Central sleep apnoea: not just one phenotype

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Shareable abstract (@ERSpublications)
Underlying aetiologies, pathophysiological and prognostic characteristics allow for phenotyping of central sleep apnoea. They substantiate treatment indication and selection of new pharmaceutical, neurostimulatory options and adaptive servo-ventilation. https://bit.ly/3SIHL2n

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Abstract

Recent scientific findings in the field of sleep disordered breathing have characterised a variety of phenotypes in obstructive sleep apnoea. These findings have prompted investigations aiming to achieve a more precise differentiation and description of the entities of central sleep apnoea (CSA). There is increasing evidence for the heterogeneity of CSA in terms of underlying aetiology, pathophysiological concepts, treatment response and outcome. Assigning patients to these phenotypes allows for the selection of individualised therapies. Major pathophysiological characteristics include loop gain, apnoeic threshold, breathing regulation and neuromuscular mechanics. Chronic heart failure is the most important underlying disease, leading to nonhypercapnic CSA based on increased loop and controller gain. Although many questions remain, this review tries to describe the current knowledge on the pathophysiology of the clinical entities. The description of prognostic aspects may guide treatment indication and the selection of pharmacotherapy and invasive options. In addition, the paper provides an update on the current understanding of adaptive servo-ventilation and its role in the treatment of CSA.

Definition of central sleep apnoea

Central sleep apnoea (CSA) encompasses a group of sleep-related breathing disorders (SRBDs) that often emerge from other medical conditions, including chronic heart failure (CHF), stroke and the use of medications or substances such as opioids. CSA is characterised by reductions (hypopnoea) or complete cessation of ventilation (apnoea) and related ventilatory effort occurring during sleep. The International Classification of Sleep Disorders (ICSD) categorises six types of CSA in adults, as follows [1]:

- primary CSA
- CSA with Cheyne–Stokes breathing (CSB)
- CSA due to a medical disorder without CSB
- CSA due to high-altitude periodic breathing
- CSA due to a medication or substance and
- treatment-emergent CSA (TE-CSA).

Full polysomnography is the gold standard not only for the diagnosis of CSA but also for its differentiation from other sleep disorders. This is clinically relevant as insomnia or movement disorders are associated with arousals that induce CSA in sleep–wake transitions. Although oesophageal pressure measurement or diaphragm electromyography is recommended to measure effort directly [2, 3], in clinical settings, surrogates of respiratory effort can be used, such as strain gauges, respiratory inductive plethysmography, pulse transit time [4] or belts with piezoelectric or polyvinylidene fluoride sensors [5].

In adults [1], the polysomnographic criteria defining CSA are >5 apnoeas or hypopnoeas per hour of sleep (apnoea–hypopnoea index (AHI)), with more than 50% being central events.

Precise descriptions of the polysomnographic patterns of flow and respiratory effort are helpful for discerning underlying and sometimes overlapping aetiologies. This represents a crucial step from both diagnostic and therapeutic perspectives. The American Academy of Sleep Medicine (AASM) defines CSB [5] as 1) ⩾3 consecutive central apnoeas and/or hypopnoeas, separated by a crescendo and decrescendo change in breathing amplitude (periodic breathing (PB)) with a cycle length of at least 40 s (typically 45–90 s) and 2) ⩾5 central events per h associated with the PB pattern recorded over a minimum of 2 h. The European Respiratory Society recommends using the term PB to describe this typical polysomnographic pattern and to reserve the term CSB for PB associated with CHF [2].

Refining the current ICSD description, a recent protocol and cohort profile has proposed a more precise CSA classification [6] based on the indication of adaptive servo-ventilation (ASV). The authors proposed adding treatment-emergent or persistent CSA and coexisting CSA/obstructive sleep apnoea (OSA), commonly defined by a percentage of central events between 20 and 50% of total AHI. They also suggested differentiating patients according to the associated medical condition. This approach is, however, quite artificial as many patients exhibit more than one possible aetiology of CSA. Therefore, clinical CSA definitions may benefit from a holistic approach using phenotypes (*i.e.* clusters of multiple variables) defined and validated based on clinical parameters and relevant outcomes.

What are the problems and limitations of the current definitions?

At least five major limitations mitigate the use of current definitions of CSA for both clinicians and researchers:

- there is no well-defined CSA-related symptomatology
- a majority of sleep scorers are not confident enough to differentiate central from obstructive hypopnoeas
- the precise number (percentage) of central events to define CSA is unknown
- the classification of CSA highly depends on CSA-associated comorbidities and
- the night-to-night variability of CSA severity has been insufficiently explored [7].

The two main determinants of clinical presentation are the CSA subtype and the underlying aetiology [8]. In a cross-sectional analysis of baseline data from the Sleep Heart Health Study (n=5804) [9], individuals diagnosed with CSA were more likely to be male, older and have lower body mass indexes (BMIs) and Epworth sleepiness scale (ESS) scores than individuals with OSA. In idiopathic CSA, two studies reported complaints of excessive daytime sleepiness (EDS), insomnia or difficulty breathing during sleep [10, 11]. In conditions such as CHF, CSA symptoms may overlap with those of the underlying medical condition [12]. Thus, patients with heart failure (HF) and CSA may not spontaneously report symptoms such as sleepiness or sleep disruption due to their attribution to HF *per se* [13]. Following stroke, male sex, a lower degree of obesity and a lower frequency of cardiovascular comorbidities are reported in CSA compared with OSA patients [14].

CSA symptoms are mainly explored through the lens of complaints usually associated with either OSA or an underlying condition. To some extent, symptoms of OSA and CSA may overlap, especially in hypercapnic CSA where EDS and morning headaches can be reported. Insomnia, fatigue, frequent awakenings and poor sleep quality are the most common sleep-related symptoms, corresponding to the usual clinical presentation [15–17]. The extent of daytime sleepiness highly varies between studies. Sleep partners may witness a breathing pattern of periodic breathing or breathing pauses. Patients frequently report shortness of breath, paroxysmal nocturnal dyspnoea and nocturia, typical symptoms of CHF or diabetes.

To date, no CSA-specific symptoms or signs have been identified and no specific questionnaires have been developed to screen for CSA. Studies often failed to demonstrate sufficient sensibility and specificity in specific populations, such as CHF [18] or stroke patients [14]. Thus, polysomnography should be requested when SRBD symptoms are present. Despite a lack of evidence, single-channel screening tests can be considered in populations at high risk of CSA but without symptoms.

In OSA, and due to the high night-to-night variability documented in the AHI, single-night sleep studies are estimated to misdiagnose and misclassify OSA severity in 20–50% of patients [19]. The night-to-night variability of CSA severity has been, to date, poorly explored. In stable CHF patients (n=50), Oldenburg

et al. [20], using cardiorespiratory polygraphy over two consecutive nights, showed that sleep apnoea diagnosis reproducibility was dependent on its severity, with low variability regarding its type (*i.e.* CSA and OSA) for an apnoea index ⩾10 events·h^{-1}. Vazir *et al*. [21] assessed over four consecutive nights the severity and type of sleep apnoea. Besides minimal variations in AHI, they demonstrated a shift in the type from CSA to OSA and reversely in 42% of the included patients. In stroke patients, by using repeated polysomnography performed within 1 week and 3 months following the stroke, Ott *et al*. [22] showed a greater decrease in AHI in predominantly central and mixed sleep apnoea patients compared to predominant OSA. Only a trend in the decrease in central apnoea (central apnoea index (CAI)) over the whole cohort (n=105) was observed [22]. Altogether, these results highlight the need for further studies assessing night-to-night variability in CSA. This is crucial for improving CSA diagnosis and classification and, *in fine*, refining treatment indication and ventilatory support.

How to differentiate obstructive and central hypopnoeas?

In an agreement analysis among nine international sleep centres the intraclass correlation coefficient (ICC) for CAI was 0.46 (95% CI 0.27–0.70), ranging from a CAI of 0.9±1.4 to 7.3±10.2 [23]. An agreement on specific events found an ICC of 52.4% (k=0.41) [24]. These discrepancies are even higher for central hypopnoea. While apnoeas can be discriminated clearly in clinical practice, hypopnoeas are often uncritically considered as obstructive. This underestimates the severity of central disturbances and may mislead therapeutical decisions. Analysis of polysomnographic parameters—flattening of the inspiratory flow curve, shape of the increase of ventilation at the end of an hypopnoea, thoraco-abdominal paradox of effort, position of associated arousal and sleep stage (rapid eye movement (REM) *versus* non-REM (NREM))—allows for reliable differentiation of the majority of hypopnoeas [25]. When compared to oesophageal pressure, an algorithm based on these parameters showed an overall accuracy of 68% and a correct definition of 76.9% of central hypopnoeas. These findings were substantiated by Dupuy-McCauley *et al*. [26], who additionally found similar results for another noninvasive differentiation based on the AASM criteria [25–27]. Parekh *et al*. [28] developed an automated algorithm to determine the probability of obstruction on a breath-by-breath basis. The targeted parameter proved to correlate with upper airway resistance on an individual basis with low night-by-night variability. Javaheri *et al*. [29] added the prolongation of the inspiratory duty cycle as an additional marker of obstructive hypopnoeas, building upon previous findings.

Epidemiology of CSA

CSA prevalence is estimated to reach 5–10% of patients with SRBD with idiopathic CSA prevalence, representing 4–7% within the sleep centre population (table 1) [8, 30]. The prevalence of CSA may be underestimated as epidemiological data are largely based on the AASM criteria [5]. Despite its lower prevalence in the general population compared to OSA [31], CSA is over-represented in specific subpopulations [17]. If CSA is significantly more prevalent among males than females [32], gender differences and gender-based phenotypic presentations of CSA remain poorly documented [7].

CHF

Both OSA and CSA are common in CHF; however, generally, one ventilatory phenotype tends to predominate [33]. Variations in the haemodynamic profile of CHF patients predispose to day-to-day differences of the predominant ventilatory phenotype of apnoea [34]. The predominance of CSA may also

TABLE 1 Epidemiology of central sleep apnoea (CSA) in specific subpopulations [140]

Condition	Prevalence (%)	References
Idiopathic CSA	4–7	[8, 30]
Chronic heart failure		
Asymptomatic left ventricular systolic dysfunction	55	[36]
Preserved ejection fraction	23–27	[33, 36]
Reduced ejection fraction	34–69	[33, 38, 39]
Stroke	8–12	[46, 47]
Pulmonary hypertension	39	[2, 49]
Chronic kidney disease	10	[50, 51]
Drug-induced CSA		
Opioids	24	[59]
Methadone	30	[60]
Treatment-emergent CSA	10–25	[60]

shift throughout the night and, in patients predominantly exhibiting CSA with left ventricular dysfunction, both the frequency and duration of CSA increase during the later segments of NREM sleep [35].

Left ventricular ejection fraction (LVEF) plays a determinant role in the prevalence and severity of CSA associated with CHF. In patients with asymptomatic left ventricular systolic dysfunction [36], the prevalence of moderate-to-severe CSA assessed by polysomnography reaches 55% compared to 11% for moderate-to-severe OSA [37]. In HF with preserved LVEF (HFpEF), CSA prevalence reaches 23–27% [33, 36], whereas in HF patients with reduced LVEF (HFrEF), CSA prevalence ranges between 34 [33] and 69% [38, 39]. This range was confirmed by data from Borrelli *et al.* [40] who included 700 CHF patients in a prospective study. The prevalence of CSA was highest in HFrEF (66%) as compared to HFmrEF (48%) and HFpEF (42%). Male gender and BMI were independent predictors of CSA in HFrEF [40]. Arzt *et al.* [41] studied 3289 CHF patients in a prospective registry using polygraphy of cardiorespiratory parameters. As compared to previous studies, they found a lower prevalence of 15% in HFrEF, 12% in HFmrEF and 7% in HFpEF [41]. Notably, if the prevalence values are reported for stable, compensated CHF, CSA severity and prevalence can be dramatically increased in the case of decompensation [42].

Gender may also play a role in the heterogeneity of clinical presentation, ventilatory phenotype and treatment adherence of CHF patients. In the FACE trial [43], Tamisier *et al.* [44] investigated sleep apnoea clusters in 482 CHF patients. Females were over-represented in the third cluster, characterised by a moderate AHI and moderate adherence to ASV treatment. At 2 years follow-up [45], this cluster was associated with an intermediate risk of all-cause death, life-saving cardiovascular intervention or unplanned hospitalisation (or unplanned prolongation of a planned hospitalisation) for worsening of chronic HF.

Stroke

Data regarding the frequency of CSA associated with stroke are contradictory [14] and may evolve from the acute to the chronic phases of stroke [22]. According to data from a systematic review [46] (37 cohort studies, n=3242 ischaemic stroke patients) and a meta-analysis [47] (13 original interventional and observational studies reporting a CAI, 15% of the included studies), CSA prevalence ranged between 8% (95% CI 6–15) [46] to 12% (95% CI 6–23) [47], respectively. More longitudinal studies are required to confirm the temporal evolution of CSA severity following stroke [14]. Moreover, the causative role of ischaemic stroke in CSA is unclear and studies investigating the association of stroke lesion location and ventilatory phenotype found inconsistent results [14]. Ventilatory instability, however, seem to be a predisposing factor for persistent CSA following stroke [48].

CSA due to a medical disorder, medication or substance

- Related to ventilatory instability: Although the clinical significance is unclear, CSA is found to be associated with pulmonary hypertension, either idiopathic or linked to chronic thromboembolic disease, with a prevalence of 39% [2, 49]. In chronic kidney disease, CSA prevalence can reach 10% [50, 51]. By increasing ventilatory drive, ticagrelor induced CSA both in naïve patients and continuous positive airway pressure (CPAP)-treated OSA patients [52, 53].
- Related to central nervous system depression or respiratory muscle peripheral weakness: Several neurological conditions, such as multiple-system atrophy [54], amyotrophic lateral sclerosis [55], multiple sclerosis [56] and neuromuscular disease [57], are associated with CSA, resulting from impaired central command and/or peripheral muscle weakness. There is insufficient prevalence data for CSA in these populations to form robust conclusions [17, 58].

Opiates and opioids are known respiratory depressants. Available data support a dose–response relationship between daily opioid dose and the severity of SRBD [17]. In a systematic review (eight studies, n=560) [59], the mean prevalence of CSA associated with chronic opioid use reached 24%. For methadone, prescribed for pain management, CSA prevalence reached 30% [60].

TE-CSA

TE-CSA is observed in approximately 10% of positive airway pressure (PAP) titration studies [61]. In a large observational study including >130 000 patients, 55.1% presented transient and 25.2% persistent TE-CSA 13 weeks after CPAP initiation [61]. Male gender, a high AHI, arousal index or CAI at the baseline study, hypertension, opioid use, coronary artery disease, stroke, and CHF all appear to be risk factors for TE-CSA [62, 63].

Pathophysiology

The phenotypes of CSA can be divided into those with reduced ventilatory output and minute ventilation (V'_E) (hypercapnic CSA) and those with overshooting ventilatory drive and breathing instability, resulting

in increased V'_E (nonhypercapnic or hypocapnic CSA). The various phenotypes of nonhypercapnic CSA, including idiopathic CSA, CSA in CHF, CSA emerging under treatment of OSA and CSA at high altitude represent the majority of CSA patients. Drug-induced CSA can be either hypercapnic or nonhypercapnic. Current pathophysiological concepts are based on the following three components: loop gain (LG), apnoea threshold (AT) and CO_2 reserve.

- The term LG describes the interplay between the compartments of the ventilatory system. It quantifies the reactivity of the ventilation to any disturbance, *e.g.* an arousal. Components of the system include the lungs (representing the plant gain), the peripheral chemoreceptors (feedback gain) and the brain stem (controller gain). The pulmonary component (plant gain) indicates the change of CO_2 in response to a change of V'_E, while the chemosensitivity (feedback gain) describes the change in ventilation to a change of CO_2 [64]. The circulatory delay between plant and feedback gain also influences the LG. Other authors describe the LG by the components of plant gain, controller gain (central and peripheral chemoresponsiveness) and mixing gain (circulation) [65, 66]. Huge swings of the system between hyperventilation and central apnoea – an overshoot and undershoot of ventilation – characterise a high LG. The ventilatory system becomes unstable, often associated with hyperresponsiveness of the chemoreceptors and extreme swings of brainstem activity. While a high LG is typical in PB, a lower LG represents the dampening of the ventilatory system in hypoventilation disorders [67].
- The AT is an important parameter to explain the association between the current ventilation and its transition to central apnoea. It describes the CO_2 level below which breathing ceases. As long as the CO_2 level is above the AT, respiration is maintained. When hyperventilation, through heightened CO_2 excretion, reduces the CO_2 level below the AT, ventilation ceases [68, 69].
- The difference between the actual CO_2 level and the AT defines the CO_2 reserve. If narrow, minor increases in V'_E may reduce the prevailing CO_2 below the AT, leading to a central apnoea. Thus, narrowing of the CO_2 reserve increases the probability of central apnoeas and destabilises respiration.
- Breathing regulation receives inputs from central and peripheral chemoreceptors, intrapulmonary vagal afferents, muscle sensors and proprioceptors as well as cortical inputs. Hypoxaemia and hypercapnia, fluid accumulation in the lung parenchyma, muscle stretching, and psychological stress are examples of respiratory stimuli. These inputs are integrated in the retro-trapezoid nucleus and the pre-Bötzinger complex, which determine the rhythmicity of breathing.

Based on the concept of the LG, Javaheri and Badr [66] proposed another classification system. They described two groups of CSA with high LG, one with increased controller gain, the other with increased plant gain, and added a group based on rhythm generation failure and a miscellaneous group. As shown in the next sections, the different pathophysiological components characterise the various clinical entities. This may guide therapeutical decisions, *e.g.* they have to avoid additional hyperventilation in phenotypes with increased LG or disturbed sleep a in low arousal threshold. Although the pathophysiological components can hardly be detected in daily routine, clinicians should focus at least on the differentiation of hypercapnic and nonhypercapnic phenotypes. Moreover, the amplitude of the ventilatory overshoot and the length of the apnoeic as compared to the hyperventilation part of the respiratory cycle give an idea of the LG [70].

CSA in CHF

CHF is the most common cause of CSA and PB and is associated with nonhypercapnic CSA and CSA with increased LG and increased controller gain [66]. CHF patients present with chronic hyperventilation, possibly because of the activation of vagal J-receptors in the lung parenchyma due to pulmonary congestion. These afferents stimulate brain stem activity, increase V'_E [67, 71] and reduce the CO_2 reserve. In addition, the increased hypercapnic and hypoxic ventilatory responses represent the elevation of chemoresponsiveness, which exaggerates hyperventilation in reaction to mild increases in CO_2 and hypoventilation or even apnoeas in response to hypocapnia (increased feedback gain) [72].

The crescendo–decrescendo pattern of tidal volume and respiratory effort reflect these mechanisms: hyperventilation reduces the actual CO_2 level below the AT, which dampens neural drive and induces CSA. The consecutive increase of CO_2 and decrease of oxygen levels stimulate ventilation. This vicious circle may be amplified by a prolonged circulation time [73], resulting in delayed reception of blood gas changes and consecutive overshooting of hyperventilation or prolonged apnoea.

TE-CSA

TE-CSA describes the appearance of CSA in patients treated with PAP or other treatments counterbalancing OSA, as it can also occur in patients treated with mandibular advancement devices [74]. Historically, “complex sleep apnoea” [75] (defined initially as the persistence or the emergence of CSA

during CPAP treatment in patients with OSA) was described in congestive HF patients (n=192, LVEF ⩽45%, New York Health Association (NYHA) ⩾2), diagnosed with OSA (AHI ⩾15 events·h^{-1}) and treated by CPAP [76]. Complex sleep apnoea developed in 18% of the patients already during CPAP titration, with evidence of higher respiratory controller gain before the application of CPAP [76].

Although CSA may often appear in HF patients under treatment of OSA, the question arises of whether this is a specific entity or an expression of the same pathophysiology of CSA in CHF described above. Recent evidence suggests that the trajectories of TE-CSA appear to be a dynamic process [61] and JAVAHERI and BADR [66] recently differentiated CPAP-resistant, CPAP-emergent and CPAP-persistent CSA (figure 1).

CPAP-resistant CSA describes central breathing disturbances that exist prior to treatment initiation and are in addition to OSA. In these patients, the pathophysiology follows the underlying cause of CSA but does not represent a unique disease. Most of these may overlap with the group of coexisting CSA/OSA patients.

In the huge majority of TE-CSA patients, CSA emerges under OSA treatment, but disappears within the first weeks of therapy (TE-CSA). This indicates that the increased LG may resolve over time [77, 78].

- The increased upper airway resistance stimulates the elevation of ventilatory drive in untreated OSA. Although V'_E is reduced during hypopnoeas or apnoeas, the overshoot of ventilation at the end of the obstructive event leads to a net reduction of the end-tidal CO_2 in NREM sleep. The CO_2 reserve is reduced, promoting unstable ventilation.
- During the early period of sufficient OSA treatment, the ventilatory drive is still elevated, leading to increased V'_E and CO_2 excretion through the re-opened airways. The end-tidal CO_2 falls below the AT and induces CSA.
- After a period of sufficient treatment, ventilatory response, CO_2 excretion and CO_2 level normalise, leading to disappearance of central events.

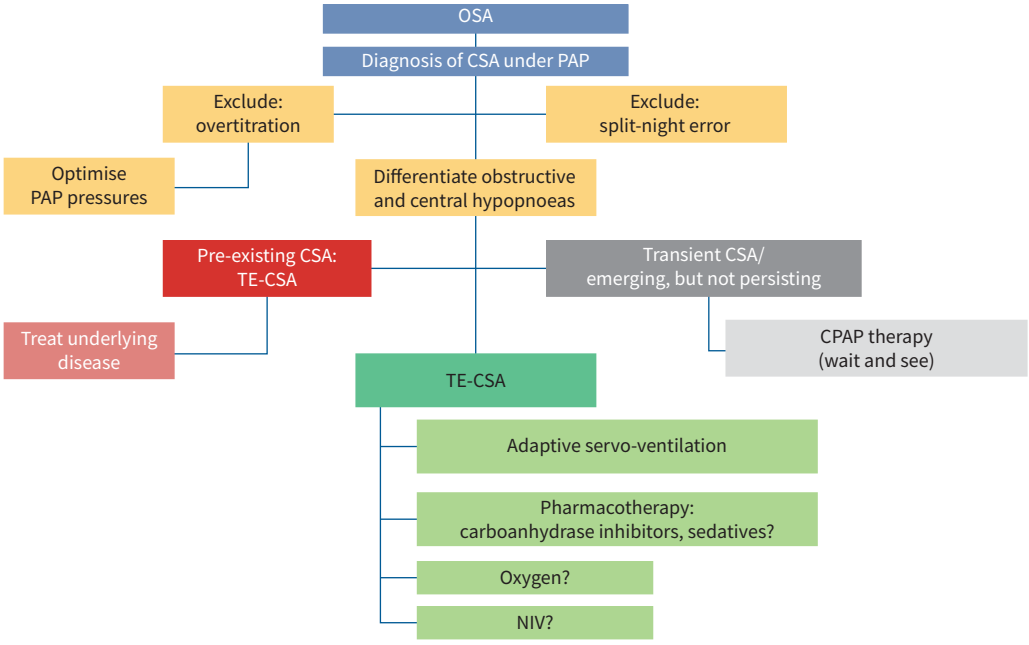

FIGURE 1 Algorithm for the differentiation of central sleep apnoea (CSA) emerging under treatment of obstructive sleep apnoea (OSA). A minority of central breathing disturbances emerging under effective treatment of OSA represent a specific entity (treatment-emergent CSA (TE-CSA)). Prior to diagnosing TE-CSA, artificial induction of central breathing disturbances, for example, by excessive therapeutical pressure or misinterpretation of polysomnography data, have to be included. In addition, pre-existing CSA, for example, due to chronic heart failure with reduced or preserved ejection fraction as well as transient CSA in the first weeks of positive airway pressure (PAP) treatment, should also be excluded. Therefore, a precise differentiation between obstructive and central hypopnoea is of crucial importance to avoid misclassification of pre-existing CSA. NIV: noninvasive ventilation; CPAP: continuous positive airway pressure

Finally, there is a minority of patients with CPAP-persisting CSA (1.6% in the study by Westhoff *et al*. [79]). In contrast to PAP-emergent and -resistant CSA, these disturbances appear under OSA treatment, but do not disappear over time. The pathophysiology is not yet clear [63, 80, 81].

Idiopathic CSA

Although the pathophysiology of idiopathic CSA is unclear, patients present with nonhypercapnic CSA. The LG is elevated and the hypercapnic ventilatory response (HCVR) increased [82, 83].

High-altitude CSA

High-altitude CSA, a nonhypercapnic CSA, is a physiological phenomenon with increasing prevalence according to the altitude above sea level. It frequently occurs above 2500 m and affects all persons at 6850 m. The hypobaric hypoxia leads to hypoxaemia and stimulates peripheral chemoreceptors. The consecutive hyperventilation reduces the actual carbon dioxide tension below the AT. LG and controller gain are increased [66]. In contrast to CSA in CHF, circulation time is not increased, resulting in shorter apnoeas and cycle lengths [66].

Drug-induced CSA

To the best of our knowledge [84], opioids influence neurons of the pre-Bötzinger complex and the cranial and bulbospinal motor neurons of the diaphragm and the upper airway muscles (table 2) [85, 86]. There is a heterogeneous effect of opioids on central and peripheral chemoresponsiveness. While they dampen the HCVR and the LG, methadone additionally increases the hypoxic response (HCR). Moreover, the induced impaired neuromuscular activity predisposes to hypoventilation and upper airway obstruction. Opioids also reduce breathing frequency and influence the rhythmogenesis in the pre-Bötzinger complex, leading to the typical pattern of ataxic breathing with chaotic changes of amplitude and breathing frequency [87, 88]. CSA has also been reported under treatment with baclofen, valproic acid and sodium oxybate, which all interfere with gamma-aminobutyric acid. It has been hypothesised that they may act on inspiratory neurons [66, 89–91].

There are several reports on the effect of ticagrelor on central breathing disturbances. The antiplatelet agent may directly inhibit P2Y12 receptors in the central nervous system. In addition, ticagrelor stimulates pulmonary vagal C-fibres, inducing hyperventilation [33, 92–94].

Hypercapnic CSA

CSA in chronic hypercapnic disorders differs substantially from nonhypercapnic conditions. It is associated with neurological or musculoskeletal disorders, including spinal cord injuries [95], and follows the pathophysiology of hypoventilation diseases, characterised by diminished brainstem output, impairment of the neural command *via* the spinal cord or peripheral nerves or their translation into muscle activity. Hypercapnic CSA can be also classified as CSA with increased LG and increased plant gain,

TABLE 2 Drugs that induced central sleep apnoea (CSA) and their putative pathophysiological mechanisms

Drug promoting CSA	Pathophysiological mechanism	References
Opioids	Loop gain: ⇩ HCVR: ⇩ loop gain; methadone: ⇧ HVR Failure of rhythm generation (pre-Bötzinger complex, direct action on the inhibitory opioids-mu receptor) Impairment of motor neuron output: cranial and bulbospinal motor neurons (hypoventilation and upper airway obstruction)	[84–86]
Sodium oxybate	Failure of rhythm generation (pre-Bötzinger complex, GABA B actions at noradrenergic and dopaminergic neurons)	[66]
Baclofen	Failure of rhythm generation (pre-Bötzinger complex, agonist of GABA B receptors)	[66]
Valproic acid	Failure of rhythm generation (pre-Bötzinger complex, blocks voltage-gated sodium channels and hence leads to increased brain levels of GABA)	[66]
Ticagrelor	⇧ loop gain: ⇧ HCVR Hyperventilation through the stimulation of pulmonary vagal C-fibres	[33, 92–94]

GABA: gamma-aminobutyric acid; HCVR: hypercapnic ventilatory response; HVR: hypoxic ventilatory response.

i.e. heightened ventilatory response to changes in CO_2 [66]. Chronic hypercapnia shifts ventilation to the right side of the hyperbolic ventilation curve, where small variations of ventilation may switch the current CO_2 above or below the AT and induce CSA as described above [96]. Hypercapnic failure can also be caused by neurodegenerative, ischaemic or inflammatory damages of the respiratory centres in the brainstem [97].

Prognostic impact of CSA

There is increasing evidence from longitudinal studies indicating the relevance of OSA and CSA on long-term outcome, especially in CHF (table 3). Based on registry-based longitudinal data of a cardiac centre, Khayat *et al.* [98] studied numbers and costs of readmission at 3 and 6 months post-discharge in 1547 HF patients without SRBD (25%), with CSA (28%) or OSA (46%). The mean±SD LVEF was 38.7±16%. Both types of SRBD were associated with an increased readmission rate and mortality. These results confirm previous data from a prospective cohort of 1117 patients hospitalised for acute HF with an LVEF ⩽45%. During 3 years of follow-up, untreated CSA or OSA were independently associated with mortality [14]. As discussed in detail below, the SERVE-HF study showed poorest survival in patients with predominant PB and in patients with LVEF >30%. Based on these findings, the question arises whether phenotypes of CSA should also be defined based on outcome.

- Sands *et al.* [99] showed a heterogeneous response to PAP treatment according to the LG. Patients with a low LG had a significantly better response to PAP therapy as compared to those with a high LG.
- Kazimierczak *et al.* [100] analysed the prognostic impact of the exercise oscillatory ventilation (EOV) in CSA patients. EOV is a common pattern and indicator of poor prognosis in CHF. The authors showed that EOV associated with CSA/CSR was highly prevalent in CHF and correlated with the severity of cardiac impairment at rest and exercise, *i.e.* significantly lower LVEF, peak oxygen uptake and ventilatory anaerobic threshold and a significantly higher left ventricular diastolic diameter, slope of ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}), AHI, central AHI and N-terminal pro-brain natriuretic peptide concentration. EOV can thus be described as another marker of unstable breathing.
- Giannoni *et al.* [101] investigated 110 HFrEF patients (31±7%). They analysed the HCR and HCVR and found that patients with the combined highest chemosensitivity (both HCR and HCVR) had significantly worse outcome as compared to those with less increased chemosensitivity. This holds even after adjustment for univariate predictors, namely V'_E/V'_{CO_2} slope, CSB, LVEF and brain natriuretic peptide.
- Brack *et al.* [102] and Perger *et al.* [103] analysed differences in the end-expiratory lung volume (EELV) and described two patterns of hypopnoea in PB. The positive pattern was defined by an EELV higher than the functional residual capacity, while the negative pattern showed an EELV lower than the functional residual capacity. Cardiac function was reduced in patients with negative CSA patterns. The authors speculated that the positive EELV might support left ventricular stroke volume.
- In addition, the extent of hypoxaemia over the night, the hypoxic burden, may influence survival in CHF with CSA. Granitza *et al.* [104] discriminated two patterns of desaturations in 11 patients with HFrEF and PB. One group showed a homogeneous distribution of oxygen desaturations. In contrast, other patients showed a bi-modal distribution with two peaks on a low and high desaturation level.

TABLE 3 Pathophysiological factors associated with prognosis in central sleep apnoea (CSA)

Outcome	Pathophysiological factor	Impact	References
Survival and MACEs	Hypoxic and hypercapnic ventilatory response	Increased chemosensitivity to both hypoxia and hypercapnia is a very serious adverse prognostic marker in HF	[101]
	Overnight desaturation patterns	Bi-modal distribution of oxygen desaturation is associated with a higher risk of mortality	[104]
	Hypoxic burden	Cumulated time with oxygen desaturation below 4% is predictive of mortality	[105]
Cardiac function	EELV	"Negative pattern" (EELV lower than the functional residual capacity) was associated with reduced cardiac function	[102, 103]
Response to ventilatory support	LG	Ventilatory instability measurement by LG effectively stratifies responders (low LG) and nonresponders (high LG) to the first night of CPAP treatment	[99]
Periodic breathing during exercise	EOV	EOV, which is associated with poor prognosis in HF patients, can be reversed with ASV treatment	[100]

ASV: adaptive servo-ventilation; CPAP: continuous positive airway pressure; EELV: end-expiratory lung volume; EOV: exercise oscillatory ventilation; HF: heart failure; LG: loop gain; MACEs: major adverse cardiovascular events.

Patients of the latter group had a substantial higher mortality risk as compared to the former group. WATANABE *et al*. [105] showed that the cumulative time with oxygen desaturation below 4% was the best predictor of mortality.

The FACE study focused on the heterogeneity of CSA patients with CHF regarding symptoms, clinical and biological parameters. TAMISIER *et al*. [44, 45] described six phenotypes differing in terms of survival and severity of morbidity at 3-month and 2-year follow-up. Male patients with HFrEF and predominant CSA had the worst outcome. Adding cardio-respiratory variables and use of latent class analysis improved phenotyping and helped to individualise health trajectories characterised by different prognosis. In addition, response to treatment may be included in CSA definitions as it may be harmful, neutral or positive depending on the initial clinical presentation [44, 45, 106, 107]. Two additional studies are ongoing, the multicentre European registry, Read-ASV [6] using an ASV device from a single brand, and the multicentre French registry, FACIL-VAA, using the three brands of ASV devices currently available on the market. These two studies have similar designs and will produce data of significant benefit in term of symptoms characterisation, quality of life and prognosis in all different aetiologies of CSA.

Treatment

These considerations urge clinicians to offer dedicated therapeutical options to overcome symptoms and, if possible, to improve outcome. These include positive pressure therapies, oxygen supplementation, but also invasive approaches and pharmaceutical options. The promptness with which to initiate therapy for CSA may be dependent upon phenotypes and the presence of daytime symptoms prior to treatment initiation [108]. Indeed, the severity of daytime and nocturnal symptoms and the degree of pathophysiological repercussions (sleep disruption and hypoxic burden) may be an argument that should be considered for therapy management.

CPAP

CPAP represents the first therapeutical option proposed for CSA. Indeed, CPAP might be sufficient to control CSA as it optimises ventilation–perfusion mismatch and improves oxygenation, reduces sleep fragmentation related to coexisting obstructive events, increases breathing dead space slightly, reduces work of breathing and left ventricular afterload, and improves haemodynamics. However, there is no large study or data supporting that CPAP improves cardiovascular outcomes or mortality in CSA. To date, the largest randomised control trial (RCT) investigating CSA associated with CHF proved that CPAP reduces the number of SRBDs by 50% and improves oxygen saturation, left ventricular ejection fraction, CHF status and 6-min walking test) and sympathetic tone, but has no effect on prognosis [109].

Oxygen

Oxygen supply dampens HVR, diminishes LG and is thus supposed to stabilise breathing. Nocturnal oxygen has been tested in different studies but has little impact on AHI and outcomes of CHF [110–112]. However, there is no data supporting improvement in prognosis to date and the LOFT-HF trial (NCT03745898) has recently been prematurely concluded after recruiting 98 HF patients.

Noninvasive ventilation

Noninvasive ventilation (NIV) should be dedicated to hypercapnic CSA associated with central hypoventilation syndromes due to congenital disorders (PHOX2B mutations), central nervous system lesions or medication. Bilevel PAP (BPAP) without back-up rate should be used cautiously as it may not control central apnoeas [113]. Moreover, fixed-pressure support may worsen nonhypercapnic CSA as hyperventilation decreases the CO_2 level below the AT. Therefore, NIV with back-up rate is frequently used in hypercapnic CSA showing evident clinical and quality of life improvement. However, data from RCTs showing improved prognosis are lacking. There is no evidence for NIV or BPAP in patients with nonhypercapnic CSA [114].

ASV

ASV is a type of positive pressure support ventilation composed of three components (figure 2):

- a variable or fixed expiratory pressure (expiratory PAP (EPAP)) to overcome upper airway obstruction;
- a variable inspiratory pressure support (difference (Δ) between EPAP and inspiratory PAP (IPAP)) to counterbalance PB and stabilise ventilation, IPAP is increased during hypoventilation and decreased during hyperventilation; and
- a back-up frequency of mandatory breaths to avoid central apnoeas.

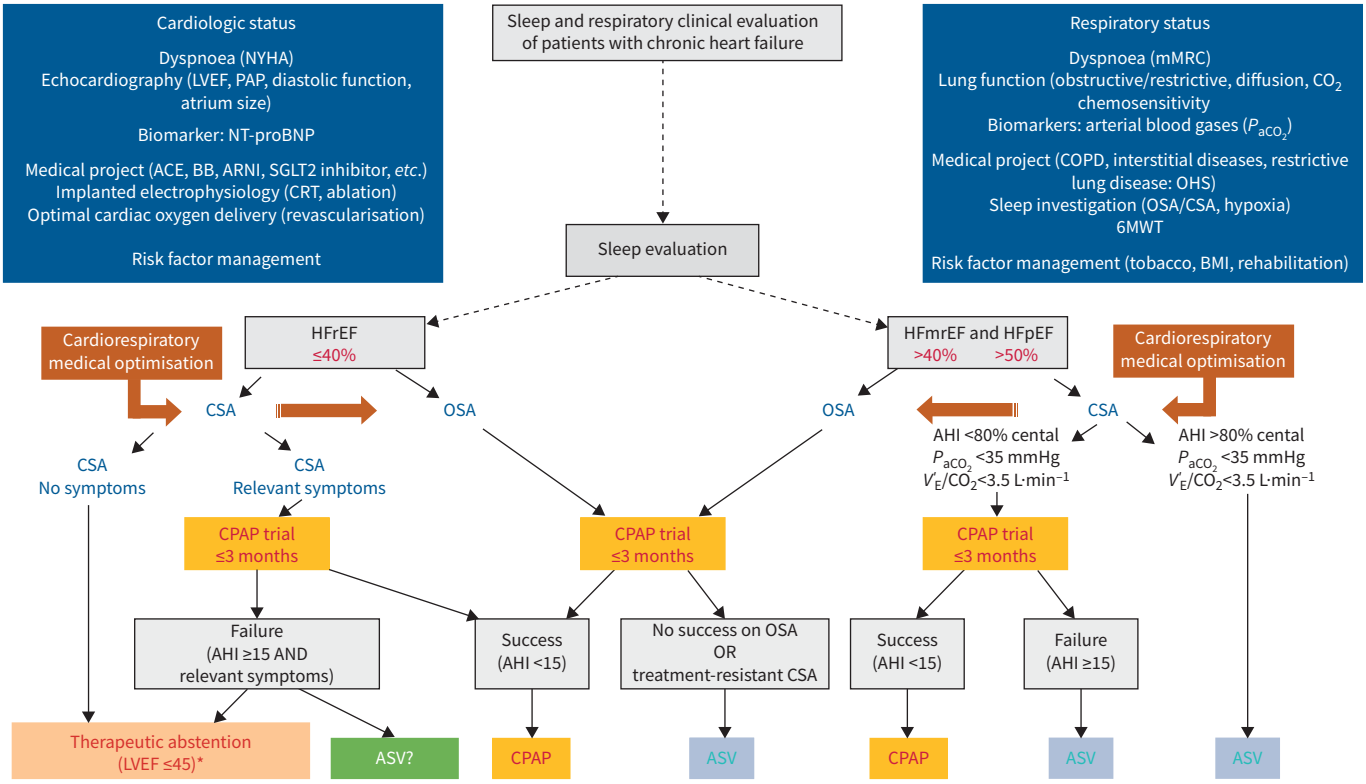

FIGURE 2 Sleep apnoea therapeutic strategy in chronic heart failure. Management of sleep apnoea (SA) in chronic heart failure patients, following the identification of SA phenotype, mainly relies on cardiac left ventricular ejection fraction status (*i.e.* reduced (ejection fraction (EF) ⩽40%), mildly reduced (40%<EF⩽50%) and preserved (EF>50%)). A proper assessment and management of both respiratory and cardiologic status, integrating risk factors management is a prerequisite for an efficient management. For obstructive sleep apnoea (OSA), continuous positive airway pressure (CPAP) is always the first line therapy. For central sleep apnoea (CSA), cardiorespiratory medical optimisation is a prerequisite for ventilatory support therapy. We recommend that adaptive servo-ventilation (ASV) as a first line ventilatory support in CSA should be reserved to heart failure patients with an EF >40%, in case of hypocapnic CSA, with at least 80% of apnoea–hypopnoea index (AHI) at diagnosis being of central origin. There is a current contraindication for ASV in patients with predominant CSA and left ventricular ejection fraction (LVEF) <45% based on the SERVE-HF study. This may be discussed based on the findings of ADVENT-HF and other data regarding the level of LVEF in the sub-analysis of SERVE only showed an increased risk in LVEF <35% [139]. Note that awaited results from ongoing studies may extend ASV indications. 6MWT: 6-min walking test; ACE: angiotensin conversion enzyme; ARNI: angiotensin renin neprilysin inhibitor; BB: β-blocker; BMI: body mass index; CRT: cardiac resynchronisation therapy device; HfmrEF: heart failure with mildly reduced ejection fraction; HfpEF: heart failure with preserved ejection fraction; HfrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; mMRC: modified Medical Research Council; NT-proBNP: N-terminal pro-brain natriuretic peptide; OHS: obesity hypoventilation syndrome; P_{aCO_2}: arterial pressure of carbon dioxide; PAP: pulmonary artery pressure; V'_E/CO_2: minute ventilation–carbon dioxide ratio, calculated based on the hypercapnic ventilatory response test.

All ASV devices measure a target parameter to calculate current ventilation on a breath-by-breath basis and compare it in a moving window of 3 or 4 min throughout the night. The technical solutions from various manufacturers mainly differ by the targeted parameter (peak flow (ASVpf), V'_E (ASVmv) or relative V'_E (ASVrmv)) and the weighting of these data to adapt ΔIPAP (for details see Javaheri *et al.* [115]). The currently available devices allow for a minimal pressure support of zero in periods of hyperventilation, meaning that the ASV works as an automatic PAP device. In contrast, the first ASV devices applied a minimal ΔIPAP of 3 mbar, even if there was no need of pressure support. The differences between manufacturers and between old and current algorithms may have relevance regarding clinical outcomes.

ASV has proven being the most effective option to treat PB [116]. Sharma *et al.* [117], in a systematic review and meta-analysis of eight RCTs, showed that ASV significantly improved AHI and LVEF in HF patients with CSA and PB compared to subtherapeutical ASV, continuous or bilevel pressure ventilation, oxygen therapy, or no treatment. ASV also significantly improved AHI, LVEF and 6-min walking distance when compared to guideline-directed medical therapy, but with no improvements in peak O_2 % predicted, V'_E/V'_{CO_2} slope or quality of life. More recently, Iftikhar *et al.* [118] performed a network meta-analysis

on the effects of CPAP, BPAP with back-up rate and transcutaneous phrenic nerve stimulation (TPNS) on AHI and sleepiness (as measured by the ESS). Statistical ranking of treatments showed the relative superiority of both ASV and TPNS over BPAP and CPAP [118].

The FACE trial showed that ASV was effective in improving the combined endpoint of death or hospitalisation for decompensated HF or heart transplant in those groups with older, overweight patients with predominant CSA and preserved LVEF and in older, hypoxic patients with combined OSA and CSA [45].

NAGASAKA *et al*. [119] studied the effect of ASV in 141 patients with CHF due to ischaemic heart disease. After adjustment for demographic and cardiovascular risk factors, ASV was associated with reduced incidence of supraventricular and ventricular arrhythmia and improvement of renal function. SUN *et al.* [120] retrospectively studied the effect of ASVmv and ASVpf on mortality in 90 patients with HFrEF and CSA. After a median follow-up of 64 months, ASV compliant patients showed significantly better survival (hazard ratio 0.44, 95% CI 0.20–0.97; p=0.04). Recently, WANG *et al.* [121] performed a meta-analysis to study the effects of ASV on cardiovascular and all-cause mortality, and major adverse cardiac events (MACEs). Based on three RCTs and five comparative observational studies (n=2208), the authors showed no difference in all-cause and cardiovascular mortality and the risk of MACEs in patients with LVEF <33% and NYHA stages III/ IV. ASV was associated with reduced risk of MACEs under ASV in patients with LVEF ⩾33% and NYHA I/ II and those with nadir arterial oxygen saturation (S_{aO_2}) <80% [121].

There are controversial results emerging from the two major prospective RCTs, SERVE-HF and ADVENT-HF (table 4). SERVE-HF was a multinational, parallel group RCT with a 2-year follow-up. 1325 patients with symptomatic CHF (LVEF ⩽45%, AHI >15 events·h^{-1}, predominant central apnoea) under optimal cardiac therapy were treated with or without ASVmf. The device applied a minimal pressure support of 3 mbar and a fixed EPAP. While there was no difference in the primary combined end-point, all-cause mortality and cardiovascular mortality were significantly higher under ASVmf [106]. Additional analyses showed no difference in muscle sympathetic nerve activity (MSNA) during follow-up, whereas a low level of MSNA was associated with decreased cardiovascular mortality in the control but not the ASVmf group [107]. Additionally, the respiratory arousal index was significantly lower, while periodic limb movements (PLMS) and PLMS-related arousal index were significantly higher under ASVmf [122]. Interestingly, in a sub-study of the SERVE-HF trial, there was no significant effect on nocturnal ventricular ectopy or tachyarrhythmia over a period of 12 months in living patients with HFrEF and CSA. Hence, these do not support the hypothesis that ASV may lead to sudden cardiac death by triggering ventricular tachyarrhythmia [123]. The findings of SERVE-HF have been criticised due to technical differences and limitations of the study performance [124]. These concerns included the unavoidable pressure support and invariable EPAP, the high number of protocol violations, and the low treatment adherence (40% below 3 h).

ADVENT-HF is another multicentre, multinational RCT in HFrEF (LVEF ⩽45%) and SRBD (AHI ⩾15), studying standard medical therapy for HFrEF alone as compared to the standard medical therapy plus ASVpf. It included not only patients with >50% CSA, but also nonsleepy patients with ⩾50% obstructive events. The study was discontinued prematurely due to the Philips recall and the severe acute respiratory syndrome coronavirus 2 pandemic after 731 randomised patients. ADVENT-HF used a different ASV algorithm based on peak flow (ASVpf) as well as allowing for zero pressure support and variable EPAP. While the ADVENT-HF population included fewer patients in NYHA stages III and IV, the mean LVEF was similarly and severely reduced in both studies (table 4).

Having the statistically underpowered study size in mind, there was no significant difference in the in the pre-defined end-points, although the hazard ratio was in favour of ASVpf at the pre-calculated level (0.78). In contrast to SERVE-HF, ADVENT-HF does not show harm based on the results of the study population. ASVpf increased the PLM index but reduced total and respiratory arousals and sleep stages N2, N3 and REM sleep significantly. In addition, it improved ESS score in the full population and the OSA and CSA subgroups. In addition, there is an urgent need to better understand the discrepancies between the SERVE-HF and ADVENT-HF results, which may be due to the differences in algorithms (ASVpf *versus* ASVmf), settings (minimal pressure support 0 *versus* 3 mbar), adherence and population (mixed OSA and CSA *versus* CSA) [125].

Phrenic stimulation

Transvenous unilateral phrenic nerve stimulation is a relatively new therapy. In the largest trial to date, encompassing 151 randomised patients and not limited to those with CHF and reduced ejection fraction (64%), phrenic nerve stimulation decreased the AHI by nearly 50% (from 49.7 to 25.9 events·h^{-1}), increased nocturnal oxygen saturation and improved quality of life [126]. However, no data supports an improved prognosis.

TABLE 4 Comparison of the two major randomised controlled studies on adaptive servo-ventilation in patients with chronic heart failure (CHF) and central sleep apnoea (CSA) [125, 141, 142]

Characteristic	SERVE-HF		ADVENT-HF	
Design	Multinational, parallel-group RCT		Multinational, parallel-group RCT	
Follow-up	24 months		Maximum of 5 years Mean follow-up 2.7 years	
SRBD (inclusion)	Polygraphy or polysomnography; AHI >15 events·h^{-1} with ⩾50% central events and cAHI ⩾10		Polysomnography, AHI ⩾15 events·h^{-1}, stratified into: OSA if ⩾50% of events were obstructive and ESS was ⩽10 CSA if >50% of events were central	
CHF (inclusion)	LVEF ⩽45%; with CHF for at least 12 weeks, NYHA III or IV, NYHA II with ⩾1 hospitalisation for HF in the previous 24 months		LVEF ⩽45% AHA stages B–D HFrEF due to ischaemic, idiopathic or hypertensive causes for at least 3 months	
Primary end-point	Time to first event: all-cause death, unplanned hospitalisation (or unplanned prolongation of a planned hospitalisation) for worsening chronic HF, cardiac transplantation, resuscitation of sudden cardiac arrest or appropriate life-saving shock for ventricular fibrillation and fast ventricular tachycardia in ICD		Cumulative incidence rate of composite of all-cause mortality, first hospitalisation for CV diseases, new-onset atrial fibrillation/flutter requiring anticoagulation but not hospitalisation and delivery of an appropriate discharge from an ICD not resulting in hospitalisation	
Co-primary/ secondary end-point	"CV death" instead of "all-cause death"; "all-cause unplanned hospitalisation" instead of "unplanned hospitalisation for heart failure"		Cumulative incidence rate of all-cause mortality; cumulative incidence rate of all CV hospitalisations, new-onset atrial fibrillation/flutter requiring anticoagulation but not hospitalisation or delivery of an appropriate discharge from an ICD not resulting in hospitalisation; number of days alive not hospitalised; additional single outcome measures	
Time	2008–2015		2010–2022	
Device	ASVmf		ASVpf	
Mask	Full-face recommended		NA	
Core lab evaluation	Only during training		Central reading	
	Control	**ASV**	**Control**	**ASVpf**
Population (enrolled)	659	666	375	356
Population (completed)	578	583	332	324
Protocol violation (discontinuation/switch to other arm)	98 (17%)	168 (29%)	13 (4%)	83 (26%)
Male sex (%)	90.9	89.9	87.2	89.3
Age (years)	69.3±10.4	69.9±9.5	63.6±10.1	62.7±11.1
BMI (kg·m^{-2})	28.6±5.1	28.4±4.7	30.7±5.6	30.8±6.1
AHI (events·h^{-1})	31.7±13.2	31.2±12.7	42.8 ±20.9	43.3±20.5
cAHI (events·h^{-1})	46.5 ±30.0	44.6±28.9	NA	NA
Central events (%)	NA	NA	31	30
T90% (min)	55.7 (events·h^{-1}) 73.9	50.5 (events·h^{-1}) 68.2	NA	NA
Minimum saturation (%)	NA	NA	79.2±10.2	78.1±11.8
LVEF (%)	32.5 ±8.0	32.2±7.9	33.3±7.9	33.1±7.7
NYHA III (%)	69.4	68.9	18.7	22.0
NYHA IV (%)	0.9	1.7	2.1	0.8
ESS	NA	NA	6.4±3.3	6.0±3.5
EPAP mode	NA	Fixed	NA	Variable
EPAP applied baseline (mbar)	NA	Median 5.5 (95th percentile 3.0–11.0)	NA	NA
Minimal pressure support (mbar)	NA	3	NA	0
Average usage (h·day^{-1})	NA	3.7	NA	CSA: 5.2±3.5 OSA: 4.1±4.7 12 months

Data are presented as mean±SD, n or n (%), unless otherwise stated. AHA: American Heart Association; AHI: apnoea–hypopnoea index; ASV: adaptive servo-ventilation; ASVmv: minute ventilation targeted ASV; ASVpf: peak flow targeted ASV; BMI: body mass index; cAHI: central apnoea–hypopnoea index; CV: cardiovascular; EPAP: expiratory positive airway pressure; ESS: Epworth sleepiness scale; HF: heart failure; HFrEF: chronic heart failure with reduced ejection fraction; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; NA: not applicable/available; NYHA: New York Health Association; OSA: obstructive sleep apnoea; RCT: randomised controlled trial; SRBD: sleep-related breathing disturbance; T90%: time below 90% oxygen saturation.

Medications

On the one hand, clinicians should be aware of and consider removing medications inducing CSA (table 2) [66]. On the other hand, several pharmacological agents have been tested to treat CSA, targeting specific pathophysiological mechanisms. The translation to clinical practice is limited due to small sample sizes and short follow-up periods of the studies. Hypnotic agents (*i.e.* triazolam, temazepam, zolpidem and clonazepam) [10, 127] may increase the arousal threshold. Despite inconsistent results, hypnotics may reduce PB and CSA in different settings including CHF or high altitude [128–130].

The effects of acetazolamide, a carbonic anhydrase inhibitor that decreases LG, has recently been reviewed and meta-analysed. Acetazolamide reduces total AHI and CAI in patients with and without CHF, but with significant heterogeneity between studies [131]. Although acetazolamide demonstrated no effect on respiratory event duration, it improved respiratory related arousal index, total sleep time, sleep efficiency, arterial carbon dioxide tension levels and S_{aO_2} values at night [131].

Interestingly, in HFrEF with iron deficiency, supplementation with intravenous iron reduces HCVR and thus stabilises ventilation during sleep [132]. However, most of the studies conducted to date were performed over a short-term period (up to 1 month of treatment).

Rocha *et al*. [133], in a recent Cochrane review, evaluated benefits and harms of pharmacological treatment for CSA in adults compared with active or inactive controls. Four cross-over RCTs and one parallel RCT were included (n=68), of which four recruited patients with CSA in CHF and one included primary CSA [133]. The pharmacological agents tested were acetazolamide, buspirone, theophylline and triazolam for a duration ranging between 3 days and 1 week. The small number of participants (5–18), the short study duration and the lack of concrete evaluation of quality of life, sleep quality, serious adverse events and overall mortality currently prevent the use of pharmacological therapy in the treatment of CSA [133].

Therefore, there is a need for high-quality trials evaluating the longer-term effects of pharmacological interventions. Along with the progression in the identification of the underlying phenotypes of CSA, an interesting perspective would be also to test the effect of pharmacological treatments in combination with different kind of ventilatory support.

Practical approach and algorithm of treatment

Several studies have contributed to establish treatment algorithms to guide clinicians towards an effective and personalised treatment for CSA in CHF patients. We provide herein an updated version of the algorithm initially published by the European Respiratory Society Task Force [2]. This algorithm has been updated to integrate the FACE study results, showing that the major impact of CSA treatment with ASV may occur in patients with HFmrEF and HFpEF [44, 45]. The results of Advent-HF will help to complete the algorithm for HFrEF patients, especially for those with predominant OSA or CSA.

There is a lack of robust evidence for patients without chronic HF. Although these patients represent the majority of ASV users, only few studies are available [134, 135]. Data from the Read-ASV (n=801) [6, 108] and the FACIL-VAA (n=520) cohort studies (NCT03032029 and NCT02835638 on https://clinicaltrials.gov) will certainly provide important knowledge to improve and refine the treatment algorithm. The Read-ASV study recently showed that ASV improves sleepiness and quality of life in symptomatic patients, which may guide clinicians in their therapeutical decisions [108].

Three steps need to be considered while implementing CSA treatment. Firstly, as mentioned above, clinicians should particularly focus on defining and addressing the underlying aetiology of CSA. Secondly, particular attention should be paid to haemodynamic changes during the initiation of CSA treatment in patients with CHF [136]. The last step is to monitor treatment efficacy. Patients with CSA suffer from multiple conditions and therefore may be more likely unstable regarding ventilation and haemodynamics. To our knowledge, there is no specific recommendation on how these patients should be monitored. The *post hoc* analysis of the CanPAP study, although, demonstrated a much worse prognosis in patients with CSA not controlled by CPAP [137]. Therefore, follow-up polysomnography or at least ventilatory polygraphy may be considered to ascertain sufficient stabilisation of ventilation during the first months of therapy. In addition, the maintenance of this treatment success should be monitored during treatment follow-up on a yearly basis. The benefit of the addition of a telehealth system for patients and sleep healthcare needs to be investigated. This may include monitoring of PAP devices as automatically detected changes of respiratory disturbances or adherence may indicate serious cardiac events [138]. However, especially in the sensitive group of CSA patients, it is of crucial importance that these data are supervised closely by experienced medical staff.

Conclusion

A more precise differentiation and description of the entities of CSA embracing the heterogeneity of underlying aetiology, pathophysiological concepts, treatment response and outcome is emerging. The identification of CSA phenotype is key for selecting individualised therapeutic approaches, which should be based on the dominant underlying pathophysiological characteristics (*i.e.* LG, AT, breathing regulation and neuromuscular mechanics) and on a more wider phenotype evaluation including socio-cultural factors. The most prevalent CSA-associated medical condition is CHF, leading to nonhypercapnic CSA. In this case, the indication of ASV should be carefully evaluated and rarely represents a first-line therapy. However, ASV indications may be extended, based on results of ongoing trials. Future research should focus on describing the prognostic aspects associated with CSA and its associated clinical entities, as well as refining treatment indication, including pharmacotherapy and invasive options. Finally, the present review is solely based on our own opinions and does not represent formal guidelines. Indeed, given the multitude of new publications and upcoming studies, there is an opportunity to employ the appropriate methodology to create updated guidelines, updating those produced in 2017 [2].

Provenance: Commissioned article, peer reviewed.

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