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ABSTRACT

Sleep-disordered breathing (SDB) describes a group of disorders characterised by abnormalities in the frequency and/or depth of breathing while asleep. The most common type is the obstructive sleep apnoea/hypopnoea syndrome (OSAHS); it affects 2–4% of the adult population and is an independent risk factor for hypertension. Another type is central sleep apnoea (CSA), which includes Cheyne–Stokes respiration; it is most commonly seen in patients with congestive heart failure and other critical illnesses including cerebrovascular accidents. There is accumulating evidence that both these types of SDB are associated with cardiac failure, arrhythmias and coronary artery disease. Treatment of OSAHS with continuous positive airway pressure (CPAP) has lowered blood pressure, reduced the frequency and severity of some arrhythmias, and improved markers of endovascular inflammation. CPAP has had a mild positive effect on left ventricular function in chronic heart failure by treating co-existent SDB, but it has not improved mortality, possibly because it does not fully treat associated CSA. Clinicians need to be aware of the increasing associations of SDB, especially OSAHS, with cardiovascular dysfunction, as treatment of co-existent SDB will not only improve sleepiness, quality of life, and driving risk, but there is growing evidence that it may also improve cardiovascular risk itself, even in non-sleepy subjects.

Sleep-disordered breathing (SDB) was first described in the medical literature in 1936,[1] but has been described as far back as the 4th century BC, when Dionysius, tyrant of Heraclea, "lived in fear of suffocation from fat".[2] Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is the most common type of SDB, affecting ~4% of men and 2% of women aged 30–65 years with a total population prevalence of 1–2%, making it as least as common as type I diabetes.[3]

There are several different types of SDB, including:

▶ OSAHS
▶ Obesity hypoventilation syndrome
▶ Central sleep apnoea (CSA)
▶ Upper airway resistance syndrome
▶ Cheyne–Stokes respiration (CSR)

In this review, we concentrate on the association between the most prevalent type of SDB, namely OSAHS, and cardiac dysfunction, but, unlike in other reviews, we also describe some associations between CSA and CSR and cardiovascular disease.

OSAHS is defined as the coexistence of excessive daytime sleepiness with irregular breathing at night due to complete or partial closure of the upper airways.[4] An apnoea is the absence of airflow at the nose and mouth for at least 10 s (due to complete airway occlusion), and a hypopnoea is a major reduction (>50%) in airflow also for at least 10 s (partial airway narrowing).[5] These are diagnosed during limited-channel sleep studies or polysomnography. The Apnoea/Hypopnoea Index (AHI) is the total number of apnoeas and/or hypopnoea events per hour of sleep. The 4% dip rate is the number of oxygen desaturations (from baseline) of at least 4% associated with the apnoeas/hypopnoeas.

CSA has two distinct types. Hypercapnic CSA results from a chronically depressed respiratory drive associated with hypercapnia in wakefulness and sleep.[6] The more common hypocapnic CSA is caused by a nocturnal pattern of breathing typified by regular crescendo–decrescendo oscillation of tidal volume, thought to be caused by dysfunction of central respiratory control. As the central drive to breathe fades, ventilation temporarily ceases before resuming again. Apnoeas and/or hypopnoeas can occur in CSA also.[7] CSR refers to a type of normocapnic CSA followed by periodic hyperventilation, with both hypopnoeas and apnoeas. The presence of this respiratory pattern appears to be a particularly poor prognostic indicator of the presence of heart failure.

CSA occurs when there is cessation of inspiratory effort, but, in contrast with upper airway collapse, occurs sporadically and repetitively during sleep. Inspiratory efforts continue in obstructive sleep apnoea (OSA) but are ineffective because of upper airway obstruction. In OSAHS, apnoeas are terminated by recurrent arousals from sleep, which are needed to increase the tone of dilator muscles and open the upper airway; these recurrent microarousals cause sleep fragmentation, which often (but not always) causes the hallmark symptom of daytime tiredness and therefore the OSAHS.

Treatment of OSAHS with continuous positive airway pressure (CPAP) decreases the excess healthcare costs incurred by patients[8][9] and reduces the risk of car accidents from an excess risk of 2–7 times greater than to equal to the background population.[10] In the UK, CPAP is currently only recommended for treatment in symptomatic patients (ie, excessive daytime somnolence) and with an AHI >15/h or a 4% oxygen dip rate of >10/h.[4][11] Why would CPAP reduce the medical costs incurred by patients with OSAHS independently of reducing driving/occupational accidents? There is increasing evidence of an association between OSAHS and cardiovascular disease, and numerous reviews reflect this.[12–16] OSAHS is certainly an independent risk factor for hypertension,[17][18] but, not only is there growing evidence

that OSAHS is linked to other cardiovascular illnesses such as stroke, arrhythmias, coronary artery disease (CAD) and heart failure, but treating OSAHS may also improve these conditions.[19–24]

Given the widespread prevalence of heart disease and potential of undiagnosed sleep pathology, any associations would have implications for the current provision of sleep services. There is still much debate about whether SDB, in particular OSAHS, is an independent risk factor for cardiovascular dysfunction or a marker of another disease state. This review summarises the present evidence on cardiovascular risk and SDB, with particular emphasis on OSAHS and CSA. We suggest situations where it may be useful to screen for SDB and when treatment of co-existent SDB would be of benefit in patients with cardiovascular disease.

OSAHS AND CARDIOVASCULAR DISEASE

Many studies have alluded to a link between SDB and cardiovascular disease, but both (particularly OSAHS) may purely co-exist with type 2 diabetes, for example,[25] therefore proving that SDB as an independent risk factor for cardiovascular disease is not straightforward. Previous cross-sectional and longitudinal population-based studies (Wisconsin Sleep Cohort,[3] Pennsylvania Sleep Cohort[26 27] and the Cleveland Family Study[28 29]) confirmed only an association with OSAHS and multiple cardiovascular risk factors such as hypertension and diabetes. However, a large, prospective (11-year follow-up), multicentre, cohort study called the Sleep Heart Health Study[30] showed excess cardiovascular mortality and morbidity in those with OSAHS after correction of results for known confounders. The Swedish 7-year cohort study of Peker et al[31] showed a higher incidence of adverse cardiovascular events in untreated patients with OSAHS (who refused/or had poor CPAP compliance) than in both subjects without OSAHS and OSAHS patients with good CPAP compliance.[31] Two more-recent studies confirmed excess cardiac events over a 10-year period in patients with untreated severe OSAHS.[32 33] Recent data from more than

15 000 subjects suggest that cardiovascular events are particularly prevalent in younger patients with OSAHS.[34] However, these studies were not randomised controlled trials, as such long-term studies (needed to measure mortality) cannot be justified on ethical grounds because of the proven benefit of CPAP for hypertension, quality of life, and driving risk. Table 1 summarises the results of the main trials.

OSAHS AND HYPERTENSION

There is stronger evidence that OSAHS is an independent risk factor for hypertension than any other cardiovascular disease state and, moreover, that treatment with CPAP can reduce blood pressure.[18] Previous work estimated that ~40% of patients with OSAHS are hypertensive while awake[35] and 40% of patients with refractory hypertension have OSAHS.[36] More-recent cohort studies have suggested that OSAHS is present in up to 83% of patients with uncontrolled hypertension, despite taking three or more antihypertensive agents at optimum doses.[37] Four large population-based studies have shown that OSAHS is an independent risk factor for hypertension.[38–41] All four studies were able to adjust for age, body mass index (BMI) and sex. The Sleep Heart Health Study reported that the adjusted odds ratio for hypertension was 1.37 (95% CI 1.03 to 1.83; p for trend = 0.005), comparing subjects with an AHI >30 events per hour with those with an AHI <1.5 events per hour.[39] The Wisconsin prospective sleep cohort of 709 subjects confirmed that those with "minimal", "mild-moderate" and "moderate-severe" SDB had adjusted odds ratios of developing hypertension of 1.42, 2.03 and 2.89, respectively, over the next 4 years, compared with subjects without SDB. This was after adjustment for baseline hypertension status, age, sex, BMI, waist and neck circumference, and weekly alcohol and cigarette use.[41] Table 2 summarises some of these studies.

Two interventional (randomised controlled) studies showed a significant fall in blood pressure (BP) in patients receiving therapeutic CPAP (set at a pressure that abolished OSAHS) but no change in BP with "placebo" CPAP, set at sub-therapeutic

Table 1 Prevalence studies on cardiovascular disease and obstructive sleep apnoea/hypopnoea syndrome (OSAHS)

Reference	Study type	Type of SDB	Sample size	Outcome	Comments
Sahar et al[30] 2001	CS	OSAHS	1023	Relative odds (95% CI) for: ► OSAHS and heart failure 2.38 (1.22 to 4.62) ► OSAHS and stroke 1.58 (1.02 to 2.46) ► OSAHS and coronary heart disease 1.27 (0.99 to 1.62)(where no OSAHS (= AHI of 0–1.3) to definite OSAHS (AHI >11))	Representative population selection. Multivariate analysis (as opposed to true matching)
Peker et al[31] 2002	C	OSAHS	182	The incidence of at least one cardiovascular disease was observed in 36.7% of cases with OSA (4% dip rate >30/h) vs 6.6% subjects without OSA (p<0.001)	All subjects (controls and OSAHS) free from cardiovascular disease/hypertension at baseline. 7-year follow-up
Marin et al[32] 2005	C	OSAHS	1044	Multivariate analysis. Odds ratios (95% CI) for cardiovascular events in untreated severe OSAHS vs healthy participants: ► fatal events 2.87 (1.17 to 7.51) ► non-fatal events 3.17 (1.12 to 7.51)	Control group matched for age and BMI. Not matched for hypertension or diabetes. "Untreated" CPAP group may be poor compliers with other treatments, also 10-year follow-up
Doherty et al[33] 2005	C	OSAHS	168	Total cardiovascular events (ie, death and new cardiovascular disease combined). More common in the untreated group (31%) than in the CPAP-treated group (18%) (p<0.05)	Average follow-up period of 7.5 years. Matched for BMI. Follow-up of OSAHS patients only. No "healthy controls". "Untreated" CPAP group may be poor compliers with other treatments

AHI, Apnoea/Hypopnoea Index; BMI, body mass index; C, cohort; CPAP, continuous positive airway pressure; CS, cross-sectional; OSA, obstructive sleep apnoea; SDB, sleep-disordered breathing.

Table 2 Prevalence studies on hypertension and obstructive sleep apnoea/hypopnoea syndrome (OSAHS)

Study	Type	Subjects	Outcome	Comments
Hla et al[42] 1994 (Wisconsin)	CS	147	OR for hypertension above background population: mild OSAHS, 2.0 moderate/severe OSAHS, 5.0	Workplace population selection
Grote et al[40] 1999	PC	1190	RR for hypertension increased with SDB severity. OR for hypertension in severe OSAHS vs no OSAHS = 4.15 (95% CI 2.7 to 6.5)	Large numbers, confounders controlled for. Statistics based on logistic regression, groups differed in BMI/age
Lavie et al[38] 2000	CS	2677	Multiple logistic regressions showed that each additional apnoeic event per hour of sleep increased the odds of hypertension by about 1%, and each 10% decrease in nocturnal oxygen saturation increased the odds by 13%	Subgroup analysis. OSAHS patients and controls matched for age and BMI , but had higher BP. No mention of sleepiness symptoms. Multiple logistic regression
Nieto et al[39] 2000	CS	6132	OR (95% CI) for hypertension in severe OSAHS vs no OSAHS: 1.37 (1.03 to 1.83), p = 0.005	Large numbers, confounders controlled for. Stats based on logistic regression, groups differed in BMI/age
Peppard et al[41] 2000 (Wisconsin cohort)	CS and C	709 (4-year follow-up) and 184 (8-year follow-up)	Relative to AHI of 0 at baseline, OR (95% CI) for the presence of hypertension at follow-up: ▶ 1.42 (1.13 to 1.78) for no OSAHS ▶ 2.03 (1.29 to 3.17) for mild OSAHS ▶ 2.89 (1.46 to 5.64) for moderate OSAHS	Large numbers, confounders controlled for. Logistic regression, but groups differed in BMI/Age
Bixler et al[43] 2000 (Pennsylvania)	CS	1741	OR for OSAHS and hypertension: 6.8 for moderate to severe SDB 2.3 for mild SDB	Representative population selection. Not matched for BMI, diabetes, smoking, gender

AHI, Apnoea/Hypopnoea Index; BMI, body mass index; BP, blood pressure; C, cohort; CS, cross-sectional; PC, prospective cohort; SDB, sleep-disordered breathing.

pressure settings (table 3).[35][45] In one study, the improvement in BP correlated as strongly with improvement in sleepiness as with OSA severity.[35] The study of Kaneko et al[44] compared CPAP and optimal medical therapy with optimal therapy alone in OSA patients with heart failure. The fall in daytime systolic BP was ~10 mm Hg after 4 weeks of treatment in the CPAP group. All three studies not only suggest that OSAHS contributes to hypertension but that a fall of this magnitude in BP could potentially reduce the risk of a coronary heart disease event by 37% and the risk of a stroke event by 56%.[45]

The pathogenic mechanism(s) linking SDB to hypertension are still not clear. Chronic hypoxia has been implicated, but a study comparing CPAP, sham CPAP and nocturnal oxygen showed no improvement in BP in the oxygen group, despite a significant improvement in mean saturations, a mean AHI (61 to 44) and reduction in time spent with saturations <90% in the oxygen group. The group receiving therapeutic CPAP spent a similar amount of time with saturations <90% to the oxygen group, but showed much greater improvements in mean AHI (66.1 to 3.4) and BP. This suggests that it is actual recurrent changes in saturation (or some other marker such as sleepiness) rather than mean saturations that are important in determining BP.[46] An alternative theory whereby OSAHS may cause hypertension is overactivity of the sympathetic nervous system. Repetitive episodes of upper airways obstruction in OSA, resulting in intermittent hypoxia, and large swings in intrathoracic pressure

(needed to overcome upper airways obstruction) have both been shown to trigger autonomic responses rather than hypoxia per se.[47] Markers of this sympathetic overactivity (eg, urinary norepinephrine concentrations) are raised in untreated OSAHS and can be reversed by CPAP therapy.[48] Even if the mechanisms are still being debated, the association between OSAHS and BP is now so clear that the US Joint National Committee on Hypertension puts OSAHS first on the list of the causes of secondary hypertension.[49]

SDB AND HEART FAILURE
SDB (in particular CSA) is common in heart failure, and these patients seem to have a worse prognosis than those without SDB.

Heart failure is becoming more common, affecting 1–3% of the UK population (rising to 10% in the elderly).[50] In 2006, Javaheri[51] found that 49% of patients with a left ventricular (LV) ejection fraction of <45% had severe SDB (defined as an AHI >44/h) with 37% having CSA and 12% OSA, with or without daytime tiredness (OSAHS) (table 4). The Sleep Heart Health Study found that heart failure was 2.38 times more prevalent in "mild–moderate" OSA than in "mild–no" OSAH.[30] Two previous studies suggested that SDB was present in 68%[52] and 72%[53] of patients with heart failure, but many of these patients were not optimally treated, in particular, β blocker use only in the range 0–33%. Wang and colleagues[54] followed 164

Table 3 Intervention studies on hypertension and obstructive sleep apnoea/hypopnoea syndrome

Study	Type	Subjects	Outcome	Comments
Pepperall et al[35] 2002	RCT	95	Mean BP fall 3.3 mm Hg	Sham CPAP. 4/52 of "Treatment". Some subjects on antihypertensive drugs
Becker et a[45]l 2003	RCT	32	Mean BP fall 9.9 mm Hg	Partially therapeutic sham CPAP in placebo group. 9/52 of "Treatment". All subjects had more severe disease. Two-thirds on antihypertensive drugs
Kaneko et al[44] 2003	RCT	24	Reduction in daytime systolic BP from a mean (SE) of 126 (6) mm Hg to 116 (5) mm Hg (p = 0.02)	Both groups matched for BMI/AHI/sleepiness scores/ejection fraction at baseline. Small numbers. All had poor LV function. No sham CPAP

AHI, Apnoea/Hypopnoea Index; BMI, body mass index; BP, blood pressure; CPAP, continuous positive airway pressure; LV, left ventricular; RCT, randomised controlled trial.

Table 4 Prevalence studies of heart failure and sleep-disordered breathing (SDB) (both obstructive sleep apnoea (OSA) and central sleep apnoea (CSA))

Reference	Study type	Subjects	Outcome	Comments
Sinn et al[53] 1999	RCA	450	In a cohort of patients with heart failure, 70% of subjects had SDB: ▶ 32% had predominantly CSA ▶ 38% had predominantly OSAHS	Patients recruited from referrals to sleep clinic, ie, selected for sleepiness. Not all patients had an ejection fraction <45%; initial diagnosis made clinically
Sahar et al[30] 2001	CS	1023	Relative odds (95% CI) for OSAHS vs no OSAHS in heart failure patients, 2.38 (1.22 to 4.62)	Screening of over 6000 subjects from general population
Ferrier et al[52] 2005	PC	53	SDB (AHI >10) demonstrated in 36 of 53 patients with heart failure (68%). OSA (53%) and CSA (15%)	Unselected patients with stable heart failure. High proportion of local ethnic subjects (Maori) and only men studied
Javaheri[51] 2006	PC	100	Severe SDB seen in 49% of patients who had a LVEF of <45%. 37% had CSA and 12% had OSA. Most were not sleepy	Patients recruited from cardiology clinics and primary care
Wang et al[54] 2007	PLC	218	In a cohort of patients with heart failure, 46% had definite SDB (45 subjects with CSA and 56 with OSA): ▶ 21% had predominantly CSA ▶ 25% had predominantly OSA	Death rate higher in the untreated SDB group, but these consisted of those who were unable/unwilling to use CPAP which may be a marker of poor compliance with other health behaviours. A mean 2.9-year follow-up

AHI, Apnoea/Hypopnoea Index; CPAP, continuous positive airway pressure; CS, cross-sectional; LVEF, left ventricular ejection fraction; OSAHS, obstructive sleep apnoea/hypopnoea syndrome; PC, prospective cohort; PLC, prospective longitudinal cohort; RCA, retrospective cohort analysis.

patients with heart failure over a mean of 3 years and found the death rate was significantly higher in the 37 untreated patients (AHI >15) than in the 113 patients with mild or no SDB (AHI <25/h), even after controlling for confounding factors (age, LV ejection fraction and New York Heart Association functional class), with 8.7 vs 4.2 deaths per 100 patient-years (p = 0.029).

One important aspect of SDB in heart failure is the occurrence of CSA (including CSR), which is estimated to occur in 40–63% of patients[51 53] and, when present, is associated with a particularly poor prognosis.[55] The pathophysiology (including effect on LV volume and the sympathetic nervous system) of CSA is important but beyond the remit of this paper; it has been described elsewhere.[56–58] OSAs can adversely affect cardiac function through large intrathoracic pressure swings occurring during respiratory efforts, increasing venous return and therefore ventricular afterload. Sympathetic activation, secondary to hypoxia and arousal, further increases BP and therefore myocardial oxygen consumption at the end of apnoeas. These adverse effects on LV function can be at least partially reversed by CPAP.[59 60] CPAP is now recommended in the acute treatment of cardiogenic pulmonary oedema irrespective of the presence of SDB; it works by improving intrathoracic fluid dynamics.[61] Standard treatments for symptomatic SDB associated with chronic heart failure are oxygen (for CSA) and CPAP (for OSA) in their own right, but evidence for their use in improving longer-term cardiovascular outcomes in non-sleepy patients is still equivocal. Nocturnal oxygen has been found to improve the AHI and some sympathetic parameters of patients with OSAHS,[62 63] but it has had no effect on quality of life[64] or LV ejection fraction.[65] (Both studies were short term and so could not look at mortality.) The results from trials with CPAP in chronic heart failure have been only slightly more promising, but by no means conclusive (table 5). Early studies showed an improvement in LV ejection fraction of up to 7%, but they all had small numbers in both the CPAP and conventional treatment arms, and many patients were not prescribed drugs (especially β blockers) according to current heart failure guidelines.[66–68] The largest trial so far to address sample size, adequate duration and maximising medical treatment is the multicentre CANPAP trial. Here, over 400 patients with congestive cardiac failure and SDB were randomised to best medical care or CPAP

in addition to best medical care. The improvement in LV ejection fraction in the CPAP arm was only 2.2%, but there was a statistically significant improvement in the 6 min walk test by 20 m, compared with a mean deterioration of 0.8 m in the optimal treatment group, over the same time period. The study was stopped early because of lower than expected enrolment rate, a falling primary event rate (because of advances in management of congestive cardiac failure), and concerns after increased mortality in the CPAP arm at 3 months. However, the early divergence in survival curves reversed after 18 months to favour the CPAP group, but the overall mortality was no different after 18 months. When assessing differences in ejection fraction, it is important to note that 70% of subjects in this trial were prescribed β blockers (compared with 20% or less in previous studies) which may render some of the beneficial effects of CPAP on sympathetic activation redundant.[69] Others suggest that, although the prevalence of CSA remains high in patients with LV dysfunction, there was no difference in prevalence in those prescribed β blockers compared with those not using β blockers, but this was a small study (n = 14).[70]

In summary, the current data do not support routine use of CPAP in chronic stable congestive cardiac failure unless there is co-existent OSAHS. Bi-level pressure support using newer devices that may more effectively treat both CSA and OSA (which often co-exist) are being evaluated (K E Lewis and M Arzt, personal communication).

OSAHS AND ARRHYTHMIAS
Cyclic variation in heart rate is typical in SDB. Apnoea and hypoxaemia-induced bradycardia is often followed by tachycardia during the post-apnoeic hyperventilation. This section reviews the current evidence for a strong association between arrhythmias and SDB and shows how treatment of the SDB can potentially abolish the arrhythmia.

The association between OSAHS and arrhythmias was first documented over 30 years ago. In the study of Guilleminault et al,[71] of 400 patients with OSAHS, 48% had documented cardiac arrhythmias, including sustained ventricular tachycardia in 2%, sinus arrest in 11%, second-degree atrioventricular block in 8%, and frequent premature ventricular contractions in 19%.

Table 5 Summary of the treatment of sleep-disordered breathing (SDB) in subjects with heart failure

Reference	Study type	Subjects	SDB type	Outcome	Comments
Naughton et al[68] 1995	RCT	29	CSA	Greater improvement in LVEF in the CPAP group (7.7%) than in the control group (−2.2%), p = 0.019	Groups similar at baseline. Study performed before widespread introduction of β blockers
Sinn et al[66] 2000	RCT	66	CSA	CSA subjects on CPAP had a 7% improvement in LVEF after 3 months and a relative risk reduction of 81% (+26% to 95%) in mortality after 4 years	2–4 year follow-up. Allowed for CPAP usage in controls and subjects with SDB. Small numbers in each group. Blinding not possible. Only 3-month echocardiogram changes
Artz et al[65] 2005	PCT	26	CSA	CSA subjects on CPAP had improved ventilatory efficiency and greater improvement in LVEF (to mean 35%) after 12 weeks, vs oxygen alone (mean LVEF 32%), p = 0.04	Looked at both ventilatory efficiency and echocardiographic changes. Comparison of CPAP and oxygen (no controls). Assignment to groups not randomised
Bradley et al[69] 2005	RCT	258	CSA	CPAP-treated group had an improvement in LVEF of 2.2% vs controls 0.4%, p = 0.02, and distance walked in 6 min (20.0 m vs −0.8 m, p = 0.016). No difference in primary endpoint of survival rates/time to transplant	Largest trial to date, powered to look at survival. Stopped early because of slow recruitment and falling primary event rate

CPAP, continuous positive airway pressure; CS, cross-sectional; CSA, central sleep apnoea; LVEF, left ventricular ejection fraction; OSAHS, obstructive sleep apnoea/hypopnoea syndrome; PC, prospective cohort; PCT, prospective controlled trial; PLC, prospective longitudinal cohort; RCT, randomised controlled trial.

Tracheostomy in 50 patients cured the OSAHS and abolished these arrhythmias. This study only looked at patients with OSAHS, and 246 patients were already prescribed amphetamine for daytime sleepiness, which is pro-arrhythmogenic. Other weaknesses of this study are that no distinction is made between patients with pre-existing cardiac disease. The 1995 study of Beckers et al[72] revealed that 7% of 239 patients with OSAHS had significant bradyarrhythmias, and, of these 17 patients, only one continued to experience bradyarrhythmias after CPAP therapy. Most of these patients had established or newly diagnosed cardiac abnormalities (hypertension, congestive cardiac failure, pulmonary hypertension), so any independent effect of OSAHS is difficult to establish. In a much smaller study, Tilkian et al[73] found bradyarrhythmias in five out of 15 patients with OSAHS. In most of these prevalence studies, arrhythmias were diagnosed in patients with OSAHS using simple 24–48 h cardiac Holter monitoring. However, in an elegant study (albeit again with small numbers), Simantirakis et al[74] inserted loop recording devices in 23 patients with OSAHS in whom other cardiac and pulmonary disease was first excluded with exercise tests, invasive electrophysiological studies, echocardiography, and lung function tests, and diabetes was also excluded. Over 2 months of continuous recording, 48% had significant rhythm disturbances, mostly occurring at night. They also noted a near-total failure of 48 h Holter monitoring to detect events during the same time period. On an intention-to-treat basis, there was a significant improvement in rhythm disturbances within 8 weeks, and all rhythm disturbances were abolished after 6 months of CPAP therapy, although the background prevalence of undiagnosed arrhythmias was not reported and there was no control group not receiving CPAP in the arrhythmia group, nor a description of CPAP usage.

Atrial fibrillation (AF) is another arrhythmia widely reported to be associated with OSAHS. A subgroup analysis of the Sleep Heart Health Study revealed a fourfold increase (odds ratio 4.02; 95% CI 1.03 to 15.74) in the prevalence of AF in subjects with an AHI >30 compared with patients with no SDB matched for age, sex, ethnicity and BMI.[75] Gami et al[76] used the Berlin Sleep Questionnaire to estimate the prevalence of OSAHS in 468 cardiology patients. They found that AF occurred in 49% of patients with OSAHS compared with 32% of general cardiology outpatients deemed at low risk of OSAHS but matched for age, gender and comorbidity (p = 0.0004). Sleep studies were only

performed in 44 patients (to validate the questionnaire, and the AF group had a larger neck size, an independent predictor of OSAHS). A smaller Finnish study from the same year, using objective sleep studies, disagreed and actually found no difference in the prevalence of OSAHS in 59 patients with lone AF compared with 56 controls matched for age, gender and cardiovascular morbidity.[77] Increased rates of recurrence of AF (after cardioversion) have been shown in inadequately treated patients with OSAHS compared with non-OSAHS and well-treated OSAHS patients.[78] The bradyarrhythmias in patients with OSAHS possibly reflect the reflex parasympathetic activity evoked by apnoeas, but AF may be caused by increased sympathetic activity after apnoeas or increased atrial size seen in patients with OSAHS.[47] Even if the causal mechanisms are not yet clear, the overlap between arrhythmias and OSAHS should at least prompt clinicians to ask about OSAHS symptoms in patients with cardiac rhythm disturbances.

OSAHS AND CORONARY ARTERY DISEASE

Patients with SDB have a high prevalence of CAD, and patients with CAD have a high prevalence of SDB.

The case–control study of Peker et al[79] looked at 62 patients with CAD and 62 patients without CAD, matched for age, sex, BMI, hypertension, hypercholesterolaemia, diabetes mellitus and current smoking. In a multiple logistic regression model, the presence of OSAHS remained independently associated with CAD (odds ratio 3.1vs 9.8 for current smoking and 4.2 for diabetes mellitus). The large Swedish cohort studies of Mooe et al[80 81] also suggested that OSAHS was much more prevalent in the 142 patients with established CAD (angiography) than in the 50 controls (with normal angiography). This was true for both men[80] and women,[81] even after adjustment for confounders.

Cross-sectional results from the population-based Sleep Heart Health Study[30] showed that, in patients with SDB, the multivariable-adjusted relative odds (95% CI) with self-reported coronary heart disease was a more modest 1.27 (0.99 to 1.62) (comparing upper with lower quartiles of severity of SDB).

Sudden cardiac death is more common in patients with OSAHS, after adjustment for confounders. Gami et al[82] looked at 112 subjects who had undergone polysomnography over a 5-year period; sudden death from cardiac causes (between the hours of midnight and 6 am) occurred in 46% of patients with

Review

Main messages

- ▶ Sleep-disordered breathing (SDB) consists of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and central sleep apnoea (CSA).
- ▶ OSAHS in particular appears to be an independent risk factor for cardiovascular disease and should be considered in patients with cardiovascular dysfunction, especially hypertension, as treatment with continuous positive airway pressure (CPAP) can lower blood pressure by as much as 10 mm Hg in symptomatic patients. A sleep history and referral would be useful in the workup of hypertensive patients, especially those with refractory hypertension.
- ▶ SDB (especially CSA) is common in patients with heart failure. These patients tend not to have the typical excessive daytime sleepiness of OSAHS. At present, only patients with OSAHS who have heart failure are recommended for CPAP therapy.
- ▶ The presence of OSAHS should be considered in patients with arrhythmias (especially atrial fibrillation or bradyarrhythmias), particularly those who are obese or hypertensive.
- ▶ Future research will be directed to improving cardiovascular outcomes by treating SDB (including CSA) more effectively in non-sleepy patients. Larger studies will be performed to see if improvements in blood pressure and endovascular outcome translate to mortality benefits in all forms of SDB.

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OSAHS compared with 21% of tired people with negative sleep studies (p = 0.01) and 16% of the general population (p<0.001). There was no excess of sudden cardiac death in the patients with OSAHS during waking hours. Mooe et al[83] followed 408 patients with verified CAD (on angiogram) for 5 years after they all had sleep studies. Subjects with SDB had an adjusted risk ratio of 1.70 (95% CI 1.2 to 2.5, p = 0.008) for the composite endpoint of death, cerebrovascular events and myocardial infarction. The authors concluded that SDB in subjects with known CAD is associated with a worse long-term prognosis.

Peker et al[84] followed 105 patients with OSAHS who were free from CAD at baseline for 7 years. CAD occurred in 16% compared with only 5% of 203 snorers without OSAHS free from CAD at baseline. This study also suggested a protective effect of CPAP within the OSAHS group: CAD developed in 25% of the 65 incompletely treated patients, but in only one (4%) of the 26 well-treated patients.[84] Such studies are not prospective randomised trials and are weakened by the possibility that poor acceptance/compliance with CPAP may be a marker for poor compliance with lifestyle modifications and other treatments shown to reduce cardiovascular risk. A smaller but much longer (10 year) prospective study showed equal cardiac death rates (four of 25) in people with established CAD whether they had OSAHS or not, but groups were not matched for age, BMI, hypertension, etc.[85] OSAHS can cause CAD indirectly via hypertension or directly by generation of free radicals, activating endovascular inflammation during the recurrent episodes of deoxygenation–oxygenation.[12]

To summarise, there is an association between OSAHS and anatomical CAD, but the clinical significance and effect of CPAP treatment remain unclear.

CONCLUSIONS

Many cardiovascular diseases are independently associated with SDB. Early cross- sectional and observational studies suggested links, but were open to selection and reporting bias and may not have adequately controlled for important confounders such as obesity and hypertension. However, well-designed randomised controlled (intervention) trials have now established that OSAHS is an independent and treatable risk factor at least for hypertension. Further prevalence studies and now interventional trials suggest that SDB, and OSAHS in particular, may cause and exacerbate other cardiovascular dysfunction, particularly cardiac failure, arrhythmias and possibly CAD.

The mechanism(s) behind these associations are biologically plausible and, together with the direction of cause-and-effect, are still being elucidated.

Awareness of the association of cardiovascular disease and SDB will prompt the general practitioner to look for both illnesses when presented with one of them. There is no doubt that CPAP and other treatments for SDB will make symptomatic patients who happen to have a cardiac disease feel better. It may be that CPAP will be used to improve cardiac outcomes in their own right, and randomised controlled trials of CPAP in patients with cardiovascular risk and OSAHS but who are not sleepy are being designed.

TRUE (T)/FALSE (F) QUESTIONS (ANSWERS AFTER THE REFERENCES)

(A) OSAHS can be diagnosed from a history of irregular breathing at night.

(B) OSAHS is an established independent risk factor for hypertension as well as heart failure, stroke, arrythmias and coronary artery disease.

(C) Treatment of OSAHS with CPAP can cause a drop in blood pressure.

(D) All patients with heart failure and sleep disordered breathing should be treated with CPAP.

(E) There is growing evidence linking OSAHS and arrythmias.

Competing interests: None.

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Answers

(A) FALSE (OSAHS requires a positive sleep study and daytime sleepiness to make a diagnosis).
(B) FALSE (At present OSAHS is only an independent risk factor for hypertension).
(C) TRUE (Potentially up to 8–10 mm Hg in some hypertensive patients).
(D) FALSE (Treatment is only recommended in those who have coincidental OSAHS).
(E) TRUE (Important, as treatment of underlying sleep disorders can abolish the arrhythmia).

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