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Sleep-Disordered Breathing in Patients with Heart Failure

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Abstract Breathing disturbances during sleep play a significant role in patients with cardiac diseases due to their high prevalence and impact on outcome. Obstructive sleep apnea (OSA) is a major risk factor of arterial hypertension and is associated with atrial fibrillation. A majority of heart failure (HF) patients suffer from OSA or central sleep apnoea (CSA), both associated with impaired prognosis. The application of continuous positive airway pressure has proven to improve symptoms and outcome in severe OSA. However, optimal therapy of CSA in heart failure is under discussion. Adaptive servoventilation (ASV) allows for counterbalancing the shift between hyperventilation and hypoventilation in periodic breathing. It has been shown to be superior to oxygen, continuous positive airway pressure therapy (CPAP) or other therapeutical options in HF patients with CSA. However, due to recent data, its use should be adapted closely to current indications and contraindications.

Keywords Sleep breathing disorders · Obstructive sleep apnea · OSA · Heart failure · Central sleep apnoea · Adaptive servoventilation

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Introduction

Breathing disturbances during sleep on one hand and heart failure (HF) on the other are associated in a bidirectional relationship. Obstructive sleep apnea (OSA) has been identified as an important risk factor of arterial hypertension, stroke, HF and arteriosclerosis. At least 50 % of HF patients present with varying combinations of sleep-related breathing disturbances (SRBDs), predominantly central sleep apnea (CSA) and Hunter-Cheyne-Stokes breathing (HCSB) [1]. There is a broad consensus to recommend continuous positive airway pressure therapy (CPAP) in OSA with and without HF aiming at the improvement of daytime sleepiness, neurocognitive deficits and risk of accidents, but also to improve oxygenation and sympathetic activity and therefore reduce cardiovascular consequences. However, recent months were characterized by an intensive and controversial discussion about the indication and optimal treatment of CSA/HCSB in HF patients.

Obstructive Sleep Apnea

Moderate to severe OSA, as defined by a number of ≥15 apneas or hypopneas per hour of sleep, reaches a prevalence of 17 % in men and 9 % in women between 30 and 70 years of age [2]. The obstructive events are associated with repetitive oxygen desaturations and reoxygenations, brief increases of the carbon dioxide (CO_2) partial pressure and arousals from sleep. Breathing effort and work of breathing increase during the upper airway obstruction until the event terminates abruptly. The immense chemical and mechanical stress of the respiratory system is associated with an overnight increase of the sympathetic and a decrease of parasympathic activity [3–11]. The numerous shifts between hypoxia and reoxygenation, the production of reactive oxygen species and the blood gas alterations increase muscle sympathetic nerve activity, blood

pressure, vascular resistance, endothelial dysfunction and arteriosclerosis [3, 5, 12, 13]. Therefore, OSA represents a risk factor for arterial hypertension and vascular diseases, independent of known confounders [9, 10, 14–16].

Most studies on the association of SRBD in heart failure focus on patients with reduced left ventricular ejection fraction (HFrEF), i.e. systolic dysfunction. However, the consequences of OSA, especially arterial hypertension, may also contribute to the development of diastolic HF. This is characterized by preserved left ventricular ejection fraction (HFpEF) but increased end-diastolic left ventricular pressure and consecutive pulmonary fluid overload [4, 8–10, 17]. As noted, OSA is also associated with coronary artery disease, stroke and—as a consequence of the cardiovascular morbidity—increased mortality. Survival is significantly impaired in patients with an AHI ≥30/h [15, 16, 18–24].

Treatment of OSA focuses at the abolishment of underlying predisposing factors, which increase the pressure of the surrounding tissue, e.g. fat or fluid accumulation. However, upper airway obstruction has to be counterbalanced by elevating the intraluminal pressure with positive airway pressure (PAP) treatment in the majority of patients [13]. Several studies have demonstrated that PAP may reverse remodelling of myocardial structure [8, 10, 25]. CPAP has been shown to improve survival in observational studies [21, 26]. Javaheri et al. analysed more than 30,000 data sets of newly diagnosed HF patients. They showed a significant improvement of survival in those patients diagnosed and treated for sleep apnea as compared to those with sufficient but undiagnosed and untreated breathing disturbances [27]. Mandibular advancement devices (MADs) have proven to reduce obstructive SRBD significantly but less efficacious as compared to PAP therapy. Although measures of daytime sleepiness and quality of life have shown similar results with MADs and PAP, compliance data are in favour of oral appliances. However, more data on cardiovascular outcome parameters are needed. Taking these aspects together, CPAP is the treatment of choice in HF patients with predominant OSA. However, so far, there are no randomized clinical trials showing any beneficial outcome, such as improved quality of life, decreased hospitalization and improved survival.

Central Sleep Apnea and Hunter-Cheyne-Stokes Breathing

Recurrent cessations or reductions of airflow with simultaneous proportional reduction of breathing effort characterize CSA [13, 28, 29]. The term Hunter-Cheyne-Stokes breathing describes the pattern of periodic breathing in HF patients [28–30]. Central disturbances generate from reduced, lacking or overshooting and undershooting generation of the ventilatory impulses from the peripheral and central chemoreceptors. Central apneas with HCSB characteristically have a long cycle, typically 40 s or more. However central apneas, without the prolonged cycle time, are also observed during sleep with exposure to high altitude, with brainstem lesions, stroke, endocrine disorders and use of opioids [31–36]. However, cardiovascular diseases are by far the most relevant causes of central disturbances, especially HF and atrial fibrillation [30–32, 37–40].

The pathophysiology of OSA is based on narrowing and occlusion of the upper airways, and multiple mechanisms are involved. In HF patients with HCSB, central apneas are best explained by an increase in loop gain, with several characteristics including increased chemoresponsiveness resulting in shift between hypoventilation and hyperventilation with overshooting and undershooting of the ventilation and the pattern of periodic breathing [32, 37, 41–45]. The instability of the respiration is aggravated by changes of the reactivity of cerebral vessels and also by arousals from sleep.

Treatment of Central Sleep Apnea

Prior to specific treatment of central SRBD, therapy of the underlying cardiac disorders should be re-evaluated critically. Interventional treatment of coronary or valvular diseases, electrotherapy of bradyarrhythmias or tachyarrhythmias and pharmaceutical therapies according to current guidelines remain the cornerstones of care of HF patients. However, patients with remaining CSA/HCSB may require additional therapies after optimizing conventional options. Sufficient data showing a survival benefit in these patients treated with PAP therapy based on large, long-term randomized controlled trials are lacking. However, if a patient suffers from daytime sleepiness, neurocognitive deficits and impaired quality of sleep, specific treatment may be justified.

Oxygen

The application of oxygen improves oxygen supply to cardiac and respiratory muscle cells and thus improves their efficacy. Moreover, oxygen reduces the hypoxic and hypercapnic respiratory drive which—theoretically—may dampen the increased loop gain and the ventilatory overshoot and undershoot. However, large, long-term trials on the efficacy of oxygen in HF with CSA/HCSB are not available [46]. Administration of supplemental nasal oxygen reduces the number of respiratory disturbances by 50 % [46–49]. In a randomized, but open clinical trial of 12-week duration, Sasayama et al. [49] described significant improvement not only in SRBD but also in cardiac function and quality of life. This was confirmed in another small study [48] of 3-month duration which in addition showed diminution in cardiac sympathetic turnover. Previously, another study reported a decrease in urinary norepinephrine [47]. Large randomized controlled trials on the oxygen therapy are badly needed,

particularly in view of the failure of the SERVE-HF trial discussed below.

Drug Therapy

The respiratory stimulants theophylline and acetazolamide are discussed in the treatment of CSA/HCSB [50–55]. Javaheri et al. performed a randomized controlled study on the efficacy of oral theophylline as compared to placebo in 15 stable patients with HFrEF and showed a 50 % reduction of the AHI. However, due to lacking long-term data and the arrythmogenic potency of the drug, it should only be reserved for selected cases under close supervision.

Acetazolamide was studied in two small placebo-controlled trials [41, 55]. Both studies showed a reduction of respiratory disturbances between 44 and 50 %. Interestingly, acetazolamide increased the hypercapnic ventilatory response significantly [41], which indicates an increased loop gain. The authors concluded that this rise in HCVR may be responsible for the incomplete resolution of central breathing disturbances during sleep.

Positive Airway Pressure Treatment

The application of PAP potentially improves SRBD in HF in several ways:

1. It stabilizes and reopens occluded upper airways.
2. It reduces the work of breathing.
3. It improves ventilation of non-ventilated lung compartments.
4. It improves the matching of ventilation and perfusion.
5. It reduces the left ventricular afterload and left ventricular function in volume-overloaded HF patients.

As a result, several clinical trials have shown improvements of the left ventricular ejection fraction under CPAP in HF patients [56–67]. However, survival benefit has not convincingly been described in large prospective randomized studies [68, 69]. The Canadian continuous positive airway pressure (CanPAP) trial studied the effect of additional CPAP in 258 HF patients with severely reduced left ventricular ejection fraction and CSA on survival, respiratory disturbances and surrogate parameters. CPAP therapy over a mean of 2 years was associated with significant improvements in apneas and hypopneas, oxygen saturation, ejection fraction, norepinephrine levels and exercise performance. However, the study failed to show a significant difference in survival without heart transplantation. Interestingly, survival was superior in the control group during the first 18 months of therapy but was overtaken by CPAP during the last study period [70]. Moreover, the effect of CPAP on respiratory disturbances varied substantially. CPAP reduced the AHI by 50 % in mean. Arzt et al. performed a post hoc analysis of the CanPAP data and found a substantially better improvement in CPAP responders as compared to non-responders. However, as this analysis was not predefined, the positive results should be interpreted cautiously. For example, one can speculate that the coincidence of CPAP response and better survival is not a causal relationship but a marker of a specific phenotype [71]. Nevertheless, the first step in the therapeutical approach to symptomatic HF patients with CSA/HCSB is a CPAP trial. If effective, CPAP is advantageous due to its simplicity, lower costs and brought availability.

Adaptive Servoventilation

Taking the data on oxygen, drugs and CPAP together, none of the available therapies improved CSA/HCSB sufficiently. However, optimal reduction of breathing disturbances during sleep seems to be a precondition to improve outcome [71]. Adaptive servoventilation (ASV, also called auto servoventilation, anti-cyclic modulated ventilation) has been designed to counterbalance the pathological breathing pattern of hyperventilation and hypoventilation and to avoid central apneas. Commonly, the available ASV devices anti-cyclically adapt pressure support (i.e. the difference between inspiratory and expiratory pressure) to the patient ventilation. During periods of hyperventilation, pressure support is reduced; during hypoventilation, it is increased. Thus, the algorithms avoid hypocapnia on one hand and hypercapnia and hypoxia on the other. As a consequence, the stabilization of the respiration reduces the hypercapnic ventilatory response, which is one factor of the underlying pathophysiology [72]. The algorithms apply mandatory breaths in case of central apneas. The expiratory pressure (EPAP) stabilizes the upper airways and can compensate for obstructive components. Devices from different manufacturers and different generations of ASV algorithms differ in target parameters, sensing of the ventilatory parameters and pattern of reaction. The main differences between older and more recent devices include the application of the automatic EPAP and improvement in pressure support during inspiration. While the first generations applied a fixed EPAP predefined by the investigator, current versions use automatic adaptation of the EPAP according to the varying level of upper airway obstruction. This allows stabilizing the upper airways with the minimal required pressure level. Moreover, the first ASV devices applied a minimal pressure support of 3 mbar during inspiration. As a consequence, all patients were ventilated to some extent even in periods of hyperventilation. In contrast, the actual algorithms apply pressure support only during periods of reduced flow or minute ventilation but zero tidal volume during hyperventilation. Thirdly, the new generation device has improved algorithm for how the dynamics of inspiratory pressure support may change. This has become

relevant in the discussion of the Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF) trial (see below) [73–76].

ASV devices are often used in patients with coexisting obstructive and central sleep apnea and several phenotypes of central breathing disturbances including treatment emergent CSA, opioid induced CSA, CSA due to high altitude and primary CSA [77–81]. Although the scientific evidence for several of these situations is limited, data from cohort studies, follow-up series and some randomized controlled trials demonstrated the efficacy of ASV and its superiority to other treatment options, including oxygen, CPAP, bilevel PAP in spontaneous timed mode (BPAP-ST) [25, 56, 82, 83]. Teschler et al. applied different therapeutical options (O_2, CPAP, BPAP-ST, ASV) randomly for one night each. They used a first generation ASV device and found a significantly better improvement and normalization of central apneas under ASV as compared to the other options [51]. Pepperell et al. compared therapeutic and subtherapeutic ASV for 1 month in heart failure with reduced ejection fraction and CSA/HCSB. ASV sufficiently improved not only breathing disturbances and parameters of daytime sleepiness but also cardiac surrogate parameters, while subjective sleepiness did not change [53]. ASV has been shown to be superior to CPAP in heart failure patients with coexisting obstructive and central sleep apnea [30, 80, 81, 84]. Takayama et al. found an improvement of the 1-year survival rate in ASV-treated patients using their devices for more than 4 h/night.

Encouraged by the positive effects of ASV on respiratory disturbances during sleep, left ventricular ejection fraction, cardiac surrogate parameters and quality of life, two large, multinational, prospective, randomized controlled trials (SERVE-HF, adaptive servoventilation for therapy of central and OSA in HF trial (ADVENT-HF)) were initiated [1, 25, 53, 85–88]. The SERVE-HF trial included 1325 patients with symptomatic chronic HF (NYHA grades II–IV) with left ventricular ejection fraction ≤45 % and predominant CSA. Patients were randomized to treatment with or without ASV in addition to optimized conventional cardiac therapy. According to the design, the study was terminated when the predefined number of 651 cardiovascular events was exceeded. The combined primary endpoint included all-cause mortality, hospitalizations, decompensation of HF, heart transplantation and events of sudden cardiac death. While the primary endpoint did not differ significantly between the two groups, further analyses showed increased rates of death from any cause and cardiovascular death in the ASV group. Moreover, ASV failed to show beneficial effects on cardiac or quality of life parameters in SERVE-HF in contrast to previous findings.

The SERVE-HF trial has led to immediate reactions of the companies manufacturing ASV devices and also from health authorities. They advised sleep physicians not to use ASV in patients with symptomatic systolic HF with EF <45 % and predominant CSA. Nevertheless, several concerns have been raised (for details, see reference 78) regarding the trial and the interpretation of the results:

1. Of randomized patients, 23 % crossed over from one to the other treatment arm; 98 of 578 patients randomized to the control group started different types of positive airway pressure therapy (mostly ASV); 168 of 583 patients randomized to ASV discontinued treatment.
2. Compliance rate in the ASV group was very low with a mean average usage of 3.7 h/night. Of the patients, 27 % used their devices less than 1 h/night; 40 % of the patients used their devices less than 3 h/night.
3. There was a significant higher usage of anti-arrhythmic drugs in the ASV group as compared to controls. This might be clinically relevant as anti-arrhythmic drugs themselves may destabilize cardiac cells. It may also indicate more sensitive patient phenotypes.
4. Subanalyses of the study showed mortality rates only in patients with high usage of anti-arrhythmic drugs and in patients with a left ventricular ejection fraction <30 %.
5. Diagnosis of sleep apnea and differentiation of respiratory events were based mostly on polygraphy. Obviously, due to missing neurologic parameters, polygraphy cannot detect sleep-wake transitions or events during wakefulness. This leads to misinterpretation of respiratory disturbances which can influence inclusion of the patients.
6. The investigators used an older version of the ASV devices with fixed expiratory pressure and a minimal pressure support of 3 cm H_2O. Therefore, patients were ventilated even in periods without any need of ventilatory support which may lead to hypocapnia and electrolyte imbalance.

Unfortunately, the investigators presented only the intention-to-treat analysis by now. However, having the high crossover between the treatment arms and the low compliance rate in mind, the per-protocol analysis would be of crucial importance. If ASV was indeed the cause of the increased mortality, one would expect the poorest outcome in those patients who used the devices according to the protocol and achieved best compliance rates. For more detailed discussion, the interested reader is referred to reference 78.

Meanwhile, the 'ADVENT-HF' is being continued after an independent board performed an interim analysis of the safety data. ADVENT-HF differs from SERVE-HF in several aspects: It uses a more recent ASV version from another manufacturer, which allows variable adaptation of the expiratory pressure and also a zero pressure support. Thus, the risk of overtreatment is minimized. Inclusion is based on polysomnography and core-lab evaluation of all studies. The majority of patients included today suffer from HF with non-hypersomnolent OSA, while one third suffers from CSA.

Cowie et al. discussed if the elimination of CSR might be unfavourable in HF patients and be responsible for the excess mortality [89]. These considerations are based on Naughton's hypothesis that CSR might be a compensatory mechanism of the failing heart [90]. Data from animal trials, mathematical models and studies in healthy persons indicated that high tidal volume and high positive end-expiratory pressure in CSR might improve lung ventilation and blood oxygenation and reduce work of breathing (with central apnea), sympathetic activity and cardiac mechanics. However, the application of positive airway pressure has similar effects: PAP has been shown to stabilize upper airways and increase alveolar pressure, prevent collapse of small airways, improve pulmonary ventilation and reopen atelectasis. It is associated with fluid shift from alveoli and interstitial space into pulmonary vessels, improve fluid overload in the lung and lung oedema. As a consequence, PAP improves functional residual capacity, gas exchange and oxygenation [91–99]. Moreover, positive effects of PAP therapy on work of breathing and ASV on sympathetic activity have been shown. PAP reduces cardiac output in healthy persons and volume-depleted HF patients. In contrast, PAP improves left ventricular transmural pressure and stroke volume in volume-overloaded HF patients [100, 101]. In addition, the number of respiratory disturbances (both, obstructive and central) correlates with the pulmonary capillary wedge pressure and the fluid shift from the lower to the upper body compartments [37, 62].

Alternative Hypotheses for the Excess Mortality

Patients with substantially reduced left ventricular ejection fraction who are additionally treated with anti-arrhythmic drugs and diuretics are at high risk of life-threatening cardiac events. As discussed before, the application of PAP may reduce cardiac function in volume-depleted HF patients. It cannot be excluded that an undefined number of patients in SERVE-HF were overtreated with diuretics leading to increased sensitivity to pressure application.

Several factors may destabilize the clinical situation of the high-risk population (NYHA III–IV, II with hospitalization, anti-arrhythmic therapy, severely impaired heart function) and impaire the prognosis of these patients. The acid base balance can be influenced by the use of diuretics, leading to metabolic alkalosis, and by both extremes of ventilation. Chronic hyperventilation is associated with respiratory alkalosis, while hypoventilation with retention of CO_2 is compensated by metabolic alkalosis. These acid base imbalances are known arrythmogenic factors. On one hand, the application of a fixed expiratory pressure (in the older ASV versions) may have led to hypoventilation by insufficiently stabilizing upper airways. On the other hand, these devices inevitably apply a minimal pressure support of 3 cm H_2O during inspiration, ventilate patients mechanically even in situations of stable respiration and thus potentially induce hyperventilation and alkalosis.

Conclusions

The association between sleep-disordered breathing and heart failure is a major clinical problem due to the high prevalence and the impact on morbidity and prognosis. OSA is a major risk factor for cardiovascular diseases and should be treated primarily with positive airway pressure in order to improve quality of life and outcome of affected patients. Heart failure is the most frequent cause of central breathing disturbances including Hunter-Cheyne-Stokes breathing. Based on the results of the SERVE-HF trial, patients' history, the polysomnographic pattern and cardiac function findings have to be evaluated precisely to optimally stratify the therapeutical algorithm. There is no prognostic rationale to treat asymptomatic heart failure patients with CSA/HCSB. However, treatment may be indicated if patients suffer from daytime sleepiness, neurocognitive deficits, fatigue and other sleep-related limitations. Heart failure patients with preserved left ventricular affection (ejection fraction ≥45 %) can undergo a trial of CPAP or—if it fails—adaptive servoventilation. In contrast, ASV is contraindicated in patients with predominant CSA/HCSB if the LVEF is >45 %. These patients should only be treated in clinical trials, such as ADVENT-HF, as no recommendations for clinical practice can be given at this moment. The limitations of SERVE-HF underline the necessity of further trials with ASV, oxygen and newer treatment modalities, such as phrenic nerve stimulation.

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Compliance with Ethical standards

Conflict of Interest Winfried Randerath has received personal fees from Resmed, Inspire, Heinen & Löwenstein and Philips Respironics.

Shahrokh Javaheri has received honoraria for speaking from Philips Respironics and Resmed. He is on advisory board of Respircardia and Leve Nova.

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