International Journal of Cardiology 139 (2010) 7–16

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Obstructive sleep apnea and cardiovascular disease

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ARTICLE INFO

Article history:
Received 14 March 2009
Received in revised form 7 May 2009
Accepted 11 May 2009
Available online 7 June 2009

Keywords:
Obstructed sleep apnea
Cardiovascular diseases
Endothelial dysfunction
Nasal continuous positive airway pressure
Bi-level positive airway pressure

ABSTRACT

Obstructive sleep apnea (OSA) is a common yet an under-diagnosed sleep related breathing disorder affecting predominantly middle-aged men. OSA is associated with many adverse health outcomes, including cardiovascular disease. Common OSA associated/induced cardiovascular disorders include coronary artery disease, heart failure, hypertension, cardiac arrhythmias and stroke, which further increase morbidity and mortality in the OSA population. Endothelial dysfunction, coagulopathy, impaired sympathetic drive, oxidative and inflammatory stress are the pathophysiological pathways suggested for the development of cardiovascular disease in OSA.

The evidence would suggest that OSA should be considered as a cardiovascular risk factor, and is a treatable condition. Multiple studies using Continuous Positive Airway Pressure (CPAP) have shown improvements in the clinical state as well as retardation of disease progression. Therefore, patients with cardiovascular disease should be proactively screened for OSA and vice versa.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by episodes of total and/or partial collapse of upper airways alternating with normal breathing, leading to chronic intermittent hypoxia, oxygen desaturation, sleep fragmentation and cortical arousal. OSA is an important health problem [1] and its significant impact on the cardiovascular status underscores the importance of understanding the natural history of this syndrome. A selection of the many epidemiological studies establishing association between OSA and cardiovascular disorders is summarized in Table 1.

Apart from a full clinical assessment, the apnea hypopnea Index (AHI) (apneas and hypopnea per hour of sleep), level of oxygen desaturation and sleepiness during day hours are used commonly for OSA severity assessment. Indeed, the AHI is probably the most useful and objective way of classifying the severity of OSA as 'mild' (AHI 5–15), 'moderate' (AHI 15–30) or 'severe' (AHI>30) [2].

Of late, OSA has gained a lot of attraction as a cardiovascular risk factor. Although OSA coexists with other cardiac risk factors, a strong association with cardiovascular disorders independent of all confounding factors is seen and screening has been recommended for cardiovascular diseases such as hypertension amongst newly diagnosed OSA patients [3]. Convincing data emerging from numerous randomised controlled trials in OSA patients with hypertension (Table 2) or heart failure (Table 3) have demonstrated that the treatment with continuous positive airway pressure (CPAP) not only reduces the risk of developing cardiovascular disorders but also disease severity, hence improving symptom score.

In this review article, we will focus on epidemiological and complex pathophysiological connections of OSA with the initiation, development and progression of cardiovascular disease (CVD). We will also critically appraise the therapeutic and prognostic role of CPAP and other management options for OSA.

2. Search strategy

We searched using electronic databases [MEDLINE, EMBASE, DARE] for words 'Obstructed sleep apnea', 'cardiovascular diseases', 'endothelial dysfunction' 'nasal continuous positive airway pressure' and 'bi-level positive airway pressure'. Additionally, abstracts from national and international cardiovascular meetings were studied to identify unpublished studies. Animal studies were added exceptionally, as the literature search was focused and completed on studies carried out in human studies. We preferably added randomised controlled trials, meta-analyses and epidemiological studies, although – where relevant– practice guidelines and extra ordinary case reports have also been mentioned. Where necessary, relevant authors of these studies were contacted to obtain further data.

3. Epidemiology

OSA affects 9–15% of middle-aged adult population [4] and is more common in men [5]. It is therefore not surprising that the majority of epidemiological studies demonstrated male preponderance (Table 1) although some large studies have predominantly recruited females

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doi:10.1016/j.ijcard.2009.05.021

Table 1
Epidemiological studies on the relationship between obstructive sleep apnea and cardiovascular disease.

Author	Reference	*n*	Predominant gender with sleep apnea	Associated disease	Study design and findings
Shahar et al.	[16]	6424	Male	Stroke, heart failure, coronary artery disease	Large study, questionnaire based assessment, overnight polysomnography used to detect apnea hypopnea index, supported
Nieto et al.	[6]	6132	Female	Hypertension	Multi centre study, interview based assessment, manual blood pressure, demonstrated dose dependent rise in systolic and diastolic blood pressure with worsening sleep related breathing measures across all ages and ethnic groups
Peppard et al.	[88]	709	Male	Hypertension	Four year follow up study, Manual blood pressure monitoring, independent dose dependent response in hypertension was seen in association with sleep disordered breathing
Lavie et al.	[92]	2677	Male	Hypertension	OSA is independently and profoundly associated with hypertension
Hoffstein et al.	[19]	458	Male	Cardiac arrhythmias	Arrhythmia assessment by isolated ECG lead analysis, prospective study, prevalence of arrhythmia was comparable to nocturnal hypoxemia but not snoring. Rules out snoring as a cause of cardiac arrhythmias
Laaban et al.	[118]	169	Male	Heart failure	Left ventricular assessment by MUGA scan, prospective study of patients with polysomnographically diagnosed OSA, suggested impact of OSA on day time left ventricular systolic function
Peker et al.	[171]	62	Male	Coronary artery disease	Questionnaire based assessment, OSA and non-OSA patients were identified by full overnight sleep study, small study but statistically significant higher risk of CAD development in OSA group
Arzt et al.	[180]	1475	Male	Stroke	4 year follow up, apnea/hypopnea index of 20 or more was associated with increased risk of stroke ($p = 0.02$)

OSA= obstructive sleep apnea; CAD= coronary artery disease; MUGA scan= multi gated acquisition scan; ECG= electrocardiogram.

[6]. The prevalence and severity of OSA is probably higher in older age groups compared to the middle-aged population [7–9]. Given that many cardiovascular diseases increase with age, the coexistence of OSA with cardiovascular disease is common, sometimes making it difficult to appreciate if OSA causes cardiovascular disease or whether they are merely epiphenomenon.

Although a number of studies demonstrate the effect of age on the *development* of OSA independent of other confounding factors, precise data addressing the absolute change in disease *severity* with ageing in a given population, are lacking. The variations amongst different studies are large, where some authors claim limited [10] whilst others suggest marked deterioration in disease severity — as much as doubling after 10 years (calculated using AHI) in a given OSA population [11]. Like the increasing age, weight gain has also been shown to be a strong predictor of worsening OSA [12]. Of note, increased prevalence of OSA is seen in patients with congestive cardiac failure (CCF) [40%] [13], stroke [60%] [14] and end stage renal failure [50%] [15]. Indeed, OSA has been increasingly implicated in the initiation and progression of a myriad of cardiovascular disorders such as coronary artery disease (CAD), CCF [16], systemic hypertension (HTN) [17], pulmonary hypertension [18], cardiac arrhythmias [19] and stroke [20].

4. Pathophysiology

Although the association between OSA and CVD has been well known for decades, the underlying pathophysiological mechanisms have begun to unfold only recently. Endothelial dysfunction, systemic inflammation, metabolic dysregulation and coagulopathy are some of the potential mechanisms which have been proposed to explain this complex link. Whilst vascular, metabolic, humoral and autonomic factors have their own relative impact; it is yet unclear which one plays the central role (Fig. 1).

4.1. Endothelial dysfunction

A large body of evidence suggests that impaired endothelial function accompanies OSA [21–23]. The relationship between endothelial dysfunction and CVD is also well established and endothelial damage/dysfunction has a key role in the development of CVD [24]. Since the existence of endothelial dysfunction in OSA and CVD is probably not simply a mere coincidence and may well point to the possibility of a close underlying pathological links, it is imperative to understand the cellular biology and physiology of the endothelium in OSA.

The endothelium is a live tissue which is more than merely a separation between the blood and the vessel wall. The role of endothelium in the maintenance of vascular tone, cellular growth, coagulation and the modulation of the activity various blood constituents such as platelets and monocytes by secreting various vasoactive substances, is well recognized [25–29].

How and what starts the process of endothelial dysfunction in OSA? Although the precise causes of endothelial perturbation in OSA remain unknown, it is believed that hypoxia, inflammation or oxidative stress initiates the process [30,31]. The inter-relationships are probably multifactorial. For example, NO is a vasodilator secreted by endothelium, and a reduction in NO is associated with endothelial dysfunction [22], with an impairment of quantifiable endothelial mediated vasodilatory response [32–34]. OSA patients also have reduced NO levels as well as impaired endothelial mediated vasodilatation [35]. Nonetheless, it is uncertain what precisely leads to the reduced NO bioavailability in OSA. Inflammation and other cytokines may potentially play a role. Since the endothelium keeps a balance between several mediators and hormones, any imbalance per se – perhaps caused by inflammation – would result in adverse effects.

C-reactive protein (CRP), a marker of inflammation and an important predictor of cardiovascular events, has also been reported to be significantly elevated in OSA patients [36]. CRP has been shown to directly reduce NO synthase levels [30], supporting the role of inflammation in the development of endothelial dysfunction. On the other hand, an endogenous NO antagonist – asymmetric dimethylarginine (ADMA) – is higher in OSA patients [35] perhaps suggesting a different route to the development of endothelial dysfunction.

Nonetheless, there remains some uncertainty whether endothelial dysfunction is the cause or the effect of some cardiovascular problems (such as hypertension) found in OSA. However, studies have shown a strong association between OSA and endothelial dysfunction, even in normotensive patients [37]. Furthermore randomised trials using nasal CPAP have shown beneficial effects on endothelial dysfunction in OSA [38].

4.2. Autonomic dysregulation

A dysfunctional autonomic system has been associated with OSA [39] and though the autonomic nervous system plays a key role in

Table 2
Randomised clinical trials of use of continuous positive airway pressure in obstructive sleep apnea patients with hypertension.

Author	Ref	Study design	Findings	Comment
Mills et al.	[98]	50 patients were randomised to therapeutic or sub-therapeutic CPAP for 2 week, to detect any effect on catecholamine clearance	Significant reduction in systolic as well as diastolic blood pressure and concurrent increased nor epinephrine clearance in CPAP arm suggest role of latter in hypertension in OSA	Single blinded study, short duration, manual blood pressure recordings
Faccenda et al.	[99]	Placebo controlled cross-over study of the effects of 4 weeks of CPAP or oral placebo on 24-hour blood pressure in 68 patients (predominantly male)	Improvement in diastolic blood pressure ($p=0.04$) was noted especially in patients with nocturnal desaturation or with prolonged CPAP use. Daytime sleepiness also improved	Normotensive study population, deduction of mild OSA from study, lack of washout period and short study duration
Robinson et al.	[156]	Double blind trial randomising 35 patients to either therapeutic or sub-therapeutic CPAP for 2 months with ambulatory blood pressure monitoring	CPAP does not reduce mean blood pressure in non-sleepy hypertensive OSA patients	Small study, does not individually comment on systolic and/or diastolic blood pressure. Does not involve mild OSA
Becker et al.	[157]	32 patients were randomised to therapeutic or sub-therapeutic CPAP. For 9 weeks.	Interestingly reduction in AHI was noted in both groups however significant drop in mean, systolic and diastolic blood pressure was only noted in therapeutic CPAP arm	First study to suggest drop in blood pressure with CPAP, good compliance in groups, small study size, however ambulatory blood pressure monitoring may give spuriously low readings
Dorkova et al.	[158]	32 OSA patients were given CPAP for 8 weeks with pre and post CPAP assessment of various inflammatory and endothelial dysfunction markers with blood pressure changes	Reduction in systolic as well as diastolic blood pressures was noted	Small study, investigated the role of metabolic syndrome, oxidative stress and inflammation in the causation of CVD
Vgontzas et al.	[159]	In this study of 16 obese OSA patients several plasma markers and blood pressure were assessed with its response to CPAP	Improvement in overall blood pressure was recorded after 3 months on CPAP	Small study, emphasis of the link between OSA and inflammation
Barnes et al.	[163]	Comparison of the effects of CPAP and oral placebo or mandibular device (MAS) amongst 110 OSA patients, for 3 months. Objectives were to observe any improvement in sleepiness and quality of life	Small nocturnal reduction of blood pressure noted with MAS compared to CPAP besides symptomatic improvement	Considerable female population, this is one of the first studies to show significant improvement in OSA hypertensive patients with MAS, though the correct method to use was questioned in some. Included mild OSA as well.
Campos-Rodriguez et al.	[172]	In this double blind trial 4 weeks randomisation of OSA patients with treated hypertension, to therapeutic CPAP verse sub-therapeutic CPAP was done	Statistically insignificant drop in mean blood pressure in CPAP group but no change in systolic, iastolic or nocturnal blood pressure.	Reasonable size double blind study, short duration, inadequately powered to detect blood pressure variations
Hia et al.	[173]	24 men with hypertension and with or without OSA were randomised to CPAP for 3 weeks.	CPAP arm showed reduction in nocturnal systolic and diastolic blood pressure.	Small study, only male investigated,
Barnes et al.	[174]	28 predominantly male patients with mild to severe OSA randomised to CPAP or oral placebo for 8 weeks to assess neurobe havioral improvement and reduction in blood pressure.	Neurobehavioral indices improved in both arms however subsidiary analysis for blood pressure did not show significant difference.	Single blinded study, high rate of patients' with drawal and doubts about CPAP compliance. only 7 patients were hypertensives and analysis failed to show significance of CPAP is such a small group.
Barbé et al.	[175]	To detect the effect of CPAP on blood pressure and quality of life of non-sleepy OSA patients, 54 patients with severe OSA were randomised to nasal CPAP or sham CPAP for 6 weeks	Non-sleepy patients with severe OSA do not get worthwhile benefit from CPAP such as reduction in blood pressure and improvement in cognitive impairment	Multicenter placebo controlled blinded study, short CPAP duration.
Campos-Rodriguez et al.	[176]	In this prospective long-term trial (24-month follow up) ambulatory blood pressure monitoring was carried out to investigate any improvement in blood pressure parameters	CPAP has a dose dependent response with reduction in blood pressure	Small study, same group published opposite findings in a double blinded but similar trial in short term (4 weeks of CPAP)

CPAP= continuous positive airway pressure; MAS= mandibular advancement splint; OSA= Obstructive sleep apnea; CVD= cardiovascular disease.

mediating cardiovascular changes during OSA, parasympathetic nervous system activity during sleep has not yet been sufficiently investigated. As previously considered, a dysfunctional autonomic system could be due to obesity, although robust data are limited [40]. Instead, repetitive hypoxia due to airway collapse in OSA patients may be the cause of an overactive sympathetic system [41]. Similarly, central and peripheral chemorecepters have a close yet complex relationship with ventilation/breathing [42] and the overactivation of such mechanisms found in OSA patients contributes to exaggerated sympathetic activity [43], which continues even during the day hours [44]. An altered cardiovascular variability, reflecting deranged autonomic cardiovascular regulation, may not only predict morbidity and mortality in patients with diabetes [45], heart failure [46], and myocardial infarction [47], but also represent an independent risk factor in normal and hypertensive subjects [39,48]. This may be the case also for patients with OSA, who are characterized both at night and during wakefulness by increased plasma levels of norepinephrine, elevated muscle sympathetic nerve activity, and altered heart rate variability [48,49], Similarly, widely prevalent hypertension and blood pressure oscillations in OSA are considered poor prognostic signs and predict target organ damage in hypertensive patients [50,51].

Evidence is available that long-term treatment with continuous positive airway pressure (CPAP) results in a significant improvement of these autonomic indices in OSA patients [43]. Treatment of OSA with oxygen reduces sympathetic tone, and the correction of hypoxia with 100% oxygen (not necessarily with CPAP) results in chemoreceptor deactivation, thus reducing sympathetic activity and normalizing haemodynamic parameters. Larger studies are required to assess the effects of interventions for OSA on autonomic function.

4.3. Haemostasis

Coagulopathy and abnormal platelet aggregability play important roles in the pathogenesis of atherothrombotic disease [52]. Although the impact of OSA on platelets per se is controversial; as any effect may be secondary to endothelial dysfunction [53], raised nocturnal catecholamine levels [28], or be simply a response to apnoeic episodes [54]. Regardless of the aetiology of platelet dysfunction, most studies have noted improvements in platelet status with the correction of hypoxia using CPAP [55].

The effects of sleep disturbed breathing on red blood cells are less well studied, and in an observational study of 624 OSA patients, small

Table 3
Studies using continuous positive airway pressure in obstructive sleep apnea patients with heart failure.

Author	Ref	Study design	Conclusion	Comments
Mansfield et al.	[115]	Open trial using CPAP for 12 weeks in OSA patients in middle-aged population to detect improvement in heart failure	Substantial improvement in cardiac failure and quality of life	predominantly male, large number of drop outs, manual blood pressure recording, diastolic dysfunction not assessed
Kasai et al.	[155]	Aim of the study was to detect any prognostic benefits of CPAP in heart failure with OSA. 88 OSA patients with moderate to severe disease were randomised to CPAP or observations	CPAP treatment group significantly reduces morbidity and mortality depending upon strict compliance	Good comparative study for assessing the prognostic significance of CPAP in this particular group
Kaneko et al.	[160]	24 OSA patients were randomised to either CPAP with medical therapy or medical therapy alone for 1 month	CPAP significantly reduced heart rate, blood pressure and left ventricular dimensions and ejection fraction	Well conducted open study, inclusion of ischaemic and non-ischaemic patients, small study
Wang et al.	[161]	To see any effect of CPAP on mortality in heart failure patients with OSA, 164 patients were recruited and control group involved untreated OSA patients	Untreated OSA with heart failure is high risk for mortality	A good prospective study with median follow up of over 7 years
Alchanatis et al.	[177]	CPAP was randomised again observation in fifteen of twenty six patients for 3 months with regular transthoracic echocardiogram	CPAP significantly improves ventricular function especially diastolic, also drop systolic blood pressure	Small study. Echocardiography induced possible observer bias, control group comprised of non-OSA individuals, mild disease excluded from study
Arias et al.	[181]	In this study of 42 patients sham CPAP against effective CPAP in moderate OSA patients for 12 weeks	Impaired relaxation is a prominent finding in OSA patients. Effective CPAP treatment improves E/A ratio considerably (p(0.01)	Double blind yet small study, only male population included, echocardiography related observer bias may be another factor

OSA= obstructive sleep apnea; CPAP= continuous positive airway pressure.

yet statistically significant hematocrit changes were observed in patients with lower nocturnal oxygen saturations [56]. Finally, other coagulation factors, such as plasma fibrinogen, are elevated in OSA [57] and long-term CPAP appears to reduce coagulation factor VII activity [27]. Nevertheless, the effects of OSA on haemostasis and thrombosis still remain a controversial area due to inadequate evidence [58].

4.4. Oxidative stress

OSA is a state of increased oxidative 'stress' and the latter has a diverse role in the development of cardiovascular disorders. [59]. Repetitive hypoxic episodes lead to intra-cellular structures to adapt to lower oxygen levels. Therefore, the availability of normal oxygen concentration to these cells during the normoxic phase leads to the production of reactive oxygen species (ROS), which have the ability to oxidize cellular products, lipids and proteins. ROS from neutrophils and monocytes is augmented in OSA patients and has a close relationship with classical inflammatory mediators (such as bradykinin) which also suggests that systemic inflammation is one of the contributory factors in ROS production [60]. Interestingly, ROS contributes to endothelial dysfunction by upregulating adhesion molecules and diminishing NO synthase activity, thus augmenting NO breakdown and ultimately, leading to diminished NO levels [61]. If not corrected, the resultant endothelial damage/dysfunction leads to atherosclerosis [62]. Case control studies have shown the tendency of neutrophils to produce more ROS in OSA, a phenomenon which is reversible with CPAP therapy

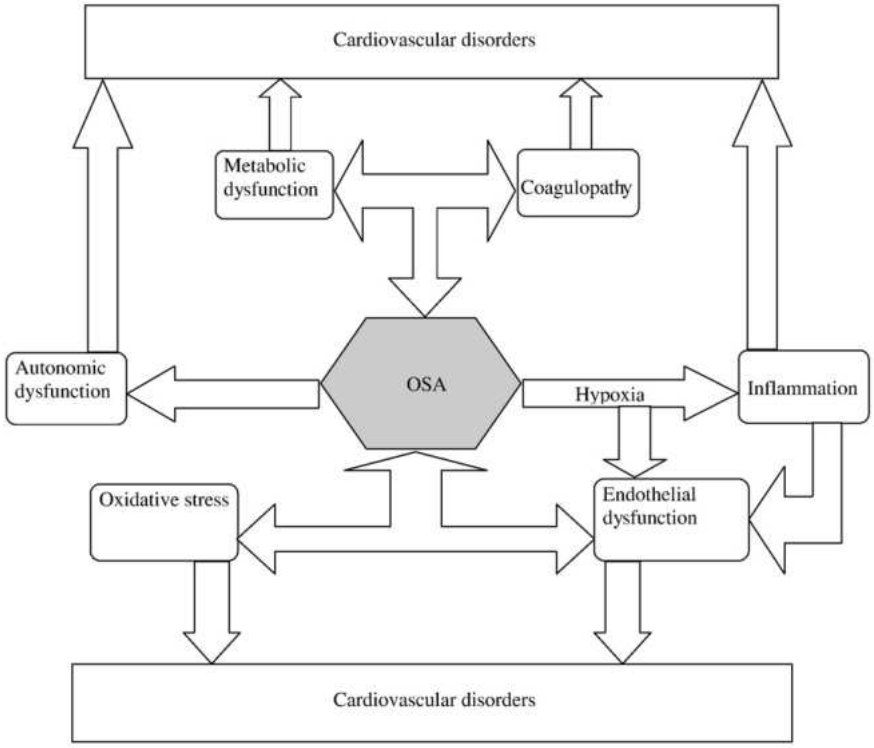

Fig. 1. Pathophysiological mechanisms linking obstructive sleep apnoea to cardiovascular disorders. OSA = obstructive sleep apnoea.

[63]. Similarly, an enhanced expression of adhesion molecules in monocytes and an increased ROS production in OSA patients that responds to CPAP also indicates inflammation related oxidative stress [64]. Hence, both experimental and human studies are consistent with the concept that intermittent hypoxia, associated with recurrent apneas, represents a form of oxidative stress. Whatever the source of ROS, these studies beg the question of whether scavengers can be used as an effective therapeutic intervention in alleviating the cardiovascular disturbances associated with recurrent apneas.

4.5. Inflammation

Observational studies have shown that inflammation is associated with various vascular disorders [65–67], as well as OSA [68]. Raised CRP levels result in the direct as well as indirect (by monocytes activation) reduction of NO synthase [30,69]. OSA increases levels of various adhesion molecules, such as intercellular adhesion molecule [70] and vascular cell adhesion molecule [71], in endothelial cells as well as in neutrophils, thus promoting endothelial cell adhesiveness and oxidative stress. Hypoxia and sleep deprivation also modulates the expression of inflammatory mediators, such as interleukins and tumor necrosis factor alpha [68]. CPAP therapy reduces inflammation, evident by its reducing various circulating inflammatory mediators such as Inter-cellular adhesion molecule-1 (ICAM-1), Interleukin-8 (IL-8) [70] and CRP [72].

4.6. Metabolic dysfunction

There is a well-recognized association of insulin resistance with OSA [21] as well as with atherosclerosis [73], suggesting that metabolic disturbances may well be a significant link between OSA and CVD. The severity of sleep apnea appears to correlate with the degree of insulin resistance. Indeed, severe OSA is accompanied by a 5-fold increase in the risk of overt diabetes mellitus [74]. High insulin levels in non-obese OSA patients [75] have been reported and worsen with increasing AHI and oxygen desaturation levels [73]. Thus, obesity per se may not the sole determinant of insulin resistance, as previously believed [76].

Leptin is a hormone involved in satiety, body weight control and fat distribution [77] is also regarded as an independent risk factor for CAD [78]. Although leptin is also elevated in obese individuals [79] it increases platelet aggregability regardless of the body fat distribution [80]. Correction of OSA reduces leptin levels, as well as intra abdominal fat levels [81]. However, treatment with CPAP does not show any consistent improvement in glucose tolerance [82].

5. Obstructive sleep apnea and cardiovascular disease

The most serious complications of OSA include heart failure, coronary artery disease (CAD), arrhythmias, stroke, systemic hypertension and pulmonary hypertension. Animal as well as human studies have revealed that acute haemodynamic disturbances in physiological parameters [83, 84] and adverse effects on left ventricular pressures and dimensions are associated with the changes in intrathoracic pressures related to OSA [85,86].

5.1. Hypertension

Large epidemiological studies have demonstrated a strong and consistent link between OSA and hypertension (Table 1) [87–90]. A vast proportion of OSA population (up to 95%) has been reported to have hypertension [91,92]. Though the causative pathways remain debatable; cross sectional analyses of several studies suggest that OSA is an independent risk factor for high mean, systolic and diastolic blood pressures [6,40,92]. Therefore, current hypertension management guidelines have acknowledged OSA as an identifiable and independent cause of hypertension and recommended blood pressure screening amongst OSA patients [3].

There are several theories on the underlying mechanism of raised blood pressure in OSA patients. Oxygen desaturation during apnea/hypopnea increases sympathetic activity [39,40,48] secondary to micro-arousal at night, and nocturnal fluctuations in catecholamines [93–95] are some of the more prominent factors in the causation of hypertension. Carlson et al. [96] reported augmented sympathetic activity in non-hypoxic OSA patients even during day hours, which were later supported by other studies [41]. Finally, endothelial dysfunction – leading to failure of endothelial dependent and independent vasodilatation of resistant vessels – results in raised peripheral vascular resistance and consequently, hypertension.

Increasing evidence suggests that CPAP therapy in OSA could improve blood pressure [97] in part by improving endothelial dysfunction as well as the correction of triggering factors, such as sympathetic system overactivation [98] and hypoxia [99]. CPAP therapy has been shown to improve autonomic balance in small studies [100]; however concomitant reduction in blood pressure in OSA has been questioned by some [144]. Indeed in some isolated studies hypertensive OSA patients on antihypertensive therapy concluded that beneficial effect of CPAP on lowering blood pressure extends beyond pharmacological therapy [101]. Others report improved nocturnal catecholamine levels [102] with improvements in nocturnal as well as daytime blood pressures with the use of CPAP. Owing to the link between severity of OSA and incidence of hypertension [101], CPAP therapy has been extensively studied in patients with moderate to severe OSA (Table 2). Although mild OSA is also linked with elevated blood pressure, limited evidence suggests that use of CPAP is not been associated with a significant decline in blood pressure [103].

5.2. Coronary artery disease

Many epidemiological studies link OSA with CAD [104–107] (Table 1). These consistently report a close and strong presence of CAD in OSA patients regardless of other risk factors [107]. Circulatory physiology is greatly affected by change in sleep pattern, OSA related hypoxia, hypercapnia, blood pressure surges due to sympathetic overactivation, and the acute imbalance of vasoactive hormones. These changes cannot only provoke acute coronary syndromes but also, their persistence ultimately leads to chronic consequences such as heart failure. Interestingly, reversible Electrocardiogram (ECG) changes can be noted in OSA patients without significant CAD [108]. The use of CPAP in OSA patients reduces incidence of new coronary events compared to controls, as observed by a large prospective trial [109]. Moreover, in a randomised study, CPAP has been found to reduce mortality [110], though the mechanism largely remains unknown.

5.3. Heart failure

Many observational studies have linked OSA with systolic as well as diastolic impairment of the left ventricle (Table 1) [111,112]. Patients with heart failure per se have a high prevalence of OSA [113]. The precise reasons are uncertain but odema of neck soft tissues makes pharyngeal tissue prone to collapses thereby leading to further tightening of airways [114].

Since OSA is strongly associated with CAD and hypertension, this makes it difficult to sketch out the direct relationship between systolic dysfunction and OSA. A direct link is suggested by normalization of left ventricular (LV) function with CPAP treatment, even in normotensive patients [115]. Furthermore, OSA associated hypertension, exaggerated adrenergic responses and hormonal imbalance may all predispose to hypertensive heart failure. In addition, increased aortic stiffness [116] and rapid changes in intrathoracic pressures inducing LV pressure changes [117] may all contribute to myocardial stress, leading to systolic dysfunction.

As in most studies transthoracic echocardiography (TTE) has been used as diagnostic tool, however in OSA patients where obesity is commonly prevalent, the efficacy of TTE has been questioned.

Nevertheless, Laaban et al. [118] studied a large cohort of OSA patients without known coronary artery disease and investigated cardiac functions using multiple-gated equilibrium cardiac imaging (MUGA). Poor LV systolic function was reported amongst OSA.

Mechanisms leading to diastolic dysfunction in OSA are less clear. Animal studies have shown intermittent hypoxia induces myocardial hypertrophy and persistently high blood pressure in rats [119]. Another theory suggests that a rise in afterload and a reduction in fractional shortening occur in response to intermittent airway collapse, leading to impaired relaxation [120]. Impaired relaxation could also be due to increased left ventricular thickness and hypertrophy which has been reported even in normotensive OSA patients [121]. Other studies based on the echocardiographic findings have concluded that OSA independently does not show any adverse impact on ventricular function in OSA [122]. Reduced right ventricular contractility, as well as impaired ejection fraction (EF) [123] and hypertrophy [124] have all been reported in OSA patients. These findings may be a direct consequence of OSA related disturbed haemodynamics [125] or secondary to pulmonary hypertension, which itself is prevalent in OSA [126,127]. Successful treatment of OSA also improves right ventricular function [128], and improvement in LV dimensions and contractility have been noted after CPAP (Table 3). The effect of CPAP one exercise capacity in OSA patients with CCF has not been studied extensively. I Nonetheless, in some small studies, CPAP seems to increase exercise capacity in heart failure patients regardless of coexistence of OSA [129,130].

5.4. Cardiac arrhythmias

A wide spectrum of conduction disturbances, ranging from premature ventricular contractions (PVCs) to complex arrhythmia such as complete heart block and ventricular tachycardia, have been reported in OSA [131]. In one small study ($n=71$), there was a higher incidence of life threatening ventricular arrhythmias amongst patients with sleep disordered breathing [131], which may possibly explain the observed abnormal circadian pattern of sudden death amongst OSA patients [132,133]. Epidemiological studies demonstrating the arrhythmia burden of OSA are summarized in Table 4.

The conclusions of these studies are hugely variable – some have found a high risk of benign ectopics [134] whilst others suggest an increased risk of more sinister conduction disturbances – such as complex heart block and ventricular tachyarrhythmias – amongst OSA patients. It is therefore difficult to conclude whether bradyarrythmias are more common as compared to tachyarrhythmias.

Emerging evidence supports a strong association between tachyarrhythmias, especially atrial fibrillation (AF) and OSA [135]. Of note, OSA and AF share risk factors such as hypertension, coronary artery disease and heart failure. Studies in heart failure patients suggest an increased prevalence of AF in patients with sleep apnea [13,113] and the presence of OSA also predicts pre-discharge AF after cardiac surgery [136] and recurrence post ablation [137]. Although the exact mechanism of development of AF in OSA is unclear, OSA associated intermittent fluctuations in blood pressure, structural myocardial remodeling [121], increased sympathetic activity and changes in blood gases [113] can make the patient more susceptible to AF. Although CPAP treated OSA patients have better outcomes with regard to reduced risk of recurrent AF after electrical cardioversion [138], the role of CPAP in primary prevention of AF in OSA patients is unknown.

Bradycardia is highly prevalent in OSA patients [139,140]. Although pauses up to 2 s can be observed in apnea episodes in otherwise healthy individuals [141], the prolongation of pause duration has been noted in OSA patients [142]. Some degree of conduction block has been described in up to 10% of OSA patients, especially during REM sleep [143]. Recently a small study using insertable loop recorder in 23 OSA patients with at least moderate disease questioned the usefulness of 24-hour holter monitor, as the results suggest that bradyarrythmias are more frequent in OSA and the loop recorder was superior to 24-hour holter in detecting significant pauses (>3 s) ($p=0.03$); furthermore consistent with the most available data, CPAP significantly ameliorates these arrhythmias [144].

Hypoxia probably plays an important role in the genesis of bradycardia with improvement in heart rate on oxygen administration [145]. CPAP – even in the absence of sinus or AV nodal disturbances – reduces apnea associated bradyarrythmias [131]. Atrial overdrive pacing [146], perhaps by reducing the number of arrhythmias, significantly reduces these episodes in OSA as well as CSA, further lowering the risk of sleep associated rhythm disturbances.

5.5. Cerebrovascular disease

Epidemiological studies link OSA independent of other risk factors, with increased risk of stroke (Table 1) [20,147,148]. Sleep disordered breathing is also highly prevalent amongst stroke patients [149] due to associated sub-total/total paralysis of facial and pharyngeal muscles. Unsurprisingly, OSA is also regarded as a poor prognostic marker in stroke patients [150] partly due to poor ventilation secondary to posture related problems amongst stroke patients. In addition, OSA is regarded as a marker of poor outcome in stroke patients. A small study of 24 stroke presence of OSA was significantly associated with adverse prognosis [20,150]. Nevertheless further data is needed to determine whether OSA is related to cerebrovascular morbidity independent of other vascular risk factors.

Hypertension, atherogenesis, hypercoagulability, impaired endothelial dysfunction, strong association with AF and changes in cerebral haemodynamics may all contribute [151]. In some instances the changes in haemodynamics may cause up to 80% fall in cerebral blood flow [152], contributing to cerebrovascular events in the OSA population. Currently there are little data on the effect of CPAP in OSA in post stroke settings to establish any symptomatic and/or prognostic benefits. Limited data indicates poor outcome with CPAP use in OSA [153]. Finally larger studies targeting primary risk reduction of stroke with the use of CPAP in OSA patients are much required.

6. Management strategies

OSA is an emerging health challenge partially because of its strong association with many cardiovascular disorders but more importantly due to its individual recognition as an established cardiac risk factor. Close involvement of OSA in the development of heart failure and hypertension might suggest that treatment of OSA might ameliorate these secondary conditions. The current general consensus is that OSA should be treated with CPAP for ventilatory support as well as a tool for the secondary prevention of cardiac problems [151]. Whilst limited data suggest reduction in the incidence of cardiac manifestations with early use of CPAP [154]; existing and/or secondarily induced cardiovascular diseases should still be treated on their own merit.

OSA is a relatively under-diagnosed condition and hence, the majority of OSA patients would have developed a cardiovascular condition before a formal diagnosis of OSA is made. Indeed CPAP emerged as a novel therapeutic tool; its prognostic advantages have also been demonstrated

Table 4
Observational studies on the obstructive sleep apnea and its association with cardiac arrhythmias.

Author	Reference	*n*	Tachyarrhythmias %	Bradyarrythmias %	Ectopics %
Guilleminault et al.	[139]	400	3	19	0
Becker et al.	[141]	239	0	10	0
Flemons et al.	[140]	76	0	6	1
Miller et al.	[178]	23	0	13	9
Bolm-audorff et al.	[179]	20	15	0	36
Tilkian et al.	[143]	15	13	46	67

in recent trials [155]. From the cardiac perspective, most of the studies on OSA have been done in population with preexisting hypertension or other cardiovascular disorders. The efficacy of CPAP in hypertension in some open, single and double blind studies has been challenged by some, whilst investigating a range of blood pressure parameters such as systolic, diastolic, mean 24-hour, nocturnal and day time blood pressure [156,157]. Indeed most of the current evidence supports the use of CPAP in reduction of blood pressure with concomitant improvement in patients' cognition and daytime sleepiness [98,99,149,154,158,159].

In the last decade, various studies have determined the effect of nasal CPAP on heart failure associated with OSA [115,160]. Although most were of a small size, they have shown improvements in symptoms, LV dimensions and systolic (as well as diastolic) cardiac function. However, assessments were based on TTE which is not infallible; also, there were significant gender differences and in some, mild OSA was excluded. Few studies have focused on the prognostic significance of nasal CPAP but the results are promising, with a reduced mortality and hospitalization in patients treated with nasal CPAP [155,161]. However, compliance with CPAP is a well-recognized issue [162] which necessitates an acceptable alternative with at least similar or more advantages. Barnes et al. [163] have used a mandibular assisted splint (MAS) with improvements shown in clinical outcomes, although this was not superior to nasal CPAP, and the impact on prognosis has not been determined. The oral appliances have also been studied in 28 OSA patients to determine the impact on brain natriuretic peptide (BNP) and left ventricular dimensions [164]. Though the author concluded significant reductions in elevated BNP levels, these benefits do not seem to translate into (echocardiographic) cardiac functional improvements, at least in this small study. Surgical treatment of OSA [165] has not gained much popularity, due to potential operative risks and no prognostic value. A small randomised trial investigated the effects of vocal training with the didgeridoo on AHI and OSA symptoms [166], and found a significant beneficial reduction of AHI with the use of the instrument. However it is not clear whether the instrument was used as 'add on' or as 'first line' therapy.

Antihypertensive drugs have shown to have beneficial effects on endothelium, whether directly or indirectly [167,168]. As inflammation and coagulopathy caused by OSA induced hypoxia leads to atherogenesis, the use of aspirin and statins may help [169,170].

7. Conclusion

Observational studies have demonstrated that OSA is a highly prevalent condition in all age and gender groups, carrying a serious risk of cardiovascular morbidity and mortality. Now regarded as an independent cardiac risk factor, OSA also leads to the development of other cardiovascular risk factors, such as hypertension. Hypoxia, oxidative stress, autonomic dysfunction and endothelial dysfunction have all been attributed to sleep associated disturbed ventilation, and implicated in atherogenesis. The dysfunctional endothelium also plays a pivotal role, by hormonal imbalance and impairment of vasomotion which lays the foundations for CVD. Moreover, the coexistence of OSA with metabolic syndrome, obesity and diabetes mellitus makes cardiovascular complications a logical consequence. OSA related symptoms such as insomnia, day time somnolence and poor exercise capacity could profoundly affect individual daily life. Therefore early recognition and treatment of OSA, supplemented by educational, behavioral and supportive interventions, may improve clinical status as well as the long-term outcome. Further understanding of basic pathophysiology behind the generation of cardiovascular disorders in OSA patients may identify possible new targets for adjunct therapies such as use of anti-inflammatory drugs.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [182].

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