

Effectiveness of adaptive servo-ventilation

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Author contributions: Tomita Y and Kasai T drafted the article;
Kasai T revised it critically.

Supported by Partly supported by a Grant-in-Aid for Scientific
Research (C), No. 26507010; and a grant to the Respiratory
Failure Research Group from Ministry of Health, Labor and
Welfare, Japan.

Conflict-of-interest statement: Yasuhiro Tomita and Takatoshi
Kasai belong to endowed department (Cardio-Respiratory Sleep
Medicine, Juntendo University Graduate School of Medicine) by
Philips-Respironics, Teijin Pharma and Fukuda Denshi.

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Received: January 24, 2015
Peer-review started: January 25, 2015
First decision: March 6, 2015

Revised: April 16, 2015

Accepted: June 9, 2015

Article in press: June 11, 2015

Published online: July 28, 2015

Abstract

Adaptive servo-ventilation (ASV) has been developed as a specific treatment for sleep-disordered breathing, in particular Cheyne-Stokes respiration with central sleep apnea (CSA). Heart failure patients often have sleep-disordered breathing, which consists of either obstructive sleep apnea (OSA) or CSA. Other medical conditions, such as stroke, acromegaly, renal failure, and opioid use may be associated with CSA. Continuous positive airway pressure (CPAP) therapy is widely used for patients with OSA, but some of these patients develop CSA on CPAP, which is called treatment-emergent CSA. CPAP can be useful as a treatment for these various forms of CSA, but it is insufficient to eliminate respiratory events in approximately half of patients with CSA. As compared to CPAP, ASV may be a better option to treat CSA, with sufficient alleviation of respiratory events as well as improvement of cardiac function in heart failure patients. In patients without heart failure, ASV can also alleviate CSA and relieve their symptom. Recently, ASV has been widely used for patients with various forms of CSA. ASV may be also used in the setting without CSA, but it should be assessed more carefully. Clinicians should have a better understanding of the indications for ASV in each setting.

Key words: Adaptive servo-ventilation; Central sleep apnea; Cheyne-Stokes respiration; Continuous positive airway pressure; Heart failure; Positive airway pressure; Sleep disordered breathing

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Core tip: Adaptive servo-ventilation (ASV) is a form of positive airway pressure device that is used to treat Cheyne-Stokes respiration and central sleep apnea with various etiologies. Accumulating evidence supports the use of ASV in patients with heart failure. However, some existing data suggest that ASV should be used in other situations. In this review, we highlight the clinical applications and effectiveness of ASV and describe future perspectives regarding its applications.

Tomita Y, Kasai T. Effectiveness of adaptive servo-ventilation. *World J Respir* 2015; 5(2): 112-125 Available from: URL: <http://www.wjgnet.com/2218-6255/full/v5/i2/112.htm> DOI: <http://dx.doi.org/10.5320/wjr.v5.i2.112>

INTRODUCTION

Adaptive servo-ventilation (ASV) is one form of non-invasive positive airway pressure (PAP) therapy and was originally developed to treat sleep disordered breathing (SDB), or more precisely Cheyne-Stokes respiration with central sleep apnea (CSR-CSA), which is typically observed in patients with heart failure (HF)^[1]. Teschler *et al.*^[2] first mentioned ASV in 2001 and reported that it was superior to other treatment options including supplemental oxygen, continuous PAP (CPAP) and bi-level PAP in the suppression of CSR-CSA in patients with HF. Furthermore, several studies have shown that treatment of CSR-CSA with ASV improved underlying cardiac dysfunction in patients with HF^[3,4]. ASV can also be used to treat various forms of central sleep apnea (CSA), such as idiopathic CSA, treatment-emergent CSA, opioid-induced CSA and CSA observed in patients with other medical conditions^[4-7].

CSA often coexists with obstructive sleep apnea (OSA), another form of SDB, especially in patients with HF. Because ASV provides expiratory positive airway pressure (EPAP), which can maintain an open upper airway, in addition to inspiratory pressure support (PS), it can alleviate coexisting OSA and CSA^[8].

More recently, ASV has been applied in various clinical settings beyond just SDB treatment. Some Japanese groups have suggested the use of ASV for the treatment of pulmonary congestion and improvement of hemodynamics in patients with HF regardless of the presence or absence of SDB^[9-13]. Another group reported the efficacy of ASV use combined with deep sedation during the pulmonary vein isolation procedure for atrial fibrillation. Thus, ASV is widely used in the field of cardiology and respiratory medicine.

In this review, we describe the fundamental mechanisms and effects of ASV on respiratory and cardiovascular systems, the utility of ASV in various clinical settings, and future perspectives.

FUNDAMENTALS OF ASV

ASV can be considered as an advanced mode of bi-level PAP. ASV devices automatically provide altering PS for each inspiration, ranging from a pre-set minimum to a pre-set maximum level to maintain the moving target ventilation determined by the current breathing of the patient, in addition to back-up ventilation with automatically determined respiratory rates (Figure 1A). ASV devices also provide an EPAP that is sufficient to maintain an open upper airway. More recent ASV devices can automatically alter EPAP levels based on algorithms that aim to alleviate snoring, flow limitation, and obstructive apneas and hypopneas (Figure 1B).

Three ASV devices are manufactured by ResMed Inc., Philips-Respironics Inc. and Weinmann Geräte für Medizin GmbH+Co. KG (Table 1). In the latest version of all of the devices, EPAP automatically varies to eliminate obstructive events. PS is also dynamically adjusted breath-to-breath as necessary to ensure that the actual ventilation matches the target value in addition to the auto-titration of EPAP to maintain airway patency. The main differences between devices are the triggers to determine the target level. ResMed and Weinmann devices provide volume-triggered ASV. The ResMed device establishes a target minute-ventilation that is 90% of the recent average minute volume from a 3-min collection period and attempts to maintain ventilation at the target level. The Weinmann device has no fixed target level of minute volume, but it calculates the relative minute volume of the current breath and attempts to predict future values of minute volume based on a moving window that is focused by 50% on the last 2 min and by 50% on the previous time to stabilize the relative minute volume. The Philips-Respironics device is a flow-triggered ASV that monitors the peak inspiratory flow of the patient over a recent moving 4-min window, calculating an average peak flow at every point within this window to establish a target peak flow. It compares these data to an internal target and maintains a target peak inspiratory flow. There are some minor differences in other features across these three devices.

Other than ASV devices themselves, the important equipment necessary for ASV therapy is patient interfaces include nasal masks, nasal pillows, and oro-nasal (full-face) masks that cover the nose and mouth, and the optional heated humidifier system (Figure 2). The choice of mask rather than the choice of device is the most important issue for patient comfort and tolerance to ASV therapy. Poorly fitted masks decrease the efficacy and adherence to ASV therapy. In addition to the mask itself, headgear or straps are used as a harness. Headgear that are too tight may worsen the air leak and interfere with patient comfort and adherence. The optional heated humidifier can be easily connected to the ASV device and helps to minimize the effects of nasal dryness.

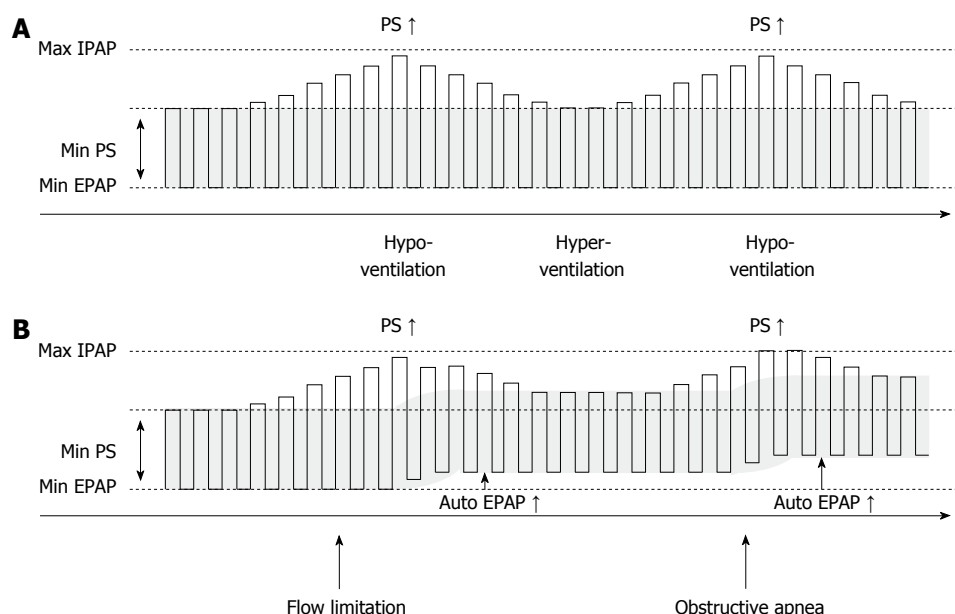


Figure 1 Adaptive servo-ventilation can be considered as an advanced mode of bi-level positive airway pressure. A: In response to central events, adaptive servo-ventilation increases pressure support during hypoventilation and decreases pressure support during hyperventilation, with the goal of stabilizing ventilation; B: In response to obstructive events (apneas, airflow limitation, and snoring), adaptive servo-ventilation increases expiratory positive airway pressure, with the goal of suppressing obstruction.

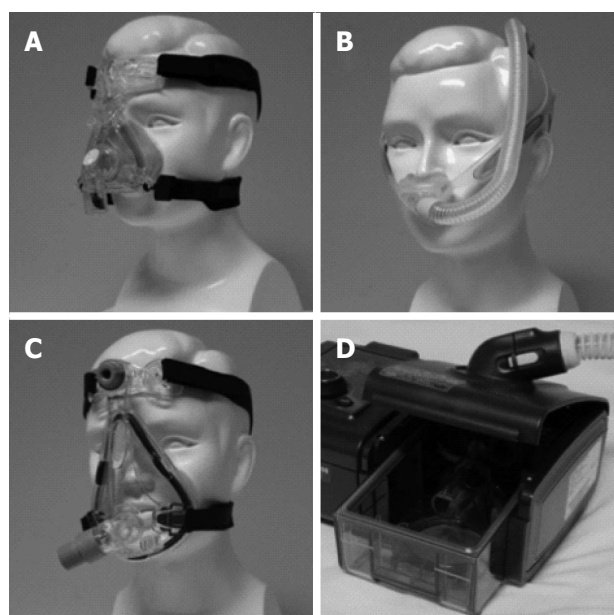


Figure 2 Several types of masks are available as an adaptive servo-ventilation interface for patients to discover a more comfortable fit: nasal masks (A), a pillow mask (B), an oro-nasal mask (C), and an optional heated humidifier connected to an adaptive servo-ventilation device (D).

EFFECTS OF ASV ON RESPIRATORY AND CARDIOVASCULAR SYSTEMS

Effects on the respiratory system

ASV devices, which provide EPAP (more recently auto EPAP), auto-adjusted PS and servo-ventilation, have several effects on the respiratory system.

EPAP prevents alveoli from collapsing in the end-expiratory phase and improves gas exchange and

oxygenation through alveolar units, which is a common effect across PAP devices^[14]. EPAP also prevents upper airway obstruction in patients with OSA^[15], consequently decreasing respiratory events and arousals and improving sleep architecture. Auto-adjusted PS, which is provided based on the target minute volume or target peak flow, can reduce respiratory muscle loading of breathing^[16] and alleviate CSR-CSA and other forms of CSA. Each ASV device has different algorithms, but all of them provide auto-adjusted PS during inspiration and servo-ventilation, with the goal of stable ventilation. Because breathing instability leads to enhanced sympathetic nervous system activity (SNA)^[17,18], ASV may reduce SNA by alleviating CSR-CSA and other forms of CSA and maintaining stable ventilation^[9]. Such sympathoinhibitory contributions of ASV may provide beneficial effects on hemodynamics, which may be unique to ASV^[19].

Effects on the cardiovascular system

ASV devices have several direct effects on the cardiovascular system. Some small studies in patients with HF suggest acute effects of the short-duration use of ASV, whereas wakefulness will help us understand the hemodynamic effects of ASV. After 30 min of ASV, blood pressure and heart rate were significantly decreased, whereas stroke volume and cardiac output were significantly increased^[19]. These findings indicate that in patients with HF, ASV can reduce systemic vascular resistance and consequently reduce left ventricular (LV) afterload, potentially by maintaining a consistent ventilation and providing a related reduction of SNA. ASV also reduces right ventricular (RV) preload, thus diminishing the systemic venous

Table 1 An overview of the features of the three adaptive servo-ventilation devices

Manufacturer	ResMed	Philips-Respironics	Weinmann
Current version	S9 VPAP Adapt, AutoSet CS-A	BiPAP autoSV Advanced System One	Prisma LINE CR
EPAP (default)	4-15 cmH ₂ O auto	4-15 cmH ₂ O auto	4-20 cmH ₂ O auto
(min EPAP)	4-15 cmH ₂ O	4-25 cmH ₂ O	4-20 cmH ₂ O
(max EPAP)	min EPAP-15 cmH ₂ O	min EPAP-25 cmH ₂ O	min EPAP-20 cmH ₂ O
IPAP	Max 30 cmH ₂ O	Max 25 cmH ₂ O	Max 30 cmH ₂ O
PS	0 to 30-prevailing EPAP	0 to 25-prevailing EPAP	0 to 30-prevailing EPAP
Calculation	The recent 3-min average minute volume	The recent 4-min average peak flow	The average of the minute volume in the recent 2-min and an earlier interval
Target for PS	90% of the average minute volume	90%-95% of the average peak flow (without SDB) 60% percentile of peak flow (with SDB)	Relative minute volume of the current breath to the average
	Approximate the minute volume to the target	Approximate the peak inspiratory flow to the target	Stabilize the relative minute volume
Backup rate	Auto (cannot be established manually)	Auto (default) or fixed rate	Auto (default) or fixed rate

EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PS: Pressure support; SDB: Sleep disordered breathing.

return by increasing the intrathoracic pressure. These cardiac unloading effects are favorable in HF patients. However, in subjects without HF who are usually dependent on preload^[20], the cardiac output may decrease in response to ASV.

Another favorable effect of ASV on the cardiovascular system is the improvement of SDB. Both OSA and CSR-CSA, or other forms of CSA, may lead to a deterioration of cardiac function. OSA exaggerates the negative intrathoracic pressure during inspiratory efforts against upper airway obstruction^[21]. Therefore, the LV transmural pressure increases (*i.e.*, intraventricular minus intrathoracic pressure), leading to an elevated LV afterload. The sympathetic nervous system is activated in patients with OSA as well as CSA^[22,23], leading to a surge in BP and HR. An absence of breathing eliminates the sympathoinhibitory reflex from pulmonary stretch receptors, enhancing SNA. Intermittent hypoxia and arousals also lead to cyclical surges in SNA. Attenuation of SDB by ASV will alleviate these adverse effects on hemodynamics. However, the maintenance of a consistent respiration by auto PS and servo-ventilation, even in cases without SDB, may play a role in the attenuation of SNA.

UTILITY OF ASV IN VARIOUS CLINICAL SETTINGS

SDB in heart failure

As mentioned previously, ASV was originally developed to treat CSR-CSA in patients with HF. CSR-CSA is characterized as a cyclic pattern of crescendo-decrescendo respiration superimposed by central apnea or hypopnea.

HF patients with an increased left ventricular filling pressure are likely to present CSR-CSA^[22]. An elevated pulmonary capillary wedge pressure (PCWP) results in pulmonary congestion, stimulating pulmonary vagal irritant receptors and leading to hyperventilation in association with an increased chemosensitivity^[24].

This effect is observed in patients with HF and is most likely due to an increase in SNA^[25]. When PaCO₂ falls below the apneic threshold due to such hyperventilation because of an increase in the apneic threshold during the transition from wakefulness to sleep^[24], central apnea ensues. Apnea persists until PaCO₂ rises above the apneic threshold; subsequently, ventilation resumes, ventilatory overshoot occurs, and PaCO₂ decreases below the apneic threshold in association with arousal during the ventilatory phase and increased chemosensitivity. The length of the ventilatory phase following central apneas is directly proportional to the lung-to-chemoreceptor circulation time^[26] and inversely proportional to cardiac output^[27], reflecting a delayed transmission of change in arterial blood gas tension from the lungs to the chemoreceptors in association with impaired cardiac output in HF patients. This phenomenon could also contribute to the pathogenesis of the Cheyne-Stokes respiration (CSR) pattern by facilitating a ventilatory overshoot and undershoot.

As described above, CSR-CSA occurs secondary to HF, but CSR-CSA itself also contributes to the deterioration of cardiac function. HF patients with CSA exhibit an increased SNA during sleep, and this effect persists during wakefulness^[23]. In HF, patients with CSR-CSA are associated with a worse prognosis. Thus, CSR-CSA could be a therapeutic target in patients with HF. However, treatment for CSR-CSA in patients with HF should be considered after optimization of HF therapy because CSR-CSA results from HF and pulmonary congestion. Because HF patients with CSR-CSA have associated pulmonary congestion and increased LV filling pressures, CPAP was initially applied to improve pulmonary congestion and decrease the LV filling pressure *via* cardiac unloading^[28]. However, studies regarding the effects of CPAP on the suppression of CSR-CSA in HF patients produced inconsistent results: some of them alleviated CSR-CSA significantly, but others did not^[29]. Nevertheless, if CPAP was titrated gradually, then CSR-CSA was alleviated in most of the

Table 2 Clinical trials assessing the effects of adaptive-servo ventilation on cardiac function in heart failure patients with central sleep apnea

Ref.	Study design	n	Duration (mo)	Baseline		Device usage (h)	Changes	
				AHI	EF		AHI	EF
Pepperell <i>et al</i> ^[36]	RCT							
	Subtherapeutic	15	1	17.7	35.7	3.9	-3	0.5
	Therapeutic	15		21.9	36.5	5.0	-16.5	1.8
Philippe <i>et al</i> ^[3]	RCT							
	CPAP	13	6	40.5	30.0	4.2	-20	-2
	ASV	12		47.0	29.0	5.8	-45	7
Fietze <i>et al</i> ^[37]	RCT							
	Bi-level PAP	15	1.5	34.9	25.5	4.8 ¹	-18.5	5.6
	ASV	15		31.7	24.6		-20.5	1.9
¹ Kasai <i>et al</i> ^[4]	RCT							
	CPAP-mode	11	3	23.0 ²	33.0	3.3	0.1	-1
	ASV-mode	12		25.0 ²	32.0	4.7	-23	5.8

¹Patients with residual AHI ≥ 15 on CPAP were included; ²AHIs on CPAP were described. AHI: Apnea-hypopnea index; ASV: Adaptive-servo ventilation; Bi-level PAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; EF: Ejection fraction; RCT: Randomized controlled trial.

cases^[30] accompanied by an increase in PaCO₂^[31], a reduction in SNA^[32], and improvements in respiratory muscle function^[33] and LV systolic function^[34].

However, The Canadian Continuous Positive Airway Pressure for Treatment of Central Sleep Apnea in Heart Failure (CANPAP) trial^[34], which included 258 patients with HF and CSA to assess the long-term survival benefit of CPAP treatment for CSR-CSA, reported that CPAP did not improve survival. A post-hoc analysis of the CANPAP trial^[35] revealed that patients with CSR-CSA that was sufficiently suppressed [*i.e.*, apnea-hypopnea index (AHI) < 15] by CPAP at 3 mo had a significantly better survival, which indicated that treatment that can suppress CSR-CSA more sufficiently and consistently might improve survival in HF patients with CSR-CSA. Because ASV has been recognized as the most effective technique to suppress CSR-CSA, even in patients with an AHI ≥ 15 on CPAP, the effects of ASV on cardiac function during the treatment of CSR-CSA were assessed in several short-term randomized controlled trials (RCTs). Small RCTs investigating the effects of ASV on cardiac function in HF patients with CSR-CSA are summarized in Table 2. Pepperell *et al*^[36] reported that ASV decreased AHI, improved excessive daytime sleepiness and lowered the level of brain natriuretic peptide (BNP) and urinary metadrenaline excretion compared with subtherapeutic use of ASV. However, there was no difference in improvement of cardiac function.

Philippe *et al*^[3] compared ASV with CPAP and concluded that ASV provided a greater benefit in attenuating CSR-CSA and improving cardiac function. Although volume-targeted ASV devices were used in these two studies, Kasai *et al*^[4] investigated the effects of flow-targeted ASV devices on cardiac function by comparing two settings for the same ASV: ASV-mode and CPAP-mode. This study included only patients with CSR-CSA that was not sufficiently suppressed (*i.e.*, AHI ≥ 15 on CPAP) despite ≥ 3 mo of CPAP. In

these populations, ASV-mode was superior to CPAP-mode in reducing AHI and improving cardiac function. Bi-level PAP has also been reported to be effective in attenuating CSR-CSA. Fietze *et al*^[37] compared the effects of ASV and Bi-level PAP using the standard spontaneous/timed (S/T) mode. They concluded that both PAPs could reduce AHI and increase LVEF. Between the two PAPs, AHI decreased more in the ASV group, whereas LVEF increased more in the Bi-level PAP group, although these differences were not significant. Based on these studies, ASV can attenuate CSR-CSA more than other PAPs in HF patients with CSR-CSA. ASV can also improve LVEF in HF patients with CSR-CSA after 3 to 6 mo use with good adherence, which indicates that the nightly usage is more than 4 h.

The effects of ASV treatment for CSR-CSA on the long-term prognosis of HF patients will be determined by two ongoing large-scale RCTs: Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (Serve-HF)^[38]; Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure (ADVENT-HF)^[39].

The prevalence of OSA is also high in patients with HF, and coexisting OSA with CSR-CSA is common in patients with HF. Therefore, CPAP may not sufficiently alleviate SDB, particularly in patients with a greater proportion of CSR-CSA than OSA. However, ASV can suppress OSA by modifying the EPAP levels in addition to suppressing CSR-CSA. Thus, ASV, particularly more recent ASV devices equipped with auto-titrating EPAP, may be a therapeutic option for SDB without the need to distinguish between OSA and CSR-CSA. Several short-term RCTs have assessed the effects of ASV on cardiac function in HF patients with coexisting CSR-CSA and OSA (Table 3). Two studies comparing the effects of CPAP and ASV on cardiac function suggested different results. Kasai

Table 3 Clinical trials assessing the effects of adaptive-servo ventilation on cardiac function in heart failure patients with central sleep apnea and coexisting obstructive sleep apnea

Ref.	Study design	n	Duration (mo)	Baseline		Device usage (h)	Changes	
				AHI	EF		AHI	EF
Kasai <i>et al</i> ^[40]	RCT							
	CPAP	15	3	38.6	36	4.4	-23.2	1.9
Randerath <i>et al</i> ^[41]	f-ASV	16		36.3	35.7	5.25	-35.4	9.1
	RCT							
Yoshihisa <i>et al</i> ^[42]	CPAP	34	12	41	43	4.3	-24.0	4.9
	f-ASV	36		47	47	5.2	-36.0	-1.9
Birner <i>et al</i> ^[43]	RCT							
	Control	18	6	36	54	-	-8.2	-2.0
Birner <i>et al</i> ^[43]	v-ASV	18		37	56.1	5.6	-30.2	5.1
	RCT							
	Control	35	3	43	29	-	0	3.0
	f-ASV	37		52	30	4.2	-41.0	1.0

AHI: Apnea-hypopnea index; ASV: Adaptive-servo ventilation; CPAP: Continuous positive airway pressure; EF: Ejection fraction; f-ASV: Flow-targeted ASV; v-ASV: Volume-targeted ASV; RCT: Randomized controlled trial.

et al^[40] reported that ASV significantly reduced AHI more completely and significantly increased LVEF compared with CPAP. Randerath *et al*^[41] reported that ASV reduced AHI and BNP levels, but there were no significant differences in exercise performance and cardiac functions. Another two studies^[42,43] comparing an ASV group and a control group without ASV failed to show an improvement of LVEF, although ASV improved SDB in both studies. However, both studies demonstrated a significantly greater reduction of the BNP level in the ASV group, and a study by Yoshihisa *et al*^[42] demonstrated significant improvements in diastolic function and event-free survival (against cardiac death and worsening HF). We should note that the studies by Randerath *et al*^[41] and Yoshihisa *et al*^[42] included HF patients with preserved LVEF, whereas the studies by Kasai *et al*^[40] and Birner *et al*^[43] included only HF patients with reduced LVEF (LVEF < 50%, < 40%). Moreover, residual AHI on ASV was higher than 10/h in the studies conducted by Randerath *et al*^[41] and Birner *et al*^[43]. Differences in the etiology of HF could have led to differences in LVEF improvement. The studies reported by Randerath *et al*^[41] and Birner *et al*^[43] contained a high proportion of ischemic heart disease, whereas those by Kasai *et al*^[40] and by Yoshihisa *et al*^[42] included only 26% and 28%, respectively. The long-term prognostic effects of SDB were greater in HF patients with ischemic heart disease^[44]. However, greater short-term reductions in RV and LV volumes were observed in HF patients with idiopathic dilated cardiomyopathy compared with those with ischemic cardiomyopathy^[45]. Based on the findings of these studies showing that ASV provides consistent effectiveness to reduce AHI and maintain good compliance in HF patients with coexisting OSA and CSR-CSA, ASV should be recommended to patients with symptoms that are related to their SDB and be considered to improve cardiac functions if the SDB can be alleviated with ASV (*i.e.*, AHI on ASV < 10/h), as well as in some select cases (possibly HF

patients with non-ischemic etiologies). Kasai *et al*^[40] also showed a significant correlation between the nightly usage of devices (*i.e.*, ASV and CPAP) and the increase in LVEF; the longer the nightly usage, the greater was the increase in LVEF. 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. We should note that OSA can be alleviated by CPAP and that CPAP can alleviate CSR-CSA in approximately 50% of the patients with CSR-CSA^[34]. In addition, considering the difference in cost between CPAP and ASV, CPAP should be attempted as a first-line therapy. The effects of ASV on both types of SDB will be determined in an ongoing large-scale RCT that includes HF patients with predominant OSA in addition to those with CSR-CSA (*i.e.*, ADVENT-HF)^[39].

Although most of the previous data regarding SDB involve HF patients in the chronic phase, it has been recently reported that hospitalized patients with HF following acute decompensated HF (ADHF) also frequently have SDB and that the presence of either severe OSA or moderate-to-severe CSR-CSA identified during hospitalization following ADHF is a predictor of readmission and mortality^[46]. Thus, ASV therapy can be considered in such patients. An ongoing study, Cardiovascular Improvements With MV ASV Therapy in Heart Failure (CAT-HF), may elucidate whether ASV therapy improves outcomes in these patients^[47].

Treatment-emergent CSA

Some patients with OSA develop central respiratory events or a periodic breathing pattern similar to CSR after the removal of upper airway obstruction. This phenomenon has been reported in patients with OSA treated by CPAP and described in various ways, such as "treatment-emergent CSA", "CPAP-emerged CSA", "complex SDB", or "complex sleep apnea syndrome (SAS)". The term "complex SAS" was first used by Morgenthaler *et al*^[48] and has been most widely applied

since that time. However, this term is sometimes misunderstood as solely a mixture of OSA and CSA observed in one patient during a diagnostic sleep study rather than CSA that has emerged in response to treatment. Thus, we use “treatment-emergent CSA” in this review, which is consistent with the term in the third edition of the International Classification of Sleep Disorders (ICSD-3).

In general, studies including patients with CPAP therapy for OSA have found that the prevalence of treatment-emergent CSA ranged from 1.6%-18.0%^[6,49-52]. Most residual events during the initial CPAP titration are transient and may disappear over 2 to 3 mo of continued CPAP use^[53]. Residual events lead to CPAP intolerance, and therefore, patients with treatment-emergent CSA may sometimes discontinue CPAP prior to alleviating the residual respiratory event. The residual respiratory events that emerged in response CPAP were associated with dyspnea and inadvertent mask removal^[54]. More careful follow-up is needed to continue CPAP for such patients.

A prospective study^[55] suggested that patients with treatment-emergent CSA were significantly older, but some other studies found no significant difference between patients with and without treatment-emergent CSA. In several retrospective studies^[48-50], treatment-emergent CSA was more frequently observed in men than in women. In addition, most epidemiological investigations suggested that body mass index (BMI) did not differ between patients with and without treatment-emergent CSA^[49,50,53,55]. In terms of polysomnographic findings, although some studies suggested that greater AHI, central apnea index, or the arousal index during diagnostic sleep studies could be predictors for the development of treatment-emergent CSA, these results were not consistent with those of other studies. One case report suggested that dissociation between apnea termination and arousal during diagnostic sleep study might be suggestive of the presence of treatment-emergent CSA^[56]. However, this phenomenon should be studied using a larger sample size.

Bitter *et al*^[6] described that 18% of patients with HF develop treatment-emergent CSA defined as more than 15 episodes of central apnea or periodic breathing per hour when undergoing CPAP titration. When defined as more than 5 episodes, 37% of the patients presented treatment-emergent CSA, which indicates that treatment-emergent CSA is quite common in patients with HF. However, Westhoff *et al*^[57] assessed the prevalence of treatment-emergent CSA among patients with CPAP treatment for OSA with BNP levels that were within the normal range. The prevalence (1.6%) was much lower than that in patients with HF. Thus, HF is one of the risk factors for the development of treatment-emergent CSA. However, this feature may be explained by an underlying CSR pattern of respiratory events with an obvious obstructive phenotype. Such respiratory events were scored as

obstructive during diagnostic studies. However, in a CPAP titration study, alleviation of the upper airway obstruction resulted in a prominent underlying CSR^[56].

The mechanism underlying the development of treatment-emergent CSA remains to be elucidated and is assumed to be multifactorial. Minute ventilation is determined by the level of PaCO₂ via stimulating chemoreceptors. When PaCO₂ falls below the apnea threshold, central apnea occurs. Patients with treatment-emergent CSA may be susceptible to frequent arousal due to the intolerance to CPAP, and this effect is secondary to an elevated nasal resistance^[58], including a mask leak and mouth breathing^[59]. Other comorbidities of the patients can also trigger frequent arousals, leading to unstable sleep and oscillation of PaCO₂, which may cause treatment-emergent CSA^[60]. Excessive pressure may activate lung stretch receptors, which inhibit central respiratory motor output, and lead to central apnea via the Hering-Breuer reflex^[61]. The efficiency of CO₂ excretion in patients with OSA is usually reduced but is improved with the application of CPAP. Even if the pressure is appropriate, improved CO₂ excretion can induce transient hypocapnia, triggering CSA. The CO₂ apnea threshold, which is usually 2–6 mmHg below the eucapnic sleeping CO₂ level, may improve to the lower level as the eucapnic sleeping CO₂ level decreases over several weeks of CPAP use, resulting in a resolution of the central apnea^[62]. This phenomenon may be one of the reasons why most treatment-emergent CSA is transient and may disappear over several weeks^[53].

ASV has been reported to be effective for the treatment of treatment-emergent CSA. However, the success rate, defined as the total AHI that was attenuated under 10 events per hour, varies from 76% to 92%^[63,64]. Supplemental oxygen plus CPAP or the use of bi-level PAP alone rather than CPAP have also been reported to be effective, but Allam *et al*^[63] reported that ASV was more successful than either CPAP with oxygen or bi-level PAP (including either spontaneous/timed-mode or spontaneous-mode). A retrospective study^[65] in which the mean nightly use of ASV was assessed at the first visit (at 4–6 wk following initiation of ASV) revealed good adherence to ASV (5.0–6.0 h per night). In another retrospective study, attenuation of residual AHI on CPAP using ASV resulted in an improvement of sleep fragmentation and a reduction of the arousal index^[64]. These findings do not indicate that all patients with treatment-emergent CSA should be treated with ASV because CSA may disappear over several months^[53], but they suggest that some patients with treatment-emergent CSA will benefit from ASV in reducing AHI and improving sleep architecture and adherence. In general, we should try to optimize the setting of CPAP, improve nasal resistance, and control mask leaks. Following these efforts and after the confirmation that treatment-emergent CSA remains after several weeks, an upgrade from CPAP to ASV could be considered. We should also consider the cost effectiveness of ASV in patients with treatment-emergent CSA.

In the study by Bitter *et al.*^[6] of HF patients with treatment-emergent CSA, all 34 HF patients with treatment-emergent CSA used ASV, and only one of them failed to show a reduction of AHI below 15 events per hour of sleep at 3 mo following the initiation of ASV. As described above, HF patients with treatment-emergent CSA may include some patients with a clear obstructive phenotype and underlying CSR. In such patients, ASV should be recommended in those patients with symptoms that are related to their residual SDB and be considered in cases in which SDB can be successfully alleviated with ASV, as well as in some select cases, similar to HF patients with coexisting OSA and CSR-CSA. Even in these populations, the patients should continue to use CPAP for several weeks with careful observation to exclude "transient" treatment-emergent CSA.

Idiopathic CSA

Idiopathic CSA is categorized as one form of primary CSA with underlying causes or disorders (*i.e.*, HF, cerebrovascular disease, and renal failure) that are not identified. The prevalence of idiopathic CSA is not reported. Although it is not strictly limited to "idiopathic", the prevalence of CSA in the general population has been reported to be only 0.4%^[66], which suggests that the prevalence of idiopathic CSA could be much lower than other forms of primary CSA. The prognosis of idiopathic CSA is also unknown, but it is speculated to be a relatively benign condition due to the absence of other comorbidities^[67].

The pathogenesis of idiopathic CSA has not been fully elucidated. However, it has been reported that increased ventilatory responses and hypocapnia play important roles^[68]. Arousal and the accompanying hyperventilation have also been reported to be one of the mechanisms that triggers hypocapnia^[69].

The patterns and features of respiratory events in patients with idiopathic CSA are not the same as those of typical CSR. Patients with idiopathic CSA exhibit a periodic breathing pattern with a shorter cycle length^[26] and less severe desaturations associated with central apneas^[70]. In patients with idiopathic CSA, insomnia (difficulty in initiating and maintaining sleep) or hypersomnolence have not been reported to be common presenting symptoms^[70,71].

ASV may also be effective for idiopathic CSA. However, there are no solid reports in which the effectiveness of ASV in patients with idiopathic CSA was completely evaluated. Three cases of idiopathic CSA that did not respond well to either CPAP or oxygen were reported to benefit from ASV^[5]. In that case series, ASV decreased the mean abnormal breathing event index from 35.2 to 3.5 per hour of sleep, and it also reduced the mean number of arousals caused by the abnormal breathing events from 18.5 to 1.1 per hour of sleep. Moreover, subjective daytime alertness and mood improved after 6 to 12 mo of using ASV.

These cases indicated that ASV could be effective in improving symptoms for idiopathic CSA and should be used to relieve symptoms. The efficacy must be verified in larger numbers of patients.

Opioid-induced CSA

Individuals who are either acute or chronic opioid users can develop CSA^[72,73]. The prevalence of opioid-induced CSA is unknown, but previous reports suggested that CSA was present in 30%-60% of patients who received methadone, a long-acting μ -opioid agonist, for the treatment of substance abuse^[74,75]. It has been reported that methadone overdose is associated with the presence of CSA and a worse prognosis, but whether the reported worse prognosis in association with methadone overdose indicates the presence of CSA or underlying comorbidities remains unclear^[76].

Walker *et al.*^[73] reported that symptoms of sleep apnea in the opioid group and in the control group were similar. There were no significant differences in the Epworth Sleepiness Scales or prevalence of comorbidities between the two groups. Specific symptoms of opioid-induced CSA have not been reported. The pattern of CSA observed in patients with opioid use is not similar to that observed in patients with HF, who typically display a CSR pattern. However, the pattern of CSA observed in patients who are taking opioids is similar to ataxic breathing. Ataxic breathing is distinguished from CSR by its irregularity. In addition, there is no cyclical change in tidal volume like that in CSR. The pathophysiology of developing CSA as a result of opioid use is unknown. However, it has been suggested that the inhibitory effects of opioids on the μ -opioid receptor of carotid bodies may play an important role in the development of CSA.

Various forms of PAP have been used for opioid-induced CSA. A systematic review^[77] based on five articles including a total of 127 patients who were using opioids for at least 6 mo showed the effectiveness of PAP for the treatment of opioid-induced CSA. In most of the cases, CPAP therapies were ineffective for the alleviation of CSA. However, ASV was more effective than CPAP. Approximately 60% of the patients with opioid-induced CSA attained a central apnea index of < 10 per hour of sleep on either the bi-level PAP or ASV^[77]. In general, the presence of ataxic breathing can be a predictor of a poor response to PAP therapy^[77]. Javaheri *et al.*^[7] reported the results of a study in which twenty patients with chronic opioid therapy who showed persistent CSA on CPAP underwent ASV titration. In that study, the diagnostic polysomnography showed an average central apnea index (CAI) of 32 per hour of sleep. On the CPAP, in contrast, CSA was not attenuated, and the average CAI was 20 per hour of sleep. However, during ASV titration, the average CAI was 0 per hour of sleep for the final pressures. During the follow-up for a minimum of 9 mo and up to 6 years in 17 of the 20 patients, the adherence to ASV was

good (average nightly usage was > 5 h). Long-term RCTs are needed to validate the mortality benefit of ASV in patients with CSA associated with opioid use.

Ischemic stroke-related CSA

SDB is common after ischemic stroke and can be found in more than half of the patients, especially in the acute phase^[78,79]. Preexisting OSA has been reported to be a predictor of the development of ischemic stroke. A longitudinal cohort study suggested that a higher obstructive AHI could be predictive of future incident ischemic stroke^[80]. Such OSA remains in the acute phase following the stroke attack. In contrast, CSA is likely to occur in the post-acute period of ischemic stroke, and there might be a cause and effect relationship between stroke and CSA during the acute phase following the stroke. This hypothesis is supported by observations in which SDB disappeared after the acute phase of stroke^[78,81]. However, there are reports showing that CSA remains in approximately 50% of the ischemic stroke patients at 3 mo after the onset of stroke^[78,82,83]. Injury in the brain or central nervous system, which may or may not be reversible, could be a possible explanation for such inconsistent results. In addition, a prospective study assessing 93 patients with stroke demonstrated that the presence of CSA was associated with a decrease in LVEF but was not related to the location or type of stroke. This study suggested that CSA after stroke was only a coexisting phenomenon of underlying cardiovascular diseases^[84].

Limited data suggest that the presence of CSA during the acute stroke phase might have a prognostic impact. Rowat *et al.*^[85] reported that central periodic breathing patterns, such as CSR, were common in acute stroke (24%) and were independently associated with a poor outcome after stroke. They found that 91% of the patients with central periodic breathing were dead or physically dependent compared with 53% of those without this condition.

However, the treatment of CSA related to stroke has not been well established. ASV has also been applied for CSA related to stroke. Speculation regarding the similarities of the pathophysiology of CSA in relation to stroke and HF has led to the consideration that ASV may be effective in the treatment of CSA after stroke. A single-center retrospective analysis of ASV treatment for CSA in post-acute ischemic stroke patients suggested that ASV was well tolerated and clinically effective in such patients^[86]. In that study, the role of ASV was evaluated in the treatment of CSA in post-acute stroke patients, most of whom were treated with other PAPs with insufficient reduction of AHI. ASV significantly improved AHI and reduced daytime sleepiness after 3 to 6 mo.

Other clinical applications of ASV

HF patients without SDB may also benefit from PAP therapy as a result of its cardiac unloading effects.

In fact, the short-term application of CPAP (*i.e.*, 5-10 cm H₂O) can increase cardiac output in stable HF patients with pulmonary congestion^[87]. This possibility has been further assessed in a subgroup analysis of a small randomized trial investigating the effects of CPAP on cardiac function and clinical outcomes in HF patients with and without CSA^[88]. In a subgroup analysis of patients without CSA, CPAP had no effect on either LVEF or the composite endpoint of mortality and the cardiac transplantation rate. However, based on recent data showing the acute beneficial effects of the short-term application of ASV on sympathetic nervous system activity^[9,89] and hemodynamics^[11,19], it has been suggested that ASV and not CPAP may be an effective option for HF patients beyond just as a treatment for SDB. In fact, Takama *et al.*^[10] reported that ASV treatment for HF patients resulted in almost equal improvements in BNP levels and LVEF regardless of the severity and type of SDB. Moreover, Koyama *et al.*^[13] reported that ASV was associated with better clinical outcomes regardless of the presence or absence of moderate CSA (*i.e.*, AHI < 20 or ≥ 20). In addition, a multicenter, retrospective, observational study that included 115 Japanese HF patients treated with ASV, regardless of the presence or absence of SDB, examined the effects on their symptoms and hemodynamics. Improvements in LVEF and New York Heart Association (NYHA) class after ASV therapy were not influenced by the severity of SDB^[90]. The possible benefits of ASV on cardiac function are being assessed in an ongoing randomized clinical trial in which HF patients with and without SDB are being randomized to either ASV treatment or medical therapy to assess changes in the LV ejection fraction at 6 mo (SAVIOR-C)^[91].

In general, the acute hemodynamic effects of PAP therapy are more prominent in HF patients with pulmonary congestion or increased LV filling pressure (*i.e.*, pulmonary capillary wedge pressure ≥ 12 mmHg)^[11]. Therefore, HF patients with a low filling pressure and those without hypervolemia should not be treated with PAP therapy including ASV, or they should at least be treated with caution^[90].

The acute effects of ASV in patients with acute cardiogenic pulmonary edema have also been evaluated^[12]. In an observational study, Nakano and colleagues found that after one hour of ASV with supplemental oxygen, plasma catecholamine concentrations fell significantly with declines in blood pressure, heart rate and respiratory rate compared with supplemental oxygen alone. These findings suggest that the use of ASV, in comparison to supplemental oxygen alone, may relieve dyspnea and improve hemodynamics, possibly through the modulation of sympathetic nerve activity. However, this hypothesis remains to be confirmed in a larger-scale randomized study comparing ASV and other PAPs.

In Japan, ASV is sometimes used during pulmonary

Table 4 Summary of recommendations for the use of adaptive-servo ventilation in various settings

Settings	Indication	Improvement other than AHI	Supporting evidence
With SDB			
HF	After optimization of HF, with CSA not suppressed by CPAP	Daytime sleepiness LVEF BNP Event-free survival	RCTs (<i>vs</i> CPAP) ^[3,4,40,41,43] RCTs (<i>vs</i> control) ^[36,42] RCT (<i>vs</i> Bi-level PAP) ^[37]
Treatment-emergent CSA	With HF Without HF	Same as HF Sleep architecture Adherence of PAP	Retrospective studies (pre-post study, <i>vs</i> CPAP) ^[64,65]
Idiopathic CSA	With symptoms	Daytime alertness and mood	Case series (pre-post study, <i>vs</i> CPAP or oxygen) ^[5]
Opioid-induced CSA	Benefit unknown		
Stroke-related CSA	Post-acute phase	Daytime sleepiness	A single-center retrospective study (pre-post study) ^[86]
Without SDB			
HF	Regardless of the presence or absence of SDB	LVEF NYHA class	A multi-center retrospective study (pre-post study) ^[91]
Acute cardiogenic pulmonary edema	With elevated filling pressure	Dyspnea High blood pressure	An observational study (<i>vs</i> supplemental oxygen alone) ^[12]
Atrial fibrillation	During PVI	Procedural time	On-off study ^[93]

AHI: Apnea-hypopnea index; ASV: Adaptive-servo ventilation; BNP: Brain natriuretic peptide; CPAP: Continuous positive airway pressure; CSA: Central sleep apnea; HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; PAP: Positive airway pressure; PVI: Pulmonary vein isolation; RCT: Randomized controlled trial; SDB: Sleep disordered breathing.

vein isolation (PVI) by catheter ablation for atrial fibrillation to maintain stable respiration. During the PVI procedure, the use of deep sedation with analgesia (propofol and pentazocine hydrochloride) suppresses respiration and/or results in upper airway collapse, leading to unstable respiration with a large variation that interferes with the PVI procedure, such as catheter positioning. The use of deep sedation with analgesia in combination with ASV lowers the frequency of restless body movements and stabilizes respiration, leading to a decreased total electrical energy supply, shorter fluoroscopy and procedural times, and a decreased rate of recurrence of atrial fibrillation^[92]. These findings should be confirmed in a larger-scale randomized study comparing ASV and other PAPs.

FUTURE PERSPECTIVES

We should note that indications for ASV and anticipated clinical outcomes in response to ASV are different in each situation (Table 4).

In HF patients with SDB, one can anticipate improvements with ASV use in cardiac function in addition to symptom relief due to SDB. If the long-term prognostic impacts of ASV for such patients are demonstrated in the future, a benefit of ASV will be more pronounced. Still, we should not overlook the following points: CPAP or ASV should be chosen appropriately, considering the cost-benefit of CPAP rather than ASV because approximately half of the HF patients with CSA can be sufficiently attenuated by CPAP; efforts to maintain adherence to devices should be implemented to derive the maximal benefit from them. In terms of maintaining adherence, intensive support for CPAP use, including a 3-night

trial of CPAP in the sleep center, education regarding home use of CPAP for patients and their partners and an additional home visit after initiating home use of CPAP, increased the duration of usage and improved symptoms compared with standard support^[93]. Thus, the strategy of initiating ASV for HF patients following admission due to acute decompensated HF is reasonable because more intensive support is available during hospitalization for ADHF. RCTs investigating the application of ASV for ADHF patients are needed, and we should also validate the usefulness of this strategy in the maintenance of adherence.

When treatment-emergent CSA is observed in HF patients, the same indication for HF patients with SDB can be applied. However, in patients without HF, we should avoid the routine use of ASV for treatment-emergent CSA, considering the high cost of ASV. We can apply ASV in such patients only to relieve symptoms of treatment-emergent CSA. We must determine the long-term prognostic impact of changing from CPAP to ASV for HF patients with treatment-emergent CSA. We must also determine which patients will experience prognostic benefits following such changes.

The impacts of ASV for idiopathic CSA or opioid-induced CSA are limited. ASV can attenuate CSA in such patients, but the significance of the effect for patients with no symptoms should be investigated further. The regular use of ASV in these situations may represent overuse and should be avoided.

Other situations of ASV use have been introduced in several reports. However, whether the clinical benefits of ASV exceed those of other PAP devices remains to be clarified. At present, additional evidence is needed to support the use of ASV rather than that of other PAP devices in such situations.

CONCLUSION

As discussed herein, the effectiveness of ASV in the field of cardiovascular and respiratory care is currently being established, and it will be more widely used if positive results are obtained in several large-scale RCTs. Therefore, clinicians should have a better understanding, for instance, of which patients should be targeted for ASV, how to apply it, and what is the anticipated outcome of ASV, with insightful consideration of the cost-effectiveness in each case.

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