Assessment of sleep disordered breathing in patients with heart failure

Sandhya Matthes [1,2] and Winfried Randerath [1,2]

[1]Institute of Pneumology, University of Cologne, Solingen, Germany. [2]Hospital Bethanien Solingen, Clinic of Pneumology and Allergology, Center for Sleep Medicine and Respiratory Care, Solingen, Germany.

Corresponding author: Winfried Randerath (randerath@klinik-bethanien.de)

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When to look for sleep disturbances in heart failure patients and how best to treat them: a practical and evidence-based expert opinion https://bit.ly/3LpCnNP

Cite this article as: Matthes S, Randerath W. Assessment of sleep disordered breathing in patients with heart failure. *Breathe* 2022; 18: 220153 [DOI: 10.1183/20734735.0153-2022].

Received: 6 June 2022
Accepted: 14 Sept 2022

Does obstructive sleep apnoea play a relevant role in heart failure or do patients mainly show central sleep apnoea?

As we all know, sleep apnoea is divided into the two main groups of obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). OSA is a sleep-related breathing disorder characterised by repetitive collapse of the upper airways, leading to apnoea and hypopnoea accompanied by oxygen desaturation and arousal from sleep. Breathing effort is preserved, but inefficient, identifiable by opposite excursions of thorax and abdomen. CSA is caused by a disruption of breathing regulation at the brain stem and occurs in many pathophysiological conditions. Breathing effort and flow are reduced or interrupted in parallel, leading to central hypopnoeas or apnoeas. CSA can be seen for example in patients with heart disease, during a high altitude stay, or with the use of opioids.

Both OSA and CSA can have a negative impact on cardiovascular function through activation of the sympathetic nervous system during sleep, leading to the elevation of blood pressure [1], increased oxidative stress [2], inflammation [3] and endothelial dysfunction [4]. Longitudinal observational studies have documented an increased long-term cardiovascular mortality in patients with untreated OSA [5].

Heart failure (HF) can be classified at echocardiography according to the left ventricular ejection fraction (LVEF) as follows [6]:

- Heart failure with reduced ejection fraction (HFrEF): symptomatic HF with LVEF ⩽40%
- Heart failure with mildly reduced ejection fraction (HFmrEF): symptomatic HF with LVEF 41–49%
- Heart failure with preserved ejection fraction (HFpEF): symptomatic HF with LVEF ⩾50%

The majority of data regarding sleep disordered breathing (SDB) in HF comes from patients with HFrEF. About 50% of HF patients show SDB, with both types of sleep apnoea being fairly equally represented [7, 8].

It is now recognised that the partial or complete collapse of the upper airway that characterises OSA is not solely due to anatomical pre-disposition. New findings show that there is an underlying disruption in the regulation of breathing, a failure in the correct muscular response as well as the development of arousals [9].

The underlying pathophysiology of CSA and periodic breathing in HF is based on the destabilisation and overdrive of the breathing cycle, described as an increase in loop gain. One convincing hypothesis is that fluid accumulation in the pulmonary interstitium may affect afferent receptors and stimulate the breathing centres in the brain stem, known as controller gain. As a result, minute ventilation increases, which is indicated by arterial carbon dioxide tension levels at or below the lower limit of normal (plant gain). Higher responsiveness of the chemoreceptors leads to excessive reactions to changes in oxygen or carbon dioxide levels with hypocapnia dampening the system and hypoxia leading to increased stimulation

(feedback gain) [10, 11]. The system oscillates between hyperventilation with hypocapnia and consecutive cessation of ventilation, again leading to hypoxaemia with hyperventilation. This is seen in the crescendo-decrescendo pattern of tidal volumes at polysomnography, with central apnoea or hypopnoea occurring at the end of the cycle.

CSA, especially periodic breathing which is a common manifestation of CSA in HF, is seen frequently (21–37%) in HFrEF, and although less well studied, at a similar rate (18–30%) in those with HFpEF [12]. There is growing evidence that OSA and CSA relate to each other. The unstable breathing pattern of CSA may provoke obstructive apnoeas and hypopnoeas [13].

Are there clues in the history and clinical findings of HF patients that may point to underlying SDB or do we have to conduct sleep studies for reliable results?

It is a common misconception that patients with sleep apnoea are all obese and sleepy. Although increased body mass index is a risk factor for OSA (along with older age and male sex) only 50% of OSA patients suffer from daytime sleepiness and 50% are not obese [14, 15].

HF patients with periodic breathing do not generally present with typical symptoms of SDB such as daytime sleepiness [16]. Therefore, widely used screening tools, including questionnaires, do not represent helpful tools to detect SDB in this population. Age older than 60 years, male sex, atrial fibrillation, diuretic use and daytime hypocapnia are risk factors for CSA among patients with chronic heart failure (CHF) [17].

The systematic screening of patients with a predisposition to SDB with simple techniques such as a 1- or 2-channel system (flow and/or oxygen) may be useful to uncover SDB in asymptomatic high-risk patients who may benefit from more detailed polysomnographic studies.

Are you convinced that SDB has a definite impact on prognosis in patients with HF? Do you recommend screening in a stable phase of the disease or would you also conduct sleep studies following, for example, an acute myocardial event?

There is a broad consensus that when symptoms and signs of sleep apnoea appear, we should be aiming for a definitive diagnosis with further sleep studies in our HF patients. Screening in an asymptomatic patient on the other hand becomes more complex as we need to not only prove a prognostic benefit from early detection but also be able to provide an effective and proven therapy.

SBD in acute HF certainly seems to have a relevant impact on prognosis. Khayat and co-workers [18, 19] studied patients admitted with acute HF over a 3-year period and found three-quarters of the patients suffered from OSA or CSA. Mortality was higher when the SDB remained untreated. In this particular study, patients were screened following cardiac compensation. Studies suggest similarly that the presence of CSA and OSA in CHF also have a negative prognostic implication [20, 21].

There is a high prevalence of sleep apnoea following acute myocardial infarction [22]. The outcome following acute myocardial infarction in patients with OSA has been shown to be impaired [23, 24], although of note, others have discussed that intermittent hypoxaemia may have protective effects on the heart because of ischaemic preconditioning and development of collateral vessels [25].

In terms of effective therapy though, there is a lack of prospective, randomised-controlled data which prove a prognostic benefit of the available therapies. Most of the data is longitudinal [18, 19]. This makes the case for screening, particularly in an asymptomatic group, less robust.

How long do you treat with conservative therapies such as drugs and nocturnal oxygen supplementation before you would consider a ventilator therapy? Do you always start with continuous positive airway pressure?

Treatment of any underlying cardiovascular disease with for example drugs to reduce fluid overload and strengthen the left ventricle, or necessary cardiac interventional techniques, lead to a clear reduction in SDB [26–28]. It is acknowledged that cardiac therapy should be optimised prior to the initiation of specific therapy for the SDB. However, once these options have been exhausted, there is no need to wait.

There is insufficient data to show that either nocturnal oxygen therapy or bi-level therapy improve the prognosis of our HF patients. In fact, based on pathophysiological considerations, bi-level may even worsen breathing instability.

Automatic positive airway pressure has been shown to reduce CSA by 50%. Smaller studies suggest positive effects of continuous positive airway pressure (CPAP) treatment in HF patients with attenuation of sympathetic nerve activity associated with reduced hypoxaemia at 3 months [29], improvements in cardiovascular parameters (a significant drop in heart rate and blood pressure, and improved LVEF) [30], and reduced all-cause mortality [31]. The large randomised controlled Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial (CANPAP) failed to show that the documented improvements in physiological parameters led to an extended life for these patients [32].

The more recent SAVE trial randomly assigned 2717 patients either to CPAP or usual care and found no significant difference in the primary end-point of death or hospitalisation for a cardiovascular cause between the two groups [33].

In summary, in non-sleepy patients with OSA and stable coronary artery disease, randomised controlled trials have, so far, failed to show that CPAP treatment protects against cardiovascular events [32].

What is the role of adaptive servoventilation in patients with SDB and HF? Has the SERVE-HF trial changed your clinical practice? Do you have a set algorithm or do you tailor to each individual patient?

Adaptive servoventilation (ASV) is considered the optimal algorithm to normalise central breathing disturbances including periodic breathing, consequently improving both sleep fragmentation and cardiac function [34, 35]. ASV applies mandatory breaths during CSA. ASV varies inspiratory pressure support anti-cyclic to the patient's own breathing, thus levelling out the overshoot of ventilation from hyperventilation to apnoea. The difference in pressure support is increased during the period of hypoventilation and decreased during hyperventilation. Newer algorithms can also adjust expiratory pressure automatically in order to stabilise the upper airways and prevent OSA.

The results of the large, randomised trial evaluating the treatment of SDB with predominant CSA by ASV in patients with HF (SERVE-HF) [36] reported a neutral primary end-point result (the composite primary end-point was the first event of death from any cause, a life-saving cardiovascular intervention or hospitalisation for worsening CHF) when ASV was added to optimal medical therapy in patients with HFrEF. Further analysis showed that all-cause mortality and cardiovascular mortality were higher in the ASV group than in the control group.

There were many limitations to the SERVE-HF trial: a high switch between treatment arms, an unexpectedly low adherence, missing data on LVEF and the unbalanced use of antiarrhythmic drugs [37]. Nevertheless, based on the SERVE-HF data, ASV can currently not be used in the setting of patients with predominant CSA and LVEF <45%. However, on 27 August 2022, the results of the ADVENT-HF trial were preliminarily published. This prospective, multinational, multicentre randomised controlled trial included patients with obstructive or central sleep apnoea, with a LVEF <45%. The ADVENT-HF trial used a different ASV device, which allows adaptation of the expiratory pressure automatically to the current patient requirements. Moreover, it allowed application of a pressure support of zero. This avoids unnecessary mechanical ventilation. The study had to be terminated prematurely, as a consequence of the COVID-19 pandemic and the Philips recall. However, in contrast to SERVE-HF, the study did not show any harm of ASV. Data on quality of life are still under evaluation.

The results of a European Respiratory Society task force addressing the diagnostic and therapeutic standards of central breathing disturbances during sleep (including for causes other than HF) provided an algorithm (figure 1) [12] for the initiation of CPAP, which is a fair reflection of routine clinical practice. Following diagnosis, we start with a CPAP trial for one night. When the apnoea–hypopnoea index remains above 15 events·h^{-1} under CPAP, we switch to ASV in HF patients with an ejection fraction of >45%. There is no robust evidence for the therapy of patients with an ejection fraction ⩽45%. In this group CPAP can be used. However, no alternative treatment can be recommended at the moment. It would be reasonable to continue CPAP when there is either a subjective benefit or an improvement in central breathing.

The FACE trial investigated a prospective cohort of unselected HF patients predominantly with CSA (⩾50% central disturbances) or coexisting CSA and OSA. The aim was to assess the effect of ASV in CHF patients with different phenotypes of breathing disturbances with different grades of severity and underlying causes of HF. The primary end-points were mortality, hospitalisation due to worsening of HF, cardiac transplantation or implantation of a ventricular assist device. 258 ASV patients were followed up over a period of 21 months and grouped into six separate clusters based on LVEF, age, comorbidities and

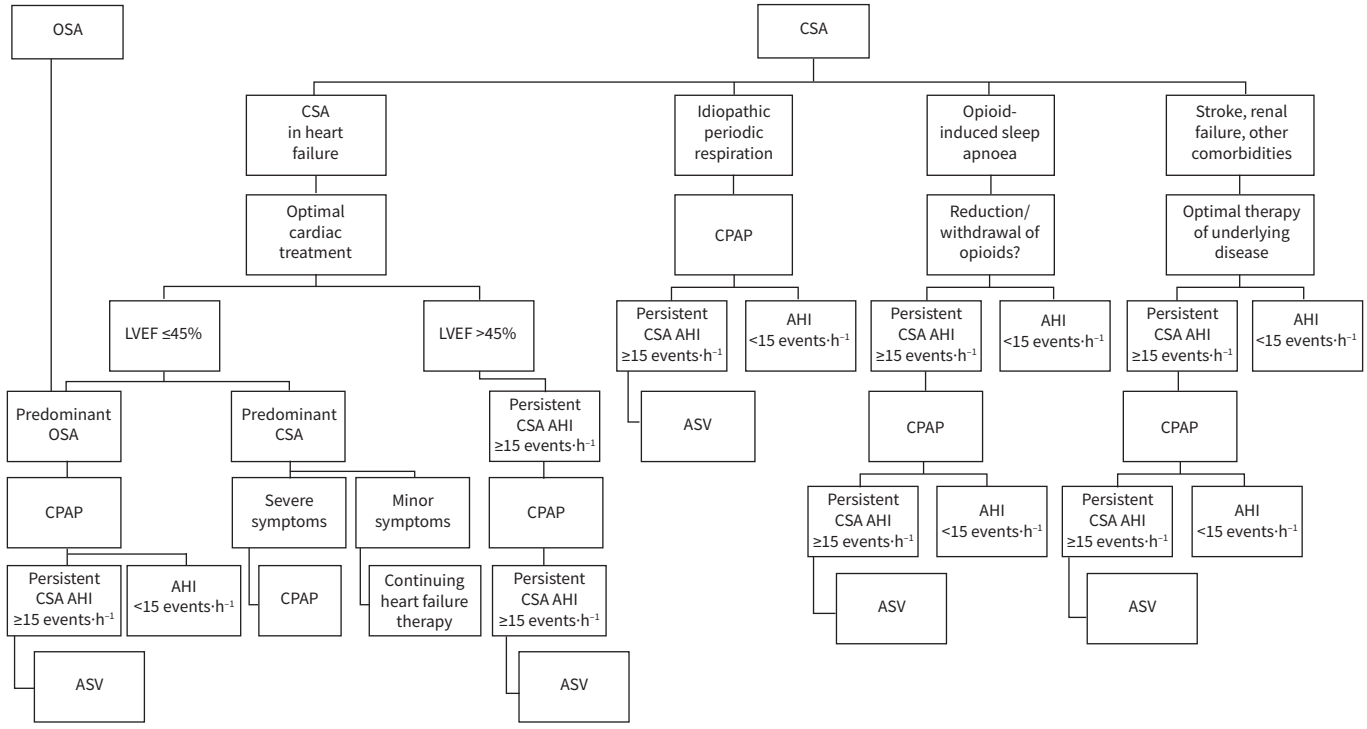

FIGURE 1 Treatment of central sleep apnoea (CSA) in heart failure. OSA: obstructive sleep apnoea; CPAP: continuous positive airway pressure; AHI: apnoea–hypopnoea index; ASV: adaptive servoventilation; LVEF: left ventricular ejection fraction. Reproduced from [12].

ASV acceptance. Results showed significantly more end-points in the cluster of male, low LVEF and severe HF patients [11].

It seems possible that treatment response and outcome differ in different phenotypes of CSA/periodic breathing, which require further definition and evaluation.

How do you improve adherence in patients, especially in those who do not suffer from daytime sleepiness and nightly waking? Is education the key or regular follow-up?

We discuss openly with non-sleepy patients that we don't know for sure if their life expectancy will be improved through the use of CPAP. In our experience, most patients are keen on a CPAP trial.

The usual factors that influence adherence are addressed. In our institute this involves patient education (including their partners), a hotline for queries, a drop-in support service for technical issues, and the readiness to refit masks and fine-tune the settings to improve patient comfort. We offer close follow-up in our sleep laboratory.

Is there a role for phrenic nerve stimulation?

In phrenic nerve stimulation (PNS), an implanted pulse generator delivers an electrical stimulus to the phrenic nerve, leading to diaphragm contractions. Stimulation is based on the measurement of the patient's respiration using transthoracic impedance.

PNS reduces CSA by ~50%, which is comparable to oxygen therapy and CPAP [38]. It cannot, however, treat concurrent upper airway obstruction and its influence on prognosis remains unclear [39, 40]. We don't yet have the long-term data to support its use. The unexpected outcome from the SERVE-HF trial highlights that we can make no assumptions that a therapy is harmless in this cohort of patients just because there is a lack of a viable alternative therapy.

Conflict of interest: S. Matthes has nothing to disclose. W. Randerath reports the following relationships outside the submitted work: consulting fees received from Jazz Pharmaceuticals (ongoing), Bioprojet (ongoing) and Philips (until 2021); payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or

educational events received from Jazz Pharmaceuticals, Bioprojet, Philips Respironics and Desitin (in 2020); and support for attending meetings and/or travel from Jazz Pharmaceuticals, Bioprojet and Philips Respironics.

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