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REVIEW

Central Sleep Apnea: An Update of Current Treatment and the Role of Positive Pressure Devices

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Abstract

Purpose of Review Central sleep apnea (CSA) is associated with increased mortality, particularly in heart failure. This review discusses current treatment options with a focus on different positive airway pressure (PAP) modalities, the clinical implication of continuous PAP (CPAP) failure, and key advancements in adaptive servo-ventilation (ASV).

Recent Findings CPAP reduces CSA by about 50% in patients with heart failure with reduced ejection fraction. The remaining patients are considered non-responsive and chronic use of CPAP has been associated with excess mortality. ASV is effective in several forms of CSA. While secondary analyses of the SERVE-HF trial limited its use in patients with predominant CSA and left ventricular ejection fraction < 45%, more recent data from ADVENT-HF using a newer ASV generation targeting peak flow has shown promising results.

Summary Physicians should consider the underlying pathophysiology, overall prognosis, and evidence base prior to selecting CSA treatment with CPAP or ASV. Promising pharmaceutical and novel device options require more studies and long-term evidence.

Keywords Periodic breathing · Heart failure · Bilevel positive airway pressure · Adaptive servoventilation · Loop gain · Apneic threshold

Introduction

Central sleep apnea (CSA) represents a heterogeneous group of sleep related breathing disorders (SRBD) characterized by the recurrent cessation of airflow associated with absence of respiratory effort. Thus far, CSA classification has been based on the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) level with disorders classified under hypercapnic and hypocapnic categories [1]. However, there is considerable overlap. For example, heart failure with reduced ejection fraction (HFrEF) is in the hypocapnic category, yet many such patients have normal $PaCO_2$ levels. In contrast, opioid-associated CSA is in the hypercapnic category, but again a number of such individuals have $PaCO_2$ values within normal levels [2].

Recently a new classification of CSA was suggested by Javaheri and Badr [3]. This classification emphasizes that there is overlap between hypercapnic and non-hypercapnic CSA and seeks to categorize CSA according to the underlying pathophysiology:

- High loop gain due to high controller gain which is the most common (e.g. heart failure).
- High loop gain due to elevated plant gain (e.g. neuromuscular disorders).
- Failure of rhythm generation at the pre-Bötzinger compex/ Kolliker-fuse parabrachial neurons e.g. opioid-associated CSA.
- Unclassified.

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The underlying cause and pathophysiology of CSA is varied resulting in a wide spectrum of clinical diseases and outcomes. CSA adversely affects cardiovascular function by causing tissue hypoxia, arousals from sleep, and activation of the sympathetic nervous system, thereby independently increasing the risk of death [1]. Heart failure (HF) is the most common condition associated with CSA such that the available literature focuses almost exclusively on this important group (Table 1). Other entities include CSA in musculoskeletal or neurological diseases, drug-induced CSA, treatment-induced CSA, high-altitude CSA and idiopathic CSA. Understanding the mechanism behind the CSA in each disease process is essential in the selection of treatment options.

Periodic breathing (PB) is a polysomnographic subtype of CSA, with Hunter-Cheyne-Stokes breathing (HCSB) denoting the presence of PB in HF [4]. CSA with HCSB is the focus of this review, being more prevalent and therefore having a greater clinical impact.

Pathophysiological Mechanism of CSA in Heart Failure

The ratio of the size of the ventilatory response to the breathing disturbance can be described using the concept of loop gain (LG). This term, which has been extensively described [5, 6], characterizes this form of CSA. LG refers to the response of the ventilatory system to any disturbance, and includes the reactivity of the ventilatory system via the lungs (plant gain) as well as the peripheral chemoreceptors at the carotids and the central chemoreceptors at the brainstem (controller gain) to a disturbance. If the ventilatory response to this disturbance is excessive (high loop gain), overshoot will occur and result in hypocapnia which can result in central apneas. Chemostimulation due to CSA (hypoxia and increased $PaCO_2$ stimulating peripheral and central chemoreceptors) leads to further overshoot and the cycle self-repeats rather than dissipates, as would be the case with a normal loop gain.

The $PaCO_2$ in the blood has a semi-linear impact on ventilation through its influence at the central chemoreceptors [7]. Hypercapnia stimulates ventilation and hypocapnia reduces it. The level of $PaCO_2$ below which breathing ceases – the apneic threshold (AT)—dictates the overall stability of the system. Whenever $PaCO_2$ drops below the AT, a central apnea occurs [8]. A small distance between the AT and the actual $PaCO_2$ (the so-called CO_2 reserve) predisposes to unstable ventilation. Under these circumstances, even mild variations in minute ventilation reduce the $PaCO_2$ below or elevate it above the AT. Hypersensitivity of the chemoreceptors and ensuing responses of the chemoreceptors induce a vicious cycle of alternating hyper- and hypoventilation. The resulting clinical and polysomnographic (PSG) pattern of PB appears with crescendo–decrescendo variations in tidal volume and respiratory effort (HCSB). Other investigators point out that sleep state instability with increased arousals can also contribute to a drop in CO_2 level due to the associated ventilatory response [9–11].

CSA is primarily a disorder of non-rapid-eye-movement (NREM) sleep when ventilatory drive and minute ventilation are metabolically controlled by $PaCO_2$ levels [3]. CSA is relatively uncommon in REM sleep.

Treatment Rationale and Therapy Options in CSA

The presence of sleep-related breathing disorders (SRBD) has been shown to have an independent impact on overall mortality regardless of the underlying disease process [12–17]. There is no convincing evidence from randomized controlled trials (RCT) to show that CSA-specific therapy improves mortality, particularly outside HF. However, large population-based studies of SRBD such as the Wisconsin sleep cohort [13] and retrospective analyses of HF patients show that those who are diagnosed and treated have better survival [18]. Several studies subsequently presented in this review do show an improvement in sleep quality and functionality and an improvement in quality of life (QoL), however the benefit is not consistently shown. The decision to initiate CSA-specific treatment should therefore be based on a combination of the severity of the breathing disorder, and the clinical and symptomatic impact based on patient-related outcome parameters.

Prior to selecting a specific therapy for management of CSA, any underlying cardiovascular, internal, neurological or pharmacological causes should be optimized, including optimal guideline directed medical therapy of HF. If CSA remains unresolved, additional therapy directed at resolving CSA should be considered. This includes careful history taking in the recognition of drug-induced CSA with drug withdrawal if possible and time for acclimatization or immediate descent in CSA associated with high-altitude.

Pharmacological Therapy

A variety of pharmaceutical agents addressing various pathophysiological components have been studied or are under current investigation. Long-term data on overall prognosis is limited with all these agents. In clinical practice, pharmacological therapy is considered in cases of primary CSA and treatment emergent central sleep apnea (TECSA) or in individual cases with either failure or inappropriateness of other treatment options [19, 20].

- Buspirone, a 5-HT-receptor agonist, reduces central chemoreceptor sensitivity to CO_2 (a decrease in controller gain) and consequently downregulates the high loop gain, stabilizing breathing [21].

Table 1 Common causes of CSA, prevalence, physiology and outcome

Clincal Phenotype	Prevalence	Origin	Pathophysiology	Mortality
CSA in Heart failure (HFrEF and HFpEF)	36–49% HF patients in cohort studies [90–92]	Stimulation of vagal afferents by excess interstitial fluid [93] Dysfunctional autonomic control [94]	Augmented chemosensitivity (increased controller gain) High loop gain, especially when associated with arousals Restrictive ventilatory effect (increased plant gain)	Independent risk factor for all-cause death and hospitalization [1, 15, 17, 91]
Drug-induced CSA Opioids GABA-receptor agonists: Xyrem, Baclofen, Valproic acid, Gabapentin Ticagrelor	24% of 392 chronic pain patients using opioids [95] Case reports in non-opioid induced CSA [96–99]	Dose-dependent Daily morphine equivalent dose > 200 mg highest risk	Co-colonization of μ-opioid receptors Dampening of plant gain and muscle activity Effect upon Pre-Bötzinger leading to ataxic breathing Ticagrelor: Increased chemosensitivity to pCO_2 (controller gain) [100, 101]	Speculative contribution to unexplained death in patients using these drugs [50]
CSA in internal medical and neurological disorders	7% of stroke patients in a meta-analysis of 2,343 patients [102]	Direct damage to the brain	Dependent on area and extent of damage High loop gain/increased plant gain (non-hypercapnic CSA) Lack of ventilatory drive through failure of rhythm generation (hypercapnic CSA)	Independent impact on overall mortality in stroke patients [12]
Treatment-emergent CSA (TECSA)	Persistent TECSA: 1–5% of untreated OSA patients [19, 103]	Occurring after PAP initiation without a back-up rate in OSA Transient (disappears), persistent (new-onset and unresolved after 3 months) or emergent (delayed onset)	PAP therapy decreases $PaCO_2$ below the apnoeic threshold Increased chemoreflex sensitivity (high loop gain/controller gain)	No direct data
Primary or idiopathic CSA	3.8% of all CSA patients in a population-based study [104]	Unknown origin	Arousals and consecutive hyperventilation (high loop gain/controller gain)	6/23 (26%) patients died in a cohort analysis (median follow-up, 4.4 years) [104]
High-altitude PB	Susceptible individuals at altitudes above 2000 m and all at > 5000 m [39]	Hypoxia induced hyperventilation Alterations to cerebral blood flow	Hypocapnia secondary hypoxic ventilatory drive (High loop gain/controller gain)	Reversible

CSA central sleep apnea, *HF* heart failure, *PAP* positive airway pressure, *OSA* obstructive sleep apnea, *PB* periodic breathing

- Acetazolamide, a carbonic anhydrase inhibitor, is a respiratory stimulant that increases alveolar ventilation and widens the CO_2 reserve, helping to stabilize breathing through decreased plant gain [22]. Short-term studies have shown improved sleep parameters, and symptom reduction with no serious adverse events [23–25]. The use of acetazolamide is well-established in high-altitude induced periodic breathing and acute mountain sickness [26].
- Theophylline, a respiratory stimulant, also works by decreasing plant gain similar to acetazolamide [27].
- Hypnotics such as Zolpidem reduce arousals and in an open label study of idiopathic CSA improved the total apnea-hypopnea index (AHI) [28]. However, in a RCT use of benzodiazepine receptor agonists reduced arousals but did not significantly reduce CSA in HF patients [29]
- Novel pharmaceutical candidates that inhibit the signaling of neurotransmitters which underlie hypoxia-induced chemosensitivity in the carotid body (CO, H_2S, and P_2X_3 receptors among others) may also eventually be used to treat PB [30–33].

Although these drugs alone may not suffice to resolve CSA completely, they may play a role in future multimodal concepts.

Transvenous Phrenic Nerve Stimulation (TPNS)

TPNS describes the use of an implanted neurostimulator to stimulate the phrenic nerve. The basic mechanism which overcomes CSA is the stimulation of the diaphragm. However, in the subtype of PB (high loop gain), the mechanism needs to be studied further. TPNS may additionally break the cycle of PB by interfering with the pathophysiology. It prevents periods of undershoot and hypercapnia, thus avoiding subsequent overshoot. RCTs as well as single-center and pooled studies have shown benefits of TPNS including significant improvement in CSA, desaturation, and arousals and quality of life (QoL). These studies also demonstrate that TPNS is well tolerated [34, 35]. A small prospective cohort study (n = 24) demonstrated safety and efficacy of TPNS as well as improvement in physical performance capacity and reduced hypoxemic burden in patients with HF [36]. Data from long-term RCTs for hard outcomes are needed concerning safety in HF. However, an adequately powered RCT along with long-term observational studies have demonstrated overall safety and effectiveness leading to Federal Drug Administration clearance of TPNS for CSA.

Nocturnal Low-Flow Oxygen Therapy

An increase in arterial O_2 works to lower the carotid-body chemosensitivity and to improve myocardial function. Low-flow nocturnal oxygen therapy attenuates CSA and lessens the augmented sympathetic activity seen in subjects with HFrEF. Physiological improvement in maximum oxygen consumption with exercise and increased LVEF and (QoL) have also been demonstrated [37]. There is evidence that oxygen therapy lowers AHI [38], but no long-term prognostic benefit has been proven. The phase 3 RCT LOFT-HF (Impact of Low-Flow Nocturnal Oxygen Therapy on Hospital Admissions and Mortality in Patients with Heart Failure and CSA) was terminated early due to low patient recruitment during the COVID-19 pandemic. Oxygen therapy is easily available and well tolerated. However, there is no evidence to show that its use is comparable to that of PAP therapy or to prove that there is no harm in HFrEF patients long-term. Therefore, it remains an individual treatment for those unable to comply with or lacking access to PAP therapy. Oxygen therapy is also used in the treatment of high-altitude CSA [39].

Positive Pressure Therapy

Continuous Positive Airway Pressure (CPAP)

CPAP mechanically supports and opens up the upper airway without addressing the shallow breathing patterns and breathing cessation characteristic of CSA. CPAP does improve oxygenation through reduction of ventilation/perfusion (V/Q) mismatch, which has an effect on the pathophysiology of CSA. CPAP also affects the preload and afterload of the heart, leading to a decrease in systolic blood pressure and an improvement in LVEF and right ventricular function (RVF) [40–42].

Evidence was initially promising that CPAP may reduce sympathoneural activity [43] and improve QoL and mortality in HF [41]. The CANPAP trial studied the effect of CPAP therapy in 258 HF patients with CSA. The first polysomnography was performed at 3 months after use of CPAP. There was an improvement in nocturnal oxygenation, the number of respiratory disturbances and the LVEF; however, there was no improvement in QoL, reduction in hospitalization at 2 years or transplant-free survival [44]. Although CPAP reduced AHI overall by 53%, 43% of the study participants still had a residual AHI of $\geq$ 15/h. A post-hoc analysis by Arzt et al. stratifying by treatment efficacy (AHI less than 15/h versus those with AHI $\geq$ 15/h) demonstrated both improvement in LVEF and transplantation-free survival in those with effective suppression of CSA with CPAP [45].

Treatment-response may indicate a specific phenotype with better outcomes to CPAP. In this regard, Sands et al. examined the question as to why CPAP is only successful in half of the patients. They designed and validated a mathematical system to efficiently analyse LG and showed that CPAP is effective in HCSB if the loop gain was < 1.10 [46]. Herkenrath et al. showed that LG also depends on

the sleep stage and body position with less ventilatory overshoot in REM sleep [47].

The practice of using automatic PAP (APAP) for home or in-lab titration for the initial treatment of obstructive sleep apnea (OSA) is well established. This allows physicians to identify the minimum pressure needed to keep airways patent. A recent large RCT of CPAP vs. APAP in the treatment of OSA was able to show that these modalities have similar effectiveness and adherence [48]. There is no similar research as to the effectiveness of APAP in the treatment of CSA so that this algorithm cannot be recommended in case of CPAP failure. As the mean pressure in APAP is substantially lower in CSA compared to when used in OSA (it is the obstruction which is the main trigger for the higher pressure), the above mentioned effects on lung ventilation and cardiac mechanics cannot be translated one-to-one to CSA [49].

CPAP may also have limited effect in opioid-associated CSA. Teichtahl et al. postulate that the dose-dependent development of SRDB with opioid use may be a cause for unexplained death in these patients [50]. Troitino et al. [51] performed a retrospective analysis and found that CPAP reduced the AHI to ≤ 10/h in only 24% of the studied patients. Similarly, evidence for the use of CPAP in the management of high-altitude CSA is limited. It may be discussed in combination with drugs and oxygen.

In routine clinical care, CPAP remains a cost-effective initial treatment option in most forms of CSA. As there is no evidence of prognostic benefit, close supervision of treatment response regarding improvement of both breathing disturbances and symptoms is required [1, 20]. If ineffective, the use of adaptive servo-ventilation (ASV) should be considered.

Bilevel Positive Airway Pressure (BPAP)

BPAP delivers two different but fixed pressure levels during inspiration and expiration. BPAP can be used in spontaneous (S), timed (T) or spontaneous-timed (ST) mode. BPAP is comparable to CPAP and APAP in that it stabilizes the upper airway, however, it also additionally provides mechanical ventilation. In contrast to S-mode, in the presence of insufficient ventilation in hypercapnic respiratory failure, the T-mode and ST-mode can apply mandatory breaths and non-invasively ventilate patients by increasing the difference between inspiratory and expiratory pressure. The fixed pressure and the pressure difference of BPAP leads to the danger of hyperventilation and may worsen central apnea by lowering the $PaCO_2$ below the AT [52]. The persistence of central apneas under CPAP treatment in some patients and the lack of an alternative therapy however culminated in trials of BPAP therapy, which initially showed some acute effect over the course of a single night [53]. A 6-month follow-up of a small cohort of CPAP non-responders (n = 7) treated with BPAP showed some clinical benefit such as an improvement in LVEF [54]. A RCT of 30 patients with TECSA (previously treated with CPAP) assigned to either non-invasive ventilation (NIV) or ASV showed that respiratory events were treated more effectively with ASV [55]. Most importantly the initial positive effects seen after the first night of BPAP were attenuated at 6 weeks follow-up.

The risk of deterioration based on our understanding of physiology combined with the paucity of clinical evidence suggests that there can currently be no recommendation for the use of BPAP therapy in the treatment of non-hypercapnic CSA (high loop-gain CSA).

Adaptive Servo-Ventilation

ASV was developed as a treatment for CSA not responsive to CPAP therapy. It is a form of NIV that delivers variable servo-controlled inspiratory pressure support (IPS) when tidal volume wanes and withdraws that support when ventilation is excessive [56]. The devices measures instantaneous inspiratory airflow in order to calculate ventilation. The continuous measurement of airflow enables the calculation and maintenance of target ventilation, set at 90% to 95% of the recent average ventilation. ASV algorithms differ in the target parameters of minute ventilation (ASVmf) or peak flow (ASVpf). Mandatory breaths are applied in a timed backup mode to abort any frank apneas.

The first generation ASV devices applied a fixed expiratory PAP (EPAP) to suppress obstructive events [57]. The EPAP was set based on data from a previous PAP titration. Newer generations of ASV apply variable EPAP according to the actual upper airway obstruction. Moreover, the previous algorithms applied a minimal pressure support of 3 cmH_2O, even during hyperventilation, while the newer algorithms allow for zero pressure support when it is not needed.

There is a large body of evidence dating back to 2001 to confirm the effectiveness of ASV in the treatment of CSA not responsive to CPAP, above all in HF, but also in CSA related to chronic opioid use and TECSA (Table 2). ASV normalizes both OSA and CSA including HCSB, reduces brain natriuretic peptide, and improves symptoms, LVEF, and sleep parameters. Treatment response appears to be superior to CPAP and oxygen. [2, 56, 58–74]. Sleep apnea is classified at PSG as either predominantly obstructive or predominantly central to guide therapy. However, the predominant mechanism of sleep apnea may vary throughout the night concurrent with changes in sleep stage and position, as well as fluid shifts due to the recumbent sleeping position. The variation of EPAP and pressure support of ASV addresses all these issues.

All of the smaller prospective cohort and retrospective studies show a positive or neutral effect of ASV on major

Table 2 Summary of ASV Studies

Year, Author	Study type, population and size	Intervention group(s)	Follow-up time	Summary of outcome	ASV type and setting range	Interpretation
2007, Fietze [59]	• RCT • HFrEF (NYHA II-III)–CSR • n = 37	• ASV • BPAP	6 weeks	• Significant reduction in AHI in ASV and BPAP	• ASVmv • EPAP 4–10 cmH_2O, Δ EPAP/IPAP 7–9 cmH_2O	Neutral • sleep parameters • symptoms
2011, Koyama [62]	• Prospective • HF–SDB • n = 59	• ASV • OMT	12 months	• Increases in eGFR and LVEF with ASV	• ASVmv • EPAP 5 cmH_2O, IPAP 3–10 cmH_2O	Positive • renal and cardiac function
2011, Yoshihisa [63]	• Prospective comparison • HF, NYHA ≥ II–CSR • n = 60	• ASV • non-ASV	6 months	• Event free rate higher in ASV group	• ASVpf • EPAP titration, set minimum and maximum IPAP	Positive • cardiovascular outcome
2011, Oldenburg [64]	• Prospective comparison • HF, NYHA ≥ II–CSA • n = 115	• ASV • OMT	3–6 months	• SDB, NYHA class, LVEF, 6MWD, NT-proBNP and exercise test improved significantly under ASV	• ASVmv • EPAP 4–5 cmH_2O, IPAP 3–10 cmH_2O	Positive • respiratory and functional indices
2012, Randerath [60]	• RCT • HF–CSA/OSA • n = 63	• ASV • CPAP	12 months	• CAI and BNP significantly more reduced with ASV	• ASVpf • EPAP titration, IPAP 4–30 cmH_2O	Positive • sleep parameters • cardiac function
2012, Takama [105]	• Prospective observation • HF NYHA II–IV–SDB • n = 85	• ASV ≥ 4 h/night • ASV < 4 h/night	12 months	• Higher survival rate and fewer cardiovascular events in good adherence group	• ASVmv • EPAP 4–cmH_2O, IPAP 3–8 cmH_2O	Positive • mortality • cardiovascular oucome
2013, Arzt [58]	• RCT • HF–SDB • n = 72	• ASV • OMT	12 weeks	• More significant reduction in AHI and NT-proBNP with ASV • Similar change in LVEF	• ASVpf • EPAP titration, IPAP max 10 cmH_2O above EPAP	Positive • sleep parameters Neutral • cardiac function
2013, Oldenburg [65]	• Prospective observation • HF–CSA/mixed • n = 45	• ASV alone	Median 3.6 ± 1.2 months	• Reduction in AHI • Improved sleep quality • Improved NYHA functional class	• ACMV • Individual titration, settings not disclosed	Positive • PSG parameters • cardiac function • symptoms
2014, Takama [61]	• Prospective comparison • HF–OSA/CSA • n = 76	• ASV in LVEF < 30% • LVEF ≥ 30%	6 months	• Improvement in LVEF • Reduction in BNP • No difference in survival/hospitalization	• ASVmv • EPAP 4 cmH_2O, IPAP 3–8 cmH_2O	Positive • cardiac function Neutral • cardiovascular outcome
2014, Morgenthaler. [66]	• RCT • Complex sleep apnea • n = 66	• ASV • CPAP	90 days	• AHI < 10 at 90 days in 89.7% versus 64.5% of participants treated with ASV and CPAP	• ASVmv • ASV titrated according to a standardized protocol	Positive • PSG parameters
2014, Javaheri [2]	• Prospective comparison • Chronic opioid use • n = 20	• ASV • CPAP	9 months to 6 years	• Significantly greater reduction in AHI with ASV	• ASVmv n = 19, ASVpf n = 1 • EPAP titration, IPS 3–8 cmH_2O	Positive • sleep parameters

Table 2 (continued)

Year, Author	Study type, population and size	Intervention group(s)	Follow-up time	Summary of outcome	ASV type and setting range	Interpretation
2014, Birner [67]	• RCT • HF–CSA/OSA • n = 32	• ASV • OMT	12 weeks	• Significant improvement in AHI with ASV • Improvement in diastolic dysfunction	• ASVpf • EPAP titration 4 cm–10 cmH_2O, IPS 1–10 cmH_2O	Positive • sleep parameters • cardiac function
2015, Cowie [75] SERVE-HF	• RCT • HFrEF, NYHA class III or IV–CSA • n = 1325	• ASV • OMT	Median follow–up 31 months	• No significant difference in time to hospitalization/ life-saving cardiovascular intervention, worsening CHF or time to death, change in NYHA class, 6MWD	• ASVmv • EPAP 5 cm H_2O, IPS 3–10 cmH_2O	Negative • mortality Neutral • cardiovascular outcome Positive • sleep parameters • symptoms
2015, Shapiro [106]	• Prospective interventional • Chronic pain (≥ 100 mg morphine)–SDB • n = 100	• ASV (with/without mandatory pressure support)	3 months	• AHI, CAI and OAI significantly reduced under ASV	• ASVpf • EPAP 4–15cmH_2O • IPS 0–21 Vs 6–21 cmH_2O	Positive • sleep parameters
2015, Momomura [107]	• RCT • HF–SDB (AHI ≥ 15/h) • n = 213	• ASV • OMT	24 weeks	• No significant difference in improvement in LVEF and BNP	• ASVmv • Settings not disclosed	Neutral • cardiac function
2016, Hetzenecker [68]	• Multicenter, RCT • HF–CSA/OSA • n = 63	• ASV • OMT	12 weeks	• ASV significantly reduced sleep fragmentation	• ASVpf • EPAP 4–10 cmH_2O, IPS 1–10cmH_20	Positive • sleep parameter
2017, Toyama [69]	• RCT • HFrEF–CSA • n = 31	• ASV • OMT	6 months	• Significant reduction in AHI, changes of LVEF and NYHA class	• ASVmv • EPAP 4–cm H_2O, IPS 3–8 cmH_2O	Positive • sleep parameters • cardiac function • exercise capacity
2017, O'Connor [70] CAT-HF	• RCT • Hospitalized unselected CHF–SDB • n = 126	• ASV • OMT	6 months	• Significantly greater reduction in AHI under ASV • No improvement in 6-month cardiovascular outcomes	• ASVmv • Setting not specified	Positive • Sleep parameters Neutral • cardiovascular outcome
2018, Piccini [108] CAT-HF	•CHFwith pacemaker/defibrillator–SDB • n = 35	• ASV • OMT	6 months	• 39% absolute reduction in AF burden	• ASVmv • Setting not specified	Positive • cardiovascular parameter
2018, Daubert [71] CAT-HF	• RCT • HF • n = 126	• ASV • OMT	6 months	• Reverse LV remodeling in both groups • Reduced LA volume under ASV	• ASVmv • Setting not specified	Positive • cardiac function

Table 2 (continued)

Year, Author	Study type, population and size	Intervention group(s)	Follow-up time	Summary of outcome	ASV type and setting range	Interpretation
2018, Cowie [109] SERVE-HF	• Sub-study of RCT • HF–CSA • n = 312	• ASV • OMT	12 months	• Addition of ASV had no effect on cardiac structure and function, or on cardiac biomarkers, renal function and systemic inflammation	• ASVmv • EPAP titration, IPS 3–10cmH2O	Neutral • cardiac and renal function
2020, Cantero [72]	• Multicentric, observational • Unselected CSA with ASV use > 3 months • n = 458	• ASV (various devices and settings)	> 3 months	• AHI normalized in 94%	• ASVmv n = 409, ASVpf n = 39, • ACMV n = 10 • Fixed and variable EPAP, min IPS 0-3cmH_2O	Positive • sleep parameters
2022, Tamisier [110] SERVE-HF	• Retrospective sub-analysis of SERVE-HF • HF–CSA • n = 312	• ASV • OMT	Baseline, 3- and 12-months	• Better sleep efficiency and lower respiratory arousal index in ASV • Increased PLMS arousal index in ASV • No change in LVEF	• ASVmv • EPAP 5 cmH_2O, IPS 3–10 cmH_2O	Neutral • sleep parameters • cardiac function
2023, Sun [111]	• Retrospective cohort • HFrEF–CSA • n = 90	• ASVpf • n = 77 • ASVmv • n = 13	Median 64 months	• No increase in mortality • Trend towards negative correlation between ASV mv with fixed EPAP and survival	• ASVmv and ASVpf • EPAP 4–14cmH_2O, IPS 0.5–12cmH_2O	Neutral • mortality
2023, Kida [112]	• Retrospective follow-up • HFpEF–SDB • n = 36	• ASV	12 months	• Significant reduction of hospitalization for HF in 12 months after ASV initiation compared to before initiation	• Details unavailable	Positive • morbidity
2023, Tamisier [113] FACE	• Prospective, observational cohort FACE study • HF with CSA or TECSA • n = 324	• ASV • OMT	2 years	• More than half of all patients benefitted with ASV • Benefit was dependent on LCA cluster	• ASVmf • Min EPAP 4–5 cmH_2O, min IPS 3mmH_2O	Positive • mortality • cardiovascular outcome
2023, Baumert [74]	• RCT • HFrEF–OSA/CSA • n = 56	• ASV • OMT	12 weeks	• ASV significantly reduced T90	• ASVpf • EPAP titration 4–10cmH_2O, • IPS 1–10cmH_2O	Positive • respiratory parameters

Table 2 (continued)

Year, Author	Study type, population and size	Intervention group(s)	Follow-up time	Summary of outcome	ASV type and setting range	Interpretation
2023, Bradley [77] ADVENT-HF	• RCT • HFrEF–CSA/OSA • n = 731	• ASV • OMT	5 years	• No significant difference in time to death or hospitalization for cardiovascular events, new onset AF/AFL or ICD shock	• ASVpf • EPAP min 4cmH_2O, min IPS 4 cmH_2O	Neutral • mortality • cardiovascular outcome
2024, Arzt [114] READ-ASV	• Prospective cohort analysis • CSA ± OSA • n = 801	• ASV	12 months	• Increased disease specific QOL measured by FOSQ in symptomatic patients and improvement in ESS	• ASVmf • EPAP median 6.9 (6–8) cmH_2O, IPAP median 10.1 (8.8 – 11.8) cm H_2O	Positive • quality of life and symptoms

The table presents the results of randomized controlled or observational trials with a number of Participants ≥ 20 and a follow-up period > 6 weeks

RCT randomized-controlled trial, *HFrEF* heart failure with reduced ejection fraction, *NYHA* New York Heart Association, *CSR* Cheyne-Stokes respiration, *ASV* adaptive servoventilation (*ASVmv* ASV minute-ventilation, *ASVpf*), *BPAP* bilevel positive airway pressure, *AHI* apnea–hypopnea index, *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *HF* heart failure, *SDB* sleep-disordered breathing, *OMT* optimal medical therapy, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *CSA* central sleep apnea, *6MWD* 6 min walking distance, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *OSA* obstructive sleep apnea, *CAI* central apnea index, *OAI* obstructive apnea index, *ACMV* anti-cyclic minute ventilation, *PSG* polysomnography, *IPS* inspiratory pressure support, *PLMS* periodic limb movements in sleep, *TECSA* treatment-emergent central sleep apnea, *LCA* latent class analysis, *T90* time spent under 90% oxygen saturation, *AF/AFL* atrial fibrillation/atrial flutter, *ICD* implanted cardioverter-defibrillator, *QOL* quality of life, *FOSQ* functional outcome of sleep questionnaire, *ESS* Epworth sleepiness scale

outcome parameters, sleep and QoL (Table 2). However, the RCT SERVE-HF of 1325 patients with a LVEF of < 45% showed ASV had no improvement in the primary outcome of all-cause mortality or lifesaving cardiovascular intervention [75]. In the secondary analysis, there was a higher all-cause and cardiovascular mortality in the ASV group. Several factors need to be critically viewed when interpreting the mortality results:

- The first generation ASV used in the SERVE-HF study may have favored ventilation over stabilization of breathing. These devices applied a minimal pressure support of 3 cmH_2O even in periods of hyperventilation. This unnecessary elevation in minute ventilation reduces the CO_2 level, which destabilizes ventilation. The accompanying electrolyte fluctuations may have precipitated arrhythmias.
- The applied fixed EPAP failed to eliminate obstructive events and desaturation in this cohort, which may in part have contributed to excess mortality. Additionally, once the upper airway opened, excessive IPAP was applied by the device and this ASV-associated excessive rise in intrathoracic pressure may have contributed to mortality.
- ASV adherence was low at only 3.4 h per night. Takama et al. showed that ASV use of < 4 h compared to ASV use > 4 h was associated with higher 1-year mortality [61].
- There was a relevant switch between the treatment arms (29% of the patients randomized to the ASV group dropped out and 16% of the control patients switched to the ASV group).

Nevertheless, the results of the SERVE-HF trial had a significant impact on the treatment of HF with CSA with national guidelines contradicting the use of ASV in HF patients with EF < 45% [1, 20] soon after the study was published.

Most recently, the results of the ADVENT-HF study were presented. Similar to SERVE-HF, it aimed to evaluate long-term outcomes under ASV [76, 77]. The trial differed from SERVE-HF in several aspects:

- It used the new generation of ASV, which allowed for a reduction of pressure support to zero in periods of hyperventilation as well as the already mentioned adaptive EPAP [57, 78, 79].
- The device was based on peak flow (ASVpf), while ASVmf was used in SERVE-HF.
- Moreover, ADVENT-HF included not only HF patients with CSA but also OSA.

The composite end-points were all-cause mortality, heart transplantation, ventricular assist device (VAD) implantation, cardiovascular disease-related hospitalization, implantable cardioverter-defibrillator shock and new atrial fibrillation. A follow-up PSG was carried out at 1 month. The centralized assessment of ASV titrations and prescription of pressure settings contributed to effective control of SRDB (the mean AHI taken from participants' ASV devices ranged between 2.8 /h and 3.7 /h over the course of the trial). Unfortunately, the study had to be terminated prematurely and did not reach the pre-calculated figures due to the COVID-19 pandemic and the Philips device recall. In total, 356 patients were recruited to ASV (completed n = 324; age: 62.7 ± 11.1 y.; LVEF: 33.1 ± 7.1%; CSA 25.8%; AHI 41.1 ± 19.9) and 375 assigned to not receive ASVpf (completed: 332; age: 63.6 ± 10.1 y.; LVEF: 33.3 ± 7.9%; CSA 28.3%; AHI 41.3 ± 22.9). The results showed no difference in the cumulative incidence of primary end-points or all-cause mortality in the OSA or CSA patients allocated to ASV use compared to the control group [77]. Under ASVpf, there was no signal of harm and a trend to improvement of survival in CSA patients. The predefined Hazard Ratio of 0.74 was achieved but did not reach statistical significance. ASV significantly improved severity of SRDB, sleep parameters, sleepiness and New York Heart Association (NYHA) class in all patients and those randomized to ASVpf for up to 2 years. The findings on the available data on ASV in HF may be summarized:

- The largest RCT (SERVE-HF) was neutral in the primary combined outcome parameter, but showed higher mortality in secondary analyses.
- Several prospective, non-randomized trials showed beneficial effects in various parameters of heart function, sleep parameters and patient-reported outcomes.
- This was supported by the results of ADVENT-HF, which did not show any harm and benefits in quality of sleep and life from ASV.

These findings warrant discussion about whether the ASV device and settings of ADVENT-HF can be applied in HF patients with EF < 45% (a contraindication to ASV based on the SERVE-HF results). There is evidence to show that the mortality risk of CSA patients with HF is influenced mainly by the phenotype and severity of HF [41]. The FACE trial examined unselected HF patients with differing degree of LV impairment [73]. A cluster analysis identified 6 clinical phenotypes based on LVEF, SRDB, age, comorbidities and ASV acceptance. The risk for the combined primary end-point of mortality, hospitalization, heart transplantation, and VAD implantation was significantly increased in the cluster of male patients with low LVEF and CSA, that is to say, the SERVE-HF phenotype. One of the clusters, however, was from the cohort enrolled in the SERVE-HF [80]. A network metanalysis of 14 RCTs

showed ASV to be the treatment of choice for decreasing AHI in patients with HF and CSA [38].

There is evidence for a worse functional outcome and increased mortality in the presence of SRBD in stroke patients [12, 81]., Whilst the evidence base for OSA in stroke supports active diagnosis and therapy, direct evidence for treatment of CSA is limited [81]. In a retrospective single-center study by Brill et al. [82] AHI and Epworth sleepiness score (ESS) improved in 15 stroke patients treated with ASV (13 of whom were previously started on CPAP or BPAP). A prospective RCT of ASV following acute stroke (eSATIS: early Sleep Apnea Treatment in Stroke) [83] has been recruiting since 2015 and aims to make an impact on stroke care. ASV has been shown to be superior to CPAP in suppressing central events in opioid-induced CSA as well [51]. Additionally, there is evidence to show that the adherence to therapy in TECSA improves early after switching from CPAP to ASV [84].

In translating this available evidence to clinical practice, we conclude that ASV is a viable and suitable option for the majority of patients with CSA who are not responsive to CPAP. As discussed above, a small group of patients should not be offered treatment, although even within this small subgroup of HF patients there is evidence suggesting that the greatest risks lie for those with a LVEF $\leq$ 30% [85]. These findings indicate that a stratification of the CSA population regarding the severity of left ventricular impairment is crucial and may be an important step in a therapeutic algorithm.

Studies have been conducted to analyze current and past use of ASV in clinical practice in relation to the SERVE-HF results. An analysis of 293 unselected patients treated with ASV showed that only a minority of patients (9.6%) fulfilled the risk criteria as described in the SERVE-HF trial [86]. A further single-center study analyzing patients already established on ASV showed the risk criteria of the safety notice were fulfilled by 10.3% of patients (13/126) [87]. Termination of ASV therapy in these patients led to an immediate return of symptoms in 60% and need for an alternative treatment. The primary analysis of 801 ASV patients recruited into a European registry between 2017 until 2021 (READ-ASV) [88] showed that the most common indications for ASV use were TECSA (56% of cases) or CSA in cardiovascular disease provided LVEF was > 45% (constituting 31% of cases). The remaining patients were post-stroke, opioid-use, unclassified CSA, CSA with concomitant OSA or OSA alone. Patients using ASV in clinical practice had severe SRDB and were often symptomatic. Prior analysis of a German databank of 285 patients also showed TECSA to be the main clinical indication for ASV prescription. Patients with LVEF $\leq$ 45% and predominant CSA in whom ASV is now contraindicated represented only 12% of all patients [89]. It is hoped that follow-up from the READ-ASV will provide data on the effects of ASV on QoL, respiratory parameters and clinical outcomes in these patients in a real-life setting.

Treatment Algorithm

Therapy decisions in CSA should be based on the definition of the subtype and its underlying pathophysiology, on the individual comorbidities and prognosis, as well as patient-reported outcomes (Fig. 1). In accordance with the European Respiratory Society guidelines [1], once the diagnosis of CSA is confirmed at PSG and the underlying medical treatment has been optimized, a trial of CPAP can be considered. If CPAP fails to normalize central breathing disturbances and symptoms, consider conversion to ASV in cases where severe HFrEF can be ruled out. This limitation may change in the future in light of recent findings. Non-PAP therapies currently represent an alternative with a limited evidence base, to be used in the event of PAP failure or unavailability. As long-term data are scarce, these individual, alternative decisions require close supervision and continuous re-evaluation.

Conclusion

CSA has a complex and diverse etiology and understanding the pathophysiology is essential for choosing the best treatment option. There is no long-term RCT data to show a reduction in mortality following initiation of CSA-specific therapy. The data discussed in this review present overwhelmingly positive or neutral benefits in terms of sleep parameters, organ function and symptoms, so that therapy can be considered on an individual basis. Once a decision to treat has been made, CPAP and ASV represent the first steps. The FACE data warns us that caution needs to be particularly exercised in specific subgroups with higher mortality. Potential harm in patients with severely reduced HFrEF has not been confirmed with newer generations of ASV devices that target peak flow (ASVpf), although available data do not allow for final conclusions. In this context, assumptions of safety of alternative treatment cannot be lightly made as larger powered studies may be required to demonstrate long-term effects. In disease processes associated with less mortality (for example drug-induced or high-altitude related CSA), there is a level of freedom with the choice of treatment and the sequence of use. In these cases, the physician can decide based on a combination of availability, cost and patient preferences.

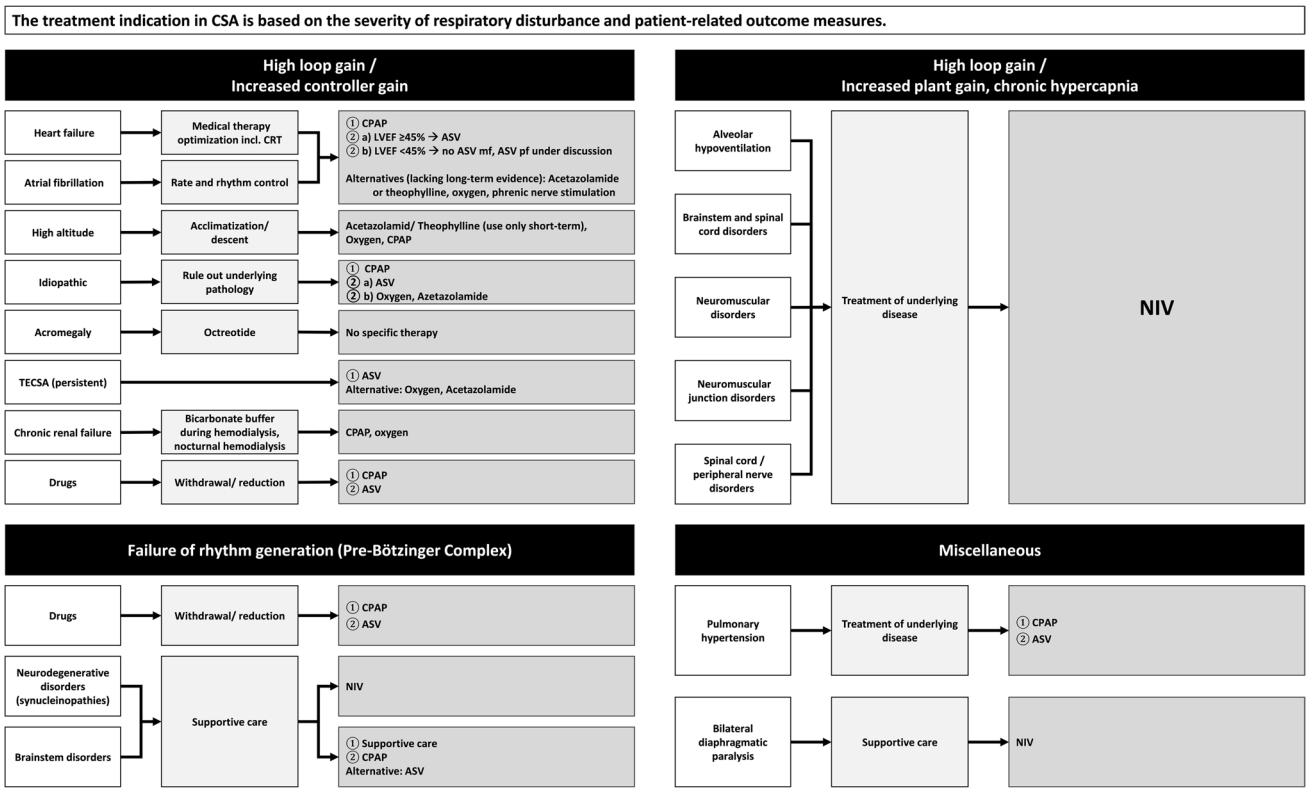

Fig. 1 Treatment algorithm for all clinical forms of CSA. *CRT* cardiac resynchronization therapy, *CPAP* continuous positive airway pressure, *LVEF* left ventricular ejection fraction, *ASV* adaptive-servo-ventilation, *TECSA* treatment-emergent central sleep apnea, *NIV* non-invasive ventilation

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