FEATURE

Cardiovascular consequences of sleep apnoea

Beyond its respiratory manifestations

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Sleep apnoea remains an under-recognised condition. Although it presents with a wide range of symptoms, both respiratory and nonrespiratory, its most serious associations are heart related. Early identification and treatment of people with sleep apnoea has the potential to not only improve quality of life but also reduce the risk of cardiovascular disease.

Key points

- **Sleep apnoea is a common but remains an under-recognised condition.**
- **The most serious associations of sleep apnoea are cardiovascular.**
- **Preliminary studies suggest that treatment of sleep apnoea may reduce the risk of cardiovascular disease.**
- **Further studies are required before the treatment of sleep apnoea can be incorporated into cardiovascular guidelines.**

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Central sleep apnoea (Cheyne-Stokes respiration) was the earliest reported sleep-breathing disorder, first noted in the 19th century in a patient with a stroke who clearly also had heart failure. Obstructive sleep apnoea (OSA) was recognised much later with the observation of cases of obese patients who had excessive sleepiness, similar to the description of the central character by Charles Dickens in his novel *The Pickwick Papers*. It was not until 1965 that the pathophysiology of OSA was recognised with snoring, upper airway obstruction and associated interrupted breathing, and heart rate and blood pressure changes.[1]

Sleep-disordered breathing represents a range of clinical disorders, from simple snoring and upper airway resistance syndrome (increased respiratory effort without airway obstruction) to its more serious forms, including OSA (airway obstruction associated with increased respiratory effort) and central sleep apnoea (apnoea without an increase in respiratory effort). Central sleep apnoea is a consequence of heart failure except in healthy people breathing at high altitude and in a minority of patients who have had a stroke. Patients can have both central and obstructive apnoeas and the type of sleep-disordered breathing can vary within a night, from night to night, and in response to changes in heart failure status.

Given that we typically spend a third of our lives asleep, the repetitive haemodynamic changes that result from airway obstruction may have adverse long-term cardiovascular consequences. This article discusses the clinical features, diagnosis and cardiovascular associations of sleep apnoea, with a focus on OSA, the most common form of sleep-disordered breathing.

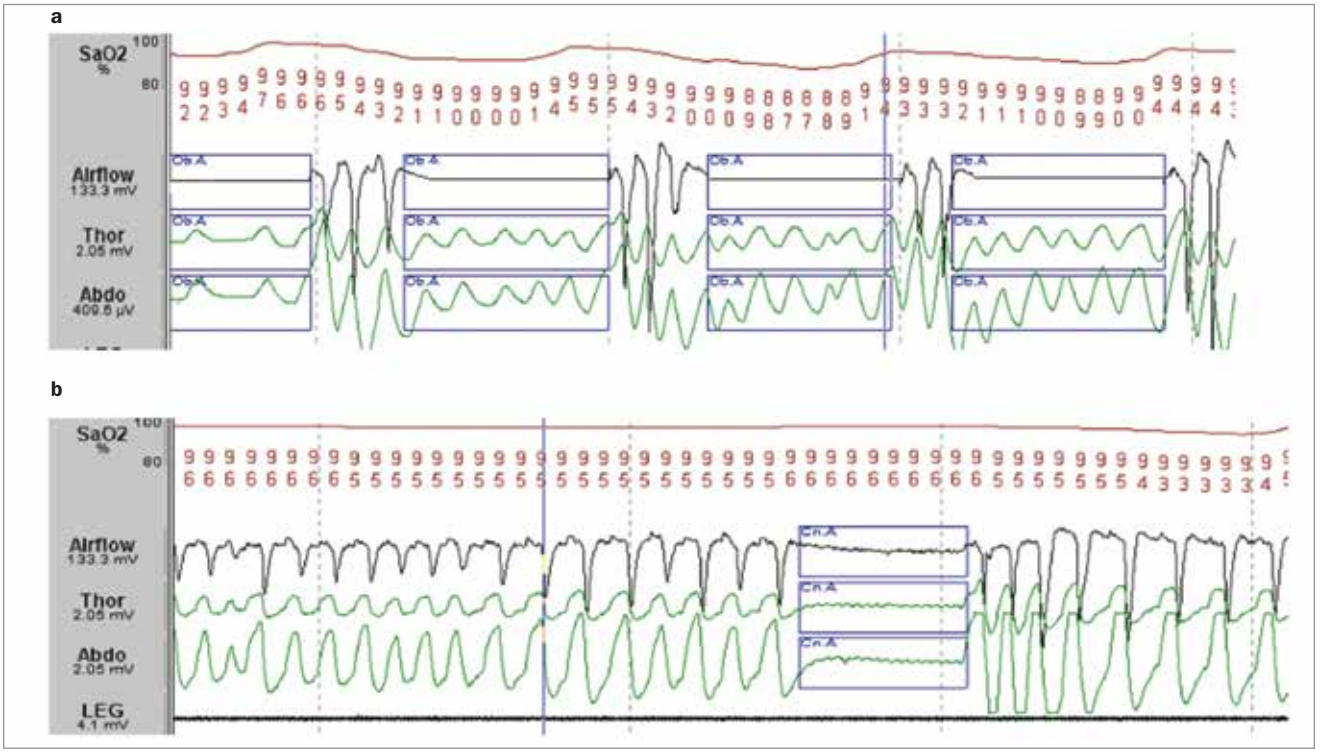

Figure 1. Examples of obstructive sleep apnoea (a, top) and central sleep apnoea (b, bottom) diagnosed on a sleep study.

Identifying patients with sleep apnoea

OSA affects men and women of all ages but the prevalence increases with age, affecting up to one in four men and one in eight women between the ages of 39 and 65 years.[2] The prevalence of OSA is two- to threefold higher in individuals 65 years or above compared with those aged between 30 and 64 years.[3] It is expected to increase in the future due to an ageing population and because obesity, which is strongly associated with OSA, is increasing dramatically in both children and adults. Although patients with sleep apnoea typically present with respiratory symptoms, including snoring, choking, witnessed apnoeic episodes, early morning headaches and daytime sleepiness, the most serious associations are cardiovascular.[4] Most patients with OSA in community-based studies are not sleepy and many have nonspecific symptoms, such as fragmented sleep, general fatigue, dry mouth, sore throat or nocturia. Nocturnal palpitations (due to post apnoeic tachycardia) are common, as are atrial arrhythmias, particularly atrial fibrillation. Awakening with shortness of breath due to choking is typical in OSA but classic paroxysmal nocturnal dyspnoea is a symptom of central not obstructive sleep apnoea.

It is important for GPs to identify people who are at risk of OSA because these people often first present to their GP for a routine medical check up. Apart from age and obesity, other known risk factors include male gender, large neck circumference, narrowed upper airway due to nasal obstruction (hay fever, septal deviation, adenotonsillar hypertrophy) and faciomaxillary abnormalities, such as maxillary constriction, smoking, high alcohol intake and use of sedatives. OSA is commonly associated with risk factors for cardiovascular disease (CVD), such as hypertension, insulin resistance and atherogenic dyslipidaemia, and with known heart disease.

Diagnosing sleep apnoea

As a large proportion of patients with OSA are either asymptomatic or present with nonspecific symptoms,[5] testing of 'high-risk' patients should be considered. Currently, the diagnosis of OSA is based on the gold-standard overnight sleep study (polysomnography). This test is usually conducted in a hospital or sleep laboratory but can be carried out as an unattended ambulatory study. The parameters measured during the study include sleep stages (by electroencephalography), respiratory effort (as evidenced by chest and abdominal wall movement), nasal and oral airflow, oxygen saturation, heart rate and rhythm, body position and sound (Figure 1). These parameters allow us to determine the severity of OSA using the apnoea–hypopnoea index (AHI), which is defined empirically as the number of obstructive respiratory events per hour of sleep (mild OSA, AHI 5 to 15/h; moderate, 15 to 30/h; severe, >30/h). However, such cut offs are arbitrary, almost certainly over simplistic, and may not be appropriate for the cardiovascular consequences of OSA.

One of the key issues in diagnosing OSA is the lack of access to the diagnostic sleep study, with waiting periods between three and 16 months in Australia.[6] Given these challenges, alternative diagnostic tools, such as the ambulatory (home-based) sleep study, have been developed and may be a useful screening tool to detect (rather than exclude) OSA. Currently, GPs can refer patients for sleep studies, with the results being reviewed by qualified sleep medicine physicians.

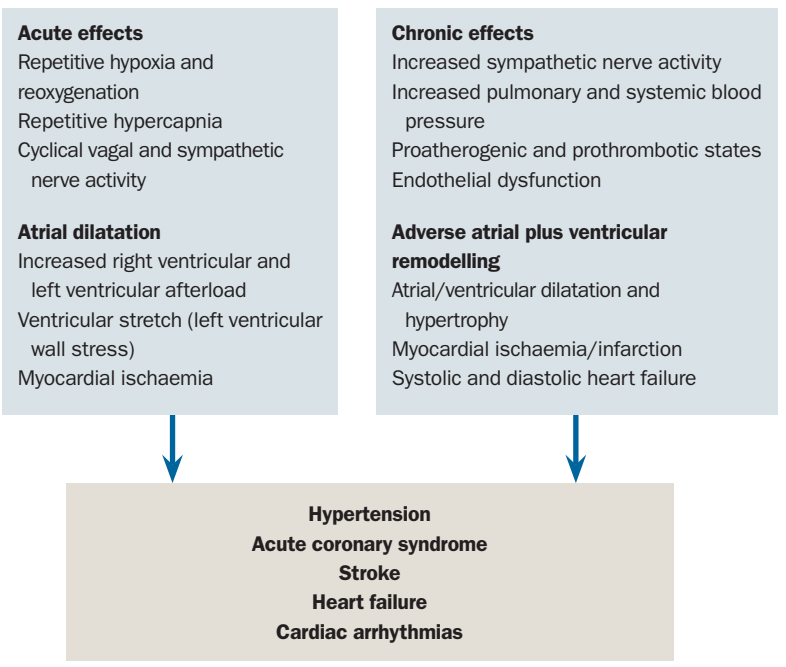

Figure 2. Adverse effects of sleep apnoea.
Adapted from: Chan K, Wilcox I. Expert Rev Cardiovasc Ther 2010; 8: 981-994.[7]

Adverse pathophysiological effects of sleep apnoea

Acute adverse pathophysiological effects from repeated obstructive apnoeic episodes are considered to be the result of three main pathological changes: hypoxaemia; the generation of excessive negative intrathoracic pressure against an occluded airway and its effects on cardiac function; and repeated arousals from sleep.[7] These changes include both vagal and sympathetic nervous system activation, with surges in heart rate and blood pressure and increased atrial and ventricular wall stress, myocardial workload and myocardial oxygen demand (and possibly myocardial ischaemia), as well as decreased myocardial contractility and cardiac output.[4,7]

Long-term adverse effects include chronic autonomic nervous system dysregulation with sympathetic activation, development of systemic (and pulmonary) hypertension, proatherogenic and prothrombotic states, and endothelial dysfunction.[4,7] These acute and chronic adverse changes are summarised in Figure 2, and may result in the development of CVD.[7]

Associations between sleep apnoea and CVD

Given the adverse acute and chronic effects of repeated apnoea, it is intuitive that sleep apnoea may be associated with a wide spectrum of cardiovascular disorders, including systemic hypertension, acute coronary syndrome, stroke, heart failure and cardiac arrhythmias (Figure 2). Studies supporting the association between sleep apnoea and cardiovascular disorders are briefly reviewed below.

Hypertension and sleep apnoea

A key part of the pathophysiology of sleep apnoea is the influence of the sympathetic nervous system on acute blood pressure changes during sleep and wakefulness as shown in a study by Somers and colleagues.[8] In this study, apnoeas were associated with cyclical increased sympathetic nerve activity, resulting in increased blood pressure (Figure 2). In addition, sympathetic nerve activation persisted during wakefulness, and treatment of OSA with continuous positive airway pressure (CPAP) resulted in diminution in sympathetic nerve activity.

Several population-based studies have also shown an association between OSA and systemic hypertension, independent of age, obesity or other confounding factors, with up to a threefold increased risk of hypertension in patients with severe OSA compared with no OSA.[9,10] Sleep apnoea is commonly associated with drug-resistant hypertension and complications of hypertension, such as heart and renal failure.

Vascular disease and sleep apnoea

Cardiac events and sleep apnoea

The association between nocturnal myocardial ischaemia and OSA was first reported by Franklin and colleagues in a small series of 10 patients in which treatment with CPAP abolished nocturnal angina.[11] A subsequent prospective study showed patients with untreated severe OSA had a threefold increased risk of both cardiovascular mortality and nonfatal cardiovascular events compared with healthy controls and those with OSA treated with CPAP, even after adjusting for potential confounders.[12]

Stroke and sleep apnoea

The association between OSA and ischaemic stroke is also significant, with a reported increased risk of at least twofold in major studies.[13,14] In the largest study to date, there was a strong adjusted association between ischaemic stroke and OSA severity.[14] Even mild OSA was associated with an increased risk of stroke. Possible mechanisms for this association include apnoea-induced atrial fibrillation (see discussion below), hypertension, heart failure, hypercoagulability, local vibrational injury to the carotid artery and proinflammatory state, all of which result in increased risk of atherosclerotic plaque rupture and thromboembolism.[7,15] In fact, any patient presenting with an unexplained thromboembolic event should probably be considered for possible OSA.[7]

Heart failure and sleep apnoea

OSA confers an approximately twofold increased risk of impaired cardiac function and heart failure.[16,17] A high proportion of patients

with heart failure have central sleep apnoea, and both obstructive and central sleep apnoea often coexist in these patients.[18] Furthermore, the presence of severe central sleep apnoea in patients with heart failure is associated with increased mortality, independent of functional class and cardiac function.[19]

Cardiac arrhythmias and sleep apnoea

Atrial fibrillation and sleep apnoea

There is compelling evidence supporting the association between OSA and risk of atrial fibrillation. A series of studies has shown OSA more than doubles the risk of atrial fibrillation.[20,21] In addition, the burden of atrial fibrillation (frequency and duration) has also been reported to be associated with OSA severity.[22] Reasons for this include both vagal and sympathetic nerve overactivity as well as atrial dilatation and remodelling due to the acute and chronic effects of repetitive obstructive apnoeas. A recent study demonstrated atrial enlargement and more extensive atrial fibrosis in patients with OSA compared with those without OSA.[23]

Bradyarrhythmias and sleep apnoea

Studies exploring the prevalence of bradyarrhythmias in patients with OSA have yielded conflicting results, with some demonstrating an increased risk[24,25] and others showing no such increase in risk.[20] A possible reason for these disparate results is the variable extent of cardiac monitoring used in the various studies so that significant bradyarrhythmias may have been missed with brief periods of monitoring.[7]

Sudden cardiac death and sleep apnoea

Seppälä and colleagues first reported that a history of habitual snoring obtained from relatives of deceased subjects was associated with a fourfold increased risk of early morning cardiovascular death compared with the general population in Finnish men.[26] This is supported by a subsequent study reporting a nocturnal predilection for sudden cardiac death in patients with OSA.[27] More recently, the severity of OSA and nocturnal desaturation was reported to predict risk of sudden cardiac death.[28] The mechanism of death may be due, in part, to an increased risk of ventricular arrhythmias in patients with OSA, with one study reporting a threefold risk of nonsustained ventricular tachycardia.[20] However, other plausible explanations include nocturnal myocardial ischaemia, sinus arrest, or heart block occurring as a result of OSA, leading to sudden death.[7]

Impact of OSA therapy on CVD

Although OSA has been reported to be associated with a range of cardiovascular disorders, it remains to be proven whether treatment of OSA will reduce the burden of CVD. Apart from lifestyle changes and weight loss, CPAP has remained the cornerstone treatment of OSA for over 30 years since its development by Australian researcher Colin Sullivan.[29] The current evidence on the impact of OSA therapy on the various cardiovascular disorders is reviewed below and summarised in the Table.[11,12,30-44]

Hypertension

The effect of CPAP therapy for OSA on blood pressure measurements has been reported, with studies showing a significant reduction in blood pressure in patients randomised to therapeutic CPAP compared with those randomised to subtherapeutic (sham) CPAP.[30,31] Importantly, the beneficial blood pressure lowering effect was seen both during sleep and wakefulness. However, these patients included normotensive subjects, and a study assessing hypertensive, nonsleepy patients with OSA failed to find a significant blood pressure improvement with CPAP therapy.[32]

Vascular disease

The evidence for CPAP therapy in reducing vascular events is more limited. As mentioned earlier, treatment with CPAP abolished nocturnal angina and reduced the frequency of nocturnal ST-segment changes in a small case series.[11] In a prospective observational study, patients with untreated severe OSA had higher rates of mortality and nonfatal cardiovascular events compared with patients with OSA treated with CPAP and healthy controls.[12] However, given the nonrandomised nature of these studies, there may have been potential confounders that influenced the results. Studies have also evaluated the effect of CPAP therapy on cardiovascular events and physical function following stroke, with conflicting results reported.[33,34] Hence, further randomised studies are required and are currently underway to evaluate the effect of CPAP therapy on cardiovascular events.

Heart failure

Nonrandomised and randomised studies have reported beneficial effects with CPAP therapy in patients with OSA and heart failure, with improvements in cardiac function and mortality seen.[35-37] However, in a randomised study involving patients with central sleep apnoea and heart failure, CPAP therapy did not result in improved survival despite improvements in cardiac function and nocturnal oxygen saturation.[38] A significant limitation of this study was that fixed pressure CPAP was much less effective in people with central sleep apnoea than in those with OSA; the AHI was only reduced from a mean of 40/h to 20/h for those treated with CPAP; and there was an undertreatment effect. A subsequent posthoc analysis of this study showed improved outcomes in people who achieved an AHI of less than 15/h when treated with CPAP therapy.[45] Hence, further randomised trials with hard clinical endpoints beyond the AHI metric are required. A more effective treatment for central sleep apnoea may be adaptive servoventilation, which is the subject of several contemporary randomised trials in heart failure (such as Serve-HF).

Cardiac arrhythmias

The potential efficacy of CPAP therapy in preventing recurrence of atrial fibrillation was first suggested by an observational study that showed treatment of OSA with CPAP therapy resulted in complete resolution of atrial fibrillation up to six months later.[24] This was supported by a study assessing the risk of atrial fibrillation recurrence

Table. Impact of sleep apnoea therapy on cardiovascular disease: a summary of the major studies to date

	Study design	Summary of results
Hypertension		
Pepperell, et al.[30]	Randomised – therapeutic versus sham CPAP	Small reductions in systolic and diastolic blood pressure, during both sleep and wakefulness
Becket, et al.[31]	Randomised – therapeutic versus subtherapeutic CPAP	10 mmHg reduction in mean, systolic and diastolic blood pressure, during both sleep and wakefulness
Robinson, et al.[32]	Randomised – therapeutic versus subtherapeutic CPAP	No effect on blood pressure lowering
Cardiac disease		
Franklin, et al.[11]	Observational	Reduction in nocturnal myocardial ischaemic events after CPAP treatment
Marin, et al.[12]	Prospective, observational	Lower rates of mortality and cardiovascular events in OSA-treated patients and healthy controls versus patients with untreated OSA
Stroke		
Martínez-García, et al.[33]	Prospective, observational	Reduction in future vascular events in patients following ischaemic stroke treated with CPAP therapy versus patients who did not tolerate CPAP
Hsu, et al.[34]	Randomised – CPAP versus no CPAP	No improvement in physical function following stroke, although CPAP compliance was poor
Heart failure		
Kaneko, et al.[35]	Randomised – CPAP versus no CPAP	Reduction in blood pressure and improvement in cardiac function
Mansfield, et al.[36]	Randomised – CPAP versus no CPAP	Improvement in cardiac function and quality of life. No changes in blood pressure
Wang, et al.[37]	Prospective, observational	Increased mortality in untreated patients with moderate to severe OSA
Bradley, et al.[38]	Randomised - CPAP versus no CPAP	In patients with heart failure and central sleep apnoea, CPAP improved nocturnal oxygen saturations, cardiac function and six-minute walk test, but did not improve survival
Atrial fibrillation		
Kanagala, et al.[39]	Observational	Untreated patients with OSA had a higher rate of AF recurrence after electrical cardioversion than treated patients with OSA and controls
Fein, et al.[40]	Prospective, observational	CPAP therapy was associated with lower rate of AF recurrence after catheter ablation versus patients with untreated OSA
Naruse, et al.[41]	Prospective, observational	CPAP therapy was associated with lower rate of AF recurrence after catheter ablation versus patients with OSA not treated with CPAP
Bradyarrhythmias		
Grimm, et al.[42]	Observational	Reduction in significant bradyarrhythmic events with CPAP therapy
Simantirakis, et al.[43]	Observational	Reduction in significant bradyarrhythmic events with CPAP therapy
Ventricular ectopy		
Ryan, et al.[44]	Randomised – CPAP versus no CPAP	Reduction in ventricular ectopy during sleep in patients with OSA and heart failure treated with CPAP therapy versus control patients

Abbreviations: AF = atrial fibrillation; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnoea.

after electrical cardioversion, which reported that recurrence was significantly more likely in patients untreated or receiving inadequate treatment for OSA compared with either OSA-treated patients or controls.[39] More recently, studies have also shown the increased risk of recurrence of atrial fibrillation after catheter ablation in patients with known OSA was normalised in those treated with CPAP therapy.[40,41] Randomised studies are currently underway to evaluate the efficacy of CPAP therapy in preventing atrial fibrillation.

Data supporting the role of CPAP therapy in preventing bradyarrhythmias or sudden cardiac death are more limited. Observational studies have shown that CPAP therapy abolishes the bradyarrhythmias in most patients with OSA.[42,43] Interestingly, patients with OSA and significant nocturnal bradyarrhythmias had either normal or mild abnormalities in sinus node function and AV conduction. Furthermore, these mild conduction abnormalities were completely reversible with atropine administration in most patients, which further supports the concept of increased parasympathetic tone in the pathophysiology of bradyarrhythmias in patients with OSA.[46]

To date, there has only been one randomised study reporting reduction in ventricular ectopy with CPAP therapy in patients with heart failure and OSA.[44] The role of OSA therapy may be important in people with implanted defibrillators in whom atrial fibrillation can trigger inappropriate defibrillator discharges or to reduce the risk of ventricular tachycardia triggering an appropriate shock.[47] Hence, further studies on the role of CPAP therapy in the management of cardiac arrhythmias are required.

Who to treat?

Traditionally, the indications for OSA therapy are daytime sleepiness and prevention of driving-related accidents due to hypersomnolence. Given the link between OSA and CVD, as well as the accumulating evidence on the cardiovascular benefits of treating OSA, management of this condition may need to be incorporated as part of the treatment guidelines for CVD, particularly in high-risk patients.

Conclusion

Sleep apnoea is prevalent and doctors should remain vigilant in diagnosing the condition, particularly in at-risk patients. Although people with OSA present predominantly with respiratory symptoms, the most serious associations of OSA are cardiovascular. There is increasing evidence that treatment of OSA may reduce the burden of CVD; however, further studies are required to establish the role and cost effectiveness of this. **CT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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