Positive Airway Pressure Therapies for Heart Failure: What Do the Trials Tell Us?

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Abstract

Sleep-disordered breathing (SDB) represents a modifiable treatment target in patients with heart failure (HF). Despite the evolution of positive airway pressure (PAP) therapy over the past several decades, randomised controlled trials have not demonstrated a consistent benefit in reducing mortality or hospital admissions related to HF. As a result, the use of PAP therapy has been primarily limited to symptom control of SDB. However, recent trials suggest that PAP therapy is safer than previously perceived and underscore an urgent need for a phenotype-based, individualised treatment approach. Stratifying patients according to sleep apnoea phenotypes or characteristic clinical clusters may enhance the identification of individuals most likely to respond favourably to PAP therapy in terms of clinical outcomes. This narrative review provides an outline of the current evidence regarding the use of PAP therapy in patients with SDB across the spectrum of HF phenotypes.

Keywords

Sleep-disordered breathing, positive airway pressure therapy, heart failure, review

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Heart failure (HF) is a clinical syndrome consisting of current or prior symptoms and/or signs, such as breathlessness, fatigue, peripheral oedema or elevated jugular venous pressure due to functional and/or structural abnormality, and corroborated by at least elevated natriuretic peptide levels or objective evidence of cardiogenic pulmonary or systemic congestion.[1] HF affects approximately 1–3% of the adult population.[2,3] Globally, it is estimated that more than 64 million individuals are living with HF.[2] Despite advances in therapy, the prognosis of HF remains poor, with 1-year mortality rates ranging from 15% to 30%.[2] The burden of HF is substantial, characterised by high morbidity and mortality, significantly reduced functional capacity, impaired quality of life and considerable healthcare costs. The chronic and progressive nature of the disease places a considerable strain on patients, caregivers and healthcare systems worldwide.[2]

HF phenotypes can be classified as HF with preserved ejection fraction (HFpEF), with impaired ventricular filling and elevated intracardiac pressure but normal ejection fraction (EF; ≥50%), or HF with reduced left ventricular function, further divided according to EF as either mildly reduced (HFmrEF; EF 41–49%) or reduced (HFrEF; EF ≤40%). The fourth phenotype, HF with improved EF (HFimpEF), is defined as HF with a baseline EF ≤40% that improves by at least 10% over time and is >40% at the time of the second measurement.[1] Approximately half of HF patients present with HFrEF, with the other half having HFpEF or HFmrEF (with the proportion varying significantly depending on the study).[2] Importantly, the incidence of HFpEF is rising and it is believed that it will exceed the incidence of HFrEF in the future.[4] One reason for this is greater awareness, better diagnostic strategies (H2FPEF score) and new, highly effective, evidence-based treatment options with sodium–glucose cotransporter 2 inhibitors.[4]

Heart Failure Treatment

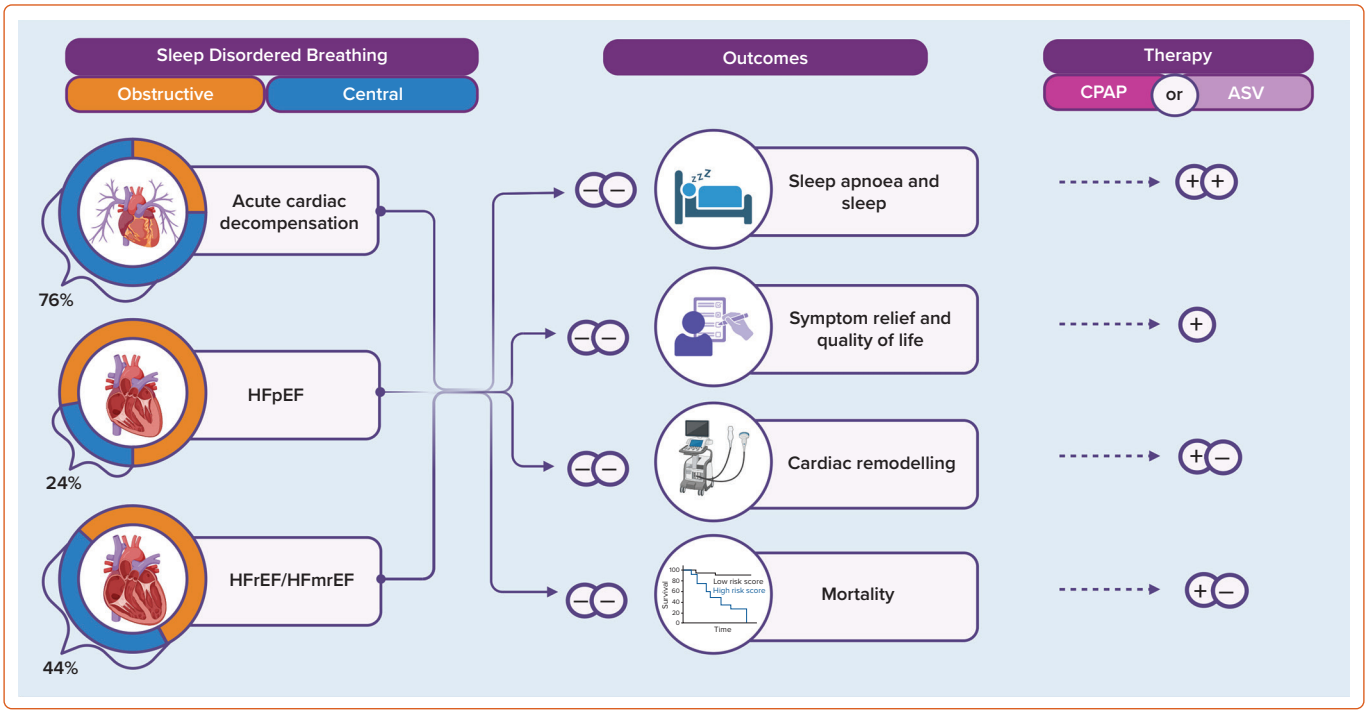
There have been significant advances in HF treatment in recent decades. The multimodal approach results in both symptomatic and prognostic improvements, and treatment strategies differ depending on the HF phenotype. In HFrEF, robust evidence supports the use of guideline-directed medical therapy, which includes angiotensin receptor–neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists and sodium–glucose cotransporter 2 inhibitors.[3] These pharmacological agents have demonstrated significant benefits in reducing mortality and hospitalisations, as well as in improving quality of life.[3] In addition to medical therapy, several device-based and intervention strategies play critical roles in select patient populations. CRT is indicated in patients with left bundle branch block and reduced EF.[3] Mitral edge-to-edge repair, particularly in patients with secondary mitral regurgitation, and catheter-based pulmonary vein isolation for AF are important adjunct treatments that can improve outcomes and functional status in appropriately selected patients.[3]

Obstructive and Central Sleep Apnoea in Heart Failure

Epidemiology and Health Burden

One-third to one-half of patients with HF are affected by moderate to

Graphical Abstract: Positive Airway Pressure Therapies for Heart Failure: What Do the Trials Tell Us?



ASV = adaptive servo-ventilation; CPAP = continuous positive airway pressure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; PAP = positive airway pressure. Created by Pec J in BioRender (https://BioRender.com/72z1kps).

severe sleep-disordered breathing (SDB).[5] In all HF phenotypes, obstructive sleep apnoea (OSA) is more prevalent than central sleep apnoea (CSA). The reported occurrence of CSA is approximately 76% in acute decompensated HF, 44% in HFmrEF/HFrEF and 24% in HFpEF.[5,6] Importantly, the presence of SDB has been associated with increased mortality, poor quality of life and higher rehospitalisation rates.[7–10]

Pathophysiology

OSA is characterised by a cessation or reduction in airflow caused by upper airway collapse due to anatomical abnormalities, obesity or rostral fluid shift to the neck (*Figure 1*). OSA leads to intermittent nocturnal hypoxia, arousals from sleep and negative intrathoracic pressure during inspiration.[10,11] Collectively, these pathophysiological mechanisms contribute to a cascade of adverse cardiovascular effects, including sustained elevation of systemic blood pressure, increased left ventricular afterload and repetitive surges in heart rate, all of which augment myocardial oxygen demand (*Figure 1*).[11,12] Intermittent hypoxia during OSA may further compromise cardiac performance by directly impairing myocardial contractility or indirectly lowering cardiac output through an increase in pulmonary artery pressure. Together, these processes create a mismatch between oxygen supply and demand, thereby placing additional stress on an already vulnerable myocardium.[11,12]

CSA, in patients with HF typically with a Cheyne–Stokes respiration pattern, is characterised by respiratory instability driven primarily by fluctuations in carbon dioxide levels, with circulatory delay playing a central role in its pathophysiology (*Figure 1*).[12–14] These fluctuations are triggered by hyperventilation caused by pulmonary congestion.[12] Oscillations in carbon dioxide drive cyclic fluctuations in heart rate and blood pressure via autonomic instability. In contrast to OSA, CSA does not generate large negative intrathoracic pressure swings.[14] However, some pressure fluctuations do occur, mainly during phases of hyperventilation. These can enhance venous return and temporarily increase left ventricular preload and stroke volume, as well as increasing myocardial oxygen demand.[14]

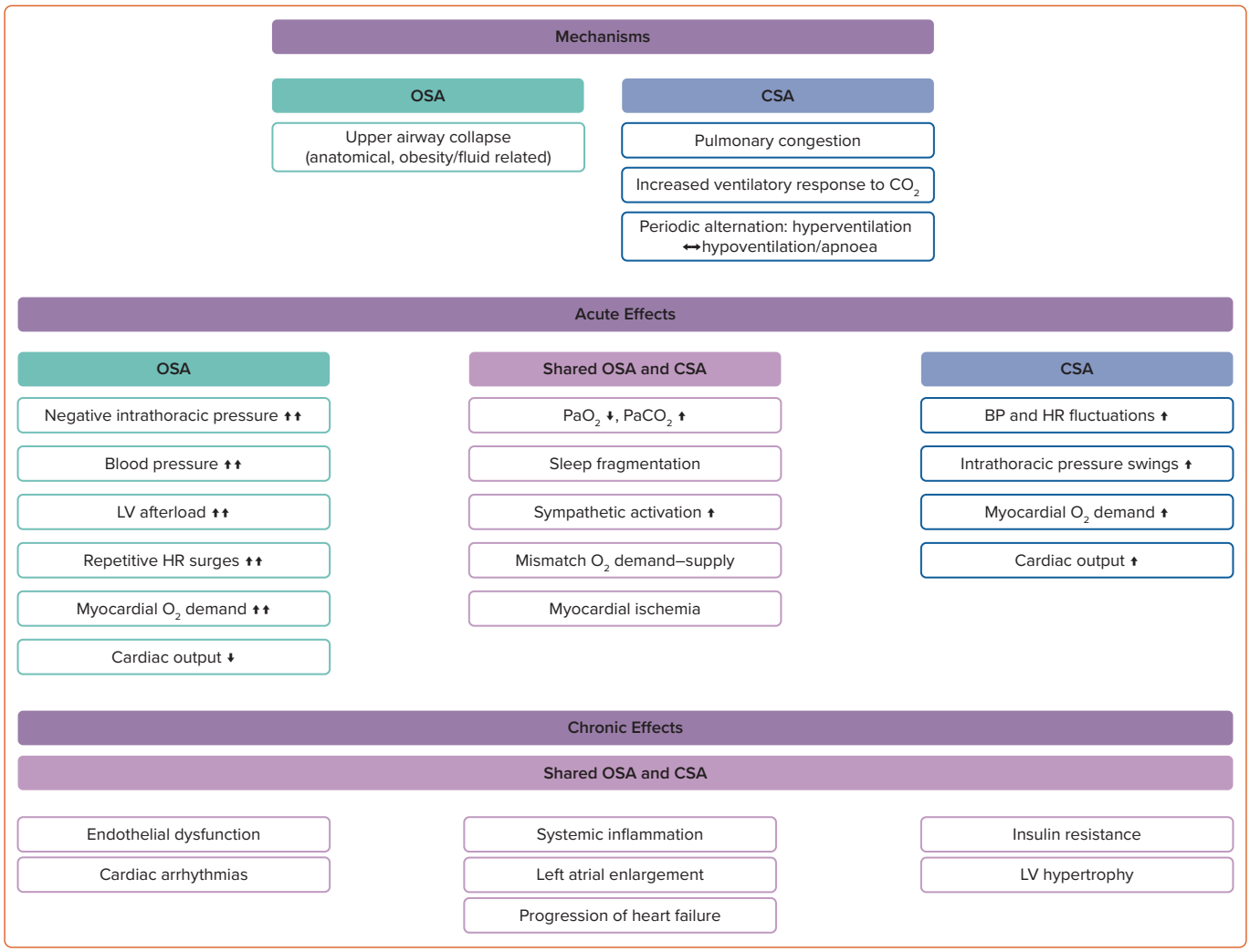
The sympathetic nervous system is activated in both OSA and CSA due to hypoxaemia, hypercapnia and arousals (*Figure 1*).[11,12,14] Sympathetic overactivity promotes tachycardia and arrhythmogenesis, raises blood pressure and thus increases left ventricular afterload and the cardiac workload.[11,12,14] In OSA, ventricular afterload is further increased by the negative intrathoracic pressure swings.[11,12] The resulting ventricular wall stress contributes to adverse remodelling, including left atrial enlargement and left ventricular hypertrophy, and progression of HF. In both forms of SDB, systemic inflammation, endothelial dysfunction and neurohumoral activation exacerbate cardiovascular injury.[10,15]

Conversely, HF itself promotes fluid overload and elevated cardiac filling pressures, whereas rostral fluid shifts during recumbency further aggravate both OSA and CSA by increasing fluid accumulation in the neck and lungs.[16,17]

Effects of Heart Failure Treatment on Obstructive and Central Sleep Apnoea

It is essential to prioritise the treatment of HF because evidence suggests that optimising standard HF therapies can lead to an improvement in CSA.[16,18,19] For example, after 6 months of optimised medical therapy, patients with CSA and HFrEF showed a reduction in pulmonary capillary wedge pressure, accompanied by a simultaneous decrease in the apnoea–hypopnoea index (AHI).[16] Intriguingly, CSA has been shown to nearly resolve after heart transplantation or left ventricular assist device implantation.[20,21] Moreover, interventional treatment options, such as mitral edge-to-edge repair for severe mitral regurgitation, also showed reductions in CSA and Cheyne–Stokes respiration.[22] Comparable results have been demonstrated for CRT in HFrEF, including enhanced sleep quality and alleviation of depressive symptoms.[23–25]

Figure 1: Mechanisms and effects of sleep-disordered breathing in heart failure



BP = blood pressure; CSA = central sleep apnoea; HR = heart rate; LV = left ventricle; OSA = obstructive sleep apnoea.

Methods

This narrative review aims to provide a comprehensive and critical overview of the current literature on positive airway pressure (PAP) therapy in patients with HF. To identify relevant studies published in peer-reviewed journals indexed in the PubMed database, the following combination of Boolean search terms was used: 'heart failure' AND 'CPAP' OR 'continuous positive airway pressure' OR 'ASV' OR 'adaptive servoventilation' OR 'auto-servoventilation' OR 'adaptive servo-ventilation' OR 'APAP'.

Additional sources were identified through manual searches. Studies were selected based on their relevance to the review topic, clinical significance and contribution to understanding current practices, physiological mechanisms and treatment outcomes. Both randomised controlled trials (RCTs) and observational studies, including cohort and registry studies, were considered if they were written in English and involved human participants. We excluded reviews and case reports.

In line with the narrative review methodology, no formal risk of bias or quality assessment was conducted for this review.

Positive Airway Pressure Therapies for Heart Failure

There are several types of PAP therapy, including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) and adaptive servo-ventilation (ASV). CPAP is typically the first-line treatment for both OSA and CSA. When CSA persists despite CPAP therapy, ASV is considered a second-line option.[26,27]

Positive Airway Pressure Therapy in Acute Decompensated Heart Failure

Sleep apnoea is highly prevalent in patients with acute decompensated HF, with two-thirds of patients exhibiting SDB at an AHI threshold of ≥15 events/h.[28–30] Importantly, newly diagnosed CSA and OSA during hospitalisation for acute HF were shown to be independent predictors of post-discharge mortality.[29,31] In patients with acute cardiogenic pulmonary oedema, non-invasive ventilation modalities such as CPAP or BiPAP are safe and effective adjuncts to standard medical therapy.[32] Moreover, BiPAP appears to be as effective as CPAP in reducing endotracheal intubation rates and mortality among patients with acute hypercapnic respiratory failure secondary to acute cardiogenic pulmonary oedema.[33] Elevated left ventricular diastolic pressure is a key factor for the increase in stroke volume and cardiac output observed with CPAP, even independent of improvement in oxygenation. In patients with high pulmonary capillary wedge pressure, CPAP has been shown to increase both the stroke volume and cardiac index.[34] Clinical trials specifically investigating sleep apnoea in the context of acute decompensated HF remain limited. In one RCT involving patients with HFrEF and OSA who received guideline-directed therapy for HF decompensation, those

randomised to CPAP and adherent to therapy (>3 h/night) experienced a 60% reduction in rehospitalisation compared with controls; however, the trial overall was neutral.[35] In the CAT-HF trial, the addition of ASV to optimised medical therapy effectively alleviated sleep apnoea but did not improve cardiovascular outcomes in patients with acute decompensated HF.[6] A subgroup analysis suggested potential benefit in patients with HFpEF. However, the trial was underpowered and was terminated early due to safety concerns raised by the SERVE-HF trial.[36] An observational trial evaluated data from ASV devices and discovered that both the AHI and the inspiratory pressure support provided by the ASV device significantly increased 10 days prior to an acute cardiac decompensation.[37] In addition, device usage time decreased during the last 2 days, indicating that respiratory data collected by the device may help both predict and prevent cardiac decompensations.[37]

In the TEAM-ASV I trial, patients with first-time acute MI and concomitant sleep apnoea were randomised to receive either ASV treatment of SDB or standard care only.[38] All patients had elevated N-terminal pro B-type natriuretic peptide concentrations and preserved to mildly reduced left ventricular EF, consistent with acute HF. The trial met its primary endpoint, showing a significant improvement in myocardial salvage index with ASV therapy.[38] In addition, a greater reduction in infarct size was observed in the ASV group (−44%) than in the control group (−21%).[38] Further research is warranted to better define the role of diagnostic screening and targeted treatment strategies for sleep apnoea in the acute setting in this high-risk clinical population, potentially tailored to specific sleep apnoea phenotypes.

Positive Airway Pressure Therapy in Chronic Heart Failure with Mildly Reduced or Reduced Ejection Fraction

Trials of ASV for central sleep apnoea in HFmrEF and HFrEF were mainly driven after neutral results in the CANPAP trial in 2005 and insufficient suppression of CSA with CPAP in that trial.[39,40] Subgroup analysis of patients in which CPAP suppressed AHI to <15 events/h showed improved heart transplant-free survival.[40] BiPAP with fixed pressure was shown in 2005 to worsen CSA, so there are no new trials.[41] Notably, even the largest RCT to date, the SERVE-HF trial in 2015, failed to demonstrate a benefit of ASV with fixed pressure settings on the primary composite endpoint in predominantly CSA patients (n=1,325).[36] Moreover, both all-cause and cardiovascular mortality were significantly higher in the ASV group.[36] Since then, few RCTs have specifically addressed the treatment of sleep apnoea in patients with the HFrEF phenotype. Several trials initiated prior to SERVE-HF were either prematurely terminated or modified to exclude patients with an EF ≤45% due to emerging safety concerns and hence became underpowered.[6,38,42] One of the more recent studies, the ADVENT-HF trial (n=731), was a multicentre, multinational, parallel-group, open-label, phase 3 RCT of peak-flow triggered ASV that enrolled patients with HF and EF ≤45%, predominantly with OSA, and randomised them to receive ASV or standard care in addition to optimised medical therapy.[42] The mean EF was 33% and the AHI was 43 events/h. There was a successful suppression of the AHI to 2.8–3.7 events/h over the course of the trial.[42] The authors concluded no significant effect of the addition of ASV to standard therapy on the primary endpoint (the cumulative incidence of the composite of all-cause mortality, first admission to hospital for a cardiovascular reason, new onset AF or atrial flutter and delivery of an appropriate cardioverter defibrillator shock), showing 180 events in the control group compared with 166 in the ASV group (HR 0.95; 95% CI [0.77–1.18]; p=0.67) or all-cause mortality as a secondary endpoint in the entire cohort or in those with OSA or CSA.[42] A clear explanation as to why there is no effect on 'hard' cardiovascular endpoints if there is an alleviation of sleep apnoea remains to be determined. The compensatory role of CSA on HF with systolic dysfunction has been questioned.[43] However, data from a larger population have clearly shown the detrimental role of CSA or Cheyne–Stokes respiration on HFrEF.[44] The potential harmful effects of PAP therapy may be related to excessive pressures resulting from fixed pressure settings. Physiological studies have investigated whether elevated PAP could lead to reduced cardiac output and hypotension in HFrEF patients with low cardiac preload, or increased right ventricular afterload due to elevated intrathoracic pressures.[34,45] Notably, the ADVENT-HF trial found that ASV was not associated with increased mortality in patients with CSA (n=198), indicating a favourable safety profile for the use of ASV devices with automated expiratory PAP in this population.[42] Furthermore, the trial was not entirely neutral, because the ASV group exhibited relevant improvements in objectively assessed sleep quality, health-related quality of life and symptom burden.[42] A recent subanalysis of the ADVENT-HF trial evaluated the effects of ASV on left ventricular structure and function, but found no improvements after 6 months of treatment.[46]

Several factors may explain the neutral outcomes with respect to mortality and major cardio- and cerebrovascular events observed in RCTs.[47] These include the relatively short duration of follow-up, the exclusion of excessively sleepy participants due to ethical concerns, suboptimal adherence to therapy and a potential overreliance on conventional sleep apnoea metrics, such as the AHI, which may not fully capture clinically relevant effects.[27]

Positive Airway Pressure Therapy in Patients with Chronic Heart Failure with Preserved Ejection Fraction

The current literature on the effectiveness of PAP therapy in patients with chronic HF is sparse. This is important because patients with HFpEF and SDB share some important comorbidities, such as hypertension, diabetes and obesity.[15] In one propensity score-matched study there was a reduction in healthcare resource use among patients adherent to PAP therapy.[48] After one small RCT with 36 patients in 2013, which showed a better event-free rate in the ASV group and an improvement of symptoms, cardiac diastolic function and arterial stiffness, there were no more RCTs to investigate the role of PAP therapy in HFpEF.[49,50] Future research should prioritise targeting modifiable factors, such as SDB, in patients with HFpEF.

Registry-based Studies in Patients with Central Sleep Apnoea with and without Heart Failure

Large registry and observational studies can serve as valuable complements to RCTs, particularly in evaluating outcomes in sleep clinic populations, including excessively sleepy patients who are typically excluded from clinical trials.[51] The large observational multicentre READ-ASV registry investigated the effects of ASV therapy in patients with CSA, including those with treatment-emergent CSA. In READ-ASV, approximately 25% of patients have HF, with vast majority of these having HFpEF.[52,53] This distribution is attributable to the indication restriction for ASV therapy for left ventricular EF ≤45% and predominantly central sleep apnoea.[36,54] The READ-ASV study demonstrated significant improvements in patient-reported outcomes, specifically in Functional Outcomes of Sleep Questionnaire and Epworth Sleepiness Scale scores, from baseline to the 12-month follow-up in patients with symptomatic CSA.[52,53] Consistent with these findings, the FACIL-VAA study, a prospective multicentre observational cohort study involving 526 patients with various CSA phenotypes, 16% of whom had HFpEF or HFmrEF, reported a significant improvement in sleep quality as

measured by the Pittsburgh Sleep Quality Index, with a median change of −1 (IQR −3, 0; p<0.001) from baseline to the 6-month follow-up, except in patients with drug-induced CSA.[55] In addition, in a propensity score-matched study of patients with HFrEF and OSA, a reduction in healthcare resource usage was demonstrated for those with higher adherence to PAP therapy.[56]

Importantly, real-world data from large-scale observational cohort studies, such as the FACE trial, have further contributed to understanding the heterogeneous effects of ASV therapy across the full spectrum of HF.[57,58] A multicentre study aimed to identify distinct patient phenotypes rather than applying a 'one-size-fits-all' approach, defining six patient clusters based on variations in left ventricular EF, SDB type, age, comorbidities and ASV adherence.[59] The primary composite endpoint was time to the first event, defined as all-cause death, life-saving cardiovascular intervention or unplanned hospitalisation due to worsening HF.[58] Two-year follow-up data from the FACE trial revealed that ASV therapy was associated with a significant reduction in cardiovascular events and mortality in patients with HFpEF and in those with a high hypoxic burden.[57] In contrast, no mortality benefit was observed among patients with HFrEF or older individuals with mild SDB.[57]

Clinical Implications

According to the 2022 American Heart Association guidelines, patients with HF and suspected SDB should undergo a formal sleep study to establish the diagnosis and differentiate between OSA and CSA (*Supplementary Table 1*).[60] In patients with HF and concomitant OSA, CPAP therapy is considered reasonable because it improves sleep quality and reduces daytime sleepiness. In contrast, the use of ASV in patients with HFrEF, New York Heart Association Class II–IV and CSA is contraindicated.[60] Since the 2022 American Heart Association guideline, new recommendations from the American Academy of Sleep Medicine guidelines and new statements from the European Respiratory Society Task Force, published in 2025, have introduced important changes to the previous recommendations on sleep-disordered breathing in heart failure (*Supplementary Table 1*).[61,62]

Based on pooled estimates of all-cause and cardiovascular mortality from RCTs in HFrEF patients, the Task Force of the American Academy of Sleep Medicine observed no effect of ASV on mortality and concluded that its potential benefits outweigh its potential harms.[61] Prior to initiation of ASV, patient–provider shared decision-making is recommended, and treatment decisions should be based on expectations of improvements in symptoms or quality of life. Treatment with ASV in patients with HFrEF should be limited to centres with experience, along with close monitoring and follow-up.[61] The Task Force of the European Respiratory Society evaluated the evidence on currently available ASV devices and stated that ASV improves CSA and quality of life across different CSA phenotypes, without evidence of adverse effects on major cardiovascular outcomes, and with beneficial effects on patient-reported outcomes.[62] According to the Task Force, ASV is considered after optimal treatment of the underlying condition and following an unsuccessful CPAP trial.[62] In CSA patients with a left ventricular EF of 30–45%, initiation should be restricted to expert centres. In severe systolic heart failure, ASV may also be evaluated within a palliative treatment approach for patients with severe symptoms and CSA.[62] The European Respiratory Society Task Force also underlined that prospective observational studies suggest that patient phenotyping is crucial for long-term outcomes independent of sleep apnoea therapy, with certain HF phenotypes potentially benefiting in terms of major adverse cardiovascular events. However, these subgroups were not represented in large RCTs, and no RCTs have specifically addressed HFpEF.[62]

Conclusion

Latest RCTs evaluating PAP therapy in patients with HF have not demonstrated significant benefits on 'hard' cardiovascular endpoints. However, consistent improvements in quality-of-life measures have been observed. A recent meta-analysis combining data from RCTs and observational studies suggested an overall positive effect of PAP therapy, although the benefit was predominantly driven by findings from observational studies.[51] The 2022 American Heart Association guidelines recommend a sleep study in HF patients with suspected SDB and support CPAP in those with OSA.[60] The latest US and European clinical guidelines now recommend considering PAP therapy, including ASV, for patients with CSA and HF, regardless of EF, to reduce disease severity.[61,62] Moving forward, clinical trials should consider alternative inclusion criteria, such as hypoxic burden, heart rate response or phenotyping via cluster analysis, to better identify subgroups of patients most likely to benefit from PAP therapy.[57,63] ❑

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