

Central Sleep Apnea in Cardiovascular Diseases



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KEYWORDS

- Central sleep apnea (CSA) • Cardiovascular diseases (CVDs) • Heart failure (HF)
- Atrial fibrillation (AF) • Cerebrovascular accidents (CVA) • Apnea threshold
- Sleep-related breathing • Pathophysiology

KEY POINTS

- Central sleep apnea (CSA) is most commonly associated with cardiovascular diseases, particularly heart failure, atrial fibrillation, and cerebrovascular accidents.
- Central apneas generally occur during sleep when arterial CO₂ levels (Paco₂) fall below the apnea threshold due to various stimuli, despite variations in underlying pathophysiology.
- In patients with CSA linked to cardiovascular conditions, Paco₂ levels are typically normal or low. This article focuses on epidemiology, clinical manifestations, prognosis and treatment.

INTRODUCTION

Central sleep apnea (CSA) most commonly occurs in association with cardiovascular diseases (CVDs), and in particular heart failure (HF), atrial fibrillation (AF) and cerebrovascular accidents (CVAs). A detailed discussion of the pathophysiology of CSA in the setting of CVD is provided in another article (see Clodagh M. Ryan and T. Douglas Bradley's article, "[Central Sleep Apnea: Pathophysiology, Classification and Diagnosis](#)," in this issue) and will not be covered in any detail herein. Although its pathophysiology varies, in general, central apneas occur when the partial pressure of arterial CO₂ (Paco₂) falls below the apnea threshold during sleep due to various stimuli.^{1,2} In patients with CSA in the setting of HF, AF and CVA are generally either normo-capneic or hypocapneic, but not hypercapneic.³ In this article, we will focus on the epidemiology, clinical manifestations, prognostic implications, and treatment of CSA in the setting of CVD.

CENTRAL SLEEP APNEA IN HEART FAILURE *Epidemiology*

Sleep-disordered breathing (SDB) is highly prevalent in patients with HF, with both obstructive sleep apnea (OSA) and CSA frequently observed across the spectrum of HF phenotypes. Contemporary studies suggest that approximately 50% to 70% of patients with chronic HF exhibit some form of SDB, although prevalence estimates vary according to patient selection, diagnostic methodology, and definitions used for respiratory events. Among patients with HF with reduced ejection fraction (HFrEF), CSA accompanied by Cheyne–Stokes respiration (CSA-CSR) is common, occurring in approximately 20% to 40% of patients. However, OSA appears to be more prevalent than CSA in this population.^{4–6} To complicate matters, CSA-CSR and OSA often co-exist in patients with HFrEF, although one type generally predominates.⁶ In addition, the predominant type of SDB can shift over time: those with predominantly OSA may

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Abbreviations	
AASM	American Academy of Sleep Medicine
ADVENT-HF	Adaptive Servo-ventilation for Sleep-disordered Breathing in Patients with Heart Failure with Reduced Ejection Fraction
AF	atrial fibrillation
AHI	apnea-hypopnea index
ASV	adaptive servo-ventilation
CANPAP	Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure
CPAP	continuous positive airway pressure
CSA	central sleep apnea
CSR	Cheyne–Stokes respiration
CVA	cerebrovascular accident
CVD	cardiovascular disease
EEG	Electroencephalogram
EMG _{sm}	submental electromyogram
EMG _{at}	anterior tibialis electromyogram
EKG	Electrocardiogram
ESS	Epworth Sleepiness Scale
HF	heart failure
HFpEF	heart failure and preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICSA	idiopathic CSA
LVEF	left ventricular ejection fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MV	minute ventilation
NYHA	New York Heart Association
OSA	obstructive sleep apnea
PaCO ₂	partial pressure of arterial CO ₂
PF	peak airflow
PLM	periodic leg movements
REM	rapid eye movement
SaO ₂	arterial oxyhemoglobin saturation
SDB	sleep-disordered breathing

convert to predominantly to CSA-CSR if cardiac function deteriorates, and vice versa.^{7,8} Nevertheless, compared to those with OSA or no SDB, those with CSA-CSR have signs of more advanced HF including older age, more male predominance, lower body mass index, lower left ventricular ejection fraction (LVEF), worse mitral regurgitation, longer circulation time, higher cardiac filling pressures, lower Paco₂, higher prevalence of AF, and rates of pacemaker and cardioverter-defibrillator implantation as well as higher mortality risk.^{4,5,9} CSA-CSR has also been associated with adverse nonfatal clinical outcomes and may serve as a

marker of disease progression in patients with chronic HF and could identify individuals who may benefit from earlier referral for advanced therapies, mechanical circulatory support, or transplantation.⁹

Compared to HFrEF, fewer studies have examined the prevalence and clinical implications of SDB in patients with HF and preserved ejection fraction (HFpEF). Similar to HFrEF, recent observational studies suggest that SDB in HFpEF is highly prevalent, often with co-existence of OSA and CSA but with one type usually predominating.¹⁰ Whether CSA is generally associated with CSR has also not been addressed. In HFpEF, OSA appears more prevalent than CSA overall.^{10–12} However, whether the predominant type of SDB can shift over time in patients with HFpEF has not been studied. As in HFrEF, this suggests some common underlying pathophysiological factors in OSA and CSA in such patients.

Data specifically addressing CSA in patients with HFpEF remain limited compared with those available for HFrEF.¹³ Although SDB is common in HFpEF, most studies have focused on OSA or combined SDB populations, making the true prevalence of CSA difficult to establish. In a prospective cohort of 233 patients with HFpEF, moderate-to-severe SDB was identified in 41% of patients, with predominantly CSA observed in 14% and predominantly OSA in 27%.¹⁴ Similarly, analyses across the spectrum of HF have demonstrated that the prevalence of central events decreases as LVEF increases, whereas obstructive events become more common. In a cohort of 700 patients with HF, nighttime central apneas were present in 66% of patients with HFrEF compared with 34% of those with HFpEF.¹³ Patients with CSA in HFpEF appear more likely to exhibit markers of advanced cardiac dysfunction, including higher filling pressures, elevated natriuretic peptide concentrations, and higher rates of AF; however, the clinical phenotype and prognostic significance of CSA in HFpEF remain incompletely characterized. Further studies specifically focused on CSA are needed to define its prevalence, mechanisms, and clinical consequences in HFpEF.

Clinical Manifestations

Patients with CSA-CSR in HFrEF frequently present differently from patients with primary OSA. For example, patients with CSA often do not report snoring or excessive daytime sleepiness (EDS). Instead, patients more commonly report fragmented sleep, recurrent nocturnal awakenings, nocturnal dyspnea, and insomnia. Since they also have more advanced HF than those with OSA or no SDB, symptoms are more often attributable to the underlying HF, rather

than to SDB per se, such as fatigue, impaired exercise tolerance, ankle edema, and physiologic evidence of more advanced HF. Repetitive cycles of hyperventilation and apnea may result in sleep fragmentation, reduced sleep efficiency, and impaired sleep quality.¹⁵ Bed partners may observe periodic breathing, pauses in respiration, or restless sleep even if patients themselves remain unaware of these abnormalities.^{4-6,16-18} The reason for relative absence of hypersomnolence in HFrEF-associated CSA-CSR is not well understood. However, studies in patients with HFrEF and OSA have demonstrated an inverse relationship between subjective daytime sleepiness and sympathetic nervous system activity in patients with HFrEF. This suggests that higher sympathetic activity may enhance alertness through activation of the reticular activating system and mask sleepiness due to sleep fragmentation.^{19,20} Since patients with HFrEF and CSA-CSR have higher sympathetic activity than those with HFrEF but with either OSA or no SDB, the relative lack of hypersomnolence may be at least partly attributable to sympathetic activation.¹⁹⁻²¹ Consequently, symptom severity does not necessarily correlate with the degree of nocturnal respiratory disturbance.

This “sleepiness paradox” has important clinical implications because reliance on excessive daytime sleepiness to screen for SDB may substantially underestimate clinically significant CSA-CSR in patients with HFrEF. Therefore, screening based solely on classical symptoms of OSA is insufficient in this population, and objective sleep evaluation, preferable by PSG, should be considered in patients with advanced HFrEF who have AF, recurrent HF hospitalizations, persistent fatigue and exercise limitation even in the absence of excessive daytime sleepiness.²²

POLYSOMNOGRAPHIC AND PHYSIOLOGIC FEATURES

Polysomnographic Features of Cheyne–Stokes Respiration

Definitions and scoring of central apneas, hypopneas, and Cheyne–Stokes respiration are based on standardized American Academy of Sleep Medicine (AASM) criteria.²³ However, variability in respiratory event definitions and scoring methodology may contribute to differences in reported prevalence and phenotypic classification across studies.

The characteristic PSG pattern of CSA in HF is Cheyne–Stokes respiration, defined by cyclic crescendo–decrescendo changes in tidal volume interspersed with central apneas or hypopneas (Fig. 1). CSA-CSR cycle length is defined as the interval from the onset of one central apnea or hypopnea to the onset of the next event. In patients with

HF, CSA-CSR cycle and hyperpnea durations are prolonged and are much longer than in those with CSA but without HF owing to longer lung-to-chemoreceptor circulation time²⁴⁻²⁶ (see Fig. 1). The prolonged crescendo–decrescendo pattern of hyperpnea is related to the gradual and prolonged transmission of blood gas changes in the lungs to the peripheral and central chemoreceptors.²⁶

CSR is generally considered to reflect instability in the respiratory control system and is associated with enhanced chemoreflex sensitivity, increased overnight fluid shift from the legs to the lungs with stimulation of pulmonary vagal irritant receptors and prolonged circulation time.^{17,24}

CSR is primarily dependent on chemical-metabolic influences and is most prominent during non-rapid eye movement (non-REM) sleep, when ventilatory control is mainly dependent on chemical/metabolic influences. In contrast, CSA-CSR becomes less prominent in REM sleep when chemical-metabolic influences are diminished, and nonmetabolic/behavioral influences predominate. Accordingly, central apneas and hypopneas are more frequent in non-REM than in REM sleep.^{1,3} In addition, overnight rostral fluid shift into the lungs during the recumbent position may contribute to hyperventilation through stimulation of pulmonary vagal irritant receptors causing hyperventilation.^{27,28} Furthermore, substantial night-to-night variability in CSA-CSR severity has been demonstrated in patients with HF,²⁹ which emphasizes the limitation of relying on single-night polysomnography for phenotyping and severity assessment. Cyclic fluctuations in ventilation, intermittent hypoxia, arousals, and intrathoracic pressure changes may further exacerbate autonomic dysregulation and cardiovascular stress.³⁰

Prognostic Implications

In patients with HFrEF, there is controversy as to whether CSA-CSR is associated with adverse cardiovascular outcomes, including increased mortality, HF hospitalization, ventricular arrhythmias, and sudden cardiac death. Some studies report such a relationship,^{9,31} whereas others do not.^{15,32,33} One mechanism through which CSA-CSR could contribute to adverse CV effects is sympathetic nervous system activation. HFrEF provokes sympathetic activation, and the greater this activation, the higher the mortality risk.³⁰ Co-existing CSA-CSR may contribute to sympathetic activation through disinhibition of sympathetic outflow by apneas and sympathetic stimulation by intermittent apnea-related hypoxia and arousals from sleep.³ Compared to patients with HFrEF and either no SDB or OSA, those with CSA-CSR

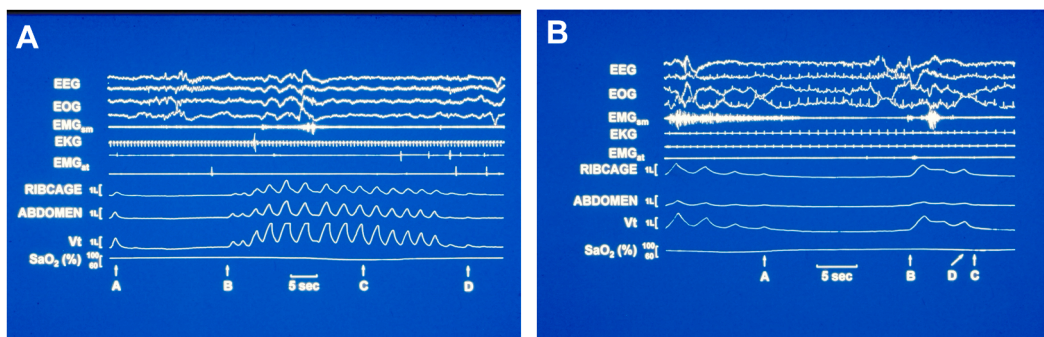


Fig. 1. (A) Polysomnographic recording of central sleep apnea with Cheyne–Stokes respiration (CSA-CSR) in a patient with heart failure. Note the absence of rib cage and abdominal motion when there is no tidal volume (V_t) excursion, indicating an absence of central respiratory drive. Following apnea, there is a crescendo-decrescendo pattern of V_t typical of CSA-CSR in association with a prolonged periodic cycle duration. A and B are the beginning and end of the of the apnea, respectively. C is the lowest arterial oxygen saturation (SaO_2) such that B to C represents the time taken for the lowest SaO_2 in the lung at end apnea to be detected by an oximeter placed on the ear (ie, lung to ear circulation time). D is the end of the hyperpnea. Compared to the subject with idiopathic CSA (ICSA) shown in the lower panel, apnea duration (A to B) is similar (21 seconds), but lung to ear circulation time (B to C = 26 seconds), total cycle duration (A to D = 65 seconds), and hyperpnea duration (B to D = 46 seconds) are much longer. This is due to lower cardiac output in this patient since total cycle and hyperpnea durations, and lung to ear circulation time are inversely proportional to cardiac output. (B) Polysomnographic recording of a central apnea in a patient with ICOSA. Note that compared to the patient with CSA-CSR in the upper panel, apnea length is similar (A to B = 18 seconds), but lung to ear circulation time (B to C = 8 seconds), total cycle duration (A to D = 25 seconds), and hyperpnea duration (B to D = 7 seconds) are much shorter. EEG, electroencephalogram; EKG, electrocardiogram; EMG_{at} , anterior tibialis electromyogram; EMG_{sm} , submental electromyogram; EOG, electrooculogram. (M J Hall, A Xie, R Rutherford, S Ando, J S Floras, T D Bradley, Cycle Length of Periodic Breathing in Patients With and Without Heart Failure, *American Journal of Respiratory and Critical Care Medicine*, 154 (2), August 1996, 376–381, <https://doi.org/10.1164/ajrccm.154.2.8756809>.)

have higher sympathetic nervous activity.²¹ However, there is some evidence that the increased sympathetic activity related to CSA-CSR is due to more advanced HFrEF.³⁴ In a recent study, Horvath and colleagues³⁵ compared mortality rates among patients with HFrEF and either OSA or CSA-CSR, and found significantly higher mortality in those with CSA-CSR. However, those with CSA-CSR also had evidence of more advanced HFrEF including lower LVEF, more severe mitral regurgitation, higher rates of AF, and higher NT-proBNP concentrations. After controlling for these factors, there was no independent effect of CSA-CSR on mortality risk. Thus, although CSA-CSR may be a marker of higher mortality risk, this may be because it is also a marker of more severe HFrEF. However, a limitation of that study is that it did not include patients with HFrEF but without SDB.

TREATMENT

Optimization of Heart Failure Therapy

Since CSA-CSR is related to HFrEF severity, the initial management of CSA-CSR in patients with HFrEF should focus on optimization of the HF therapy itself. Contemporary HF therapy, including medications, cardiac resynchronization therapy,

and exercise rehabilitation, may reduce the severity of CSA and CSA-CSR by reducing peripheral and pulmonary edema, and overnight rostral fluid shift as well as improving hemodynamic status with reduced circulation time.^{36–40}

Supplemental Oxygen

Supplemental O_2 may reduce ventilatory instability and central respiratory events by attenuating hypoxic chemoreflex activation and decreasing loop gain.⁴¹ The Impact of Low Flow Nocturnal Oxygen Therapy on Hospital Admissions and Mortality in Patients with HF and CSA (LOFT-HF) tested the hypothesis that supplemental O_2 at 3 L/min during sleep would reduce the primary composite endpoint of all-cause mortality, a life-saving cardiovascular intervention, cardiac transplantation, or unplanned hospitalization for worsening HF compared to sham O_2 .⁴² The estimated sample size was 858 patients with HFrEF and CSA-CSR. However, the trial was terminated after only 98 patients were enrolled and was underpowered to test the original hypothesis. O_2 reduced the AHI by only approximately 50%. There was a tendency to a higher primary even rate in the O_2 versus sham O_2 cohort (hazard ratio [HR] 1.46 [95% confidence interval (CI): 0.65, 3.29]) with no improvement in HF

or sleep-related quality of life indices. The reason for lack of efficacy was not determined but one possibility is that supplemental O₂ in such patients caused hyperoxia and its adverse hemodynamic effects related to oxidative stress, such as raising vascular resistance, blood pressure and left ventricular (LV) filling pressure, and lowering cardiac output.^{43,44} Taken together, there is insufficient evidence to support the use of O₂ to treat CSR-CSA in patients with HFrEF, and indeed, one must consider the possibility that supplemental O₂ may actually be harmful.

Respiratory Stimulants

Acetazolamide, a carbonic anhydrase inhibitor, induces a mild metabolic acidosis, thereby increasing ventilatory drive and widening the margin between resting PaCO₂ and the apneic threshold. Javaheri and colleagues demonstrated in patients with HFrEF and CSA-CSR, that through this mechanism, it improved respiratory control system stability and reduced the central AHI by about 50%.⁴⁵ However, this study had a small sample size and was of only 6-day duration so that long-term effects on CSA-CSR and clinical outcomes were not assessed. Because of this, the potential adverse long-term effects of metabolic acidosis and hypokalemia⁴⁶ that might precipitate arrhythmias, acetazolamide cannot be recommended for therapy of CSA-CSR in the setting of HFrEF.

Theophylline, an adenosine antagonist, stimulates central respiratory drive and augments cardiac contractility. In a 5-day randomized trial involving 15 patients with HFrEF and CSR-CSA, theophylline reduced the AHI but clinical outcomes were not assessed.⁴⁷ It must be kept in mind, however, that whereas theophylline was once used routinely for treatment of acute HF, its use for this purpose was abandoned because it increases the risk of cardiac arrhythmias and sudden death.⁴⁸ Consequently, theophylline cannot be recommended for therapy of CSR-CSA since its long-term safety and efficacy have not been demonstrated.

Inhalation of CO₂ or the addition of dead space raises PaCO₂ above the apnea threshold and thereby abolishes CSR-CSA instantaneously in patients with HFrEF.² However, because there is no evidence of long-term clinical benefits, and because CO₂ increases sympathetic nervous activity and disrupts sleep,⁴⁹ it cannot be recommended for therapy of CSR-CSA.

Continuous Positive Airway Pressure

In small short-term trials involving patients with HFrEF and CSA-CSR, continuous positive airway pressure (CPAP) has been shown to augment

cardiac output in those with elevated LV filling pressures, to reduce central AHI by about 50%, to improve autonomic function by reducing sympathetic and augmenting vagal activity and baroreflex sensitivity and improving LVEF.⁵⁰⁻⁵³

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial was the first large, long-term randomized trial to evaluate CPAP for treatment of CSA-CSR in patients with HFrEF.⁵⁴ It included 258 subjects, and although CPAP attenuated CSA-CSR by approximately 50%, improved nocturnal oxygenation, and modestly increased LVEF, reduced sympathetic activity and increased 6-minute walking distance, it had no significant effect on heart transplant-free survival or CV hospitalizations.

In a subsequent post hoc analysis of the CANPAP cohort, among those in whom CPAP reduced the AHI below 15 after 3 months, heart transplant-free survival was greater than in the control group and those in whom CPAP failed to reduce the AHI below 15.⁵⁵ These findings suggested the concept that effective suppression of CSA-CSR may be a key factor in improving CV outcomes in patients with HFrEF and CSA-CSR. Consequently, among patients with HFrEF and CSA-CSR, it would be reasonable to provide a trial of CPAP and repeat a PSG after 1 to 3 months while wearing CPAP. If the AHI falls below 15, then CPAP could be continued, but if it did not fall below 15, it should be stopped as it may worsen outcomes in those in whom it does not suppress CSA-CSR.

Adaptive Servo-Ventilation

Adaptive servo-ventilation (ASV) was initially developed specifically to alleviate CSA-CSR in patients with HFrEF through dynamic adjustment of inspiratory pressure support. In the initial version of ASV, pressure support was triggered by falls in minute ventilation (ASV_{MV}).⁵⁶ Among patients with HFrEF and CSA-CSR, ASV_{MV} was more effective in suppressing the central AHI than CPAP, BilevelPAP, and supplemental O₂.

The (Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure [SERVE-HF]) trial was the first large-scale, randomized trial designed to determine whether treatment of CSA-CSR with ASV_{MV} could improve cardiovascular outcomes in patients with HFrEF. Among 1325 participants, although ASV_{MV} effectively suppressed CSA, compared to the control group, it increased all-cause and cardiovascular mortality mainly due to an increase in sudden death (Fig. 2).⁵⁷ The cause of the increased sudden death rate was not identified.⁵⁸ It also had no beneficial effect on quality of

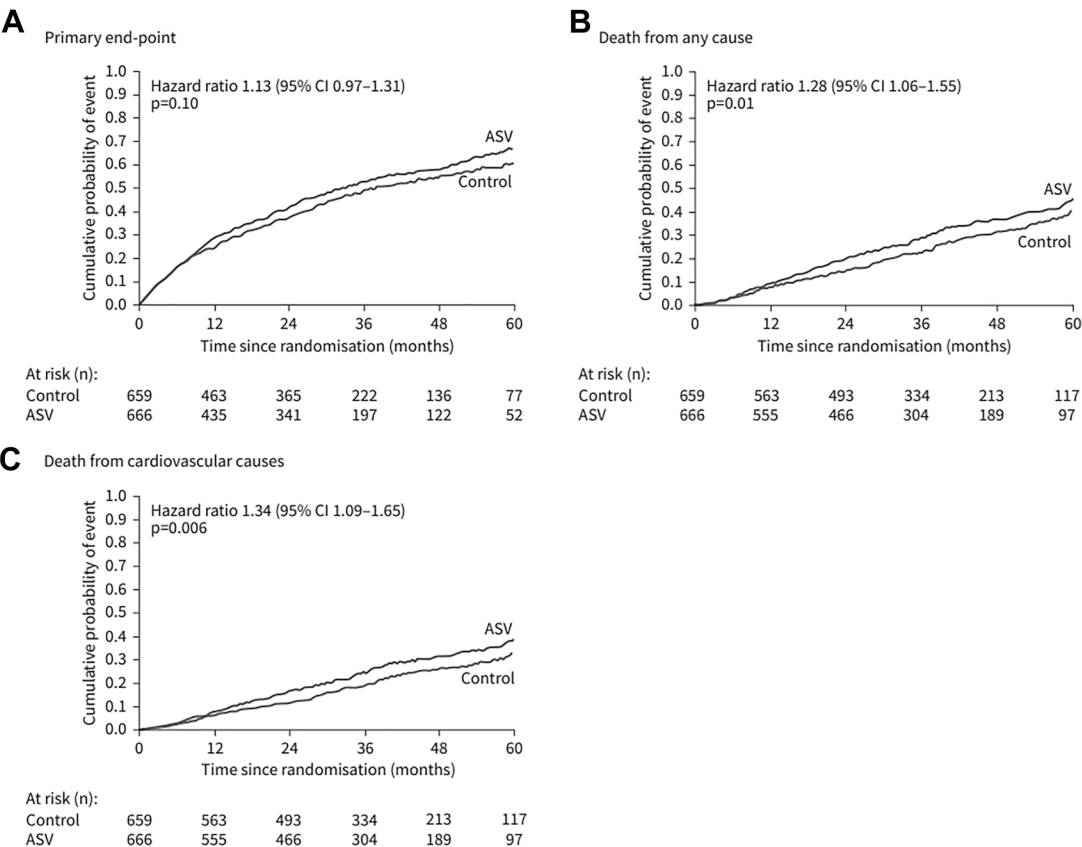


Fig. 2. (A–C) Effects of treating central sleep apnea in patients with heart failure and reduced ejection fraction by minute ventilation-triggered adaptive servo ventilation (ASV) in the SERVE-HF trial. Minute ventilation-triggered ASV had no effect on the primary endpoint, but increased both death from any cause and from cardiovascular causes. (From New England Journal of Medicine, Javaheri S et al., Effect of theophylline on sleep-disordered breathing in heart failure, 335 (8), 562-7. Copyright © 1996 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.⁴⁷)

life assessed by the Minnesota Living with Heart Failure Questionnaire, New York Heart Association (NYHA) class or the Epworth Sleepiness Scale (ESS) score. These findings led to recommendations against ASV use in patients with HFrEF and predominantly CSA.^{58,59}

Subsequent post hoc ancillary studies from the SERVE-HF trial reported that while ASV_{MV} reduced arousal frequency and stage N1 sleep time, it had no effect on stage N3 or REM sleep time.⁶⁰ ASV_{MV} also had no effect on echocardiographically assessed cardiac structure or function or biomarkers including NT-proBNP.^{60,61} Because of the adverse effects of ASV_{MV} on mortality and absence of any significant symptomatic benefits in patients with HFrEF, this iteration of ASV_{MV} is no longer available for clinical use.

In patients with HFrEF and SDB, one type of apnea usually predominates at a single point in time.^{6,12} If cardiac function changes, the predominant type can shift, in parallel: if OSA predominates,

it can convert to CSA if HF worsens and vice versa, should it improve.^{7,8,62} Accordingly, a newer version ASV, triggered by reductions in peak airflow (ASV_{PF}) was specifically designed to treat both CSA by automatically adjusting pressure support to treat central events, and unlike ASV_{MV}, by automatically adjusting end-expiratory pressure to treat obstructive events.⁶³ In a small-scale, short-term randomized trial, involving patients with HFrEF and co-existing OSA or CSA, Kasai and colleagues⁶³ tested the effects of ASV_{PF} compared to CPAP. Compared to CPAP, ASV_{PF} compliance was better; it was more effective in suppressing CSA-CSR and caused greater improvements in LVEF and quality of life.

The Adaptive Servo-ventilation for Sleep-disordered Breathing in Patients with Heart Failure with Reduced Ejection Fraction (ADVENT-HF) randomized trial evaluated the effects of ASV_{PF} on both OSA and CSA-CSR and on the primary composite endpoint of all-cause mortality, first

admission to hospital for a cardiovascular reason, new onset AF or flutter requiring anticoagulation and delivery of an appropriate cardioverter-defibrillator shock.⁶ It was stopped prematurely before reaching the estimated sample size of 860 because of COVID-19 restrictions on enrollment, and the Philips' recall of positive airway pressure devices for safety concerns related to potential disintegration of motor sound-abatement material.⁶⁴

Seven hundred thirty-one patients were enrolled: 533 with predominantly OSA and 198 with predominantly CSA.⁶ ASV_{PF} was very effective in controlling OSA and CSA such that it maintained the AHI in both groups below 5 throughout the maximum 5-year follow-up period. However, it had no significant effect on the primary endpoint either in the entire cohort or in the OSA or CSA cohorts

(Fig. 3). However, in the CSA-CSR cohort, there was a trend to lower all-cause mortality among those randomized to ASV_{PF} (HR, 0.74, $P = .25$). Importantly, comparison of all-cause mortality hazard ratios between patients with CSA-CSR in SERVE-HF and ADVENT-HF reveals that the outcomes of ASV_{MV} and ASV_{PF} therapy, respectively, in the 2 trials were qualitatively and quantitatively different (HR 1.73; 95% CI: 1.00–2.99; $P = .05$; Fig. 4), consistent with the concept that these 2 devices behave differently in patients with HFref and CSA-CSR.^{6,22} Similar to ASV_{MV} in SERVE-HF, ASV_{PF} in ADVENT-HF had no effect of LV structure or function.⁶⁵ However, in contrast to SERVE-HF, in ADVENT-HF, ASV_{PF} improved overall sleep structure with reduced arousal frequency and stage N1 sleep time and increased stage N3 and REM sleep time (Table 1).⁶ It also improved MLHFQ and ESS

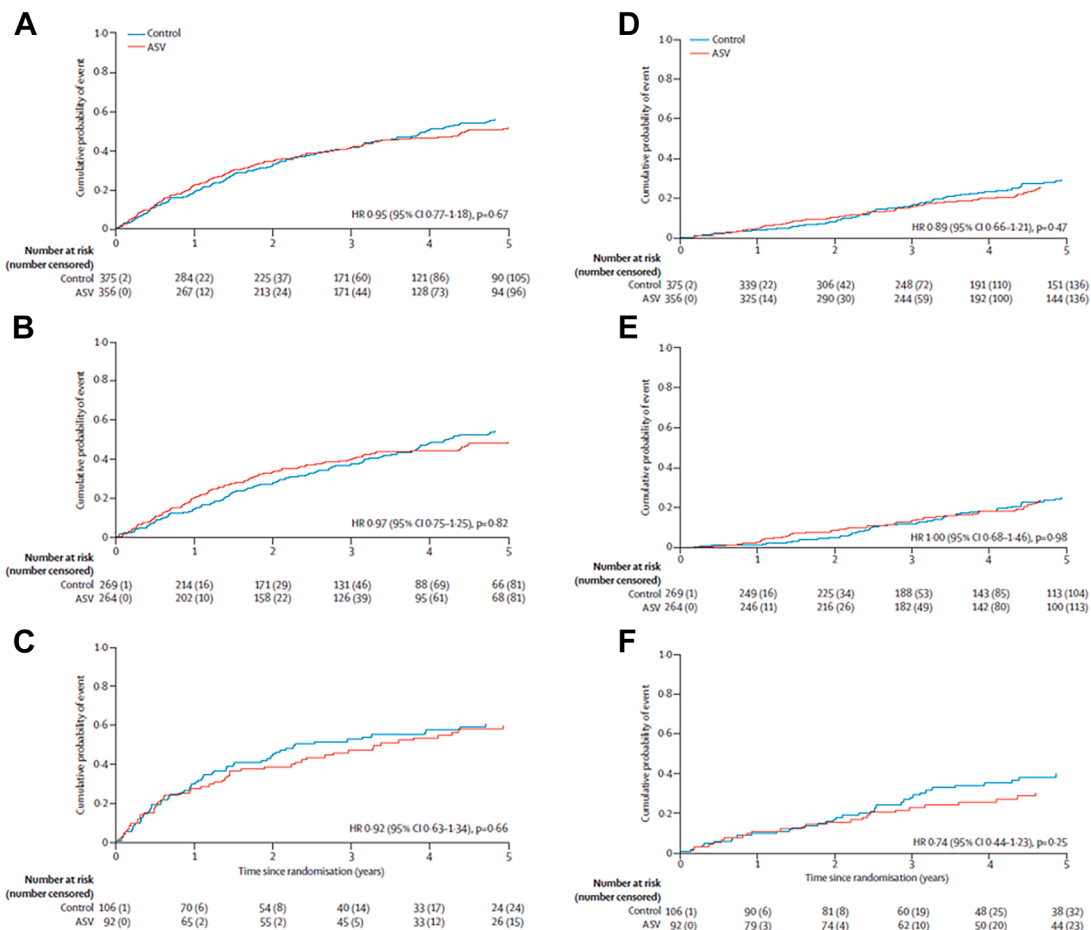


Fig. 3. Effects of treating obstructive and central sleep apnea (OSA and CSA, respectively) in patients with heart failure and reduced ejection fraction by peak flow-triggered ASV in the ADVENT-HF trial. Peak flow-triggered ASV had no significant effect on the primary endpoint in the entire cohort (A), the OSA subgroup (B), or the CSA subgroup (C). Similarly, it had no significant effect on all-cause mortality in the entire cohort (D), the OSA subgroup (E), or the CSA subgroup (F). (Reprinted with permission from Elsevier. The Lancet Respiratory Medicine, February 2024, 12 (2), 153–166.⁵⁰)

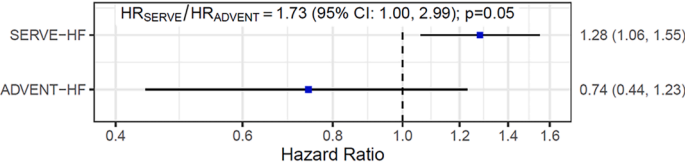


Fig. 4. Comparison of hazard ratios (HRs) for all-cause mortality in patients with CSA between minute ventilation triggered ASV in SERVE-HF and peak flow-triggered ASV in ADVENT-HF. The lower HR for peak flow-triggered ASV than for minute ventilation-triggered ASV, at a *P* value of 0.05, suggests qualitatively different effects with respect to this endpoint. (Reproduced with permission of the ERS 2026. Bradley TD, Logan AG, Floras JS. Treating sleep disordered breathing for cardiovascular outcomes: observational and randomised trial evidence. *Eur Respir J* 2024; 64: 2401033 [<https://doi.org/10.1183/13993003.01033-2024>].⁷)

scores over the duration of the trial (Fig. 5) in the entire cohort, and in both the OSA and CSA cohorts. These data suggest that effects of interventions on symptoms and quality of life are related to effects on sleep structure rather than cardiac function. Thus, assessment of sleep structure while on SDB therapy may provide further insights into how various interventions affect symptomatic responses.

A win-ratio analysis incorporating ADVENT-HF clinical and patient-relevant endpoints favors overall ASV_{PF} treatment benefit. The win ratio calculated on sequential addition of outcomes to the hierarchy, in the order death, CV hospitalizations, quality of life indices, and sleep structure was 1.18 (1.00–1.39). The win difference was 7.6%. The principal contributions to the latter were better quality of life (4.2%) and more time spent in stage 3 plus REM sleep (2.1%). Ranking quality of life second increased the win ratio to 1.22 (1.04–1.43) and the win difference to 9.1%. ASV_{PF} appeared more effective in the CSA-CSR than the OSA cohort with respect to sleep structure and quality of life.⁶⁶ Regarding safety of ASV_{PF} for therapy of CSA-CSR in patients with HFrEF, in addition to the nonsignificant tendency for lower mortality in the ADVENT-HF trial, a Bayesian interpretation of the ADVENT-HF results reveals that the probability of benefit (HR < 1) of 87.5% far outweighs the probability of harm (HR > 1) of 12.5%, and the probability that the hazard ratio is increased by more than a small amount (HR > 1.1) is very small: 6.5%.⁶⁷ Further, there was no difference in hazard ratios for ASV_{PF} between those with an LVEF of less than 30% (HR, 0.87; *P* = .52) and those with LVEF ≥ 30% (HR, 0.84; *P* = .45; interaction term 0.97, *P* = .93).^{6,68} Based on the totality of evidence, data from the ADVENT-HF indicates that ASV_{PF} can be applied safely to improve symptoms and quality of life in HFrEF patients with CSA-CSR. ASV_{PF} is available for clinical use outside of the United States.

Differences in ASV technology probably account for differences in outcomes for patients with CSA-

CSR between SERVE-HF and ADVENT-HF. By automatically controlling pressure support and end-expiratory pressure, ASV_{PF} caused a greater reduction in AHI than ASV_{MV} probably by better controlling obstructive events.^{6,58} The ASV_{MV} used in SERVE-HF had relatively high expiratory default settings of 5 cmH₂O and pressure support default settings of 3 cmH₂O, so that the minimum inspiratory pressure applied was 8 cmH₂O. The ASV_{PF} used in ADVENT-HF had a lower default minimum expiratory setting of 4 cmH₂O and minimum pressure support setting of 0 cmH₂O, such that the minimum inspiratory pressure applied would be only 4 cmH₂O. Applied pressure support up to 48 months after randomization was approximately 1.6 cmH₂O lower in patients with CSA-CSR in ADVENT-HF than in SERVE-HF.⁶ It was also reported that ASV_{PF} generates less minute ventilation overnight than the ASV_{MV} used in SERVE-HF,⁶⁹ so would be less likely to induce hyperventilation and its adverse consequences, such as hypokalemia and malignant cardiac arrhythmias.^{70,71} Taken together, these data indicate that ASV cannot be considered a generic device, but effects on outcomes in patients with HFrEF and CSA-CSR are device specific.

Transvenous Phrenic Nerve Stimulation

Modulation of ventilation by unilateral transvenous phrenic nerve stimulation via the superior vena cava is under investigation as a treatment for CSA-CSR on the premise that activation of the diaphragm during central apneas will improve cardiac function. By delivering synchronized stimulation to the phrenic nerve during central events during sleep, it can reduce the central AHI. Transvenous unilateral phrenic nerve stimulation has been studied in a randomized trial of 151 patients with predominantly CSA-CSR, only 64% of whom had HF.⁷² At the end of the 6-month trial period, the AHI fell approximately 50% in the paced group (from 49.7 to 25.9), and most of the residual events were obstructive. The AHI did not change in the control group. Oxygen desaturation improved, as

Table 1
Effect of ASV_{PF} on polysomnographic variables from baseline to 1 month following randomization

Variable	Control (n = 93)			ASV _{PF} (n = 84)			P
	Baseline	1 mo	Difference	Baseline	1 mo	Difference	
AHI, events/h	50.6 ± 18.3	49.7 ± 23.5	−0.3 ± 20.9	50.5 ± 18.1	13.6 ± 12.2	−36.1 ± 18.7	<0.001
3% O ₂ desaturation index, events/h	45.9 ± 19.8	43.8 ± 23.7	−1.5 ± 19.9	45.1 ± 18.2	10.4 ± 12.3	−34.3 ± 18.6	<0.001
Mean SaO ₂ , %	93.5 ± 2.4	93.7 ± 2.6	0.1 ± 1.6	93.5 ± 2.5	94.5 ± 2.1	1.0 ± 2.2	0.003
Min SaO ₂ , %	80.1 ± 10.0	80.4 ± 10.8	0.2 ± 7.5	78.8 ± 10.2	87.0 ± 4.8	7.8 ± 10.1	<0.001
Total sleep time, min	290.4 ± 72.0	299.8 ± 83.1	7.6 ± 74.9	286.2 ± 86.1	314.0 ± 86.3	24.6 ± 77.4	0.139
Sleep efficiency, %	67.5 ± 13.9	68.4 ± 16.1	0.8 ± 15.8	66.3 ± 18.5	72.5 ± 17.7	5.4 ± 16.2	0.054
Stage N1 sleep, min	52.0 ± 35.1	52.0 ± 34.9	−0.8 ± 29.9	46.0 ± 30.8	27.0 ± 21.3	−18.5 ± 33.0	<0.001
Stage N2 sleep, min	177.3 ± 56.4	182.2 ± 63.2	3.7 ± 61.7	181.7 ± 63.7	198.9 ± 62.1	13.2 ± 71.1	0.343
Stage N3 sleep, min	24.7 ± 22.9	24.3 ± 24.3	0.01 ± 24.0	24.3 ± 27.4	36.6 ± 29.0	12.2 ± 32.6	0.005
Stage REM sleep, min	36.9 ± 24.3	38.2 ± 26.4	0.9 ± 30.1	34.8 ± 24.8	47.7 ± 26.8	13.5 ± 25.2	0.003
Arousal index, events/h	45.4 ± 18.5	45.7 ± 21.6	0.2 ± 18.3	44.9 ± 21.3	24.9 ± 15.6	−19.3 ± 21.2	<0.001
PLM index, events/h	20.9 ± 30.3	21.7 ± 33.3	−0.2 ± 24.7	29.2 ± 34.9	43.2 ± 42.0	13.2 ± 29.3	0.001

Abbreviations: AHI, apnea-hypopnea index; ASV_{PF}, peak-flow-triggered adaptive servo-ventilation; PLM, periodic leg movements; REM, rapid eye movement; SaO₂, arterial oxygen hemoglobin saturation.

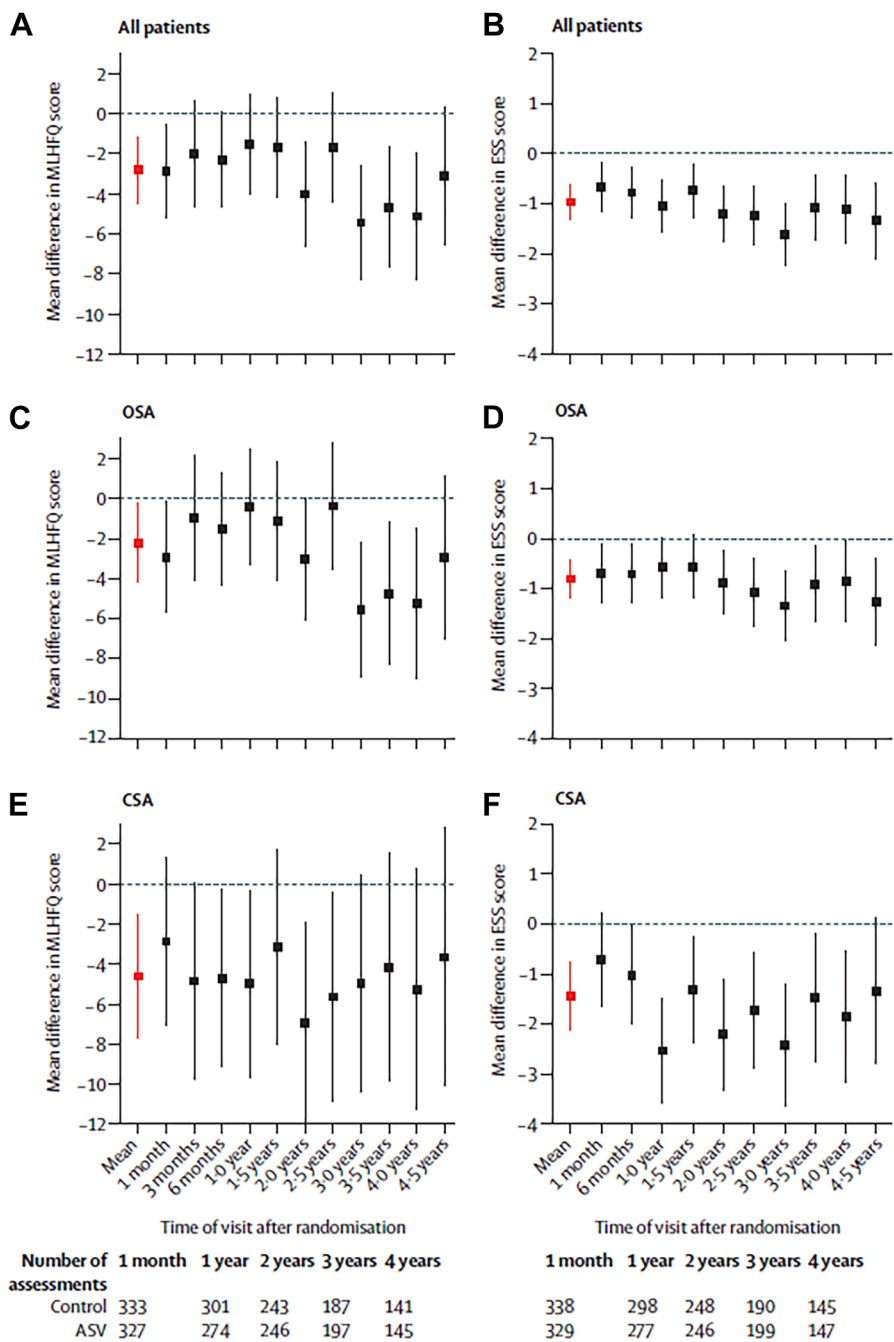


Fig. 5. (A–F) Effects of peak flow-triggered ASV on Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Epworth Sleepiness Scale (ESS) from the ADVENT-HF trial. Differences in MLHFQ score and ESS scores between the peak-flow-triggered ASV and control groups. Over the entire trial period, the ASV_{PF} group had significant improvements in mean MLHFQ and ESS scores for the entire cohort (–2.8, 95% CI –1.2 to –4.5; *P* = .0009 and –1.0, 95% CI –0.6 to –1.3; *P* < .0001, respectively); the OSA subgroup (–2.2, –0.2 to –4.2; *P* = .028 and –0.8, –0.4 to –1.2; *P* = .0001, respectively), and the CSA subgroup (–4.6, –1.5 to –7.7; *P* = .0036 and –1.4, –0.8 to –2.1; *P* < .0001, respectively). (Reprinted with permission from Elsevier. The Lancet Respiratory Medicine, February 2024, 12 (2), 153-166.⁵⁰)

did daytime sleepiness and quality of life. The trial was not powered for cardiovascular events. The high residual AHI due mainly to obstructive events is a significant limitation in patients with HFrEF who often have combinations of CSA and OSA, and whose predominant type can change over time. It is possible phrenic nerve stimulation could induce upper airway obstruction due to asynchronous activation of the diaphragm and upper airway dilator muscles.⁷³ It is also possible that unilateral stimulation is not sufficient to abolish CSA-CSR in a substantial proportion of patients. In any case, further studies will be required to determine whether this therapy will improve cardiovascular outcomes.

Per cutaneous phrenic nerve stimulation was originally developed in 1948 to treat hypoventilation syndromes⁷⁴ and can be applied either unilaterally or bilaterally, safely over many years. Accordingly, it might be explored as an alternative to transvenous stimulation, as it is less invasive and can be applied bilaterally.

CENTRAL SLEEP APNEA IN ATRIAL FIBRILLATION

Epidemiology

Among patients with HFrEF, AF is associated with increased odds of having CSR-CSA.² Among patients with CSA but without HFrEF, cerebrovascular disease, or renal disease, AF was observed in 27%.⁷⁵ CSA is a predictor of incident AF risk in older men (>65 years).⁷⁶ Cross-sectional and observational studies suggest that CSA is more prevalent in patients with AF compared with those without AF.^{75,76} The reason for the association between CSA and AF was not identified. However, the most likely possibility is that AF predisposes to CSA by mechanisms similar to those that predispose patients with HFrEF to CSR-CSA: AF lowers cardiac output and raises pulmonary venous pressure that could trigger hyperventilation and hypocapnia through stimulation of pulmonary vagal irritant receptors while recumbent during sleep.

Clinical Manifestations

Symptom profiles of CSA in patients with AF are not well described. It seems that CSA can present with nonspecific symptoms, including fatigue, and fragmented sleep.^{75,77} Excessive daytime sleepiness is variably present and may be less prominent than expected relative to the degree of nocturnal respiratory instability, similar to that described for OSA in HFrEF.^{19,20}

As a result, CSA may remain underdiagnosed in patients with AF unless actively screened using sleep studies. This underscores the importance of

maintaining a high index of suspicion for CSA in AF populations, especially in the presence of HFrEF.

Prognostic Implications

The prognostic implications of CSA in patients with AF are unknown.

Treatment

In the absence of randomized trials of therapy of CSA in AF, management of CSA in patients with AF should primarily focus on optimization of AF treatment, including pharmacologic therapy, and radiofrequency ablation as required. A trial of CPAP or ASV_{PF} might be indicated if patients have symptomatic CSA. There is, however, no evidence that treating CSA in either paroxysmal or chronic AF will improve cardiovascular outcomes.

CENTRAL SLEEP APNEA IN Cerebrovascular Disease

Epidemiology

SDB occurs in as many as 70% of patients after ischemic or hemorrhagic stroke.^{78,79} OSA predominates, but CSA is also common. The prevalence appears to be highest in the acute post-stroke period, and severity of CSA tends to decrease over time.

The pathophysiology of CSA in the post-stroke period is poorly understood. However, in the subset with CSA-CSR, it is associated with occult LV dysfunction and hypocapnia.⁸⁰ This suggests that stroke per se may not be a cause of CSA-CSR, but that co-existing asymptomatic LV systolic dysfunction may be the culprit.

Clinical Manifestations

CSA in cerebrovascular disease may present with nocturnal periodic breathing, oxygen desaturation, sleep fragmentation, and reduced sleep efficiency. Daytime manifestations often overlap with post-stroke fatigue, cognitive impairment, and reduced vigilance, making clinical recognition challenging.⁷⁹

Because these symptoms are frequently attributed to neurologic injury itself, CSA may be under-recognized unless polysomnography or respiratory monitoring is actively performed.⁷⁸ Also, CSA may dissipate over time for reason not well understood. This suggests that approaches to treatment need to take this time course into consideration and may require re-evaluation at regular intervals.

Prognostic Implications

A paucity of data on prognostic implications of CSA after stroke makes it difficult to determine its clinical significance. Prospective long-term

studies would be required to shed light on this issue.

Treatment Considerations

Because of a lack of randomized clinical trials, indications for and treatment of CSA in cerebrovascular disease remains challenging. Optimization of underlying neurologic and cardiovascular status represents the primary therapeutic approach. In an observational study of 15 patients with CSA following stroke, ASV was found to be more effective than CPAP or bilevel-PAP in alleviating CSA. ASV caused a reduction in the AHI (46.7 ± 24.3 vs $8.5 \pm 12/h$, $P = .001$) and ESS score (8.7 ± 5.7 vs 5.6 ± 2.5 , $P = .08$) with a mean nightly use of ASV of 5.4 ± 2.4 hours at 3 months after the initiation of treatment.⁸¹ However, no randomized trials have assessed effects of treating CSA post-stroke on long-term neurologic and functional outcomes.

SUMMARY

CSA and CSR are most common in the setting of HFrEF. So far, the best evidence for treatment indications comes for the ADVENT-HF trial, where ASV_{PF} alleviated CSA-CSR in association with improvements in HF and sleep apnea symptoms without causing either adverse or beneficial effects on morbidity or mortality. Thus, treatment of CSA-CSR in patients with HFrEF should be undertaken with the expectation of improvement in symptoms, but not cardiovascular endpoints. Long-term effects of phrenic pacing on cardiovascular outcomes remain to be determined. In the setting of AF and stroke, very little data are available on effects of treating CSA on clinical outcomes, such that treatment decisions need to be made on the basis of individual’s symptoms and availability of therapeutic options. Close monitoring of symptoms in such cases is warranted. In general, more larger and longer-term randomized trials of treating CSA in the setting of AF and stroke are necessary to inform management decisions.

CLINICS CARE POINTS

- Treatment of CSR-CSA in patients with HFrEF should first involve optimization of heart failure therapy, but if CSR-CSA persists, ASVPF treatment can be applied to improve sleep quality and symptoms of heart failure and sleep apnea.
- Treatment of CSA in AF should first involve optimization of AF therapy, but if CSA persists, ASV could be considered, but no randomized

- trials have demonstrated long-term beneficial effects of this or other interventions.
- For CSA following stroke, the possibility of underlying left ventricular dysfunction should be investigated, and if found, treated. Otherwise, ASV could be applied for sleep apnea symptom relief, but without randomized trial evidence of benefit.

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