, with coexisting obstructive sleep apnea and CSR-CSA, were randomly assigned to either CPAP or flow-triggered ASV. The suppression of respiratory events, changes in cardiac function, and compliance with the devices during the 3-month study period, improvements in quality-of-life and LV ejection fraction were greater in the ASV group. Compliance was significantly greater with ASV than with CPAP and there was a significant correlation between machine using time and improvement in LV ejection fraction when data from both groups were plotted on the same plane.

Thus ASV (adaptive servo-ventilation or auto servo-ventilation) improves cardiac function, exercise capacity, and quality of life, but its effect on survival in patients with heart failure is unknown. Recently, Yoshihisa reported that clinical events including cardiac death or hospitalization are significantly lower in heart failure treated with ASV compared with those not treated with ASV. Koyama et al. reported that the effects of ASV on clinical events and LV function were demonstrated regardless of the severity of sleep apnea [44]. Takama reported ASV treatment for patients with mild sleep disordered breathing resulted in almost equal improvements in BNP levels and LV ejection fraction compared to that in patients with moderate and severe sleep disordered breathing [45]. The results of these reports may indicate that ASV improves heart failure regardless of sleep disordered breathing. However, in Koyama’s study, AHI in two groups with patients with non-to-mild sleep disordered breathing were 14.2 and 15.6, which were actually not very mild. And in Takama’s report, the improvement in LV ejection fraction was relatively mild and not significant in the mild sleep disordered breathing group (AHI, 20) although there was no difference in the LV ejection fraction after ASV therapy between the groups. But these reports raise the question if the mechanism of improvement in heart failure by ASV may not be through its effect on sleep disordered breathing. Even without sleep disordered breathing, ASV decreases LV preload and afterload by supplying positive intrathoracic pressure. Expansion of the lung by breath-by-breath pressure support of ASV may ameliorate the increased sympathetic tone in patients with heart failure.

According to Haruki et al. the acute beneficial impact of ASV is mainly associated with the reduction of afterload resulting in an increase in stroke volume and cardiac output. In contrast, chronic ASV therapy produces LV and left atrial reverse remodeling resulting in an improvement in LV function and the severity of mitral regurgitation in patients with chronic heart failure [46]. These effects of ASV may well be exerted without direct effect on sleep disordered breathing.

Two randomized trials evaluating the effect of ASV on survival are ongoing currently.

Phrenic nerve stimulation

Recently Ponikowski et al. reported that unilateral transvenous phrenic nerve stimulation significantly reduces
episodes of CSA and restores a more natural breathing pattern in patients with heart failure [47]. This therapy was originally used to provide respiratory support in patients with respiratory paralysis from high cervical spinal cord injury and in patients with central alveolar hypoventilation syndrome (Ondine’s curse). This study reports the results of only a single night of therapy involving a relatively small number of patients, and the effect of chronic phrenic nerve stimulation which needs surgical procedure is not known.

**CO₂ administration**

Giannoni applied a novel automated algorithm in seven patients with heart failure and periodic breathing and found that dynamic CO₂ administration, delivered at an appropriate time during periodic breathing, can almost eliminate oscillations in end tidal-CO₂ and ventilation. This dynamic approach might be developed to treat CSA, as well as minimizing undesirable increases in end tidal-CO₂ and ventilation [48].

**References**


