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HEART DISEASE AND SLEEP DISTURBANCES (R KHAYAT, SECTION EDITOR)

Central Sleep Apnea in Heart Failure: Pathogenesis and Management

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Abstract
Sleep-disordered breathing (SDB) is a common comorbidity of heart failure (HF), which disrupts sleep. Indeed, patients with heart failure (HF) generally have quantitatively and qualitatively disturbed sleep. Central sleep apnea (CSA) is a unique feature of SDB in HF patients. CSA is likely a consequence, rather than a cause of HF, and results in further deterioration in cardiovascular function, consequently increasing morbidity and mortality. However, effects of treatment for CSA remain to be elucidated. This review article will highlight pathogenesis and pathophysiology of CSA and its management in patients with HF.

Keywords Central sleep apnea · Cheyne–Stokes respiration · Heart failure · Left ventricular ejection fraction · Adaptive servo-ventilation

Introduction

Patients with heart failure (HF) generally sleep less; total sleep time assessed by polysomnography among patients with HF is shorter by 1 to 1.5 h compared with a community sample of subjects without HF [1]. In addition to quantitative sleep issues, patients with HF are likely to have impaired sleep quality because of coexisting sleep-disordered breathing (SDB) [1, 2]. In HF, SDB is regarded as one of the common non-cardiac comorbidities that adversely affect clinical outcomes [3]. Actually, in patients with HF, prevalence of SDB, including either obstructive or central sleep apnea (OSA or CSA, respectively), is approximately 50% [4], and CSA is much more frequently observed in the general population (Fig. 1) [5, 6]. These findings imply that CSA is not just a coexisting condition in patients with HF, but instead appears to be secondary to HF. Risk factors for CSA include male sex, elderly, coexisting atrial fibrillation (AF), increased left ventricular (LV) filling pressure and LV chamber size, enhanced chemosensitivity, low arterial partial pressure of carbon dioxide ($PaCO_2$) level, and use of diuretics [4, 5]. In patients with HF, CSA typically manifests Cheyne–Stokes breathing (CSB) pattern (i.e., CSA-CSB) [2, 8]. CSB is a form of periodic breathing characterized by a crescendo-decrescendo pattern of hyperpnea, followed by central apnea or hypopnea (cycle lengths of ≥ 40 s) [9]. In patients with HF, CSA generally accompanies CSB and thus, CSA-CSB is treated as "CSA" in this chapter.

Pathogenesis and Pathophysiology of CSA in HF

An important pathogenetic factor of CSA in HF patients is respiratory control system instability, which is associated with hypocapnia and increased chemosensitivity. In HF patients with CSA, $PaCO_2$ levels are lower than in those without CSA, either when awake or asleep [10]. Such hypocapnia results from chronic hyperventilation through pulmonary vagal irritant receptor stimulation caused by pulmonary congestion [11] and increased chemosensitivity [12], in association with sympathetic overactivation in HF [13, 14]. Indeed, HF patients with CSA have greater pulmonary capillary wedge pressures, compared with those without CSA [6]. In addition, increased peripheral and central chemosensitivity contributes

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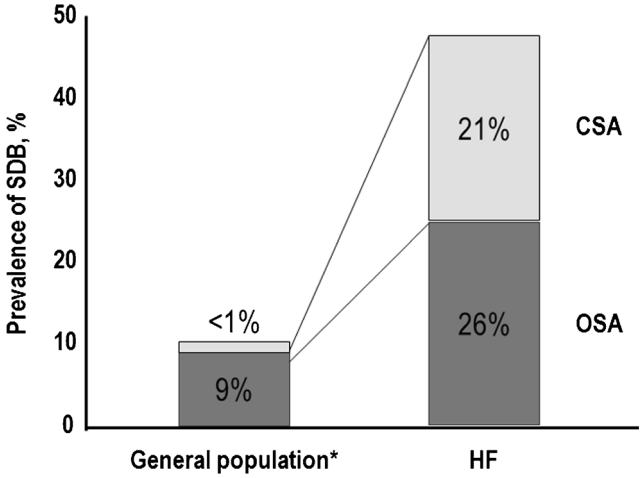

Fig. 1 Prevalence of SDB in general population and in patients with HF. Prevalence of SDB (AHI cutoff of ≥ 15), either OSA or CSA, is much greater in patients with HF [5] compared with general population [6, 7]. In particular, greater prevalence of CSA in HF patients is obvious. *Note prevalence of OSA and CSA in general population was reconstructed by data from two different reports due to a lack of CSA prevalence in one report [6] and a lack of OSA prevalence based on AHI cutoff of ≥ 15 in the other report [7]. AHI, apnea-hypopnea index; CSA, central sleep apnea; HF, heart failure; OSA, obstructive sleep apnea; SDB, sleep-disordered breathing

to promoting hyperventilation and hypocapnia [12]. In HF patients with hypocapnia, the eupneic $PaCO_2$ level borders on the apnea threshold. When $PaCO_2$ decreases below apnea threshold because of a rise in the apnea threshold during transition from wakefulness to sleep, or because of an acute increase in ventilation that is triggered by a spontaneous arousal, CSA ensues [1, 4]. Apnea persists until $PaCO_2$ rises above the apnea threshold, when ventilation will resume. However, ventilatory overshoot occurs and $PaCO_2$ will fall below the apnea threshold again in association with both arousal during the ventilatory phase and increased chemosensitivity [1]. This cycle of ventilatory overshoot and undershoot characterizes the CSB pattern. The cycle length of the CSB pattern is in proportion to lung-to-chemoreceptor circulation time and in inverse proportion to cardiac output, owing to the delayed transmission of change in arterial blood gas to chemoreceptors [15], thereby forming the crescendo-decrescendo pattern of tidal volume during hyperpnea [4].

Systemic fluid retention and related pulmonary congestion in association with HF may induce or worsen CSA. Kasai and colleagues [16] reported that in patients with HF, there is a significant relationship between CSA and sodium intake, which can cause fluid retention; the greater the sodium intake, the greater the severity of CSA. It is well known that in patients with HF, an increase in venous return while recumbent at night worsens pulmonary congestion. This may contribute to the pathogenesis of CSA. Yumino and colleagues [17] reported that severity of CSA and the apnea-hypopnea index (AHI) were correlated with the overnight reduction in leg fluid volume in men with HF. Kasai et al. [18] demonstrated that in men with HF, rostral fluid shift with shock trousers immediately induced hyperventilation and lower $PaCO_2$ level. It is therefore likely that a portion of leg fluid was redistributed into the lungs and caused pulmonary congestion that stimulated pulmonary vagal irritant receptors to elicit reflex hyperventilation and precipitate CSA [19]. CSA is triggered by pulmonary congestion and is associated with decreased cardiac output; therefore, other cardiac diseases (e.g., AF, bradycardia, mitral regurgitation [MR]) that can cause pulmonary congestion and decreased cardiac output can also cause CSA.

Patients with HF and CSA have impaired cerebral blood flow responses to CO_2, and this impaired cerebrovascular reactivity to CO_2 may play some role in the pathogenesis of CSA by contributing to respiratory control system instability [20]. Normally, arterial hypocapnia causes cerebral vasoconstriction, limits cerebral blood flow, and consequently attenuates hypocapnic signals to the central chemoreceptor. Thus, ventilatory inhibition in response to hypocapnia will be diminished. However, in HF patients with CSA, since cerebral blood flow responses to CO_2 are impaired, the central chemoreceptor will be exposed to greater hypocapnic signals than normal. Consequently, ventilatory undershoot is more likely to develop, leading to central apnea [20]. During central apnea, systemic $PaCO_2$ will rise and cerebral vasodilatation will occur. However, since the vasodilatation response to arterial $PaCO_2$ is also impaired, HF patients with CSA are likely to have ventilatory overshoot at apnea termination [20].

In patients with HF, metabolic alkalosis in association with use of diuretics can cause a decrease in the gap between prevailing and apneic threshold $PaCO_2$ and contribute to respiratory control system instability [4, 21]. Diuretics are widely used for the treatment of both acute and chronic HF; however, a fourth of patients with cardiovascular disease develop metabolic alkalosis in association with diuretic use [22]. In patients with HF, use of diuretics is a risk factor for CSA in either acute or chronic phase [5, 23].

Upper airway (UA) instability may also play a role in the pathogenesis of CSA. It was reported that UA collapse was observed at the onset and end of some central apneas [24, 25], probably due to inactivation of the UA dilator muscles in association with attenuation of central respiratory drive [26, 27]. If UA resistance increases as ventilation decreases during the decrescendo phase of hyperpnea in the CSB pattern, this may contribute to ventilatory undershoot [4, 27]. Conversely, if UA resistance decreases as ventilation increases during the crescendo phase of hyperpnea in the CSB pattern, this may contribute to ventilatory overshoot and increase the likelihood of post-hyperventilation central apnea [4, 27]. Several factors, such as low functional residual capacity and hypoxia, may further contribute to the pathogenesis of CSA [4].

Although CSA is more likely a consequence, rather than a cause of HF, CSA has the capacity to initiate a vicious cycle that could cause further deterioration in cardiovascular function through several pathophysiologic mechanisms. During central apnea, the absence of lung inflation eliminates reflex inhibition of central sympathetic nerve traffic arising from pulmonary stretch receptors, and as a result, sympathetic nerve activity (SNA) is enhanced. This effect summates with apnea-related intermittent hypoxia and with arousals to cause cyclical surges in sympathetic nerve activity and cause net increase in overnight SNA [28]. In addition, the adverse effects of CSA on SNA may persist into wakefulness. Indeed, muscle SNA during wakefulness is greater in HF patients with CSA than in those without CSA [29]. Furthermore, ventricular arrhythmias are more common in HF patients with CSA than those in without CSA in association with increased SNA [30]. In patients with HF, elevated levels of inflammatory mediators are known to have an adverse impact on cardiovascular function [31] and consequently are independently associated with worse clinical outcomes [32]. A recent study suggested that in patients with HF, severity of CSA is independently correlated with the level of C-reactive protein (CRP) [33]. Furthermore, another study demonstrated that in HF patients, severity of CSA was associated with prevalence of atrial fibrillation and sinus pauses during the night, and that severity of CSA and elevated CRP levels were independently associated with the prevalence of non-sustained ventricular tachycardia during either night or daytime hours [34]. Indeed, several reports demonstrated that patients with either acute or chronic HF and CSA had a greater risk of morbidity and mortality compared with those without CSA [35, 36].

Management of CSA in HF

Optimization of HF Condition

Optimization of HF treatment should be prioritized because CSA improves as HF improves [11]. Indeed, specific drug therapy for HF such as angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and diuretics may alleviate CSA [37, 38]. In addition, overdrive pacing and cardiac resynchronization therapy are also associated with alleviation of CSA through increased cardiac output [39, 40]. Cardiac rehabilitation may improve CSA [41], although one study found no significant change in the AHI [42], possibly due to differences in the duration or in the exercise program. Similarly, LV assist device implantation may or may not improve CSA [43]. These conflicting results may be explained by differences in the duration of follow-up and in the type of device. Nevertheless, cardiac transplantation was shown to improve CSA in patients with HF [44, 45].

Treatments for CSA

Respiratory Stimulants

Theophylline, a respiratory and cardiac stimulant, can improve CSA by stimulating central respiratory drive and possibly by augmenting cardiac contractility [46]. However, its clinical utility and actual use in HF patients are limited because it is arrhythmogenic. Acetazolamide is also a respiratory stimulant and causes metabolic acidosis. In a double-blind crossover study, Javaheri et al. [47] demonstrated that a single dose of acetazolamide before sleep reduced both the severity of CSA by 38% and CSA-related daytime symptoms. Another double-blind crossover study demonstrated reduction of CSA severity by 52% but also demonstrated an increase in the hypercapnic ventilatory response that inhibits improvement of CSA and consequently results in incomplete resolution of CSA [48]. Moreover, long-term safety and efficacy of acetazolamide remain to be elucidated. Raising $PaCO_2$ level above the apneic threshold either through carbon dioxide inhalation or adding dead space abolishes CSA instantaneously in patients with HF [49]. On the other hand, raising $PaCO_2$ may cause increase in SNA [50]; in addition, whether raising $PaCO_2$ improves cardiovascular outcomes in HF patients remains unknown. Therefore, raising $PaCO_2$ either by carbon dioxide inhalation or by adding dead space cannot be recommended as a treatment for CSA in patients with HF. Real-time dynamic carbon dioxide administration during CSA has almost completely alleviated or eliminated oscillations in end-tidal CO_2 levels and ventilation [51], which might imply a novel approach for CSA.

Respiratory Depressants

The effects of respiratory depressants such as benzodiazepines on CSA in patients with HF have been demonstrated in short-term trials. These trials aimed for the suppression of arousability and ventilatory overshoot, and consequently showed that benzodiazepines would prevent CSA following hyperventilation. Although various benzodiazepines did reduce the frequency of arousals, there was no obvious reduction in CSA severity [52].

Supplemental Oxygen

Supplemental oxygen during sleep reduces the AHI [53], plasma B-type natriuretic peptide (BNP) levels [54], and SNA [55] and increases exercise capacity [56] in HF patients with CSA. However, no randomized controlled trials showed improvement in left ventricular ejection fraction (LVEF) or long-term clinical outcomes [57]. In addition, supplemental oxygen has no advantage over either continuous positive airway pressure (CPAP) or adaptive servo-ventilation (ASV) [58–60]. In

patients with HF, OSA may coexist with CSA and supplemental oxygen is not effective for OSA, instead prolonging obstructive respiratory events due to lack of desaturation stimuli for arousals that will contribute to the termination of respiratory events (Fig. 2).

Phrenic Nerve Stimulation

Recently, the effect of phrenic nerve stimulation (PNS) has been investigated as a novel treatment for CSA [61]. For PNS, a unilateral transvenous lead was generally used. In early studies, acute positive effects of PNS on reduction in the AHI, central apnea index, arousal index, and oxygen desaturation index have been shown [62]. Improvements in quality of life in addition to similar positive chronic effects on sleep study parameters (e.g., approximately 50% reduction in the AHI) were reported in a 3-month follow-up study [61] and a 12-month follow-up study [63], and more reduction in the AHI (80%) was observed in a longer (4 years) follow-up study [64]. A randomized controlled trial (RCT) to determine the effects of CSA suppression by PNS on cardiac function or cardiovascular morbidity and mortality is warranted to confirm long-term efficacy.

Continuous Positive Airway Pressure

Several reports suggest that CPAP can suppress CSA, possibly through cardiac unloading [2, 8, 65]. In systolic HF patients with high LV filling pressure (i.e., ≥ 12 mmHg), CPAP of 5 to 10 cm H_2O acutely augments cardiac output, but in patients with low LV filling pressure (i.e., < 12 mmHg), it reduces cardiac output [66]. Since pathogenesis of CSA is associated with pulmonary congestion and increased LV filling pressures [11], limited venous return, reduced LV preload, reduced LV transmural pressure, and afterload in association with increasing intrathoracic pressure using CPAP can reduce LV filling pressure, improve pulmonary congestion, and consequently suppress CSA [2, 8, 65]. Indeed, approximately 50% of patients with systolic HF and CSA showed that CPAP suppressed CSA [67–69]. However, the effects of CPAP on CSA suppression have not been consistent [66, 70, 71]. This could be explained by the differences in study subjects and how CPAP was applied. The fact that HF patients with a high LV filling pressure [71], those with non-ischemic etiology [72], those without AF [73], and those with MR and dilated LV chamber size [74] may have greater hemodynamic benefit suggests that effective CSA suppression by CPAP can be observed in such patient populations [67–69]. In addition, if CPAP was applied acutely and at low pressure, CSA was not alleviated. [66] On the other hand, if CPAP were gradually initiated with higher pressure levels, the AHI was sufficiently reduced [66]. Alleviation of CSA by CPAP was accompanied by an increase in the $PaCO_2$ [75], a reduction in SNA [28], and improvements in cardiopulmonary function, including increases in the LVEF [76], inspiratory muscle strength [77], reduction in functional MR, and daytime plasma atrial natriuretic peptide concentration [78]. In a small RCT in HF patients with and without CSA, CPAP had no effect on either the LVEF or the composite of mortality and cardiac transplantation in those without CSA [79]. In those with CSA, CPAP improved the LVEF at 3 months and showed a trend toward a reduced event rate ($P = 0.059$, median follow-up period,

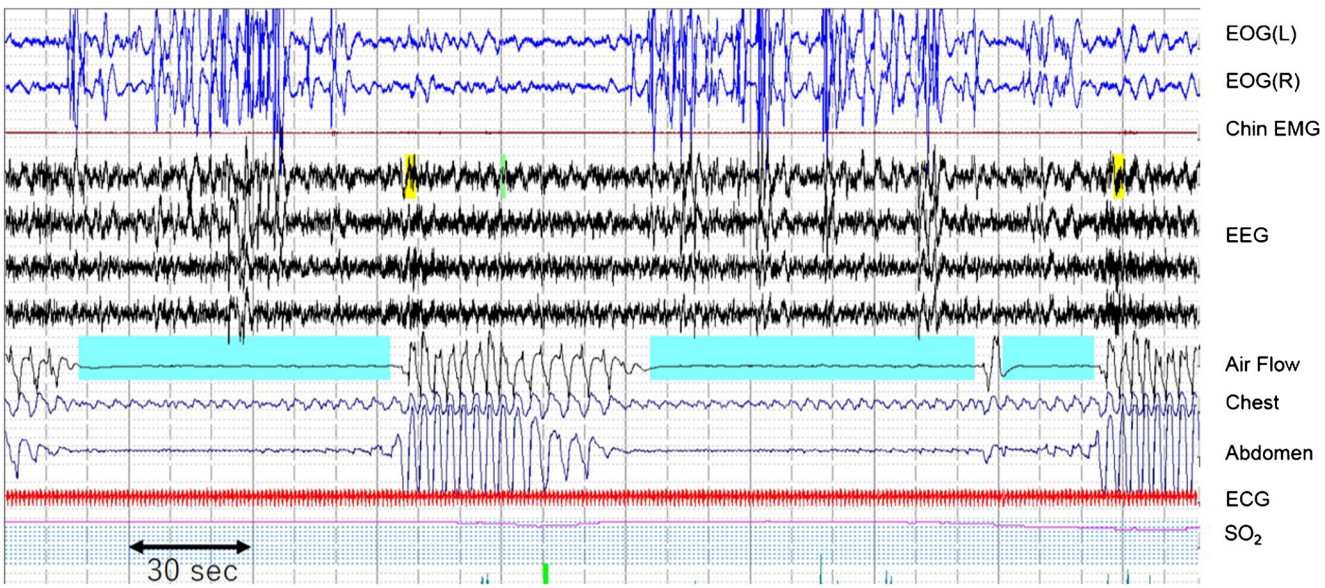

Fig. 2 Representative raw wave form of polysomnography under oxygen inhalation in HF patients with coexisting OSA and CSA. There are prolonged obstructive apneas with minimal desaturation. ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; L, left; R, right; SO_2, oxyhemoglobin saturation

2.2 years). In particular, a sub-group of patients who were compliant with CPAP had a significant reduction in the event rate. The Canadian Continuous Positive Airway Pressure for Treatment of Central Sleep Apnea in Heart Failure (CANPAP) trial sought to determine whether CPAP would improve CSA, morbidity, mortality, and cardiovascular function in systolic HF patients with CSA [80]. The CANPAP trial, which included 130 patients in a control group and 128 patients in a CPAP-treated group, reproduced previous findings that CPAP attenuates CSA, improves the LVEF, and lowers SNA [80]. However, there were no significant differences in transplant-free survival between the two groups during the mean follow-up duration of 2 years [80]. Since suppression of CSA itself appears to be one means by which CPAP could improve cardiovascular outcomes, and since there might be some patients whose CSA cannot be suppressed by CPAP, a post hoc analysis of the CANPAP trial was carried out [69]; it showed that patients whose AHI was suppressed below 15 by CPAP at 3 months have a significantly better transplant-free survival rate compared with control groups and that patients whose AHI was not sufficiently suppressed by CPAP at 3 months (i.e., ≥ 15) have similar or even worse transplant-free survival rates compared with control groups (Table 1). These observations do not support routine use of CPAP for patients with systolic HF and CSA, but confirm that CSA might be a therapeutic target in patients with systolic HF and CSA, and imply that if CSA were suppressed sufficiently by CPAP (i.e., AHI < 15), CPAP could be the first option. On the other hand, it was suggested that other forms of positive airway pressure that can suppress CSA more effectively than CPAP may provide beneficial effects in patients whose CSA was not suppressed sufficiently or in the broader spectrum of these patient populations.

Adaptive Servo-ventilation

Adaptive servo-ventilation (ASV) is an advanced mode of bi-level positive airway pressure developed for the treatment of CSB with CSA in patients with HF [81]. ASV devices automatically provide changing pressure support for each inspiration, ranging from a preset minimum level to a preset maximum level, to maintain moving target ventilation determined by the patient's current breathing, in addition to back-up ventilation with variable respiratory rates. Recent ASV devices provide changing levels of positive pressure during expiration that are sufficient to prevent upper airway (UA) collapse [82].

Several RCTs investigated effects of CSA treatment using ASV on cardiac function [83–86]. Pepperell and colleagues [83] showed that in patients with systolic HF and CSA, nocturnal urinary metadrenaline and daytime BNP concentrations were reduced significantly more by therapeutic than by sub-therapeutic ASV. Philippe and colleagues [84] showed that as compared with CPAP, ASV showed better nightly usage of the positive airway pressure devices and greater improvement of LVEF in patients with systolic HF and CSA. On the other hand, Fietze and colleagues [85] showed that treatment of CSA with bi-level positive airway pressure improved LVEF more than that with ASV, although the difference in the degree of improvement between two positive airway pressure devices was not significant. Nevertheless, in patients with systolic HF and CSA that is non-responsive to CPAP, changing the mode of the device from CPAP to ASV reduces AHI more and improves cardiac function, compared with remaining in CPAP mode [86] (Table 2).

Patients with HF and CSA often have coexisting OSA. Since ASV can prevent UA collapse by altering the expiratory pressure levels in addition to suppressing CSA, ASV can be a

Table 1 Summary of RCTs investigating effects of CSA treatment by CPAP on cardiovascular outcomes in patients with CHF

Author, year	Design	Duration	Outcomes
Naughton, 1995 [28]	RCT	1 month	Plasma and urine norepinephrine↓, LVEF↑, NYHA class↓
Naughton, 1995 [76]	RCT	3 months	LVEF↑, NYHA class↓, improve quality of life
Granton, 1996 [77]	RCT	3 months	Maximal inspiratory pressure↑, LVEF↑, NYHA class↓
Tkacova, 1997 [78]	RCT	3 months	Mitral regurgitant fraction↓, plasma atrial natriuretic peptide↓, LVEF↑, NYHA class↓
Sin, 2000 [79]	Subgroup analysis of RCT	2.2 years (median)	Better transplant-free survival in CPAP group.
Bradley, 2005 [80]	RCT (multicenter)	2 years (mean)	No difference in transplant-free survival. Plasma norepinephrine↓, LVEF↑, distance in a 6-min walk test↑ in CPAP group.
Arzt 2007 [69]	Post hoc analysis of RCT (multicenter)	23 months (mean)	LVEF↑, better transplant-free survival in patients whose AHI on CPAP < 15 compared with control subjects. Lower death and hospitalization risk in CPAP group

RCT, randomized controlled trial; *CSA*, central sleep apnea; *CPAP*, continuous positive airway pressure; *CHF*, chronic heart failure; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association

Table 2 Summary of RCTs investigating effects of CSA treatment by ASV on cardiovascular outcomes in patients with CHF

Author, year	Design	Duration	Outcomes
Pepperell, 2003 [83]	RCT Subtherapeutic Therapeutic	1 month	Plasma BNP↓, urinary metadrenaline↓ No difference in LVEF
Philippe, 2006 [84]	RCT CPAP ASV	6 months	LVEF increased more in ASV group Quality of life↑
Fietze, 2008 [85]	RCT Bi-level PAP ASV	1.5 months	LVEF increased more in the bi-level PAP group
Kasai, 2013 [86]	RCT CPAP mode ASV mode	3 months	LVEF increased more in ASV mode group
Cowie, 2015 [87] "SERVE-HF"	RCT Control f-ASV	31 months (median)	All-cause mortality↑, cardiovascular mortality↑, No difference in LVEF, chamber size, plasma NT-pro BNP

RCT, randomized controlled trial; *CSA*, central sleep apnea; *ASV*, adaptive servo ventilation; *CHF*, chronic heart failure; *BNP*, B-type natriuretic peptide; *LVEF*, left ventricular ejection fraction; *bi-level PAP*, bi-level positive airway pressure; *NT-pro BNP*, N-terminal pro B-type natriuretic peptide

therapeutic option for coexisting CSA and OSA, including either OSA or CSA. Several RCTs have assessed the effects of ASV on cardiac function in HF patients with coexisting CSA and OSA [88–91] (Table 3). Two studies compared patients with CPAP to those with ASV and another two studies compared patients without ASV to those with ASV among those with either systolic or diastolic HF. Kasai et al. [88] reported that ASV significantly reduced AHI more completely and significantly increased LVEF at 3 months, compared with CPAP in patients with systolic HF. Randerath et al. [89] reported that in patients with diastolic HF, ASV reduced AHI and BNP levels more at 12 months compared with those with CPAP, whereas there were no significant differences in exercise performance and cardiac function. Briner and colleagues [90] reported that in patients with systolic HF, BNP levels decreased significantly more in patients with ASV at 3 months compared with those without ASV. Yoshihisa and colleagues [91] demonstrated significant improvements in diastolic function, BNP levels, and event-free survival (against composite of cardiac death and worsening HF) in patients with diastolic HF. We should note that the studies by Randerath and Yoshihisa included patients with diastolic HF and follow-up

Table 3 Summary of RCTs investigating effects of CSA and coexisting OSA treatment by ASV on cardiovascular outcomes in patients with CHF

Author, year	Design	Duration	Outcomes
Kasai, 2010 [88]	RCT CPAP f-ASV	3 months	LVEF increased more in ASV group Quality of life↑
Randerath, 2012 [89]	RCT CPAP f-ASV	12 months	Greater decrease of BNP in f-ASV group No difference in LVEF, exercise capacity
Yoshihisa, 2013 [91]	RCT Control v-ASV	6 months	Improvement in diastolic dysfunction (E/e' ↓), CAVI↓, BNP↓, and NYHA class↓ Better event-free survival in ASV group
Birner, 2014 [90]	RCT Control f-ASV	3 months	No significant improvement in diastolic dysfunction
O'Connor, 2017 [92] "CAT-HF"	RCT Control v-ASV	6 months	No significant improvement in cardiovascular outcomes

RCT, randomized controlled trial; *CSA*, central sleep apnea; *OSA*, obstructive sleep apnea; *ASV*, adaptive servo ventilation; *CHF*, chronic heart failure; *LVEF*, left ventricular ejection fraction; *BNP*, B-type natriuretic peptide; *f-ASV*, flow-targeted ASV; *v-ASV*, volume-targeted ASV

duration was longer, whereas the studies by Kasai and Birner included only patients with systolic HF and follow-up duration was relatively shorter (i.e., 3 months). Moreover, residual AHI on ASV was higher than 10/h and more patients with ischemic etiology were enrolled more in studies conducted by Randerath and colleagues and by Birner and colleagues, compared with those by Kasai and by Yoshihisa. The study by Kasai and colleagues also showed a significant correlation between the nightly usage of devices whether ASV or CPAP and the increase in LVEF; the longer the nightly usage, the greater the increase in LVEF [88]. This finding indicates that maintenance of better adherence to devices is more important for improvement of cardiac function than the type of device that is used.

Nevertheless, the effects of ASV treatment for CSA on morbidity and mortality in patients with HF were further investigated in two multicenter RCTs. In the Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) [93], 1325 patients with symptomatic HF and LVEF ≤ 45% and those with predominant CSA (AHI ≥ 15 with > 50% central events and a central AHI ≥ 10) were randomly assigned to groups with or without ASV. The primary endpoint (composite of all-cause death, cardiac transplantation or implantation of ventricular assist device, resuscitation, and unplanned hospitalization of worsening of HF) did not differ significantly across two groups (hazard ratio [HR], 1.13; 0.97 to 1.31; $P = 0.10$). However, surprisingly, secondary endpoints, all-cause and cardiovascular mortalities, were significantly worse in patients with ASV compared with the control group (HR for all-cause death, 1.28; 1.06 to 1.55; $P = 0.01$; and HR for cardiovascular death, 1.34; 1.09 to 1.65; $P = 0.006$). Further analysis [94] reported that cardiovascular death occurred mainly without previous hospital admission. To facilitate understanding of mechanisms underlying the increased risk of all-cause and cardiovascular mortality randomized to the ASV group in the SERVE-HF trial, on-treatment analysis was carried out [95] and showed results similar to those of the original intention-to-treat analysis. It is thought that some aspects of CSB may be beneficial, possibly through the hyperventilation-related swings in intrathoracic pressure (normally, − 120 to + 120 mmHg) that act as an additional cardiac pump [96]. Thus, the elimination of CSA by ASV in the SERVE-HF trial may remove a compensatory mechanism and consequently adversely affect clinical outcomes. A recent study reported that HF patients have two subtypes of CSA-CSB, i.e., a positive pattern during hyperpnea, in which end-expiratory lung volume remains at or above functional residual capacity, and a negative pattern, in which it falls below functional residual capacity, and that HF patients with a negative CSB pattern have worse cardiac function compared with those with a positive pattern [97]. Greater positive expiratory pressure during hyperpnea is likely generated during the negative CSB pattern and might support stroke volume in patients with worse cardiac function, indicating that a negative CSB pattern should not be eliminated by ASV whereas a positive CSB pattern may be. However, since the SERVE-HF trial had a substantial number of patients with nonadherence to the study protocol (approximately 29% of the patients in the ASV group either discontinued use of the trial device or never used it), and since 17% of the patients in the control group crossed over to positive airway pressure therapy, results from even on-treatment analysis should be interpreted with caution. A substudy of the SERVE-HF trial [98] showed no significant differences in changes of either systolic or diastolic function on echocardiography and on cardiac magnetic resonance imaging. N-terminal pro BNP concentration was decreased but values were similar at 12 months. Other cardiac, renal, and inflammatory biomarkers were also not significantly different. These findings from the substudy at least suggest that the negative results of SERVE-HF may not be attributed to adverse remodeling or worsening of HF conditions expressed by biomarkers.

Another RCT focusing on the effects of ASV treatment for SDB in hospitalized patients following acute decompensated HF (ADHF), the Cardiovascular Outcomes with Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure (CAT-HF) [92], has been terminated earlier than planned due to negative impact of SERVE-HF study on mortality and because only 126 of 215 planned patients were randomized [87]. Primary endpoint (hierarchy of death, cardiovascular hospitalizations, and percent change of 6-min walk distance) at 6 months was not significantly different between ASV and control groups. However, prespecified subgroup analysis implied a positive effect of ASV in hospitalized patients following ADHF with preserved LVEF. Study power was quite limited for identifying differential effects of ASV in hospitalized patients following ADHF with preserved LVEF, but these findings generate further hypotheses and additional studies are warranted in this population.

One ongoing large-scale RCT is A Multi-Centre, Randomized Study to Assess the Effects of Adaptive Servo Ventilation on Survival and Frequency of Cardiovascular Hospital Admissions in Patients with Heart Failure and Sleep Apnea (ADVENT-HF) [99]. In the ADVENT-HF study, a newer ASV device from a different manufacturer provides automated expiratory pressure levels and pressure settings are determined by a core laboratory with strict ASV titration. Importantly, in the ADVENT-HF trial, frequent contact of subjects to ensure their adherence to the ASV device and frequent monitoring against safety concerns are provided throughout the study periods. In addition, the ADVENT-HF

trial included patients with predominant OSA in addition to those with predominant CSA, which covers a wide spectrum of HF patients with SDB and thus, seems to be more practical. Since there are no large-scale RCTs investigating the effect of OSA treatment on long-term clinical outcomes in patients with HF, results from the ADVENT-HF trial will be quite important. Until then, treatment of CSA with ASV in patients with HF should not be routinely recommended, especially when aiming to improve long-term clinical outcomes.

Conclusion

In patients with HF, although the pathogenesis of CSA is multifactorial, pulmonary congestion plays a central role. Although HF patients with CSA, whether hospitalized following ADHF or with chronic HF, have poor clinical outcomes, effective suppression of CSA with CPAP or ASV is at least beneficial for improving cardiovascular function in the short term; however, it remains to be elucidated whether CSA is just an epiphenomenon, perhaps related to progression of HF, or a causal contributor to worse prognosis. Therefore, we still need further RCTs in order to assess whether CSA can be a therapeutic target and whether the type of positive airway pressure affects clinical outcomes. Positive result from an ongoing RCT, the ADVENT-HF trial, may dramatically change strategy for SDB in patients with HF. In addition, in the meantime, studies investigating long-term effects of other treatments for CSA such as acetazolamide, phrenic nerve stimulation, and prevention of rostral fluid shift can also be conducted.

Compliance with Ethical Standards

Conflict of Interest Takatoshi Kasai reports no relevant conflicts of interest. Takatoshi Kasai reports financial interests in Philips-Respironics, Fukuda Denshi, and ResMed outside the submitted work.

Hiroki Matsumoto reports no relevant conflicts of interest. Hiroki Matsumoto reports financial interests in Philips-Respironics, Fukuda Denshi, and ResMed outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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