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REVIEW

The importance of sleep-disordered breathing in cardiovascular disease

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Abstract Obstructive sleep apnoea and central sleep apnoea/Cheyne-Stokes respiration are collectively referred to as sleep-disordered breathing (SDB). Rapidly accumulating evidence suggests that both forms of SDB, and often a combination of both, are highly prevalent in patients with a wide variety of cardiovascular diseases, including hypertension, heart failure, arrhythmias, coronary artery disease, acute coronary syndrome and stroke. The presence of SDB in these patients is independently associated with worse cardiac function and exercise tolerance, recurrent arrhythmias, infarct expansion, decreased quality of life and increased mortality. Recent data suggest positive effects of positive airway pressure (PAP) therapy on quality of life and cardiovascular function. In addition, ongoing clinical trials may soon provide first definitive data on PAP therapy of SDB on hard outcomes such as mortality. This review presents current data highlighting links between SDB and a variety of cardiovascular conditions, the importance of recognising and diagnosing SDB in patients with cardiovascular disease, and the effects of effective SDB treatment on cardiovascular endpoints.

Keywords Obstructive sleep apnoea · Central sleep apnoea · Cheyne-Stokes respiration · Cardiovascular disease · Atrial fibrillation · Mortality

Introduction

Sleep-disordered breathing (SDB), or sleep apnoea, is a highly prevalent co-morbidity in cardiovascular diseases (CVD) with an independent negative impact on patient quality of life and is associated with high healthcare costs [1–7]. However, the importance of SDB in cardiology goes beyond symptoms of unrestful sleep, particularly in patients with CVD. There are a number of factors that combine to compel cardiologists to pay more attention to sleep-related breathing disorders, like the high prevalence of SDB in patients with CVD (Fig. 1) [1, 3–7], the possible impact of SDB on the underlying disease, the availability of different strategies to diagnose and treat SDB, and the promising effects associated with treating SDB in patients with CVD.

What is sleep-disordered breathing?

There are three basic mechanisms for the disruption of respiration during sleep: upper airway obstruction, dysregulation of respiratory control, and hypoventilation [8]. Two main breathing abnormalities predominating in SDB are obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), which may manifest as Cheyne-Stokes respiration (CSR). Disease severity is determined by the number of respiratory events per hour of (estimated) sleep time [the apnoea–hypopnoea index (AHI)], and the number and severity of oxygen desaturations [9]. SDB is usually

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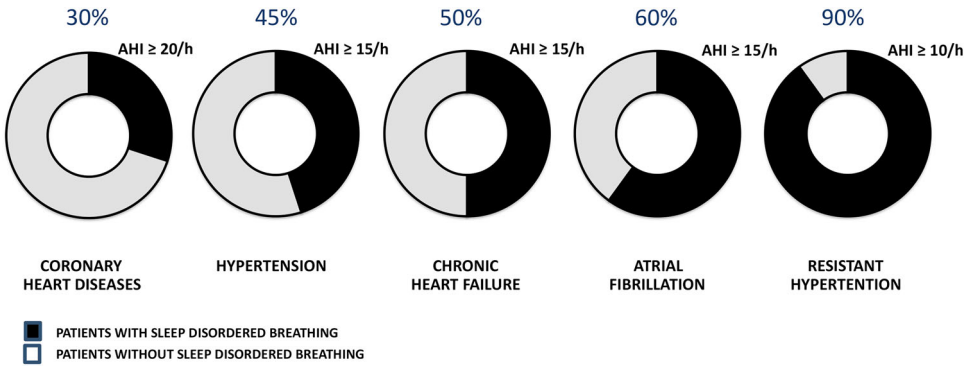

Fig. 1 Prevalence of SDB in patients with coronary heart disease, hypertension, chronic heart failure, atrial fibrillation, and resistant hypertension [1, 3, 5–7] with respective definition of sleep apnoea [apnoea-hypopnoea index (AHI)]

defined as mild if the AHI is 5–15/h, moderate when AHI is 15–30/h and severe when the AHI is >30/h.

Obstructive sleep apnoea (OSA)

Obstructive sleep apnoea is the most common type of SDB in the general population and is characterised by recurrent partial (hypopnoea) or complete (apnoea) collapses of the upper airway during sleep, even when there is respiratory effort (Fig. 2). Typical clinical symptoms of OSA in patients without CVD include excessive daytime sleepiness, insomnia, morning headaches, depression, cognitive dysfunction, nocturnal dyspnoea, nocturia, erectile dysfunction and drowsy driving. However, there is wide inter-individual variation in symptoms, especially between male and female patients [9]. Women tend to have less severe OSA and a lower AHI than males, partly due to episodes of upper airway resistance and flow limitation that do not meet the criteria for apnoeas. This may contribute to the lower rate of SDB diagnosis in women. Other factors implicated in gender-related SDB variation are differences in the upper airways, fat distribution and respiratory stability, and changes in hormones. These differences between men and women appear to decrease as age increases. Furthermore, changes in airway and lung function during pregnancy may contribute to snoring and OSA [9].

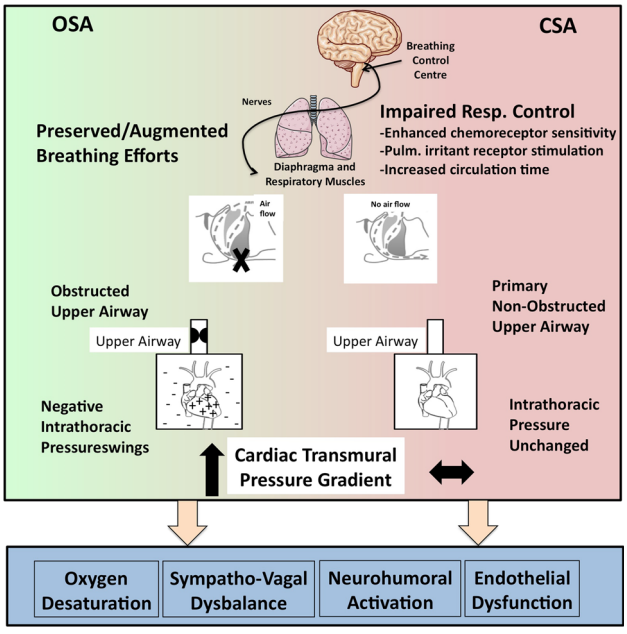

Fig. 2 Pathophysiology of obstructive (*OSA*) and central sleep apnoea (*CSA*) and the effect on the heart

At least, 50 % of patients with severe OSA do not report symptoms of unrestful sleep. This proportion is even higher in patients with OSA and CVD, who often primarily report symptoms of underlying CVD rather than typical signs of OSA [10, 11].

The gold standard therapy for OSA is continuous positive airway pressure (CPAP), which splints the upper airway and maintains upper airway patency, thus alleviating obstructive respiratory events [12] (Fig. 3). Additional beneficial cardiovascular effects of CPAP include increased intrathoracic pressure, reduced left ventricular pre- and afterload, and reduced transmural cardiac pressure gradients, all of which can ameliorate impaired cardiac function [13, 14]. Long-term compliance with CPAP therapy in symptomatic OSA patients is good, with about 70 % still regularly using treatment after 5 years [15]. In OSA patients who are unable to tolerate CPAP therapy, an effective alternative approach is the use of a mandibular repositioning device [16, 17].

Central sleep apnoea/Cheyne-Stokes respiration (CSA/CSR)

Central sleep apnoea and Cheyne-Stokes respiration are mediated by a dysregulation of respiratory control. Heart failure (HF) is the most obvious cause of CSA/CSR, but it has also been observed in patients with stroke, especially in the acute phase, and in those with renal failure [18]. CSR is characterised by periodic episodes of hyper- and hypoventilation, with a typical waxing and waning pattern [19] (Fig. 2). This form of SDB is associated with chronic

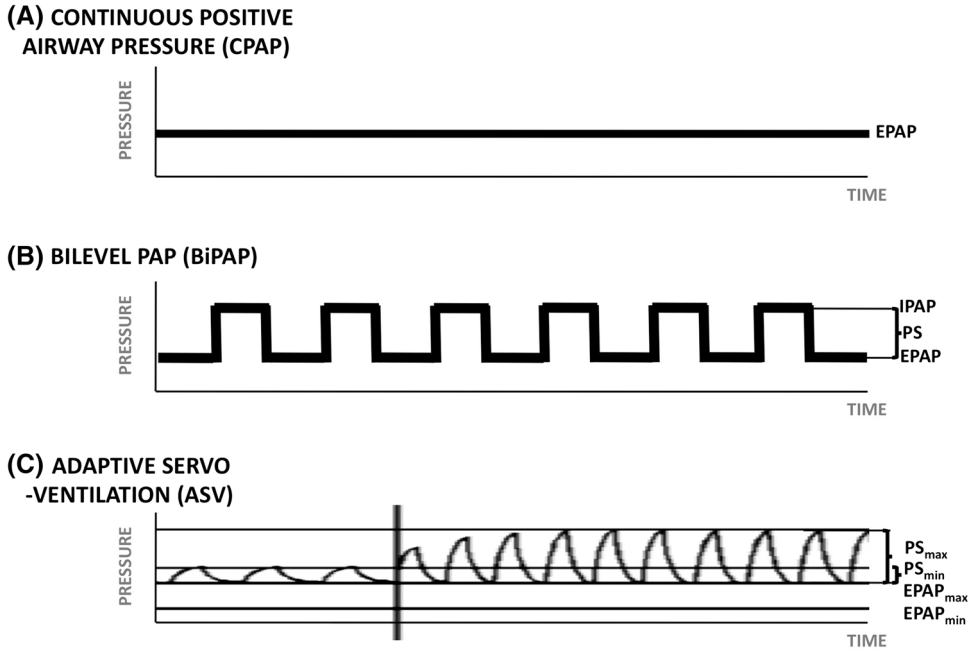

Fig. 3 Different treatments for SDB: **a** continuous positive airway pressure (*CPAP*): fixed or automatically adjusted expiratory pressure (*EPAP*). CPAP aims to maintain upper airways open. **b** Bilevel positive airway pressure (*BiPAP*): fixed EPAP and pressure support (*PS*) at inspiration [inspiratory pressure (*IPAP*)], usually with fixed backup rate. BiPAP aims to trigger breathing in respiratory insufficiency. **c** Adaptive servoventilation (*ASV*): fixed or automatically adjusted expiratory pressure [minimal ($EPAP_{min}$) and maximal ($EPAP_{max}$)] and adaptive pressure support [minimal (PS_{min}) and maximal (PS_{max})] at inspiration with servo controlled backup rate. ASV aims to stabilise all form of unstable breathing such as CSA/CSR

hyperventilation and patients usually have low carbon dioxide (CO_2) levels. Dysregulation of respiratory control is mediated by increased sensitivity of peripheral and central chemoreceptors [19]. Other contributing factors are pulmonary congestion and prolonged circulation time [19]. Interestingly, CSR is not just limited to sleep but can also occur at rest and during exercise in patients with advanced HF [20, 21]. The cycle length of CSR in HF is related to reduction in cardiac function [22]. It has been suggested that CSR with associated hyperventilation may be a compensatory mechanism that has detrimental effects in HF [23].

Standard management of CSA/CSR in CVD patients consists of optimising treatment for the underlying disease, especially HF. Effective pharmacological and device therapy has been shown to significantly improve the severity of CSA/CSR in patients with HF [24–27], and heart transplantation may eliminate CSA/CSR. A number of treatments for CSA/CSR have been studied, including oxygen, carbon dioxide, CPAP, bilevel positive airway pressure (BiPAP) and adaptive servoventilation (ASV) (Fig. 3). Oxygen therapy has been the subject of a few small-scale trials. Its use during sleep reduces the severity of CSA/CSR by approximately 50 %, but only one study has reported clinical improvements [28]. Administration of carbon dioxide reduces AHI, but at the expense of hyperventilation and poor sleep quality, and is not used clinically [29]. Although it does not trigger inspiration during central apnoea, CPAP improves CSA/CSR probably by increasing functional residual capacity (and, as a result, oxygen stores), decreasing blood volume in the lungs and upper airway when lying down [30], and reducing hyperventilation via a direct effect on the paravasal J-receptors of the lung [31]. In addition, CPAP reduces pre- and afterload and the cardiac transmural pressure [32]. However, not all patients respond to CPAP therapy, for example, due to unresolved mask leaks or unsatisfactory positive airway pressure titration. Some patients even develop CSR during CPAP administration, a finding labelled as complex sleep apnoea [8, 33, 34]. BiPAP with backup rate has been shown to be more effective than CPAP at controlling CSA/CSR [35], but it can also worsen central SDB [36]. This is because BiPAP with backup rate is designed to provide ventilation and reduce CO_2 levels, which does not ameliorate the hyperventilation and low CO_2 levels associated with CSA/CSR. For this reason, BiPAP is not considered an adequate treatment for CSA/CSR.

ASV is the most effective treatment for SDB in heart failure patients, providing the best control of nocturnal respiratory events [37]. The advantage of ASV compared to other SDB treatment options is that it treats both OSA and CSA/CSR. ASV ensures upper airway patency using a

fixed or varied amount of expiratory positive airway pressure, while a varying amount of inspiratory pressure support sustains inspiration with decreasing breathing amplitude or even ensures inspiration with sustained breathing efforts [37, 38]. Thereby, ASV also uses a 'backup rate', which acts as a respiratory pacemaker during apnoeas. Treatment with ASV can effectively suppress complex sleep apnoea and has positive effects on cardiac function and respiratory stability [33]. Phrenic nerve stimulation is a new approach to the treatment of CSA/CSR, with initial results showing that it may improve central respiratory events by about 50 % [39–41].

Physiological effects of sleep-disordered breathing

In OSA, attempts to breath against the occluded upper airways not only result in acute hypoxaemia and hypercapnia, but also in profound negative intrathoracic pressure swings, which increase cardiac transmural pressure gradients [29], sympathetic activation [42], impairment of ventricular mechanics [43], arousals, and sleep fragmentation and deprivation [44]. Additionally, in the long run, these processes could lead to structural and functional remodelling processes in the heart and may contribute to the development and progression of CVD in the context of OSA [44] (Fig. 4).

Like OSA, CSA/CSR results in desaturations and arousals, activating the sympathetic nervous system [9], which can lead to progression and deterioration of underlying CVD. In contrast, intrathoracic pressure swings and subsequent changes in transmural pressure are not observed in CSA/CSR. CSR has been shown to be an independent predictor of increased mortality in patients with HF and impaired left ventricular ejection fraction (LVEF) [45, 46].

Sleep-disordered breathing and hypertension

The potential role of OSA in the pathogenesis of hypertension has been recognised in international guideline documents [47–49]. Approximately, half of all patients with OSA have hypertension and about 30–40 % of patients with arterial hypertension also have clinically relevant OSA [9]. The prevalence is even higher (up to 90 %) in those with drug-resistant hypertension [5, 50, 51]. Cohort study data suggest that the risk and prevalence of hypertension increase as the severity of OSA increases [52–59]. CPAP alleviates intermittent hypoxia and reduces sympathetic drive in OSA patients and thus lowers blood pressure during sleep [42]. In patients with cardiovascular disease or multiple cardiovascular risk factors, the treatment of OSA with CPAP, but not nocturnal supplemental oxygen, resulted in a significant reduction in blood pressure [60]. This suggests that it is not just intermittent hypoxia alone but factors directly associated with obstructive respiratory events that are the relevant trigger for hypertension. Compared to intermittent apnoea alone, obstructive respiratory events are associated with apnoea associated changes in renal perfusion and subsequent sympathetic and neurohumoral activation which may contribute to the pathophysiology of OSA-associated hypertension [61].

Randomised clinical trials have assessed the effects of CPAP treatment on OSA in more than 1600 patients with hypertension [62]. In the majority of studies, the effect of treatment on BP has been favourable. The results of two meta-analyses, including studies that were conducted largely in normotensive patients, suggest that the reduction in BP during CPAP therapy in patients with OSA is in the region of 1.5–2.5 mmHg [63, 64]; the magnitude of effect varied from nothing up to a 10 mmHg reduction in BP [65, 66]. Regression analysis estimated that 24-h mean BP would decrease by 1.39 mmHg for each 1-h increase in effective nightly use of a CPAP device [64]. In the most recent meta-analysis of published data, which included 32 randomised controlled trials, mean reductions in daytime systolic and diastolic BP with CPAP versus no treatment were 2.6 and 2.0 mmHg, respectively; corresponding nighttime reductions were 3.8 and 1.8 mmHg [67]. The magnitude of BP reductions during CPAP therapy was at least half that attributed to antihypertensive drugs in similar analyses. Another interesting finding of this systematic review was that there was a link between baseline OSA severity and the beneficial effects of CPAP on BP—the higher the baseline AHI, the greater the reduction in systolic BP—suggesting that patients with more severe OSA may benefit the most from CPAP therapy in terms of BP reduction [67].

The greatest benefits of CPAP therapy for OSA have been seen in patients with difficult-to-treat hypertension [5, 50, 51, 68]. In patients with resistant hypertension, treatment of OSA with CPAP reduced daytime BP by 6.5 mmHg, compared with a 3.1 mmHg increase in untreated patients over the study period [51]. It is important to mention that compliance to CPAP therapy by patients with resistant hypertension plays a key role in achieving optimal BP reduction. Decreases in 24-h BP were documented in patients with resistant hypertension who used CPAP for >5.8 h per night, but not in those with lower usage [68], and another study of CPAP treatment for OSA in patients with resistant hypertension reported a significant correlation between hours of CPAP use and decreases in 24-h systolic and diastolic BP [69]. Other factors influencing the magnitude of the effect of CPAP on BP include sleepiness symptoms, severity of desaturations, compliance with CPAP therapy, and pharmacological pre-treatment [70, 71].

The evidence described above and the document antihypertensive effects of CPAP therapy in OSA patients

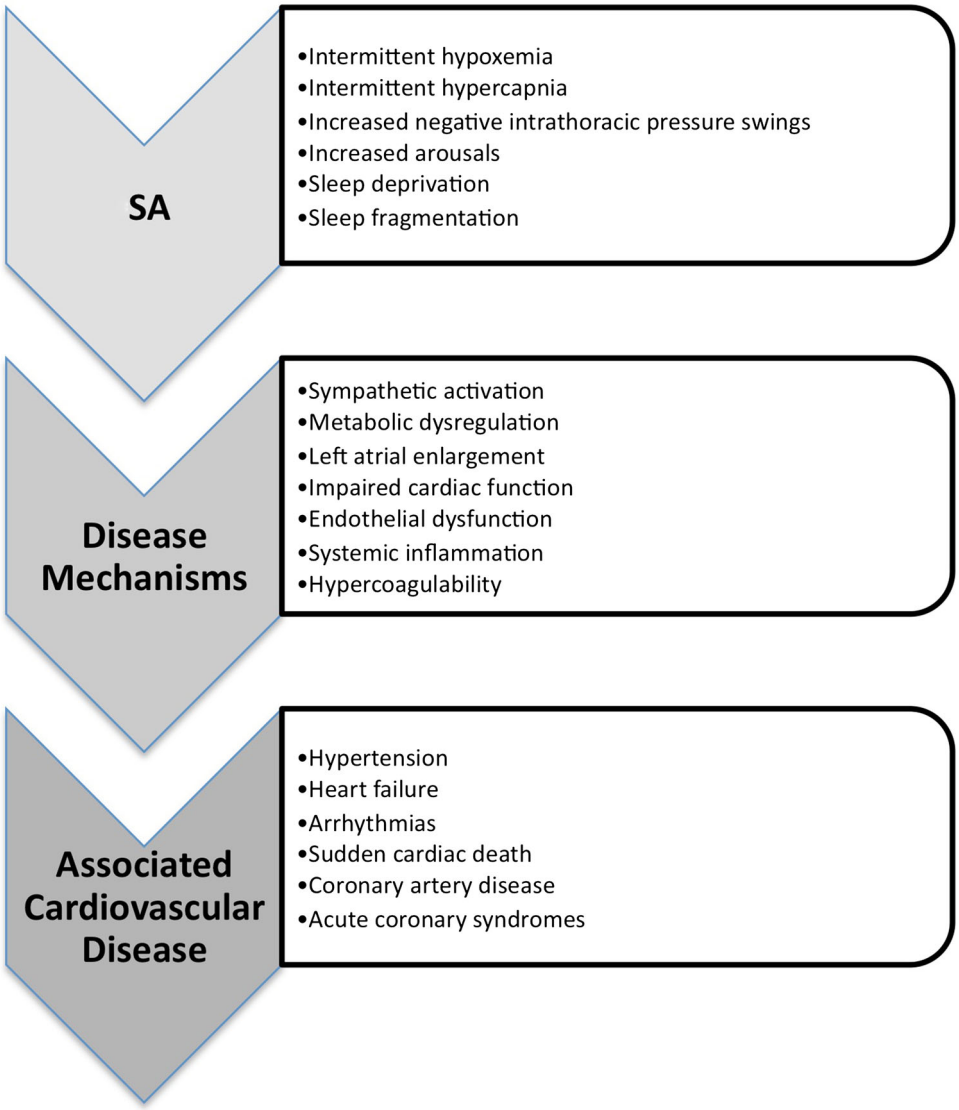

Fig. 4 Links between sleep apnoea and cardiovascular disease (adapted from Somers et al. [10]). *SA* sleep apnoea

indicate that SDB is a relevant cause of hypertension. For clinical practice, it is important to mention that it takes 3–6 months to achieve the maximum reduction in BP associated with CPAP therapy [70]. OSA is recognised as the most prevalent risk factor contributing to resistant hypertension [72], and an American Heart Association (AHA) scientific statement recommends that OSA in patients with resistant hypertension should be treated with CPAP [73].

Sleep-disordered breathing and heart failure

The Sleep Heart Health Study identified OSA as an independent risk factor for the development of HF [74], with more impact in men than in women [75]. The prevalence of SDB in patients with HF with preserved ejection fraction (HF*p*EF) or HF with reduced ejection fraction (HF*r*EF) is up to 70 and 76 %, respectively [76, 77], and 45–50 % of these have moderate-to-severe SDB [77]. OSA appears to be the predominant SDB in patients with HF*p*EF, with a prevalence of 62 % compared with 18 % for CSA [78]. Conversely, the prevalence of CSA/CSR in patients with HF*r*EF is high [79]. The severity of ventricular dysfunction is driving the risk for CSA/CSR and with increasing impairment in cardiac function, there is an increase in CSA/CSR prevalence [18] (Fig. 5).

In patients with HF and impaired LVEF, untreated OSA and CSA are independent risk factors for a worse prognosis and death [46, 80–82], and daytime CSR is a significant independent predictor of mortality in patients with severe congestive HF [83]. Even when treatment of HF is optimised, persistent low levels of CSA/CSR or OSA appear to have an important negative impact on prognosis [84].

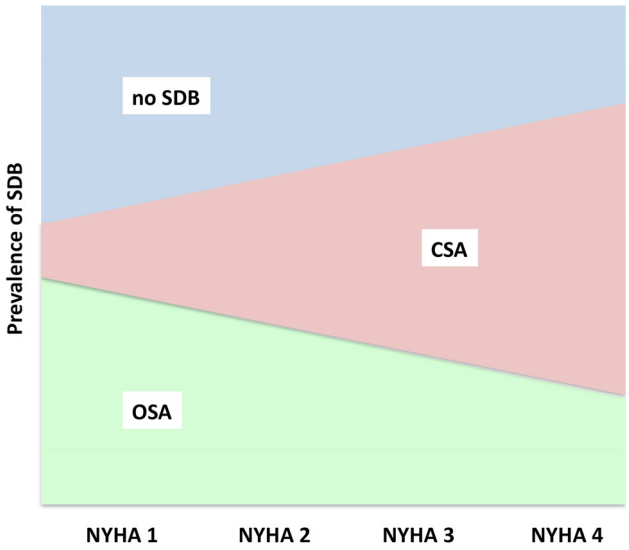

Fig. 5 Scheme of the relative prevalence of obstructive (*OSA*) and central sleep apnoea (*CSA*) according to heart failure severity. With increasing impairment in cardiac function there is an increase in CSA prevalence. *NYHA* New York Heart Association class (adapted from Oldenburg et al. [18])

It is important to note that HF patients with SDB do not usually have typical symptoms, such as daytime sleepiness [3, 10, 85, 86]. This may be the result of increased sympathetic nervous system activity secondary to SDB that stimulates alertness and counteracts the effects of sleep fragmentation and deprivation [87].

Two randomised trials evaluating the effect of CPAP therapy in patients with OSA and HF showed significant improvements in LVEF after 1 and 3 months [88, 89]. In addition, quality of life was improved and sympathetic activity was reduced. A Japanese cohort study documented a positive effect of CPAP treatment on survival in HF patients with OSA, although this was not a randomised controlled trial, and also highlighted the importance of compliance with therapy in achieving beneficial outcomes [90]. Treating newly diagnosed OSA with CPAP in men without overt cardiovascular disease was associated with improvements in echocardiographic markers of diastolic function [91].

The 2010 Heart Failure Society of America Comprehensive Heart Failure guidelines recommend screening for SDB and CPAP therapy in those with confirmed OSA [92]. The 2013 ACCF/AHA guidelines acknowledge that treating OSA with CPAP in patients with HF does have benefit [93].

Use of CPAP has been shown to alleviate CSA/CSR in patients with HF [14, 30, 94, 95]. Improvements associated with CPAP therapy include a decreased number of CSA episodes, improved oxygenation, increased LVEF, decreased noradrenaline levels and improved 6-min walk distance [96]. Nevertheless, the Canadian Positive Airway Pressure (CANPAP) study, which investigated the effect of CPAP therapy of CSA/CSR in patients with stable HF on transplantation-free survival, did not show a positive effect of treatment on either transplant-free survival or hospitalisation [96]. The trial was stopped prematurely after a prespecified interim analysis for a number of reasons, including decline in event rate, low recruitment and early increase in mortality in the CPAP group. A post hoc analysis of the CANPAP data suggested that patients who achieved normalisation of respiratory events during PAP therapy may have improved outcomes [97].

Data from studies such as CANPAP indicate that effective control of SDB may be important for improving morbidity and mortality in patients with CSA/CSR. However, a high proportion of patients with CSA have residual apnoea events despite CPAP therapy, suggesting that a more effective intervention is required [98].

ASV has been shown to be the most effective intervention for controlling SDB in patients with HF [37]. Smaller trials have documented improvements in AHI, sleep quality, quality of life, LVEF, New York Heart Association class, oxygen uptake, natriuretic peptides, inflammatory markers and exercise capacity [99–104], and a meta-analysis provides an overview of the treatment effect [105].

In randomised, controlled clinical trials, beneficial effects of ASV treatment of CSA/CSR in HF patients include significant reductions in AHI [106–111], N-terminal pro-BNP levels [107, 110–113], urinary catecholamine release [110] and left ventricular end-systolic diameter [107], increases in 6-min walk distance [107] and LVEF [106, 108, 109], and improved NYHA class [108].

ASV has been shown to be more effective than BiPAP for treating CSA/CSR in HF [114] and ASV is better tolerated than CPAP [115], resulting in improved compliance with therapy, which is an important part of successful treatment [107].

The effect of ASV treatment on morbidity and mortality is currently being investigated in the SERVE-HF and ADVENT-HF trials (clinicaltrials.gov identifier: NCT00733343 and NCT01128816). The SERVE-HF has enrolled approximately 1325 patients with chronic stable HF*r*EF and CSA/CSR, with an expected finish date of mid-2015 [116]. The Cardiovascular Improvements With Minute Ventilation-targeted ASV Therapy in Heart Failure (CAT-HF) study (clinicaltrials.gov identifier: NCT01953874) will compare the effects of targeted ASV added to optimised medical therapy compared with medical therapy alone in patients with acute decompensated HF. The primary outcome is a global measure combining survival free from cardiovascular hospitalisation and improvement in functional capacity; changes in functional

parameters, biomarkers, quality of life and sleep-disordered breathing will also be assessed.

Another area of interest is the use of ASV in patients with HF*p*EF and CSA/CSR. Early results show that ASV can improve cardiac diastolic function, improve symptoms and decrease brain natriuretic peptide levels in this group of patients [117, 118]. In addition, the proportion of HF*p*EF patients treated with ASV who were free of cardiac events was significantly higher than that in untreated patients [118].

Sleep-disordered breathing and cardiac arrhythmias

Atrial fibrillation

Sleep apnoea is highly prevalent in patients with AF. More than 50 % of those with paroxysmal AF and a high AF burden or persistent AF have been shown to have clinically relevant SDB [7]. The prevalence of CSA in patients with AF is not well described and few data are currently available. One study has reported a high proportion of CSA (79 %) in a group of pacemaker recipients with permanent AF [76]; this was probably a result of a high rate of HF and depressed LVEF in this study population. Another study in AF patients with normal left ventricular function showed prevalence rates of 31 % for CSA/CSR and 43 % for OSA [119]. Several mechanisms may contribute to the development of arrhythmias in sleep apnoea [120]. In animal studies as well as clinical observations, the negative thoracic pressure during obstructive respiratory events in particular was identified as the most relevant factor for the perpetuation and initiation of AF. Negative thoracic pressure changes result in increased occurrence of atrial premature contractions, potentially triggering AF episodes [121, 122]. In a pig model of OSA, application of negative tracheal pressure during tracheal occlusion, but not tracheal occlusion without applied negative tracheal pressure, reproducibly and reversibly shortened the atrial refractory period and strongly enhanced the inducibility of AF. These arrhythmogenic electrophysiological changes were mainly driven by a combined sympatho-vagal activation as it could be modulated by sympathetic as well as by vagal inhibition [61, 121, 122]. Additionally, repetitive obstructive respiratory events resulted in an arrhythmogenic structural substrate for AF characterised by local conduction disturbances due to increased atrial fibrosis formation and distribution of connexins in a rat model of sleep apnoea [123]. OSA substantially limits antiarrhythmic treatment strategies in AF patients. For example, the effectiveness of antiarrhythmic drugs for the treatment of AF is reduced in patients with severe OSA [124]. Additionally, recurrence of AF after initially effective electrical cardioversion is increased in patients with OSA [125]. Data from a meta-analysis reported that the risk ratio for recurrent AF after pulmonary vein isolation was 1.25 in patients with versus without OSA [126]. The risk was significantly higher (risk ratio 1.40) if OSA had been diagnosed using polysomnography, but not (risk ratio 1.07) if OSA was diagnosed on the basis of the Berlin questionnaire [126], meaning that the Berlin questionnaire is not an appropriate screening or assessment tool in this setting. Prevention of obstructive respiratory events in OSA using CPAP reduces the risk of AF recurrence after ablation therapy [127]. In a larger study ($n = 426$) [128], CPAP therapy in patients with OSA and AF undergoing pulmonary vein isolation was associated with a higher AF-free survival rate (71.9 vs 36.7 % in untreated patients) and almost similar to a group of patients without OSA. Interestingly, the effect of CPAP in patients without pulmonary vein ablation was comparable to the effect of pulmonary vein isolation in CPAP non-user OSA patients [128]. The proportion of patients who were free of AF without drug treatment or repeat ablation was also significantly higher in CPAP users versus non-users [128]. In AF management guidelines, OSA is mentioned as being associated with AF and as a factor contributing to a reduction in the success of ablation procedures [129].

Ventricular arrhythmias

An AHI of >20/h was a significant and independent risk factor for incident sudden cardiac death in a study of more than 10,000 patients referred for polysomnography [130]. Co-existing HF and SDB increase the risk of developing malignant ventricular arrhythmias [131]. Severe OSA also increases the risk of ventricular premature beats and non-sustained ventricular tachycardias (NSVT), and nocturnal sudden cardiac death [132, 133]. It has been shown that an episode of AF or NSVT was almost 18 times more likely to occur within 90 s of an apnoea or hypopnoea compared with normal breathing [134]. Registry data show that treatment of CSR with ASV in HF patients with implantable cardioverter defibrillator devices (ICDs) decreases the use of defibrillatory therapies, and improves cardiac function and respiratory stability [135].

Sleep-disordered breathing and coronary artery disease

Stable coronary artery disease

The prevalence of OSA in patients with CAD is high (up to 87 % in CAD patients referred for coronary artery bypass graft surgery), and is significantly increased compared with

healthy controls [136–141]. In a cohort of patients who had undergone revascularisation for CAD, the prevalence of OSA was higher than that of obesity, hypertension, diabetes and AF [142]. CAD patients with OSA are not usually sleepy, and OSA remains a significant risk factor for CAD even after controlling for other well-known cardiovascular risk factors, including body mass index, hypertension, hypercholesterolaemia, diabetes and smoking [143]. Data from the Sleep Heart Health Study showed that men aged 40–70 years with an AHI of ≥30/h were 68 % more likely to develop CAD than those with an AHI <5/h [74]. It has also been shown that CAD patients with versus without OSA have a higher frequency of noncalcified/mixed atherosclerotic plaques, along with more serious stenosis and higher number of affected vessels [144]. In addition, OSA has been associated with nocturnal ST segment changes, even in the absence of documented coronary artery disease (CAD) [145]. In a prospective study of patients with CAD, the relative increases in the risk of a composite endpoint of death, cerebrovascular events and myocardial infarction in patients with a desaturation index of ≥5/h and an AHI of ≥10/h were 70 and 63 %, respectively, over 5 years of follow-up [146]. Despite all this, OSA remains an undiagnosed problem in patients with CAD [147].

Acute coronary syndromes

In the several days after an acute myocardial infarction (MI), the prevalence of moderate-to-severe sleep apnoea (AHI ≥15/h) was as high as 55 % [148]. In addition, AHI has been shown to be independently associated with less myocardial salvage and a larger infarct size at 3 months [149], and the presence of OSA inhibits recovery of left ventricular function after MI [141]. In the acute setting, the presence of OSA was shown to be an independent predictor of cardiovascular events in patients with non-ST-elevation coronary syndromes (odds ratio [OR] 3.4; 95 % confidence interval [CI] 1.3–9.0; $p = 0.0002$) [150]. Cardiovascular event rates over a 5-year follow-up were 37.5 and 9.3 % in CAD patients with versus without OSA ($p = 0.018$), and the respiratory disturbance index was identified as a significant independent predictor of cardiovascular mortality [151]. Similar results were reported in another study in patients with acute coronary syndromes that had a mean follow-up of 227 days, except it was OSA that was identified as independent predictor of major cardiac events (hazard ratio [HR] 11.62, 95 % CI 2.17–62.24; $p = 0.004$) [152].

Treatment

Treatment of OSA with CPAP can alleviate nocturnal ischaemia, and has been shown to have a beneficial effect on cardiovascular event rates and mortality [153–156]. The ongoing ISAACC (NCT01335087) [157] and TEAM ASV-I (NCT02093377) studies will help to better define the role of early PAP therapy in patients with acute coronary syndromes.

Lifestyle modifications and sleep-disordered breathing

Even if prescribed non-invasive respiratory support, patients with SDB should be screened for factors that can exacerbate the condition, such as obesity or alcohol consumption. Alcohol consumption is associated with elevated morning blood pressure [158]. In addition, alcohol consumption prior to bedtime has been associated with an increase in the number and duration of apnoeas and hypopneas in adults who snore or have SDB [159, 160], requiring higher levels of CPAP to prevent these SDB events [161].

Excess weight is also associated with SDB [162] and may be complicated by obesity hypoventilation syndrome. Obesity hypoventilation syndrome is usually diagnosed in patients who have daytime alveolar hypoventilation (awake, sea-level, arterial pCO_2 >45 mmHg) and a body mass index (BMI) ≥30 kg/m^2 in the absence of other causes of hypoventilation. The exact prevalence of obesity hypoventilation syndrome among OSA patients is unknown but may range from 4 to 50 % [163]. Both bariatric surgery and non-surgical weight loss may have significant beneficial effects on OSA via reductions in BMI and AHI. However, bariatric surgery is often associated with greater reductions in BMI and AHI than non-surgical alternatives [164]. Aggressive risk factor management, including weight reduction and reducing or eliminating alcohol intake is likely to reduce some SDB symptoms and could therefore contribute to a reduction in cardiovascular complications [165, 166].

Concluding remarks

Obstructive sleep apnoea represents an independent risk factor for the development and progression of various CVD. OSA as well as CSA/CSR are highly prevalent in cardiac patients and worsen underlying CVD. Screening for SDB in patients with CVD provides important information and ongoing as well as future studies in cardiovascular patients should evaluate the effects of effective treatment of SDB on mortality, quality of life, and healthcare costs.

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Conflict of interest None.

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