Obstructive sleep apnoea and cardiovascular disease

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Abstract
Obstructive sleep apnoea (OSA) leads to both acute and chronic physiological effects on the cardiovascular system. There is now a large amount of evidence showing that OSA is independently associated with a wide spectrum of clinical cardiovascular disease (CVD). Evidence for a causative effect of OSA is strongest for hypertension, but is weaker for other cardiovascular disorders. Large prospective trials are ongoing and when results become available the link between OSA and CVD is likely to be strengthened. Treatment of OSA with continuous positive airway pressure has been shown to improve blood pressure, particularly in those with hypertension, and also left ventricular ejection fraction in those with congestive heart failure. Given the high prevalence of OSA in the community and its effects on the cardiovascular system, symptoms of this disorder should be sought in patients being investigated or treated for CVD. (Intern Med J 2004; 34: 420–426)

Key words: obstructive sleep apnoea, cardiovascular disease, continuous positive airway pressure.

INTRODUCTION
Obstructive sleep apnoea (OSA) is characterized by repetitive collapse of the upper airway during sleep. It is estimated to occur in 24% of men and 9% of women aged 30–60 years, with 4 and 2%, respectively, having symptoms of excessive daytime sleepiness and thus meeting the criteria for OSA syndrome. Patients with OSA have a high prevalence of cardiovascular disease (CVD). This is partly related to OSA patients having a high rate of comorbidities associated with vascular disease, particularly obesity; however, there is now increasing evidence that OSA is an independent risk factor for a variety of CVD.

DEFINITIONS
The severity of OSA is usually quantified by counting the total number of apnoeas and hypopnoeas and dividing this by the time asleep. This gives an apnoea-hypopnoea index (AHI), which is, therefore, the average number of respiratory events per hour of sleep. An apnoea is defined as the complete cessation of airflow for ≥10 s, whereas a hypopnoea is a significant reduction in airflow for ≥10 s, usually associated with either an arousal from sleep or a small dip in oxygen saturation.

PHYSIOLOGICAL EFFECTS OF OBSTRUCTIVE SLEEP APNOEA
A variety of adverse physiological effects occur as a result of the repetitive obstructive apnoeas and hypopnoeas that characterize OSA. Upper airway obstruction during respiration leads to the generation of excessively negative intrathoracic pressure, which has significant deleterious haemodynamic consequences (Table 1). Subsequent hypoxia and arousal from sleep have further adverse effects, particularly activation of the sympathetic nervous system (Fig 1). These haemodynamic stressors, which occur on a nightly basis, can potentially lead to chronic effects on the cardiovascular system. Table 2 summarizes the chronic physiological changes that have been shown in patients with OSA. The hypothesis that OSA is a cause of CVD is thus biologically plausible; however, the conclusions drawn in the present review are based on the clinical evidence. The current clinical literature is reviewed below.

GENERAL CARDIOVASCULAR DISEASE
The largest epidemiological community-based study of OSA and CVD is the Sleep Heart Health Study. This study has recruited and performed full polysomnography on 6424 subjects across the USA. The primary aim of the study is to follow participants prospectively to determine the effect of sleep-disordered breathing on the development of CVD. Other than being prospective in design, the strengths of the study are its size and its community-based population. It is also collecting data on all types of CVD. Results from longitudinal follow up are not yet available; however, a cross-sectional analysis of the prevalence of CVD at study entry has been
Obstructive sleep apnoea reported.

Participants have been divided into quartiles based on their AHI. After adjusting for confounding variables, those in the highest quartile (AHI > 11/h) have a 1.42-fold greater risk of reporting a history of any CVD compared with those in the lowest quartile (AHI < 1.4/h) (Table 3).

HYPERTENSION

There is now very good evidence on multiple levels that OSA is a cause of hypertension. First, the hypothesis is biologically plausible. Increased sympathetic nervous system activity, reduced baroreceptor responsiveness and endothelial damage and dysfunction (Table 1) all result from chronic OSA and all are implicated in the pathogenesis of hypertension.

Second, animal studies have demonstrated that OSA can cause sustained hypertension. Studies in which rats were exposed to repetitive intermittent hypoxia (as seen in OSA) and dogs with experimentally induced OSA have shown significant blood pressure elevations during both daytime and night-time.

Third, there is now a wealth of literature on human subjects. Many studies have shown an association between OSA and hypertension, usually independent of associated confounding variables such as age, sex, obesity, smoking and alcohol intake. However, the strongest evidence comes from a recent, large community-based prospective study. Peppard et al. showed that the presence of OSA at baseline was independently associated with the development of hypertension during a 4-year follow-up period. Furthermore, there was a dose–response relationship with the incidence of hypertension being higher in those with more severe OSA. For those with an AHI of >15 events per hour, there was a 2.89-fold greater chance of developing hypertension compared with those with no events per hour. This was independent of any known confounding variable.

OSA might also play a causal role in patients with hypertension that is refractory to standard blood pressure treatment. It has recently been demonstrated

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**Table 1** Acute physiological cardiovascular effects of obstructive sleep apnoea

1. Exaggerated negative intrathoracic pressure with airway obstruction
   - Initial inhibition then progressive increase in sympathetic outflow
   - Increased venous return to right ventricle
   - Decreased left ventricular preload
   - Increased left ventricular afterload
   - Decreased stroke volume during apnoea
   - Increased stroke volume with relief of obstruction

2. Hypoxia
   - Either vagal or sympathetic stimulation:
     - with airflow – sympathetic predominance
     - without airflow – vagal predominance
   - Ischaemia – reperfusion injury of endothelial cells

3. Arousal from sleep
   - Increased sympathetic activity
   - During apnoea – blood pressure decreases with varying effect on heart rate
   - Following apnoea – blood pressure and heart rate increase significantly

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**Figure 1** Superimposed recordings of the electro-oculogram (EOG), electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (EKG), sympathetic nervous system activity (SNA), respiration (RESP) and blood pressure (BP) during rapid eye-movement sleep in a patient with obstructive sleep apnoea. BP surges at the end of the apnoeic periods, peaking during arousal (as indicated by the increase in muscle tone; see arrows). Republished with permission from Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnoea. J Clin Invest 1995; 96: 1897–1904 (permission conveyed through Copyright Clearance Centre, Inc.).

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**Table 2** Chronic physiological effects of obstructive sleep apnoea

1. Increase in 24-h sympathetic nervous system activity
2. Decrease in heart rate variability
3. Endothelial damage and dysfunction
4. Platelet activation and increase in blood coagulability
5. Insulin resistance (controversial)
that OSA is very common in those with hypertension that is difficult to control, with a reported prevalence of 83% in a large hypertension clinic. Symptoms suggestive of OSA should therefore be sought in these patients.

However, the association between OSA and hypertension does not persist in the elderly. In subgroup analyses of the Sleep Heart Health Study and another large community cohort study, no increased risk for hypertension was seen in those aged more than 65 years. This could mean that other causes of hypertension are more important than OSA in the elderly and any association is attenuated, or it could be the result of a survivor effect— that is, the elderly subjects sampled in those studies might be inherently less susceptible to the adverse effects of OSA than young to middle aged people.

Finally, there is evidence showing an improvement in blood pressure following treatment of OSA. Continuous positive airway pressure (CPAP) applied via nasal or oro-facial mask is the gold standard treatment for OSA. If adequate positive pressure is applied, upper airway collapse can be prevented. Randomized controlled studies looking at the effect of CPAP therapy on 24-h blood pressure in general have yielded modest but significant reductions in blood pressure. Arousal from sleep frequently occurs with each cuff inflation. Studies that use cuff inflation techniques are hindered by the fact that arterial pressure is underestimated as only a minority of patients in these studies have been hypertensive and blood pressure was measured by automatic cuff inflation. Studies that use cuff inflation techniques are hindered by the fact that cuff inflation techniques are hindered by the fact that arterial pressure is underestimated as only a minority of patients in these studies have been hypertensive and blood pressure was measured by automatic cuff inflation. Studies that use cuff inflation techniques are hindered by the fact that arterial pressure is underestimated as only a minority of patients in these studies have been hypertensive and blood pressure was measured by automatic cuff inflation. This study also had a much higher proportion (65%) of patients with a history of hypertension. Patients in the active CPAP treatment arm achieved a reduction in mean systemic blood pressure of 9.9 mmHg over a 9-week period. This is a substantial blood pressure reduction and would be predicted to reduce stroke risk by 56% and cardiac event risk by 37%.

There are, however, important qualifying points about these two positive studies. First, the beneficial effect of CPAP on blood pressure could be limited to those with severe OSA. In the study by Becker et al., most subjects had severe OSA, with a mean AHI of 64 respiratory events per hour. There was a wider range of OSA severity in the study by Peppard et al., but the beneficial effect of CPAP on blood pressure was seen mostly in those with an AHI of >33 events per hour. These findings are in keeping with other studies looking at the effect of CPAP on blood pressure in those with mild

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**Table 3** Adjusted relative odds of prevalent cardiovascular disease according to quartile of sleep-disordered breathing variables

<table>
<thead>
<tr>
<th>Quartile</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arousal index</td>
<td>Full model</td>
<td>1.0</td>
<td>0.99</td>
<td>1.24</td>
<td>1.30</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td>(0.77–1.28)</td>
<td>(0.97–1.59)</td>
<td>(1.01–1.67)</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Parsimonious model</td>
<td>1.0</td>
<td>0.98</td>
<td>1.28</td>
<td>1.42</td>
<td></td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td>(0.77–1.24)</td>
<td>(1.02–1.61)</td>
<td>(1.13–1.78)</td>
<td>0.0070</td>
<td></td>
</tr>
<tr>
<td>Per cent of sleep time O&lt;sub&gt;2&lt;/sub&gt; &lt; 90%</td>
<td>Full model</td>
<td>1.0</td>
<td>0.91</td>
<td>1.05</td>
<td>1.21</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td>(0.71–1.17)</td>
<td>(0.82–1.34)</td>
<td>(0.95–1.55)</td>
<td>0.5100</td>
<td></td>
</tr>
<tr>
<td>Parsimonious model</td>
<td>1.0</td>
<td>0.90</td>
<td>1.10</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td>(0.71–1.13)</td>
<td>(0.88–1.38)</td>
<td>(1.00–1.55)</td>
<td>0.4500</td>
<td></td>
</tr>
</tbody>
</table>

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‡ The full model included the following covariates: age, race, sex, smoking status, number of cigarettes smoked per day (for current smokers), self-reported diabetes, self-reported hypertension, use of antihypertension medications, systolic blood pressure, body mass index, total cholesterol and high-density lipoprotein cholesterol. The parsimonious model excluded five variables from this list: number of cigarettes smoked per day, self-reported diabetes, self-reported hypertension, use of antihypertension medications, systolic blood pressure, body mass index, total cholesterol and high-density lipoprotein cholesterol.

§ For a linear trend from the 1st to the 4th quartiles.

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OSA. Barnes et al. recruited patients with an AHI between 5 and 30 and were unable to show any change in 24-h blood pressure following 8 weeks' treatment with CPAP.17 Blood pressure was measured with automatic cuff inflation and the number of patients completing the study was small (n = 28). A much larger trial specifically designed to assess the effect of CPAP on blood pressure in mild to moderate OSA is thus required.

It is also unclear what role the symptoms of OSA play in the responsiveness of blood pressure to CPAP treatment. All subjects in the studies by Becker et al. and Pepperell et al. rated themselves as being excessively sleepy.13,16 In contrast, Barbe et al. looked at the effect of CPAP in those with severe OSA who did not complain of significant daytime sleepiness.18 No change in blood pressure (measured by automatic cuff inflation) was seen over the 6-week study period in either the treated or placebo groups, although the authors did note that their sample size was small (n = 55) and involved normotensive persons. Nevertheless, the relevance of the symptoms of sleepiness to blood pressure responsiveness with CPAP needs further exploration.

The scale of evidence linking OSA to the development of hypertension is now comprehensive, ranging from mechanistic and animal studies to independent and prospective associations in humans, and finally, to improvement in blood pressure following treatment of severe OSA. In recognition of this evidence, the US National Heart, Lung and Blood Institute now lists OSA as a significant and reversible cause of hypertension in its recent position statement.19

CARDIAL FAILURE

There is now good evidence that OSA could worsen or contribute to left ventricular (LV) failure. Hypertension is an important risk factor for cardiac failure and, as has been seen, OSA is a cause of hypertension. However, sleep apnoea itself might affect cardiac function more directly. The exaggerated negative intrathoracic pressure and hypoxia that occur in OSA have significant adverse haemodynamic effects (Table 1). It is possible that if these effects are repeated over months or years (as occurs in OSA), then susceptible individuals could develop sustained LV dysfunction.

There is now experimental and clinical evidence to support the hypothesis that OSA is deleterious to cardiac function. First, studies in dogs have shown that 1–3 months of repetitive apnoeas can lead to impaired LV systolic function and hypertension.20 OSA is also strongly associated with systolic heart failure in studies on human subjects. In the Sleep Heart Health Study the largest cardiovascular risk from OSA was seen for a history of cardiac failure. Those with an AHI of >11 had a relative risk of 2.38 (95% confidence interval (CI) 1.22–4.62) for reporting a history of congestive heart failure compared with those with an AHI of <1.4.2

If OSA adversely affects LV systolic function, then one would expect improvement in cardiac performance following its treatment. Strong evidence supporting a beneficial effect of CPAP has now begun to emerge. A recent randomized controlled trial has shown improvements in LV ejection fraction from 25 to 34% following treatment of OSA with CPAP for 1 month in those with systolic heart failure.21 A current Australian study has shown similar results with an improvement in LV ejection fraction from 38 to 43% in the CPAP treatment group, as well as significant improvements in health-related quality of life in the active treatment arm.22 However, as yet there are no data looking at the long-term treatment effects of CPAP on cardiac function, including its effect on hospitalizations and survival.

There is also the possibility that CHF might contribute to the pathogenesis of OSA, as well as vice versa. Decreased cardiac output as a result of CHF can lead to ventilatory instability with periods of apnoea followed by excessive hyperpnoea – the classic central apnoeas of Cheyne-Stokes respiration. This instability in ventilatory drive (known as loop gain) can also lead to upper airway collapse in those susceptible to OSA.23 Indeed, it has been shown that both central and obstructive apnoeas can be improved by measures to increase cardiac output, such as atrial overdrive pacing in patients with paroxysmal atrial fibrillation or tachyarrhythmias.24

OSA is also associated with diastolic heart failure, but the link is not so clear-cut. The apnoea-induced haemodynamic changes listed in Table 1 cause acute reductions in LV diastolic function. Negative intrathoracic pressure causes increased right ventricular filling with a subsequent shift of the intraventricular septum into the LV cavity. This reduces LV diastolic compliance. Hypoxaemia leads to delays in ventricular relaxation and tachycardia,25,26 both of which also impair diastolic function. Chronically, OSA is associated with hypertension and increased LV wall thickness, which can lead to LV diastolic dysfunction.27 However, it remains controversial whether the change in LV muscle bulk occurs independently of associated hypertension, as evidence to this point in time has been conflicting.

ISCHAEMIC HEART DISEASE

OSA could be a cause of coronary artery disease (CAD). On a mechanistic level, there is now evidence that OSA causes endothelial damage and dysfunction, and thus could promote the development of generalized atherosclerosis.28

From a clinical viewpoint, there is evidence that OSA is associated with ischaemic heart disease (IHD). It was shown in 1990 that OSA is very common in patients presenting with acute myocardial infarction.29 Further controlled studies have confirmed this association between OSA and IHD. Peker et al. have published data from a 7-year follow up of a sleep clinic population. In this group, those with OSA at baseline had a 4.9-fold greater chance of developing CVD during the follow-up period, independent of age, body mass index and blood pressure.30 In contrast, the Sleep Heart Health Study showed only a modest association between OSA and...
IHD in its recent cross-sectional analysis. Those in the highest quartile of AHI (AHI > 11) had only a 1.27-fold (95% CI 0.99–1.62) increased risk of self-reported IHD compared with those in the lowest quartile of AHI. However, the small number of patients in the analysis with very severe OSA might have attenuated this effect. Ongoing follow up of the participants in the Sleep Heart Health Study will provide the first opportunity to address prospectively the issue of IHD risk from OSA in a community-based population.

A separate issue is the prognosis of patients with both CAD and OSA. Possible reasons for a worse prognosis as a result of OSA include the precipitation of nocturnal ischaemia/infarction and arrhythmias, or the acceleration of pre-existing atherosclerosis. Nocturnal ischaemia has been shown to be common in patients with both OSA and CAD, and similarly, OSA has been found to be very common in patients with nocturnal ischaemia. Furthermore, in a study with a 5-year follow up of patients known to have CAD, mortality has been shown to be significantly higher in those with OSA, independent of confounding factors. Reassuringly, however, during admission for acute myocardial infarction, in-hospital mortality and major complication rates are the same for patients with and without OSA. Another interesting observation is that the peak time of onset of myocardial infarction occurs between 00.00 and 12.00 hours – a time that includes the final hours of sleep and the transition from sleep to wakefulness. Abnormalities of coronary artery blood flow or thrombotic tendency during sleep or in episodes of OSA could play a role in explaining these associations. There is, in fact, preliminary evidence that fibrinogen levels (an independent cardiovascular risk predictor) and platelet activation are elevated in the morning in patients with OSA. These findings require more detailed study.

ARRHYTHMIAS

There are several mechanisms that could lead to either bradyarrhythmias or tachyarrhythmias in OSA (Table 1). In the initial phase of the apnoea, there is a predominance of vagal tone. Towards the end of the event and following relief of the obstruction, there is then a surge in sympathetic nervous system discharge. These neurohumoral factors as well as the mechanical stress on the myocardium from the intrathoracic pressure changes are potentially arrhythmogenic.

Bradycardia is common during apnoeas. Indeed, sinus pauses up to 2 s in duration are not infrequently seen in severe OSA and are a normal physiological response to apnoea without airflow (Table 1). Transient heart block can also occur and has been reported in up to 10% of patients with OSA. Those most at risk have pre-existing conduction disturbances or are taking negatively chronotropic medications. In addition, a high frequency of ventricular ectopic beats have been observed in patients with OSA and heart failure. Treatment with nocturnal CPAP has been shown to abolish the majority of these bradyarrhythmias and ectopic beats.

Sustained tachyarrhythmias, such as atrial fibrillation (AF), can also develop as a result of OSA. Mooe et al. reported that OSA was an independent predictor for the development of AF post coronary artery bypass surgery. More recently, Kanagala et al. demonstrated in a prospective study that the recurrence of AF at 12 months following successful cardioversion was halved for those with treated compared with untreated OSA. In those without OSA treatment, the risk of AF recurrence was related to the degree of nocturnal desaturation. Given the high prevalence of both AF and OSA, this association requires further study.

There are no data demonstrating sustained ventricular tachyarrhythmias in patients with OSA.

CEREBROVASCULAR DISEASE

OSA is very common in stroke patients, with a reported prevalence of up to 60%. This far outweighs the amount of central sleep apnoea seen following stroke. The factors that might be involved in the pathogenesis of CAD in patients with OSA might also lead to cerebrovascular disease. Hypertension is known to be a prominent risk factor for stroke and might also be a pathway through which OSA can lead to cerebrovascular disease.

There are increasing clinical data supporting an independent association between OSA and stroke. The largest trial showing a link is the Sleep Heart Health Study, which demonstrated that those with an AHI of >11 were 1.58-fold more likely to have reported a history of stroke compared with those with an AHI of <1.4. It has been controversial whether OSA is a cause or consequence of stroke, as there could conceivably be alterations in upper airway tone and collapsibility following stroke, which could predispose patients to OSA. Studies looking at whether the AHI improves as patients recover from stroke have been inconclusive, with reports of the prevalence of OSA both reducing and remaining unchanged at 2–3 months following the stroke. However, the prevalence of OSA is the same for both completed stroke and transient ischaemic attack. Given that there is no lasting neurological damage with a transient ischaemic attack, this suggests OSA is likely to have preceded the stroke. Longitudinal data from the Sleep Heart Health Study should help clarify the issue.

OSA might also be deleterious to those who have had a stroke, by adversely affecting prognosis. The ischaemic brain is highly susceptible to further injury from hypoxia, such as can occur in OSA. This could lead to more extensive cerebral damage or it could impair neurological recovery. Indeed, there is accumulating evidence that stroke patients with OSA have slower and less complete functional recovery. However, no controlled trial has looked at the effect of CPAP on stroke outcome.

SUMMARY AND FUTURE DIRECTIONS

OSA is associated with CVD and there is increasing evidence to suggest this link is causal, particularly for...
hypertension. However, doubt will remain until the results of current prospective follow-up and treatment studies become available. Other than for hypertension and more recently for cardiac failure, there has been little rigorous research assessing the effect of CPAP therapy on clinical outcomes. Such trials are urgently needed to demonstrate convincingly that OSA is an independent and modifiable cardiovascular risk factor.

Future challenges include quantifying the cardiovascular risk for people with mild to moderate OSA (particularly those with minimal oxygen desaturation and those who are asymptomatic), standardizing methods of measuring and defining sleep–disordered breathing across sleep laboratories and identifying treatment alternatives to the current gold standard (nasal CPAP). This latter point is essential if treatment of OSA is going to be recommended to those with minimal symptoms of daytime sleepiness, as the inconvenience and cost of CPAP is poorly tolerated in this group.

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