Chapter 5
Cheyne-Stokes Breathing and Diastolic Heart Failure

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Case

A 74-year-old Caucasian male (Fig. 5.1), non-smoker, usually drinking five cups of coffee per day, was referred to our sleep clinic because of mild chronic insomnia which started approximately 5 years ago. The patient was affected by stable diastolic heart failure due to atrial fibrillation and arterial hypertension. Two years before, a single-chamber rate-responsive pacemaker was implanted. He had been suffering from progressive intermittent snoring, fatigue, and mild sleepiness for years. Witnessed apneas were also reported. He complained of fragmented, unrefreshing sleep despite averaging 8.5 h of sleep per night. He also awoke to use the bathroom once a night. There was no suspicion of depression. No restless legs symptoms or periodic leg movements were reported. He did not use alcohol on a regular base. Physical examination revealed obesity (BMI of 30.5 kg/m^2, neck circumference 47 cm, waist circumference 107 cm, hip circumference 109 cm, fat ratio 29.2%) and elevated blood pressure (systolic blood pressure of 158 mmHg, diastolic blood pressure 97 mmHg). Epworth sleepiness score was 10/24, and the New York Heart Association (NYHA) class was 1. Arterial blood gas analysis was performed with the following values: pH of 7.46, $PaCO_2$ 32.1 mmHg, PaO_2 95.9 mmHg, and SaO_2 98.2%. NT-proBNP was elevated (743 pg/mL). Lung function measurements revealed an FEV1 of 4.25 L (147% of the predicted value), a Tiffeneau index of 69, and a TLC of 8.53 L (121% predicted). Diffusion capacity

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was 108% predicted. He was taking oral anticoagulant therapy, simvastatin (20 mg/day), perindopril 10 mg, and indapamide 1.25 mg a day. Echocardiography showed mild concentric left ventricular hypertrophy, a left ventricular ejection fraction (LVEF) of 50% (2D-Simpson), moderate bi-atrial and bi-ventricular dilatation, and mild elevated end-diastolic LV pressure (see Table 5.1). Polysomnography was

Fig. 5.1 De-identified photograph of the case described

Table 5.1 Echocardiographic parameters before and after ASV therapy

	At diagnosis	After 1 year of ASV	Normal value
Mean PAP (mmHg)	36	30	10–20
Left atrial diameter (mm)	51	62.8	30–40
Left atrial volume (mm)	167	130	18–58
LAVI (mL/m^2)	77.54	61.22	30–38
EE'	12.8	12	<10
LVEF (Simpson, %)	50	57	>55%
LVIDd (mm)	64	58.4	42–59
IVS (mm)	14.95	13.5	6–12
LVPWd (mm)	12	11.2	6–12

Legend: *PAP* Pulmonary arterial pressure, *LVEF* left ventricular ejection fraction, *LAVI* left atrial volume index, *EE'* the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *LVIDd* left ventricular internal dimension during diastole, *IVS* interventricular septum thickness, *LVPWd* left ventricular posterior wall dimension

performed, scoring sleep stages according to the American Academy of Sleep Medicine (AASM) 2007 criteria [1] and breathing according to AASM 2012 criteria [2].

Baseline Night

The baseline recording (Figs. 5.2 and 5.3 and Table 5.2) showed a series of central apneas (central apnea-hypopnea index (AHI) = 31/h), associated with significant fluctuations in peripheral oxygen saturation (oxygen desaturation index (ODI) = 19.1/h) in a context of Cheyne-Stokes breathing (CSB) pattern. Breathing events were prevalent in NREM sleep (AHI-NREM = 32.6/h), especially during sleep stages N1 and N2 and were less frequent in slow-wave sleep and REM sleep (AHI-REM = 21.2/h). The oxygen saturation values did not drop below 90%. Snoring was rare and few obstructive events were detected. Two short periods of periodic leg movements were recorded. Sleep architecture was disrupted, with

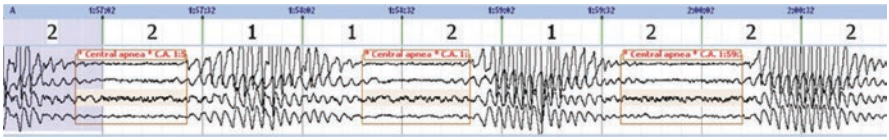

Fig. 5.2 Characteristic central sleep apneas with a crescendo-decrescendo flow pattern (Cheyne-Stokes breathing)

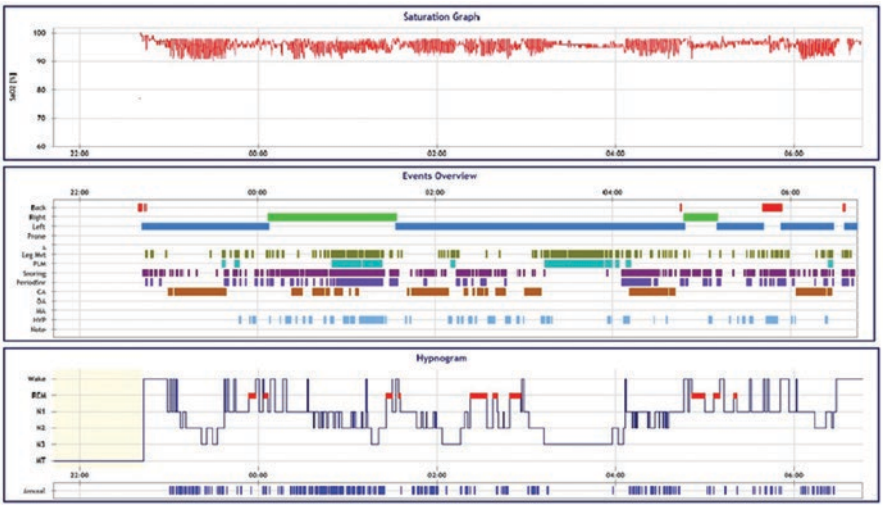

Fig. 5.3 Polysomnographic trend of the diagnostic night. Note very few central events occur during REM and N3 sleep.

Table 5.2 Polysomnographic parameters at diagnosis, during CPAP titration, and after ASV therapy

	Diagnosis	CPAP titration	ASV (2 M)	ASV (1 Y)
TST (min)	413	302	348	297
SEI (TST/TIB, %)	85.6	63.0	71.9	60.3
SL (min)	16.6	17.1	16.7	14.4
WASO (min)	36	148	85	181
NREM (%)	87.7	89.9	80.5	80.6
SWS (%)	17.7	7.3	15.7	9.6
REM (%)	12.3	10.1	19.5	19.4
AHI (#/h)	31.2	40.1	0	0.4
AHI-NREM (#/h)	32.6	42.8	0	0.0
AHI-REM (#/h)	21.2	15.7	0	2.1
OAI (#/h)	0	0	0	0
CAI (#/h)	31.2	0	0	0
HI (#/h)	12.3	40.1	0	0.4
Apnea duration (s)	31.6	0	0	0
Hypopnea duration (s)	24.8	29.5	0	33.0
Mean SaO_2 (%)	95.7	96.5	96.9	96.8
Min SaO_2 (%)	77	91	90	95
$SaO_2 < 90\%$ (min)	0	0	0	0
ODI (#/h)	19.1	40.1	1.6	0.6

TST Total sleep time in min, *SEI* sleep efficiency index in %, *SL* sleep latency time in min, *NREM* non-rapid eye movement sleep in %TST, *REM* rapid eye movement sleep in %TST, *AHI* apnea-hypopnea index, *AHI-NREM* AHI during NREM sleep, *AHI-REM* AHI during REM sleep, *OAI* obstructive apnea index, *CAI* central apnea index, *HI* hypopnea index, *ODI* oxygen desaturation index (#/h)

modest reduction in sleep efficiency, total sleep time, and percentage of slow-wave (17.7%) and REM sleep. Sleep latency was normal, while wake time after sleep onset (WASO) was longer than 30 min.

CPAP Titration Night

During the second night (Fig. 5.4 and Table 5.2), continuous positive airway pressure (CPAP) therapy was titrated from 5 to 15 cmH_2O. A full face mask was applied. There were persistent central apneas (AHI 40.0/h), again with features of CSB. The lowest oxygen saturation was 91%. Sleep efficiency, total sleep time, and percentage of slow wave (7.3%) and REM (10.1%) sleep were worse. Sleep latency was within normal limits, while WASO was 148 min.

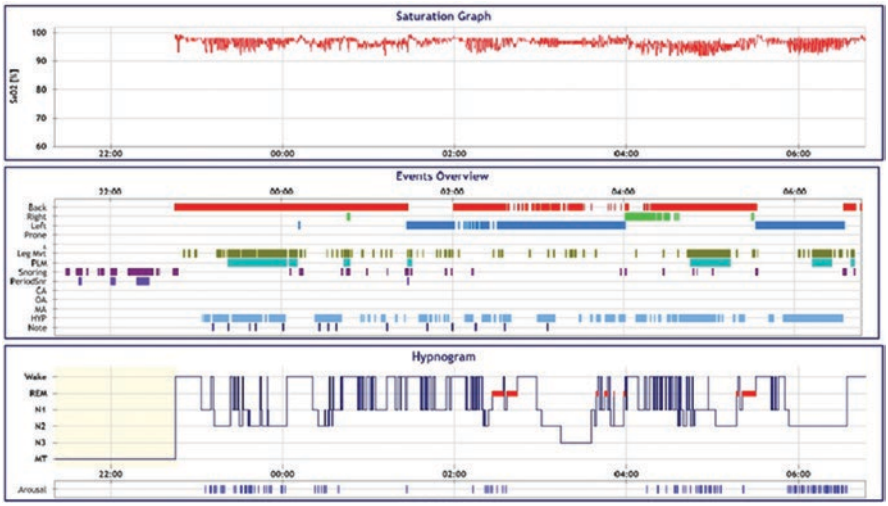

Fig. 5.4 Polysomnographic trend of the CPAP titration night

ASV Control Nights

Finally, the patient was prescribed adaptive servo-ventilation (ASV) which was set as follows: ASV, auto; expiratory positive airway pressure (EPAP), 4–8 cmH_2O, and pressure support (PS) range, 4–10 cmH_2O. A polysomnographic recording with ASV 2 months later showed improvement in respiratory events (Fig. 5.5 and Table 5.2). Breathing events were absent and the oxygen saturation remained greater than 90%. Sleep architecture was still disrupted but with an increased percentage of slow wave (15.7%) and REM sleep (19.5%). Sleep latency was still normal, while WASO improved to 85 min. After 1-year follow-up, a polysomnography confirmed the efficacy of nocturnal ventilation in controlling breathing events, while sleep quality was still not optimal (Fig. 5.6 and Table 5.2).

Chronic Follow-Up with ASV

Although the problem of maintaining sleep persisted, our patient perceived considerable improvement in sleep quality. Since the start of ASV, a progressive improvement could be observed, with more alertness and less dyspnea. Moreover, the fatigue, hypersomnia, nocturia, and restlessness during sleep—the patient's most important complaints—disappeared. Caffeine intake was lowered to two cups of coffee a day. His quality of life improved considerably, and he also experienced less discomfort when performing moderate exercise. His BMI decreased to 28.9 kg/m^2, while the Epworth sleepiness score improved to 0–5/24. The NYHA class remained

Fig. 5.5 Polysomnographic trend after 2 months of ASV therapy

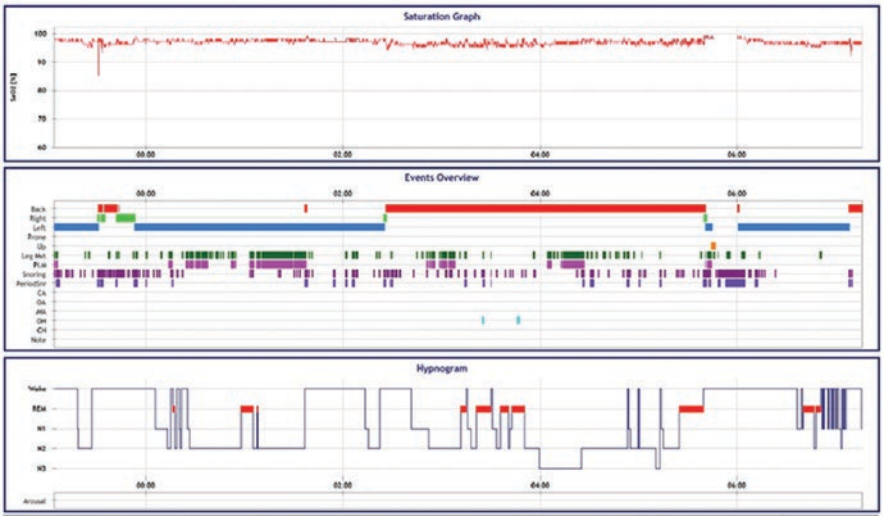

Fig. 5.6 Polysomnographic trend after 1 year of ASV therapy

1. Blood pressures decreased to 128 mmHg (systolic) and 82 mmHg (diastolic) after 2 months and to 124 mmHg (systolic) and 77 mmHg (diastolic) after 1 year on ASV therapy. LVEF substantially improved by 7%, but relative improvement was 15%. Pulmonary artery pressures also improved after chronic ASV treatment, though the NT-proBNP remained high (838 pg/mL). The treatment with ASV was generally well accepted and tolerated. He used his ASV device 7.7 h per night (approximately 90.6% of time in bed), with absence of significant leakage (2.1 L/min). In order to solve the residual insomnia problem, cognitive behavioral therapy was initiated.

Discussion

The case described in this paper is a typical presentation of CSB in association with diastolic heart failure due to atrial fibrillation and moderately severe insomnia. CSB is typically characterized by recurrent central apneas or hypopneas alternating with a ventilatory phase, presenting as a crescendo-decrescendo pattern of flow. A cycle length of >40 s and a "waxing and waning" pattern of ventilation typically distinguish CSB from other central sleep apnea (CSA) types. The majority of patients with CSB have either systolic or diastolic congestive heart failure (CHF). In 2017, the European Respiratory Society (ERS) Task Force on central sleep apnea recommended replacing the historical term "Cheyne-Stokes respiration" by "periodic breathing in heart failure" or "chronic heart failure with central sleep apnea/periodic breathing (CSA/PB)" [3]. In this chapter, we will use the terms interchangeably. CSB can also manifest following stroke or may be associated with other neurological disorders; very rarely do idiopathic cases occur. Patients with CSB usually are normocapnic or hypocapnic. According to the International Classification of Sleep Disorders – Third Edition (ICSD-3) diagnostic criteria for CSB, either symptoms or a comorbid condition must be present [4]. If neither symptoms nor comorbid conditions are present, CSB is less relevant and considered a polysomnographic finding. More than 50% of respiratory events must be of central origin and meet the criteria for CSB. Particular features can help to distinguish CSB from idiopathic CSA and can give insight in the underlying pathology. In patients with CSB, arousal from sleep tends to occur at the zenith of respiratory effort, between episodes of apneas and hypopneas, rather than at apnea termination. Overall, these patients have a longer cycle length compared to those in primary CSA, caused by a long ventilatory period. Also, the nadir of the oxygen saturation is in the middle of the apnea, which is explained by an increased circulation time as seen with decreased cardiac output. CHF with CSA/PB occurs most commonly in patients with left ventricular systolic heart failure but may also present in patients with diastolic dysfunction. In case of diastolic CHF, the cycle length of CSA/PB is shorter compared to systolic CHF, as the ejection fraction is normal. On the other hand, the worse the systolic function, the longer is the cycle length (given the longer ventilatory period between respiratory events).

Our case was known with an established diagnosis of diastolic heart failure. Heart failure is a complex clinical syndrome that results from a structural or functional impairment of contraction or filling of the heart, resulting in the inability to meet the metabolic needs of the body. Diastolic dysfunction refers to an abnormality of diastolic distensibility, filling, or relaxation of the left ventricle. If effort intolerance and dyspnea develop in such a patients, it is appropriate to use the term "diastolic heart failure." Current classification of heart failure is based on the LVEF [5]. Most recent guidelines separate heart failure with reduced ejection fraction (<40%, HFrEF) from midrange (40–49%) and preserved ejection fraction (≥50%, HFpEF) [5]. The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. On the one hand, patients with HFpEF generally do not present with a dilated left ventricle, but have increased wall thickness, increased left atrial size,

and signs of increased filling pressures. In short, impaired left ventricular filling capacity is a likely cause of heart failure in these patients (diastolic heart failure). On the other hand, HFrEF presents with dilatation of the left ventricle. These patients are characterized by symptoms of breathlessness, peripheral edema, and fatigue due to pulmonary congestions and reduced output. To make it even more complex, most patients with HFrEF also have diastolic dysfunction, while subtle abnormalities of systolic function may be present in patients with HFpEF. The prevalence of CHF is approximately 1–2% of the adult population in developed countries, rising to >10% among people >70 years of age. The proportion of patients with HFpEF ranges from 22% to 73%. Compared to HFrEF, patients with HFpEF are older and more often women and more commonly have a history of arterial hypertension and atrial fibrillation, while a history of myocardial infarction is less common. These epidemic proportions, together with the few effective treatments, make HFpEF one of the greatest unmet needs in the current field of cardiology [6]. Prognosis is equally grim in HFrEF: 5-year mortality is around 75%, which is worse than most cancers. The plasma concentration of natriuretic peptides (NP) can be used as an initial diagnostic test, especially in the non-acute setting. Plasma concentrations of BNP < 35 pg/mL and/or NT-proBNP <125 pg/mL make a diagnosis of HFpEF or HFrEF unlikely. NT-proBNP was obviously elevated in our case. Notably, the diagnosis of HFpEF in patients with atrial fibrillation is difficult, since atrial fibrillation itself is associated with higher NP levels. In such setting, higher cut-offs have to be used [5].

CSA/PB is most commonly seen in patients with HFrEF – up to 50% of these patients may have such a breathing pattern. However, the prevalence of CSA/PB in HFpEF, as in our case, is less well defined. Estimates vary between 18% and 30% depending on body weight, the different diagnostic criteria of HFpEF, and the cut-off levels used [7–10]. Prevalence of CSA/PB increases with increasing impairment of diastolic function [7]. Presence of cardiovascular comorbidities can contribute to the severity of heart failure—such as arterial hypertension, coronary artery disease, myocardial ischemia, and atrial fibrillation—and may worsen CSA/PB [11]. Patients with hypertension, such as in the present case, and particularly those with left ventricular hypertrophy, are susceptible to diastolic heart failure. They are unable to increase their end-diastolic volume, because of decreased left ventricular relaxation and compliance. Consequently, this provokes a cascade, in which the left ventricular end-diastolic pressure rises, left atrial pressure increases, and pulmonary edema develops. Evidence that CSA/PB aggravates hypertension, coronary artery disease, or atrial fibrillation is sparse. However, treatment as in our case can result in an improved blood pressure profile, suggesting a direct relationship.

Patients with CSA/PB may complain of typical symptoms of sleep apnea, including daytime sleepiness or disturbed sleep. However, the majority of the patients do not complain of excessive daytime sleepiness. Despite the lack of symptoms in CSA/PB, improvement in sleep quality and objective daytime sleepiness with successful treatment has been described. While it is recognized that CHF contributes to the development of CSA [12] and that CSA is associated with worse prognosis in these patients, the role of treatment of CSA in CHF is of debate. The recent ERS

statement paper by Randerath et al. and the extensive systematic review by Aurora et al. contain many relevant references for treatment of CSA/PB [3, 13]. The first intervention in patients with CSA/PB is always to optimize treatment for the underlying CHF. For this, diuretics can be used to reduce pulmonary congestion and cardiac filling pressures, beta-blockers to diminish excessive sympathetic activation, and angiotensin-converting enzyme inhibitors to reduce ventricular afterload. In HFpEF, the evidence that diuretics improve symptoms is similar across the spectrum of LVEF. For other drug categories, the evidence is lacking or inconsistent. Circumstantial evidence suggests that treating hypertension, often predominantly systolic, is important in HFpEF. The blood pressure targets recommended in hypertension guidelines are applicable to CHF [5]. Physical activity, salt restriction, and compression stockings can also reduce fluid retention and accumulation in the lower limbs during daytime and diminish nocturnal fluid shift to lungs and upper airways [14]. Optimal cardiac failure treatment also includes a surgical approach on cardiac vessels or valves. Atrial overdrive pacing at a rate 15 beats faster than the mean nocturnal heart rate has also been shown to improve CSA/PB. Resynchronization therapy has been shown to decrease respiratory instability and improve cardiac function, quality of life, and mortality in more advanced disease.

Pharmacological treatment of CSA/PB with respiratory stimulants has been tried, including theophylline, acetazolamide, as well as with hypnotics, but its overall impact is weak, and, hence, not widely used [15, 16].

The Canadian Positive Airway Pressure Trial for Heart Failure Patients with Central Sleep Apnea (CANPAP) trial provided evidence that about 50% of patients will respond to CPAP, with a reduction in the frequency of episodes of apnea and hypopnea, an improvement of LVEF, and 6-min walk test distance, but without improved prognosis or rate of heart failure-related hospitalizations. This warrants a trial with CPAP; in our case, however, CPAP was not unsuccessful [17, 18]. CANPAP emphasized that an improved survival may only manifest in patients whose AHI is reduced to <15/h [17]. The mechanisms of action of CPAP include decreasing venous return and unloading the left ventricle, thereby decreasing pulmonary capillary wedge pressure and increasing functional residual capacity. Moreover, in some patients with CSA, upper airway collapse occurs which is reversed by CPAP.

If CSA/PB does not respond to CPAP, ASV will usually be effective. ASV machines track minute ventilation or peak flow and adjust pressure support to stabilize ventilation or the mean amplitude of peak airflow during breathing. In our patient, CPAP was not effective for central respiratory events, but a subsequent titration with ASV reduced the AHI to 0/hr. An ASV device download after 2 months and 1 year of treatment showed an AHI close to 0/hr., and the patient felt much improved on ASV. However, we have to bear in mind that the majority of the evidence on CSA treatment with ASV in CHF is based on studies in systolic heart failure—with evidence suggesting an increased mortality in ASV users with LVEF <45%. Few data are available on treatment of CSA/PB in HFpEF (or HFrEF with concomitant diastolic dysfunction) [18–20]. In one observational, uncontrolled study [21], ASV reduced CSA/PB and improved cardiac function in diastolic heart failure. Our case is in line with these findings, demonstrating improved blood pressure profile and hemodynamic

changes. Another study addressed the potential prognostic impact of sleep-disordered breathing in 36 patients with HFpEF: ASV significantly improved the central as well as the obstructive apnea index, with an 18-month higher event-free rate [19].

However, this enthusiasm has to be tempered, when looking to the number of patients effectively achieving success, which was only 70% in a real-life study that included central sleep apnea of different etiologies [22, 23]. Moreover, ¼ of them refused to start the treatment at home. After 5 months of therapy, 84% of the patients were still using ASV, with only 50% of them reporting "much improvement" in sleep quality and 36% reporting "much improvement" in daytime sleepiness, based on a subjective survey by telephone contact. This reflects the masking of the typical symptoms of sleep apnea by the symptoms of their underlying heart disease and by an increased sympathetic activity. The heterogeneous and contradictory results on ASV ask for more accurate patient's phenomapping. Apart from the AHI and LVEF, a number of pathophysiologic traits underlying CSA/PB patterns during sleep have been suggested, including the burden of hypoxemia, the variations of oxygen desaturation, the chemoresponsiveness, the ventilatory instability during wakefulness and sleep, and the end-expiratory lung volume. The advantages of ASV have also to be weighed versus the substantial costs of ASV devices, and despite its superiority, ASV has to be prescribed in a stepwise approach. Some guidance was given by Momura S et al., who recommended ASV in those with persisting respiratory events (>15/h) during a CPAP titration night [24]. On the other hand, therapy should be considered at the earliest moment in the course when clinical symptoms (and cardiovascular burden of the disease) might be minimal [25]. The current priority is to search for phenotypes of CHF patients that may benefit most from treatment guiding individualized and personalized management.

Our case suffered from concomitant moderately severe insomnia. The prevalence of insomnia symptoms among patients with CHF is high, ranging from 23% to 73%, including difficulty maintaining sleep (34–43%), falling asleep (23–47%), and waking too early in the morning (35–39%) [26]. CHF patients are also consistently more likely to have objective findings of prolonged sleep latency and poor sleep continuity. The reasons are multifactorial. In addition to sleep-disordered breathing such as CSA/PB, symptoms of CHF itself such as orthopnea, paroxysmal nocturnal dyspnea, coughing, and nocturia often lead to insomnia, and insomnia itself may reflect the severity of CHF. Moreover, insomnia may also be an indicator of depression, which is associated with adverse prognosis of CHF. Insomnia could also be partially caused by medications used in the treatment of CHF. For example, beta-blockers may affect production of melatonin, and diuretics may cause nocturia, which all together could result in poor sleep quality. Patients with CHF who also have insomnia develop fatigue and worsening physical performance, and these symptoms are associated with decreased quality of life and low medication adherence. CHF patients with insomnia also have a significantly higher rate of cardiac events. The hyperarousal disorder is accompanied by chronic activation of stress responses with increased activity in the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to an increased secretion of cortisol and upregulation of the renin-angiotensin-aldosterone system (RAAS). Stress response

caused by insomnia is also accompanied by increased blood pressure, increased heart rate, decreased heart rate variability, secretion of catecholamines and pro-inflammatory cytokines, and impaired exercise capacity and activity, which are risk factors for the progression of CHF and prognostic factors of CHF. Thus, treatment of insomnia might improve both quality of life and overall prognosis.

In our patient, problems with maintaining sleep persisted after initiation of ASV therapy, and thus cognitive behavioral therapy was proposed, with the addition of strict sleep hygiene rules, such as minimal use of caffeine, maintaining a regular sleep schedule, going to bed only when sleepy, regular exercise, and only short naps. Such approach can lead to improvement in insomnia in 58% of the cases, and 25% can achieve remission of insomnia symptoms, along with improvement in depression and anxiety.

Key Learning Points

- CPAP and supplemental oxygen are often effective at reducing the AHI in CSA/PB associated with heart failure. These are generally considered first-line therapies, although outcomes studies have yet to show long-term benefit.
- ASV is an effective treatment modality for CSA/PB, and a valuable complement to the management of heart failure. However, ASV therapy has been associated with increased mortality in those with reduced left ventricular ejection fraction. Its long-term benefits or risks in diastolic dysfunction or heart failure with preserved EF remain unknown.
- ASV includes ventilatory support with variable synchronization dependent on flow and ventilation. This type of ventilation is anti-cyclic to the periodicity of the patient's own breathing and acts to dampen the oscillations in the ventilatory drive that underlie periodic breathing. A common feature in treating patients with CSA/PB is that only some patients respond.
- Patients whose CSA does not resolve with treatment are those with the most unstable respiratory control (or the highest loop gain). Uncontrollable CSA may be an indicator of a worse prognosis in CHF.
- Insomnia is highly prevalent in CHF. Insomnia contributes to fatigue and poor quality of life, as well as may be associated with adverse outcomes in CHF patients. CHF disease management alone may not be sufficient to ameliorate insomnia symptoms. Understanding the nature of insomnia symptoms and their associations with daytime symptoms and functional performance is necessary to guide sleep disorders treatment for CHF patients. Identification of CHF patients who may benefit from pharmacological and/or behavioral insomnia treatment is needed.

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