Obstructive sleep apnoea and its cardiovascular consequences

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Obstructive sleep apnoea (OSA) is a common disorder in which repetitive apnoeas expose the cardiovascular system to cycles of hypoxia, exaggerated negative intrathoracic pressure, and arousals. These noxious stimuli can, in turn, depress myocardial contractility, activate the sympathetic nervous system, raise blood pressure, heart rate, and myocardial wall stress, depress parasympathetic activity, provoke oxidative stress and systemic inflammation, activate platelets, and impair vascular endothelial function. Epidemiological studies have shown significant independent associations between OSA and hypertension, coronary artery disease, arrhythmias, heart failure, and stroke. In randomised trials, treating OSA with continuous positive airway pressure lowered blood pressure, attenuated signs of early atherosclerosis, and, in patients with heart failure, improved cardiac function. Current data therefore suggest that OSA increases the risk of developing cardiovascular diseases, and that its treatment has the potential to diminish such risk. However, large-scale randomised trials are needed to determine, definitively, whether treating OSA improves cardiovascular outcomes.

Introduction

Obstructive sleep apnoea (OSA) is a disorder in which loss of pharyngeal dilator muscle tone at sleep onset causes recurrent pharyngeal collapse and temporary cessation of breathing (apnoea). An abnormally narrowed or collapsible pharynx puts individuals at greater risk.[1] Such apnoeas cause repetitive hypoxia and carbon-dioxide retention, and provoke awakenings (ie, arousals) that restore pharyngeal dilator muscle tone and airflow. However, this respite is brief: pharyngeal obstruction recurs once sleep resumes, and recurrent arousals, although protective, disrupt sleep. An OSA disorder is generally defined as five or more apnoeas–hypopneas per hour of sleep (ie, the apnoea–hypopnoea index [AHI]).[2,3]

After the initial description of OSA, a proposition was made that cardiovascular stresses evoked by OSA could contribute to the pathogenesis of cardiovascular diseases.[4] However, in 1997, Wright and colleagues[5] concluded that there was insufficient evidence to support this concept. Over the subsequent decade, data from epidemiological, observational, and interventional studies have transformed our appreciation of how OSA could contribute to the burden of cardiovascular diseases, and how its treatment might lessen this burden. The purpose of this Seminar is, first, to review our current understanding of mechanisms by which OSA might contribute to the pathogenesis of cardiovascular disease; second, to assess epidemiological evidence concerning a potential link between these two conditions; third, to review cardiovascular effects of treating OSA; and finally, to identify gaps in our knowledge in need of resolution.

Search strategy and selection criteria

PubMed was searched using the search term "sleep apnoea" with relevant phrases including "cardiovascular disease", "hypertension", "cardiac hypertrophy", "heart failure", "coronary artery disease", "ischaemic heart disease", "stroke", "cardiac arrhythmias", and "cerebrovascular disease". Only papers published in English between 1997 and 2008 were used. Publications referred to in the identified articles were also reviewed and were cited if they provided important data not addressed in subsequent articles. Emphasis was placed on experimental mechanistic studies, large prospective epidemiological studies, and randomised controlled clinical trials using full polysomnography. Where data from randomised controlled trials are unavailable, non-randomised trials are discussed.

Definition and diagnosis of OSA

A diagnosis of OSA requires the presence of repetitive apnoeas and hypopnoeas during sleep. This presence is most reliably shown by attended overnight polysomnography in a sleep laboratory, in which sleep stages, arterial oxyhaemoglobin saturation, and respiratory movements of the rib cage and abdomen or respiratory effort, or both, are recorded.[2]

Apnoea is an absence of tidal volume for at least 10 s, and hypopnoea is a decrease in tidal volume of at least 50%, but above zero, for at least 10 s accompanied by at least a 4% decrease in oxygen saturation or terminated by arousal from sleep. Apnoeas are obstructive if accompanied by respiratory efforts against the occluded pharynx, and central if not.[2] In the general population, OSA is by far the commonest form of sleep apnoea, whereas central sleep apnoea is rarely recorded in the absence of heart failure.[6–10]

OSA is frequently associated with a history of habitual snoring, which is a sign of increased pharyngeal airflow resistance. An OSA syndrome is defined as an AHI equal to or more than 5 accompanied by either excessive daytime sleepiness or two or more of episodes of choking or gasping during sleep, recurrent awakenings, unrefreshing sleep, daytime fatigue, or impaired concentration or memory.[2] The severity of OSA is most often reported as the AHI for two reasons. First, because hypoxia and arousals that disrupt sleep are a direct consequence of apnoeas and hypopnoeas, the AHI provides an index of the frequency of the primary events and their immediate physiological consequences. Second, in general, the higher the AHI, the

more severe the clinical manifestations of OSA, such as daytime sleepiness, neurocognitive impairment, and the likelihood of developing cardiovascular complications.[3,11–15] The American Academy of Sleep Medicine classification of OSA severity considers both the AHI (mild defined as an AHI of 5–15, moderate as 15–30, and severe as >30) and degree of daytime sleepiness (mild: unwanted sleepiness or involuntary sleep episodes occurring during activities that need little attention; moderate: during activities that need some attention, such as during meetings; severe: during activities that need more active attention such as during conversation or driving).[2] However, these thresholds are arbitrary.

Pathophysiology

During non-rapid-eye movement sleep, metabolic rate, sympathetic nervous activity, blood pressure, and heart rate all decrease, whereas cardiac vagal tone increases from wakefulness.[16–18] OSA interrupts this cardiovascular quiescence by triggering a cascade of acute haemodynamic, autonomic, chemical, inflammatory, and metabolic effects, with chronic after-effects capable of initiating or exacerbating cardiovascular disease (figure).

These cycles of hypoxia and carbon-dioxide retention elicit oscillations in both cardiac parasympathetic and sympathetic nervous activity that affect heart rate. Although bradycardia was originally thought to be a common response to obstructive apnoeas,[19] it has subsequently been shown not to be, and heart rate has been shown to either increase, decrease, or remain unchanged during obstructive apnoeas.[20] The net response might be a function of both autonomic balance and airflow; hypoxia slows heart rate by activating the vagus only in the absence of lung stretch or airflow.[21,22] When parasympathetic tone predominates, the heart rate can slow, when sympathetic tone predominates, the heart rate can rise, and if vagal and sympathetic effects are equal, the heart rate can remain unchanged. Repetitive apnoea-induced hypoxia and carbon-dioxide retention cause ineffectual inspiratory efforts and the generation of negative intrathoracic pressure against the occluded pharynx that, by increasing the difference between intracardiac and extracardiac pressure, increase left ventricular transmural pressure (ie, afterload, a potent stimulus to left ventricular hypertrophy).[23] Negative intrathoracic pressure draws blood into the thorax, augmenting right ventricular preload, while apnoea-induced hypoxia causes pulmonary vasoconstriction, increasing right ventricular afterload.[24] These forces distend the right ventricle, causing leftward shift of the interventricular septum during diastole that impedes left ventricular filling and decreases stroke volume.[24] Hypoxia during OSA might also directly impair cardiac contractility and diastolic relaxation.[25,26] Such adverse consequences are rapidly relieved by application, via a nasal mask, of continuous positive airway pressure (CPAP) to splint the pharynx and maintain its patency.[27]

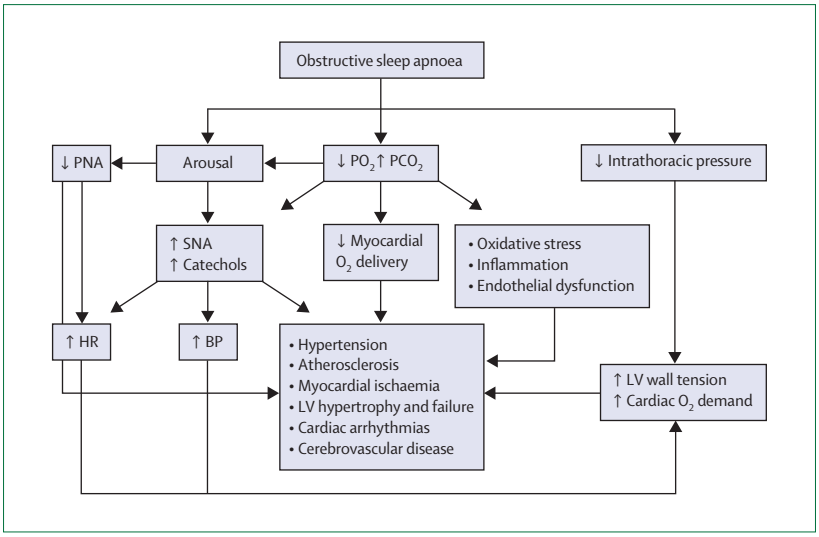

***Figure*: Pathophysiological effects of obstructive sleep apnoea on the cardiovascular system**
PNA=parasympathetic nervous system activity. PO_2=partial pressure of oxygen. PCO_2=partial pressure of carbon dioxide. SNA=sympathetic nervous system activity. HR=heart rate. BP=blood pressure. LV=left ventricular.

These cycles of hypoxia and carbon-dioxide retention elicit oscillations in sympathetically-mediated peripheral vasoconstriction that further augment afterload by raising systemic blood pressure.[28] At apnoea termination, asphyxia triggers a brief arousal from sleep that abruptly increases sympathetic activity, and suppresses vagal tone, precipitating surges in blood pressure and heart rate.[29] These acute effects can be sustained into wakefulness, causing higher blood pressure and impaired vagally-mediated heart-rate variability.[28,30–32]

Intermittent hypoxia can induce oxygen-free-radical production,[33,34] and activate inflammatory pathways that impair vascular endothelial function[35–37] and increase blood pressure independently of activation of the sympathetic nervous system.[38] Non-randomised uncontrolled trials report that CPAP lowered the nuclear-factor-κB-dependent cytokines tumour necrosis factor α (TNFα), and interleukin 8,[36,37] and also lowered plasma concentrations of interleukin 6 and C-reactive protein.[35] Individuals with OSA have attenuated endothelium-dependent vasodilation,[39,40] and decreased circulating markers of nitric oxide that increase after treatment by CPAP.[41] OSA can also promote oxidation of lipoproteins, increased expression of adhesion molecules and monocyte adherence to endothelial cells, and vascular smooth-muscle proliferation.[33,42–44] These adverse vascular effects, combined with increased sympathetic vasoconstrictor activity and inflammation, could predispose to hypertension and atherosclerosis.[45,46]

In dogs, just 8 hours exposure to severe OSA can induce acute pulmonary oedema,[47] and several weeks' exposure to OSA can induce left ventricular hypertrophy and systolic dysfunction.[48]

Platelet activation and aggregability, markers of increased susceptibility to thrombosis, are increased during sleep in patients with OSA and, in a non-randomised trial, decreased after one night of CPAP.[49] Morning fibrinogen concentration is increased, and plasminogen activator inhibitor type-1 activity is decreased in patients with OSA,[50] indicating less fibrinolytic potential.[51] Fibrinogen has been shown to decrease after one night of CPAP.[52]

Cerebral bloodflow declines significantly during obstructive apnoeas due to a decrease in cardiac output.[53] In patients with flow-limiting lesions of the cerebral arteries, this can predispose to ischaemic events.[54] Compared with control participants, patients with OSA show greater signs of early atherosclerosis, including greater carotid intima–media thickness, decreased arterial compliance, and a higher prevalence of silent brain infarcts.[55–57]

Epidemiology

Prevalence

In the USA, the prevalence of OSA (AHI≥5) in the adult, mainly white, population aged 30–60 years, has been estimated at 24% in men and 9% in women, and, at an AHI≥15, at 9% in men and 4% in women, with no major differences noted between African-Americans and White people.[58] The corresponding prevalence of OSA syndrome has been estimated at 4% in men and 2% in women.[3] In European populations, the most comprehensive data come from Spain, where 26% of men and 28% of women aged 30–70 years had an AHI≥5, and 14% of men and 7% of women had an AHI≥15.[59] In a predominantly oriental male population from Hong Kong, aged 30–60 years, the prevalences of OSA and OSA syndrome at an AHI≥5 were 9% and 4%, respectively, and at an AHI≥15, 5% and 3%, respectively.[60] These data suggest that OSA is common in several racial and ethnic groups, but that most individuals with OSA are asymptomatic. This factor could have public-health implications, because relations between OSA and cardiovascular diseases seem not to be related to the presence of symptoms of sleep apnoea.[61] Of those with OSA syndrome who could benefit symptomatically from its treatment, 75–80% remain undiagnosed in the USA.[62]

	Cross-sectional (prevalence)		Prospective (incidence)	
	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†
Hypertension	Yes[3,13,75]	Yes[3,13,75]	Yes[13]	Yes[13]
Dysglycaemia	Yes[76–78]	Yes[76–78]	Yes[78]	No[78]
Coronary artery disease	Yes[14]	Yes[14]	NA	NA
Heart failure	Yes[14]	Yes[14]	NA	NA
Cardiac arrhythmias				
Bradyarrhythmias	No[79,80]	No[79,80]	NA	NA
Atrial fibrillation	Yes[79]	Yes[79]	NA	NA
Ventricular ectopy	Yes[79]	Yes[79]	NA	NA
Cerebrovascular disease	Yes[11]	Yes[11]	Yes[11,12]	No[11,12]

Yes=available data support a significant association. No=available data do not support a significant association. NA=no data available. *Findings of univariable analyses or multivariate analyses with partial adjustment. †Findings of multivariable analyses in which adjustments have been made for all known confounding factors.

Table 1: **Summary of community-based epidemiological studies that used polysomnography to investigate potential links between obstructive sleep apnoea and cardiovascular diseases**

Risk factors

OSA is two to three-times more common in men than in women, and in those aged 65 years or more than in those aged 30–64 years.[61] The risk of OSA also increases with increasing body weight: a 10% weight gain increases the risk of developing OSA by six-times.[63] Fat accumulation in the neck, as a result of obesity, can impinge on the pharyngeal lumen and predispose its collapse during sleep.[64]

Nonetheless, OSA occurs in individuals of normal weight in whom other factors can contribute to pharyngeal collapsibility (eg, macroglossia and adenotonsillar hypertrophy).[64] Anomalies of craniofacial structure, such as retrognathia, which can retrodisplace the tongue and narrow the pharynx, can be especially important in non-obese oriental populations.[65] Nasal obstruction and smoking can also increase the risk for developing OSA, possibly by causing pharyngeal narrowing as a result of inflammation.[61] Hereditary factors can also increase risk for reasons not fully elucidated.[61,66]

Association between OSA and cardiovascular diseases

Compared with the general population, the prevalence of OSA is higher in populations with cardiovascular conditions, such as hypertension (30–83%),[67,68] heart failure (12–53%),[8,9,69] ischaemic heart disease (30–58%),[70,71] and stroke (43–91%).[72–74] However, the coexistence of these conditions with OSA does not prove causality, and potential confounding variables, such as obesity, need to be considered. Nevertheless, epidemiological data (table 1) support the concept that OSA can participate in the initiation or progression of several cardiovascular diseases.

There is compelling experimental evidence that OSA can raise blood pressure which, in turn, increases cardiovascular risk.[75] Dogs exposed to OSA developed hypertension during both sleep and wakefulness that resolved on reversal of OSA.[30] Rats exposed to intermittent hypoxia, mimicking the recurrent hypoxia of OSA, developed hypertension that was prevented by sympathectomy or peripheral chemoreceptor denervation.[46,81]

Cross-sectional studies have shown increased odds of hypertension in association with OSA, independent of obesity.[15,82] A prospective study also showed that for an AHI>15 versus 0, the odds of developing hypertension over 4–8 years was 2·89 (95% CI 1·46–5·64), independent of confounders.[13] OSA is also common in patients with drug-resistant hypertension,[68] in whom it is often associated with biochemical features of primary aldosteronism[83] that could provoke oxidative stress, inflammation, and ventricular fibrosis and hypertrophy.[84]

Dysglycaemia and diabetes also increase the risk of developing cardiovascular disease. Exposure of healthy people to sleep deprivation or intermittent hypoxia increases glucose intolerance, insulin resistance, and activity of the sympathetic nervous system.[85,86] In cross-sectional studies, involving as many as 2656 participants, those with OSA had greater resistance to insulin[76,87] and higher prevalences of both hyperglycaemia and type 2 diabetes than those without OSA,[77,78] after adjusting for confounders including weight. However, prospective data from one of these studies did not show an increased risk of incident type 2 diabetes associated with the presence of OSA during 4 years of follow-up.[78]

In mice, although exposure to either chronic intermittent hypoxia, or to a high cholesterol diet alone, did not induce atherosclerosis,[88] simultaneous exposure to both induced aortic atherosclerosis, probably by potentiating hypercholesterolaemia and worsening lipid peroxidation. In a cross-sectional analysis of the Sleep Heart Health Study, OSA at the highest AHI quartile (AHI>11) was associated with modestly increased odds of coronary artery disease (OR 1·27 [95% CI 0·99–1·62]) versus the lowest quartile.[14] Additionally, case–control studies have consistently shown a higher prevalence of OSA in men and women with coronary disease than in those without coronary disease.[89,90]

In the largest of several prospective observational studies with a mean follow-up of 10·1 years, Marin and co-workers[91] noted that, compared with healthy controls matched for age, sex, and weight, those with severe untreated OSA (AHI>30; n=235) had more fatal (1·06 *vs* 0·3 per 100 patient years; p=0·0012) and non-fatal cardiovascular events (2·13 *vs* 0·45 per 100 patient years; p<0·0001), whereas event rates in those with severe OSA treated by CPAP (n=372) did not differ significantly from the controls. Similar findings have also been reported elsewhere.[92]

Obstructive apnoeas, induced by occluding an endotracheal tube during anaesthesia, provoke myocardial ischaemia in the presence, but not in the absence, of coronary artery ligation.[93] In human beings, Mueller manoeuvres, which simulate the effects of obstructive apnoeas, cause more pronounced decreases in left-ventricular ejection fraction and stroke volume in patients with coronary artery disease or heart failure than in those without these conditions.[94,95] Thus, the adverse effects of OSA can be amplified in the presence of cardiovascular diseases.

In patients with coronary disease, cyclic apnoea-induced hypoxia, negative intrathoracic pressure, and hypertension can provoke myocardial oxygen demand–supply mismatch and ischaemic electrocardiographic changes, as well as nocturnal angina that, in an uncontrolled study, were alleviated by CPAP.[96]

In patients with coronary disease, the presence of OSA is associated with higher mortality (38% *vs* 9%; p=0·018),[97] more major adverse cardiac events (24% *vs* 5%; p=0·002), and more restenoses after percutaneous coronary interventions (37% *vs* 15%; p=0·026) than in patients without OSA.[98] Milleron and colleagues[99] did an observational study involving 54 patients with both coronary disease and OSA (AHI≥15). 25 patients accepted treatment for OSA. During 87 months of follow-up, treated patients had a significantly decreased risk for the composite endpoint of cardiovascular death, acute coronary syndrome, hospitalisation for heart failure, or need for coronary revascularisation, than did untreated patients (adjusted hazard ratio [HR] 0·24 [95% CI 0·09–0·62]). In a similar observational study of 168 patients with OSA referred to a sleep clinic, 107 were treated with CPAP. Compared with the untreated group, all-cause mortality over the mean 7-year follow-up was not decreased in CPAP-treated patients, but cardiovascular mortality was (1·9% *vs* 14·8% deaths; p=0·009).[100] Data from randomised trials are now needed to confirm or refute these findings.

Cross-sectional data from 6424 men and women showed a 2·38-times increased likelihood of having heart failure in association with OSA, independent of confounders,[14] and prospective data showed that 21 days after acute myocardial infarction, the presence of OSA was associated with impaired recovery of left-ventricular systolic function.[101] However, there are no prospective data concerning OSA and the risk of developing either left-ventricular hypertrophy or failure.

In the general population, the prevalence of OSA with an AHI exceeding 10–15 is about 7–10%,[3] but in patients with heart failure it is higher at 11–53%.[8–10,69,102] Because the prevalence of central sleep apnoea with an AHI of 15 or more in patients with heart failure is 15–37%[8–10] but less than 1%[6,7] in the general population, the overall prevalence of these sleep-related breathing disorders in patients with heart failure is about 50%. Differentiating between OSA and central sleep apnoea in patients with heart failure is important because their pathophysiologies (central apnoeas are not caused by pharyngeal occlusion, but occur when the partial pressure of carbon dioxide falls below a threshold level needed to stimulate breathing) and treatments differ, as previously reviewed.[103,104]

The finding that patients with heart failure have a lower body-mass index for a given AHI than the general population[105] suggests that factors unrelated to obesity might contribute more to the pathogenesis of OSA in patients with heart failure. One such factor might be fluid redistribution from oedematous legs to peripharyngeal tissues when moving from the upright to recumbent position, impinging on the pharyngeal lumen and predisposing to collapse during sleep.[106,107]

In addition to its chronic effects on systemic blood pressure, OSA could, through several mechanisms independent of blood pressure, promote left-ventricular hypertrophy, diastolic and systolic dysfunction, and overt heart failure. These mechanisms include the mechanical and trophic consequences of repetitive increases in left-ventricular wall stress with each obstructed inspira-

tory effort,[108] hypoxia, increased sympathetic drive to the heart, and OSA-related increases in aldosterone secretion.[83,84] Compared with patients without OSA, those with OSA, but without overt heart failure, have a higher prevalence of impaired diastolic relaxation, reversible by 3 months of CPAP therapy.[109]

Several studies reported increased left-ventricular thickness or mass in association with OSA,[109–111] but these relations were not significant after adjustment for body weight. Only two studies, one in children[112] and one in adults with non-ischaemic dilated cardiomyopathy[113] noted an independent association between OSA and left-ventricular hypertrophy. In the adult study, left ventricular thickening was more prevalent in patients with OSA than in those without. OSA might also promote the development of intrathoracic aortic aneurysms, presumably by inducing repetitive increases in intrathoracic aortic transmural pressure during obstructed inspiratory efforts.[114]

Cardiac metabolic gene expression has a circadian rhythm that anticipates diurnal variations in the ratio between workload and substrate availability.[115] Disruption of such rhythms by obstructive apnoeas can cause a temporal mismatch between increased myocardial oxygen demand, as a result of increased left-ventricular wall tension, and decreased oxygen supply, as a result of apnoea-induced hypoxia, that might aid contractile dysfunction. Findings of an uncontrolled study involving seven patients with heart failure suggest that such impaired myocardial metabolic efficiency might be improved if coexisting OSA is abolished by CPAP.[116]

In addition to these adverse effects of obstructive apnoeas during sleep, patients with heart failure and OSA have higher daytime sympathetic-nerve traffic and systolic blood pressure than those with heart failure alone,[117,118] which could promote abnormalities that worsen prognosis, such as cardiac myocyte hypertrophy, β-adrenoceptor desensitisation, and cardiac arrhythmias. In a prospective observational study involving 164 patients with heart failure who were followed up over 7·3 years,[10] mortality was significantly greater in the 37 patients with untreated OSA (AHI≥15) than in 113 patients without sleep apnoea (8·7 *vs* 4·2 deaths per 100 patient years; p=0·029) after controlling for confounders. There was also a non-significant tendency for lower mortality in those with CPAP-treated OSA compared with those with untreated OSA (p=0·07).

In a community-based study, Mehra and co-workers[79] noted no significant difference in the prevalence of nocturnal sinus pauses between patients with severe OSA (AHI≥30, n=228) and those without OSA (AHI<5, n=338; 11% *vs* 9%, p=0·34). Second-degree atrioventricular block was rare, and its prevalence did not differ between the groups. Flemons and colleagues[80] reported similar findings in patients referred to a sleep laboratory for suspicion of OSA. In 66 patients with OSA, Roche and co-workers[119] recorded a higher prevalence of sinus pauses (9·1% *vs* 0%; p<0·01), but not of second-degree heart block, than in 81 participants without OSA.

Although there might not be an overall increased prevalence of bradyarrhythmias in individuals with OSA, in non-randomised studies where bradyarrhythmias were detected, they resolved with administration of supplemental oxygen, atropine, or treatment of OSA.[19,22,120,121] Increased parasympathetic input to the heart, rather than intrinsic abnormalities of the cardiac conduction system,[122] seems to be the main nocturnal bradyarrhythmic mechanism. Thus, if OSA evokes nocturnal bradycardia, its treatment might obviate the need for cardiac pacing.

Two studies reported that the prevalence of nocturnal paroxysmal supraventricular tachycardia was not increased in OSA.[79,119] Although another study reported a higher prevalence of atrial fibrillation in those with OSA than in those without (4·8% *vs* 0·9%, respectively; p=0·003),[79] this finding was not replicated in other studies.[102,119,123] By contrast, in two of these other studies, there was a strikingly higher prevalence of atrial fibrillation in patients with central sleep apnoea, both in the setting of preserved (27% *vs* 2% in those with OSA and 3% in those without sleep apnoea; p<0·001)[123] or impaired (23% *vs* 12% in those with OSA and 8% in those without sleep apnoea; p<0·05)[102] left-ventricular systolic function. Future investigations of potential relations between sleep-disordered breathing and atrial fibrillation will therefore need careful differentiation of OSA from central sleep apnoea.

In an observational study, Kanagala and co-workers[124] reported that patients with untreated OSA had twice the risk for recurrence of atrial fibrillation within 1 year of electrical cardioversion to sinus rhythm than those whose OSA was treated with CPAP (82% *vs* 42%, respectively; p=0·013). However, in a retrospective analysis, the same group noted that obesity rather than OSA at baseline was an independent predictor of incident atrial fibrillation.[125]

Mehra and colleagues[79] also reported that the prevalence of ventricular premature beats and complex ventricular ectopy was higher in those with, than in those without, OSA (35% *vs* 21% [p=0·0003] and 25% *vs* 15% [p=0·002], respectively). By contrast, Flemons and colleagues[80] showed no significant difference in the prevalence of these ventricular arrhythmias between patients with and without OSA. Thus, uncertainty remains as to whether OSA induces ventricular arrhythmias.

Gami and co-workers[126] reported that, in patients with OSA, the relative risk of sudden cardiac death between midnight and 0600 h was 2·57 compared with the general population, whose peak risk for sudden cardiac death was between 0600 h and noon. However, whether these individuals died during sleep is unknown. Thus, although suggestive, these data do not establish a direct causal relation between OSA and an increased risk of sudden death during sleep. Indeed, in an earlier report involving 13 patients with OSA who had sudden death, none died during sleep.[127]

	Treatment	Patients enrolled, n	Patients completing trial, n	Treatment period	Treatment outcomes
Hypertension*					
Becker et al[14]	Therapeutic *vs* sham CPAP	60	32	Mean 65 days (SD 50)	10 mm Hg decrease in systolic and diastolic blood pressure
Robinson et al[138]	Therapeutic *vs* sham CPAP	35	32	1 month	No change in blood pressure
Heart failure†					
Kaneko et al[139]	Therapeutic CPAP *vs* no CPAP	24	24	1 month	9% increase in LVEF; 10 mm Hg decrease in systolic blood pressure; decrease in heart rate of four beats per minute
Mansfield et al[140]	Therapeutic CPAP *vs* no CPAP	55	40	3 months	5% increase in LVEF; no change in blood pressure; decrease in nocturnal urinary concentration of norepinephrine; improved QOL
Usui et al[141]†	Therapeutic CPAP *vs* no CPAP	17	17	1 month	17% decrease in muscle SNA; 15 mm Hg decrease in awake systolic blood pressure
Gilman et al[142]†	Therapeutic CPAP *vs* no CPAP	19	19	1 month	Increase in high frequency HRV
Ryan et al[143]†	Therapeutic CPAP *vs* no CPAP	18	18	1 month	58% decrease in frequency of VPB during sleep
Egea et al[144]	Therapeutic *vs* sham CPAP	61	45	2 months	2·7% increase in LVEF; no change in blood pressure, QOL, or 6-MWT
Type 2 diabetes					
West et al[145]	Therapeutic *vs* sham CPAP	42	40	3 months	No change in outcomes of HbA_{1c}, euglycaemic clamp, or HOMA%S
Stroke					
Sandberg et al[146]	Therapeutic CPAP *vs* no CPAP	63	59	28 days	Decrease in depressive symptoms; no change in physical or cognitive function
Hsu et al[147]	Therapeutic CPAP *vs* no CPAP	30	28	8 weeks	No change in physical or cognitive function, sleepiness, QOL, or 24-h blood pressure

CPAP=continuous positive airway pressure. LVEF=left-ventricular ejection fraction. QOL=quality of life. SNA=sympathetic nervous system activity. HRV=heart-rate. VPB=ventricular premature beats. 6-MWT=6-minute walk-test distance. Hb=haemoglobin. HOMA%S=homoeostatic model assessment. *Only trials in which most patients had elevated blood pressure at enrolment are included. †Overlap exists with some patients in these trials because these reports represent components of a larger clinical trial that was extended after the findings by Kaneko and colleagues[139] were reported.

Table 2: **Summary of randomised trials of treatment for obstructive sleep apnoea on outcomes contributing to cardiovascular diseases**

After a stroke, OSA is frequently noted, adversely affecting patients' cognitive and physical function.[73,74] However, whether OSA predisposes to stroke or vice versa remains unclear. The finding that there is no association between stroke location, type, or severity and the presence of OSA[72,74] favours the former possibility. Cross-sectional data from the Sleep Heart Health Study showed greater odds for stroke in the highest AHI quartile than in the lowest quartile (1·58 [95% CI 1·02–2·46]).[14] Subsequently, Arzt and colleagues[11] showed, in a community sample between the ages of 30 and 60 years, that, compared with patients without OSA, those with moderate to severe OSA (AHI≥20) had 4·33 (95% CI 1·32–14·24) greater odds for prevalent stroke, independent of other risk factors, and that after 4 years, an AHI of 20 or greater at baseline was associated with an increased risk of incident stroke after adjustment for age and sex (odds ratio 4·48 [95% CI 1·31–15·33]), but not for body-mass index. In an elderly population (70–100 years of age), severe untreated OSA (AHI≥30) was associated with a 2·52-times increased risk of incident stroke over a mean follow-up of 4·5 years compared with patients with an AHI of less than 30 (p=0·04);[12] however, because other risk factors were not accounted for, whether severe OSA is an independent risk for stroke in this context remains uncertain.

In a longitudinal study of 408 patients with coronary artery disease, Mooe and co-workers[71] noted that OSA independently increased the risk for incident cerebrovascular events (HR=2·98 [95% CI 1·43–6·20]; p=0·004). In an observational study, Yaggi and colleagues[128] reported an association between OSA and the combined rate of stroke, transient ischaemic attack, and all-cause mortality, independent of confounders (HR=1·97 [95% CI 1·12–3·48]). However, there was no significant association between OSA and either stroke, transient ischaemic attacks, or death alone. Moreover, treated and untreated patients with OSA were included together in this analysis. Because data from other observational studies report that treatment of OSA is associated with a decreased risk of cardiovascular and cerebrovascular events,[10,91] the data reported by Yaggi and colleagues are difficult to interpret. Hence, further studies will be needed to establish whether OSA contributes to causation of stroke independently of other risk factors.

Cardiovascular effects of treating OSA

In this section we review the findings of randomised controlled trials of OSA treatment on cardiovascular endpoints. Currently, there is no effective drug therapy for OSA. Oral appliances, electrical stimulation of the pharyngeal dilator muscles, or surgery are less effective than CPAP.[129–131] Atrial overdrive pacing, which, in an initial report, caused a modest improvement in OSA in patients with bradyarrhythmias,[132] is ineffective in those without bradyarrhythmias.[133–135] CPAP and mandibular advancement devices[136,137] are the only treatments for OSA whose effects on cardiovascular endpoints have been assessed in randomised trials (table 2).

Hypertension

Several randomised trials have assessed the effect of CPAP on daytime blood pressure in patients with

OSA.[148–153] However, most participants were normotensive[148–150] or had a history of hypertension controlled on medications at the time of enrolment.[152] These trials were short (all <3 months) and measured blood pressure by different methods at different times of day.[108] In some instances, the control for therapeutic CPAP was sham CPAP (mask applied with no pressure), which, in two such trials, tended to increase blood pressure.[150,153] In two meta-analyses, which included patients with both normal and increased blood pressure, a modest effect-size of CPAP of about 2 mm Hg in mean blood-pressure reduction was reported.[154,155] However, a third meta-analysis did not show a significant effect of CPAP on blood pressure.[156]

In a 1-month trial involving 68 patients with OSA with a history of medically-treated hypertension, in whom blood pressure was well controlled in most (mean 24-h blood pressure=130/78 mm Hg), therapeutic CPAP had no effect on blood pressure.[152] Robinson and colleagues[138] did a 1-month double cross-over trial of 35 patients with OSA who were not sleepy, most of whom had increased 24-h blood pressure at enrolment (mean 24-h blood pressure 142/86 mm Hg). Therapeutic CPAP had no effect on blood pressure.[138] By contrast, in a study[150] involving 118 patients who were mainly normotensive with hypersomnolence, a 1-month trial of CPAP significantly lowered the 24-h mean blood pressure by 2·5 mm Hg. However, in a subgroup with an AHI greater than the median (>33), mean blood pressure decreased by 5 mm Hg, and in those with a history of treated hypertension mean blood pressure decreased by 8 mm Hg. In a 2-month trial[151] involving patients with OSA and hypersomnolence, 65% of the 60 enrolled participants were hypertensive on enrolment. CPAP caused a significant 10 mm Hg decrease in both 24-h systolic and diastolic blood pressure. Taken together, these data suggest that treatment of OSA by CPAP can lower blood pressure, and is most effective in patients with increased blood pressure and more severe OSA accompanied by hypersomnolence. Because a lowering of blood pressure is more important in hypertensive than in normotensive patients, table 2 lists only the two published randomised trials in which most patients had increased blood pressure at enrolment.

Gotsopoulos and colleagues[137] compared the effects of a mandibular advancement device, adjusted to alleviate OSA, versus a sham oral appliance on 24-h blood pressure in a randomised trial. After 4 weeks, the device decreased 24-h diastolic blood pressure by 1·8 mm Hg (p=0·001), but systolic blood pressure remained unchanged. In a second randomised trial lasting 3 months, which compared an advancement device versus CPAP versus a placebo tablet, Barnes and colleagues[136] documented a 2·2 mm Hg decrease in nocturnal diastolic blood pressure only (p<0·05 compared with placebo and CPAP). Patients in both trials were predominantly normotensive.

Dysglycaemia, diabetes mellitus, and atherosclerosis

Up to now, only two randomised trials have investigated these conditions. West and co-workers[145] studied 42 men with type II diabetes and OSA who were randomly assigned to therapeutic or sham CPAP for 3 months. Therapeutic CPAP had no effect on any measure of glycaemic control or insulin resistance. Drager and colleagues[157] tested the effects of 4 months of CPAP versus no CPAP on early signs of atherosclerosis in 24 patients with severe OSA. Compared with the control group, those treated with CPAP had a 9% (p=0·04) decrease in carotid intima–media thickness, and an 11% (p<0·001) decrease in arterial pulse-wave velocity, changes that correlated significantly with concordant decreases in daytime plasma C-reactive protein and norepinephrine concentrations.

Heart failure

Kaneko and colleagues[139] randomly assigned 24 patients with heart failure and OSA (left-ventricular ejaction fraction ≤45%, AHI≥20) to either a control group on optimum medical heart-failure therapy, or to a treatment group that additionally received CPAP. Over 1 month, CPAP increased mean daytime left-ventricular ejaction fraction from 25% to 34% (p<0·001), and lowered morning systolic blood pressure from 126 mm Hg to 116 mm Hg (p=0·02). In an extension of this trial, one of the causes for this decrease in blood pressure was shown to be a CPAP-induced lowering of sympathetic vasoconstrictor nerve discharge.[141] CPAP also increased high-frequency heart-rate variability and baroreflex sensitivity in such patients, suggesting improved vagal modulation of heart rate.[142,158] In another randomised trial that involved 40 patients with heart failure and OSA, Mansfield and colleagues[140] tested the effects of 3 months of CPAP treatment. In CPAP-treated patients, left-ventricular ejaction fraction increased from 38% to 43% (p=0·04), and nocturnal urinary norepinephrine concentrations decreased (p=0·036). There were significant improvements in quality of life and sleepiness, but not in mean blood pressure. Compared with the patients studied by Kaneko and co-workers,[139] these individuals had milder systolic dysfunction and OSA, which might explain the lesser improvement in cardiovascular function. Nevertheless, the above studies are consistent in showing that treatment of OSA in patients with heart failure improves left-ventricular systolic function and lowers activity of the sympathetic nervous system.

Cardiac arrhythmias

In the only randomised trial published, Ryan and co-workers[143] reported that the treatment of coexisting OSA in patients with heart failure by CPAP for 1 month caused a 59% decrease in the frequency of ventricular premature beats during sleep (p=0·037).

Cerebrovascular disease

Sandberg and colleagues[146] did a randomised trial of CPAP versus no CPAP in 63 outpatients with OSA 2–4 weeks after a stroke. Compared with controls, CPAP-treated patients had a greater improvement in their depression score, but not in cognitive or physical function over 4 weeks. By contrast with most stroke studies, in which OSA predominates,[72–74] there were more central events in this population. Because central sleep apnoea is less likely to respond to CPAP than OSA,[159] and because CPAP was titrated only according to oximetry, sleep apnoea in this cohort might not have been treated effectively.

Hsu and colleagues[147] did a randomised trial of CPAP in 30 outpatients with coexisting OSA within 25 days of a stroke. Patients randomly assigned to CPAP had no improvement in activities of daily living, cognition, depression, sleepiness, quality of life, or blood pressure. However, the effect of CPAP on OSA was not reported and CPAP compliance was poor with overall use of only 1·4 h per night. Thus, the main conclusion to be drawn from this study might be that stroke outpatients have difficulty adhering to CPAP. The question of whether effective treatment of OSA with CPAP improves stroke recovery remains unanswered.

Prevention of OSA

The most important modifiable risk factor for OSA is excess body weight. In patients with OSA, weight loss has been shown to decrease the AHI.[160] Unfortunately, because obesity is increasing substantially in industrialised countries, the prevalence of OSA is anticipated to also increase. Thus, the most important public-health measure that could be taken to prevent OSA would be to promote avoidance or reversal of weight gain, especially in children.

Summary, controversies, and future challenges

Data from animal models, epidemiological studies, and randomised clinical trials provide strong evidence that OSA can cause hypertension, and that its treatment can lower blood pressure. Indeed, OSA might well be the commonest treatable cause of secondary hypertension. A consistent finding of trials on CPAP therapy in patients with heart failure and OSA is an improvement in left-ventricular systolic function and a decrease in activity of the sympathetic nervous system, two important clinical markers of adverse outcome in heart failure. OSA can provoke acute nocturnal myocardial ischaemia in patients with coronary artery disease, and in epidemiological studies, untreated OSA increased the risk of developing coronary artery disease. Non-randomised observational studies have consistently described an increased risk of fatal and non-fatal cardiovascular events associated with untreated OSA, independent of other risk factors, and a decrease in this risk in patients treated with CPAP for OSA. The effect of CPAP in patients who have had a stroke and who have OSA remains to be defined. Despite this substantial body of supportive evidence, large, long-term randomised trials are needed to delineate definitively the role of diagnosing and treating OSA in decreasing the incidence of, and mortality from, cardiovascular diseases (panel).

Undertaking such studies and implementing findings in clinical practice will pose several challenges. Currently, the only clear-cut indication for treating OSA is a complaint of daytime sleepiness.[2] Consequently, there is reluctance to deny such patients CPAP for extended periods in a clinical trial. Conversely, if excessive daytime sleepiness is not reported, CPAP treatment of even severe OSA has been shown not to improve neurocognitive function, alertness, or blood pressure.[138,161] Compared with the general population, patients with OSA and heart failure have significantly less subjective daytime sleepiness.[105] Nevertheless, in this population, treatment of OSA by CPAP improves surrogate markers of adverse cardiovascular prognosis.[139,140,141]

These findings give rise to complex issues. If a diagnosis of OSA depends on referral to a sleep laboratory, and if referral is contingent on symptoms of an OSA syndrome,

***Panel:* Cardiovascular consequences of obstructive sleep apnoea (OSA): unresolved issues**

Pathophysiology

- Are processes triggered acutely by OSA epiphenomena or independent pathophysiological mechanisms?
- Can animal models simulating human OSA be developed to explore its acute and chronic cardiovascular effects?

Epidemiology

- Does OSA cause or contribute independently to the development of type II diabetes, coronary artery disease, heart failure, cardiac arrhythmias, and cerebrovascular disease?
- If hypertension is an intermediary step between OSA and the development of cardiovascular diseases, how should one control for the potentially confounding effects of hypertension in examining these issues?

Treatment

- Does treating OSA decrease the risk of developing hypertension and cardiovascular diseases?
- In patients with cardiovascular diseases, does treating coexisting OSA decrease cardiovascular morbidity or mortality?
- If randomised trials are to be done to resolve these questions, how should the issue of leaving a control group with OSA untreated for lengthened periods be addressed?
- Can less cumbersome treatments for OSA be developed as an alternative to CPAP and other forms of positive airway pressure?

then contemporary approaches to screening might exclude a large population of individuals at risk of cardiovascular events from the potential benefits of participation in clinical trials, or from OSA management. Simple and cost-effective methods to screen for OSA will therefore need to be developed and tested in unselected community samples. Second, relief of sleepiness might not be the main target of treatment in many patients with OSA. If so, such patients might not sense short-term or long-term symptomatic relief from CPAP therapy and might thus abandon it. Therefore, better methods of encouraging adherence to long-term CPAP are needed. Finally, because of issues with bed-partner acceptance, nasal congestion, and nasofacial discomfort or claustrophobia, not all patients with OSA can or will accept CPAP therapy. Accordingly, there remains an unmet need for effective, well-tolerated alternative therapies for OSA.

Conflict of interest statement

Subsequent to the acceptance for publication of this Seminar, we received research grant support from Respironics Inc to develop a large clinical trial initiated and designed by ourselves.

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