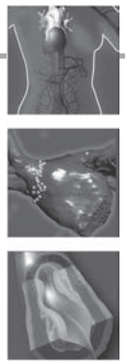

Obstructive sleep apnea, coronary artery disease and continuous positive airway pressure therapy

Obstructive sleep apnea (OSA) has emerged as a potential risk factor for coronary artery disease (CAD). At basic research and tissue levels, OSA has been shown to be associated with sympathetic hyperactivity, endothelial dysfunction, inflammation, and platelet and coagulation pathways activation. Epidemiological studies have shown a high prevalence of OSA among patients with CAD. Moreover, it appears that patients with both CAD and OSA have poorer outcomes, and this may be reversible by OSA treatment using continuous positive airway pressure therapy. The objective of this article is to evaluate OSA as a risk factor for CAD. Emphasis is placed on reviewing existing literature on the association between OSA and the effect of continuous positive airway pressure. Limitations of current studies are addressed and the required focus for future research is also highlighted.

KEYWORDS: acute coronary syndrome ■ continuous positive airway pressure ■ coronary artery disease ■ obstructive sleep apnea

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Obstructive sleep apnea (OSA), a respiratory disorder of sleep, is characterized by recurrent episodes of complete or partial upper airway obstruction, resulting in intermittent oxygen deprivation (Figure 1). The primary abnormality in patients with OSA is an anatomically small pharyngeal airway, commonly due to structural features or obesity, resulting in increased soft tissue structures. The breathing disturbances and intermittent hypoxia experienced result in sympathetic activation, surges in blood pressure, production of vasoactive substances and activation of inflammatory and procoagulant pathways. Severely affected patients have neurocognitive and neurobehavioral impairment and are at risk of adverse cardiovascular outcomes.

OSA is widely prevalent in the general population, with an estimated 3–7% in adult males and 2–4% in adult females [1]. Strong clinical evidence has demonstrated a clear association between OSA, hypertension and cardiovascular diseases [2], recognizing OSA as an emerging cardiovascular risk factor. In addition, an increased mortality in coronary artery disease (CAD) patients with coexisting OSA has been documented in several long-term outcome studies [3,4].

Acute coronary syndrome (ACS), one of the life-threatening manifestations of CAD, encompasses a spectrum of clinical presentations with varying degrees of progression to myocardial infarction. In recent years, the body of literature supporting a causal link between OSA and ACS has grown [5,6]. Identification of OSA in ACS patients is especially important as untreated severe OSA in cardiovascular disease can trigger worse cardiovascular outcomes.

In this review, the authors summarize the data on the relationship between OSA and CAD and on the potential role of OSA therapy in CAD using continuous positive airway pressure (CPAP) on cardiovascular outcomes.

Epidemiology studies

It is estimated that a minimum of 6% of the adult population has at least moderate OSA [7]. This figure varies with ethnicity, gender and age [8,9]. There is growing interest in the adverse cardiovascular consequences accompanying OSA. Marin *et al.* performed a population-based observational study comparing the incidence of cardiovascular events after a mean follow-up duration of 10 years in five groups of men: healthy men, simple snorers, patients with untreated mild or moderate OSA, patients with untreated severe OSA and patients with OSA treated with CPAP therapy [10]. Multivariate analysis with adjustments for confounding factors showed a significantly higher incidence of fatal cardiovascular events (death from myocardial infarction or stroke) and nonfatal cardiovascular events (nonfatal myocardial infarction or stroke, coronary artery bypass surgery and percutaneous transluminal coronary angiography) in patients with untreated severe OSA compared with the other groups.

This is consistent with results from the Sleep Heart Health study, which found OSA to be a significant predictor of prevalent coronary heart

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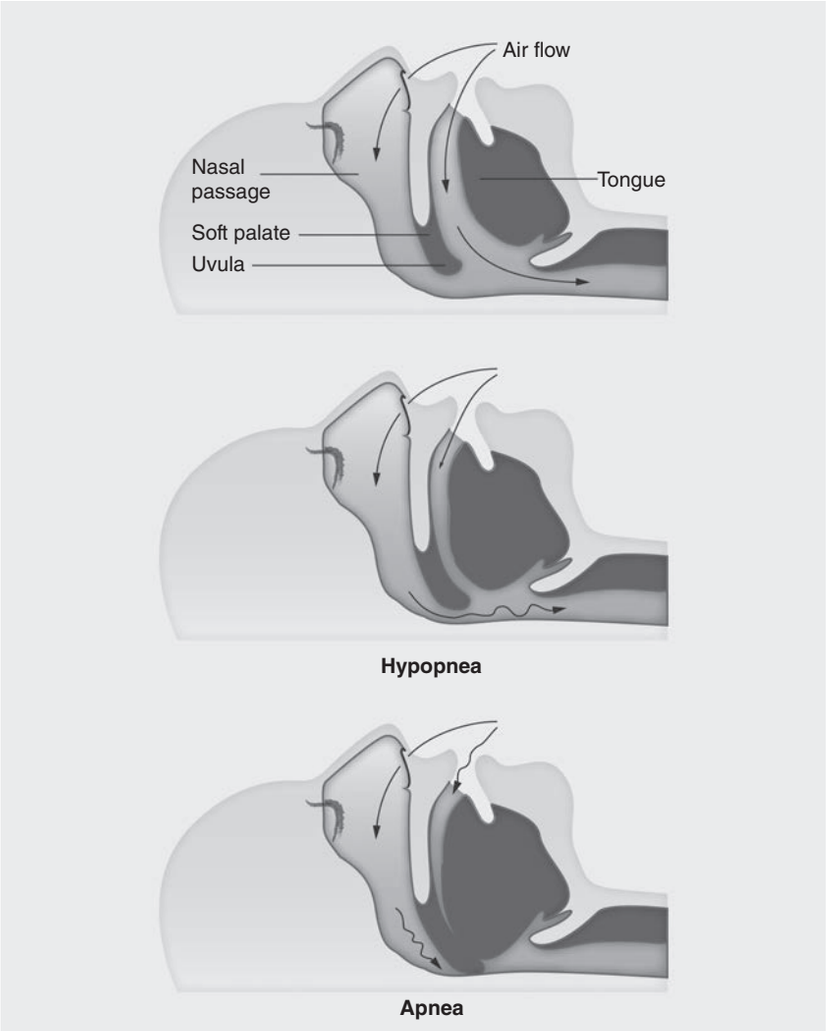

Figure 1. Pathophysiological mechanism of obstructive sleep apnea.
Adapted with permission from [81].

disease in men of 70 years of age [11]. The data also evidenced a 68% increased likelihood of developing coronary heart disease in men between 40 and 70 years of age with severe OSA (apnea–hypopnea index [AHI] 30) as compared with those without OSA (AHI <5). It is interesting to note, however, that no association between OSA and prevalent coronary heart disease in women or older men was observed in the study. It might be possible that a pathological difference in OSA response between males and females exists or that the protective effect of the female gender on cardiovascular risk may extent to OSA-related risks as well. However, a recent study found a correlation between severe OSA and cardiovascular death in women [12]. Evidence of a higher mortality from cardiovascular death in women compared with men was also previously reported [13]. Future studies to this end accounting for confounding factors are eagerly awaited.

When looking specifically at ischemic heart disease, a tightly matched case–control study on 62 acute coronary care patients confirmed OSA as an independent predictor of both angina pectoris and myocardial infarction [14]. Present reviews of OSA prevalence in ACS patients also show a much higher rate of occurrence in comparison with the general adult population.

In a cohort of 120 Asian patients presenting with acute myocardial infarction, an overnight sleep study was performed between day 2 and day 5 after admission. The prevalence of previously undiagnosed moderate/severe OSA (AHI >15) was 65.7% (Figure 2) [15]. Similarly, a clinical study performed in the USA reported that 66.4% of patients had OSA (AHI >10) in a cohort of 104 ACS patients [16]. Another sleep study carried out in Portugal found an OSA prevalence of 43.1% in a group of ACS patients [17].

The above mentioned studies indicate that OSA is more common in the CAD population and an increased risk of CAD appears to be present in OSA patients. However, whether there is a differential correlation of OSA and CAD with age, ethnicity and gender has not been determined.

Pathophysiology of OSA on atherosclerosis & thrombosis

Atherosclerotic plaque accumulation and thrombosis have been recognized as the main culprits for CAD [18]. Their mechanisms, though complex and incompletely understood, can be implicated in inflammation, sympathetic nervous system overactivity, platelet reactivity and endothelial dysfunction [19]. Such cardiovascular stressors are also part of the pathophysiological components of OSA as a result of intermittent severe hypoxemia, CO_2 retention, changes in intrathoracic pressure and sleep fragmentation experienced. The risk of CAD may be further heightened by the presence of comorbidities such as arterial hypertension and metabolic syndrome, which are evidently associated with OSA [20,21].

■ Sympathetic nervous system overactivity

During recurrent apnea episodes, peripheral and central chemoreceptors are excited, eliciting increased sympathetic vasoconstrictor activity [22]. OSA can also induce an increased chemoreflex, sleep arousal and a reduction in the sensitivity of pulmonary stretch receptors, limiting their ability to inhibit central sympathetic discharge, which further contributes to sympathetic activation [23].

It has been reported that the overactivity of the sympathetic nervous system persists during daytime as well, resulting in prolonged sharp adrenergic increases in blood pressure and heart rates [24]. Increased plasma levels of norepinephrine, elevated muscle sympathetic nerve activity and altered heart rate variability are also observed in OSA patients, both at night and during wakefulness [25,26]. Elevated plasma levels of angiotensin II and aldosterone may also contribute to the blood pressure surge of chronic intermittent hypoxia in OSA patients [27]. In the presence of coronary atherosclerosis with simultaneous hypoxemia and increased myocardial oxygen demand, such responses may trigger acute nocturnal cardiac ischemia. This association has been demonstrated in several studies [28,29].

Moreover, there is evidence of a significant role for autonomic nervous activity in the clinical outcomes of patients with CAD [30]. Such data provide substantiation that adrenergic overdrive, as a result of OSA, contributes to the development of CAD.

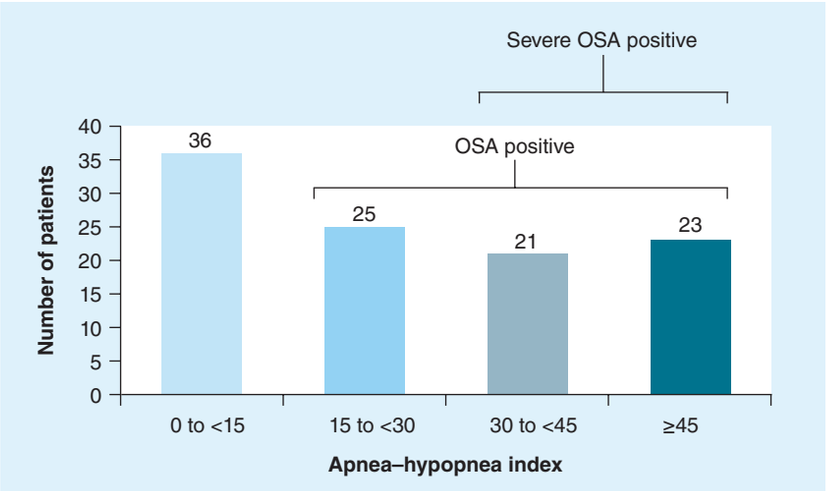

Figure 2. High prevalence of moderate-to-severe obstructive sleep apnea in patients presenting with myocardial infarction.
OSA: Obstructive sleep apnea.
Adapted with permission from [15].

■ Endothelial dysfunction

Endothelial dysfunction is believed to be a key event in the pathogenesis of atherosclerosis and atherosclerotic complications [31]. Factors of endothelial dysfunction such as increased oxidative stress, reduced nitric oxide availability and systemic inflammation are evident in OSA patients. A past study demonstrated reduced endothelial nitric oxide synthase and phosphorylated endothelial nitric oxide synthase expression in OSA patients, indicative of endothelial dysfunction [32]. This is consistent with results from experimental studies showing impairment of endothelial-dependent vasodilatation and increased endothelin secretion, a potent vasoconstrictor, in response to hypoxemia [33].

■ Inflammation

Endothelial dysfunction leads to increased macrophage activity, causing T cells to produce more cytokines and cytoxic substances. Hypoxemic stress experienced during recurrent apneas may also play a role in the activation of systemic inflammatory pathways [34]. The increased inflammatory state stimulates endothelial cells, activates more macrophages and regulates endothelial adhesion molecules [35], accelerating atherosclerosis [36]. Macrophage secretion of metalloproteinases also weakens the fibrous cap of atherosclerotic plaque, increasing the risk of plaque rupture and ACS. Multiple studies have reported an increase in the markers of systemic inflammation, such as acute phase proteins (i.e., serum amyloid A and CRP) [37,38], nuclear factor [39] and cytokines [40] in OSA patients. Widespread evidence recognizes that OSA predisposes patients to a proinflammatory state.

■ Coagulopathy & platelet dysfunction

Increased platelet activation, abnormal platelet aggregability, fibrinogen and other markers of thrombosis risk are evident in OSA patients [41]. A review comparing multiple reports justified the presence of a hypercoaguable state in OSA, despite a lack of adequate control across studies [42]. The same conclusion was drawn by a clinical study on 110 patients, which reported a positive association between OSA, plasma fibrinogen and platelet viscosity, persisting after adjustments for cardiovascular risk factors [43]. Two other trials found that OSA was correlated with an elevated plasminogen activator inhibitor-1 level, indicative of impaired fibrinolysis [44,45].

This implicates a possible important role of OSA in the pathogenesis of atherothrombotic disease. However, the impact of OSA on platelets remains controversial, as it is difficult to exclude the effects of confounding factors such as lifestyle variables, diseases and type of drug usage. Whether there is significant hypercoagulability in patients with OSA, resulting in increased risk of CAD, remains to be established.

■ Other factors

In addition to the major pathophysiological mechanisms of OSA resulting in an increased risk of CAD, several other variables may exist as

well. These components, together with the previously mentioned components, are schematically presented in Figure 3.

Impact of OSA on CAD

■ Effect on time onset of myocardial ischemia

Apnea-associated hypoxemia can reduce oxygen supply to the myocardium and increase oxygen demand by labile changes in heart rates and increased cardiac afterload. Therefore, it is reasonable to suspect that nocturnal myocardial ischemia episodes may be more common in patients with OSA.

This relationship is demonstrated by a study comparing ST-segment depression episodes among patients with OSA, snoring subjects and healthy subjects [46]. It was observed that nocturnal ST-segment depression episodes were more frequent in patients with OSA than snoring and control subjects. However, the study sample size was relatively small (n = 48) and measurement values might be biased due to lack of repeated trials. A similar investigation in a randomized group of men and women (n = 226) presenting with angina pectoris who underwent coronary angiography was conducted [47]. It was observed that 70% of nocturnal ST-segment depressions were preceded by three or more apnea–hypopnea episodes and/or oxygen desaturation. Such nocturnal ST-segment depressions were significantly present in men and in people with severely disordered breathing. Another clinical observation found that 91% of patients with myocardial infarction onset between 12:00 am and 6:00 am had OSA, suggesting the role of hypoxemic episodes on triggering coronary plaque rupture [48]. This is in concordance with a reported peak in sudden cardiac death during sleeping hours in people with OSA [28].

These studies lend support to the possibility that a relationship between the time onset of myocardial ischemia or infarction and OSA exists. Together with epidemiological and pathophysiological evidence, OSA is favored as a risk factor for CAD.

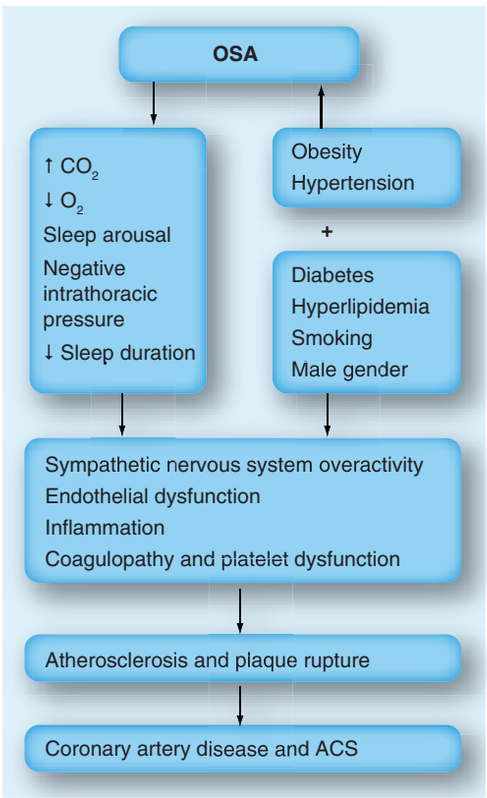

Figure 3. Effects of obstructive sleep apnea on coronary vasculature.
ACS: Acute coronary syndrome; OSA: Obstructive sleep apnea.

■ Effect on mortality & restenosis rate

Existing data indicate a high morbidity and mortality in patients with coexisiting OSA and CAD. A 5-year follow-up on intensive cardiac care patients presenting with angina pectoris or myocardial infarction, found untreated OSA to be independently predictive of increased cardiovascular mortality [4]. Recently, the authors demonstrated that among patients admitted with acute myocardial infarction, severe OSA (AHI >30) was an independent predictor of adverse cardiac events at 18-month follow-up [49]. Similarly, a study on 89 ACS patients following percutaneous coronary intervention demonstrated that the presence of OSA was an independent predictor of major adverse cardiac events (cardiac death, reinfarction and target vessel revascularization). Moreover, a high OSA prevelance of 57% was documented [5].

Several studies support an association between OSA, increased late lumen loss and restenosis. Quantitative coronary angiography at 6-month follow-up found that patients with OSA had significantly greater late lumen loss (1.28 ± 0.84 vs 0.69 ± 0.81 mm) and a higher binary restenosis rate (36.5 vs 15.4%; p = 0.026) compared with patients without OSA [5]. This is in concordance with findings from another study, which demonstrated a greater incidence of angiographic restenosis and a significantly higher late lumen loss in patients with AHI >10 compared with patients with AHI <10 [6]. However, as only bare-metal stents were implanted during percutaneous coronary intervention in both studies, an increased restenosis rate may not be of concern

with future utilization of drug-eluting stents. Nevertheless, the higher degree of late lumen loss in patients with both OSA and CAD compared with patients without OSA can be viewed as a marker of restenosis and vessel remodeling after percutaneous intervention. This is suggestive of an increased risk of acute cardiac event reoccurrence, consistent with increased mortality in OSA patients.

■ Effect on microvascular & macrovascular perfusion

Impaired microvascular perfusion in patients undergoing percutaneous coronary intervention is correlated with adverse clinical outcomes and poor recovery of left ventricular function [50]. As the pathophysiological effects of OSA appear to compromise microvascular integrity, it was proposed that the presence of OSA in patients with acute myocardial infarction will result in impaired microvascular perfusion after primary percutaneous coronary intervention. This hypothesis was investigated and impaired microvascular perfusion was defined as an ST-segment resolution of <70%, myocardial blush grade 0 or 1, or a corrected thrombolysis in myocardial infarction (antegrade flow scale) frame count >28. However, no relationship between OSA and impaired microvascular perfusion was observed [15].

A different result was obtained by a study examining left ventricular function recovery of 86 first acute myocardial infarction patients who underwent primary percutaneous coronary intervention. A significantly lower recovery of left ventricular ejection fraction and regional wall motion was reported in OSA patients, compared with patients without OSA [51]. This may also implicate impaired microvascular perfusion in OSA patients with acute myocardial infarction as the cause of poor recovery of left ventricular ejection fraction.

The evaluation of myocardial perfusion using real-time quantitative myocardial contrast echocardiography, as well as macrovascular and microvacular endothelial dysfunction, in the presence of OSA, was previously conducted [52]. Healthy subjects were matched with OSA subjects and it was observed that OSA subjects demonstrated significant impaired myocardial perfusion, attenuated brachial artery reactivity and cutaneous perfusion responses compared with normal subjects. Such evidence suggests the presence of macrovascular and microvascular abnormalities in OSA patients. When taken together, these studies highlight a possible role of OSA on myocardial perfusion, especially in the setting of myocardial infarction. Nonetheless, further studies are required to elucidate the exact implication of OSA in this context.

■ Effect on central sleep apnea, heart failure & its relation to CAD

The ventilator control instability present in OSA patients can also result in central sleep apnea, depending on the direction of airway collapse. Episodes of central sleep apnea, defined by a 10-s pause in ventilation with no associated respiratory effort, are also evidenced in patients with OSA [53]. This is observed in the CAD population as well. Sleep apneas, mainly central apneas, were evidenced in patients with ACS and patients with stable angina [54]. However, no strong relationship seems to exist between them as the pathophysiological cause of OSA and central sleep apnea are markedly different.

Nevertheless, it is possible that OSA might be an indirect cause of central sleep apnea. Cheyne-Stokes respiration, a form of central sleep apnea, is induced by and occurs mainly in patients with congestive heart failure [55]. As ischemic heart disease is the primary cause of heart failure, it is hypothesized that myocardial dysfunction might be potentiated through the adverse effects of OSA on coronary vasculature. Moreover, the multiple pathophysiological mechanisms of OSA promote heart failure through increasing cardiac afterload and left ventricle wall stress. Hypoxia experienced by OSA patients may also deteriorate heart contractibility [56]. This theory is supported by a report documenting similar prevalence of central apneas and obstructive apneas (40 compared with 36%, respectively) in 700 heart failure patients [57].

Continuous positive airway pressure

As OSA reflects counteracting forces of the upper airway dilating muscles and an imbalance of the intrapharyngeal pressure present in inspiration [58], CPAP neutralizes this by applying a continuous positive pressure through a nose mask (Figure 4). This provides an airway splint that works against the negative inspiration lung pressure, thereby preventing pharyngeal airway collapse, eliminating apnea, hypopnea and snoring episodes. Though a number of intervention approaches such as weight reduction, medical therapy or surgery are present, CPAP is the treatment of choice for all OSA patients [59]. This is because widespread evidence has recognized CPAP to be the most efficacious therapeutic option [60]. Moreover, a lack of well-designed clinical trials regarding the other treatment methods

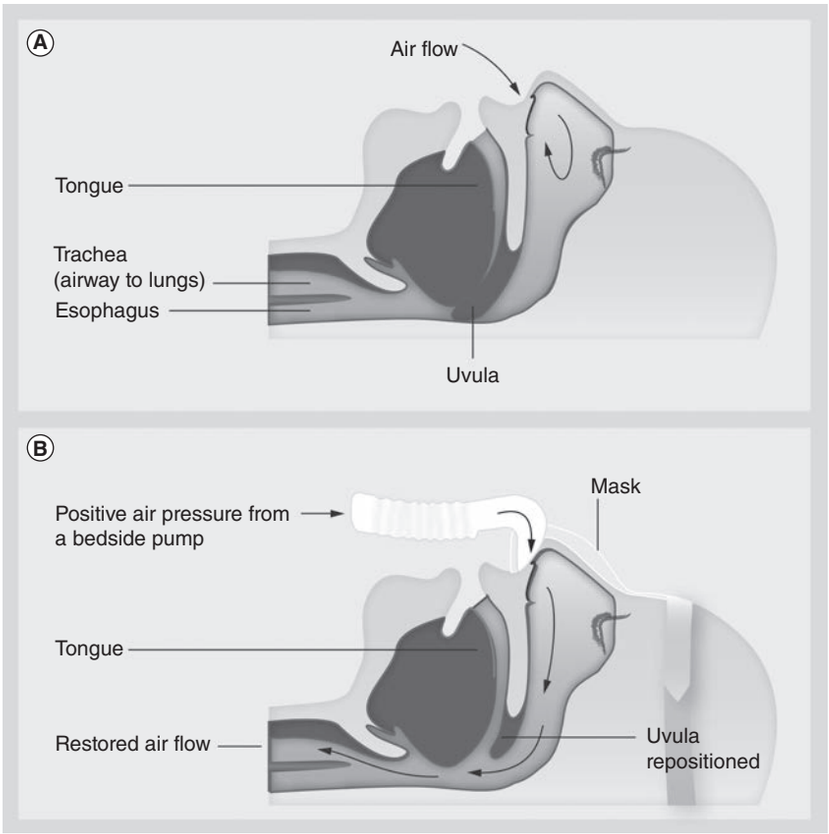

Figure 4. Continuous positive airway pressure. (A) Obstructive sleep apnea. **(B)** Continuous positive airway pressure opens airway.
Image reprinted with permission from Kathryn Born.

of OSA exist and present studies of other OSA treatment methods remain inconclusive [61].

Effect of CPAP on aforementioned mechanisms

The pathophysiological mechanisms of OSA arise from hypoxemia and CO_2 retention experienced in apneic episodes; therefore, it is reasonable to postulate that the prevention of airway collapse through CPAP therapy would eliminate these mechanisms. This is also suggested by data showing improvement in early signs of atherosclerosis with OSA treatment using CPAP [62].

■ Sympathetic nervous system overactivity

Present studies point to a reduction in sympathetic nervous system overactivity with the usage of CPAP. CPAP treatment in patients with myocardial ischemia and central sleep apnea or OSA demonstrated a significant lowering of sympathetic overactivity and nocturnal blood pressure surges through eliminating apnea episodes [63]. Results from a randomized controlled trial also showed diminished daytime sympathetic activation with CPAP therapy [64]. Furthermore, the usage of extended CPAP therapy has been shown to reduce muscle sympathetic nerve activity and biomarkers of sympathetic activity [65].

■ Endothelial dysfunction

Reversal of endothelial dysfunction may be possible with CPAP treatment. A study observed an attentuation in the reduced endothelial nitric oxide synthase and phosphorylated endothelial nitric oxide synthase expression in OSA patients after 4 weeks of CPAP therapy [32]. Moreover, an *in vitro* study demonstrated an increased adherence of monocytes to endothelial cells in OSA patients and a decrease in adherence level after CPAP treatment, suggestive of reduced endothelial dysfunction [35]. In a clinical trial on Chinese patients, a total of 28 men with moderate/severe OSA were randomized to CPAP or observation for 4 weeks. Subjects on CPAP had a significant increase in endothelium-dependent flow-mediated dilation as measured by Doppler ultrasound of the brachial artery, whereas those on observation had no change (4.4 vs -0.8%, difference of 5.2%; $p < 0.001$) [66].

When comparing markers such as VEGF and inducible nitric oxide synthase before and after 12 weeks of CPAP therapy, a significant reduction in VEGF levels and increase in nitrate–nitrate levels, suggestive of improved endothelial function, was previously reported [67]. This is consistent with results from another study demonstrating reduced endothelin levels with nasal CPAP treatment in OSA patients [68].

■ Inflammation

A significant fall in inflammatory markers in OSA patients after effective treatment with CPAP has been widely evidenced [35,38,39]. Of note, levels of CRP and IL-6, markers of systemic inflammation, have been demonstrated to be elevated in patients with OSA but decreased with CPAP therapy [38]. Neutrophil superoxide, an important contributor to inflammatory disease and ischemia, is enhanced in OSA patients. This is diminished with CPAP therapy [69].

■ Coagulopathy & platelet dysfunction

Although available literature on the role of CPAP therapy in coagulopathy and platelet function may be less persuasive due to the lack of randomization, control and limited sample sizes, present evidence is in favor of CPAP treatment. It was observed that the use of CPAP therapy resulted in a resolution of the increased platelet activation and aggregability in OSA patients [70,71]. Results also suggest a similar blood viscosity and platelet

activity level in OSA patients using CPAP and healthy control subjects [72]. Treatment with CPAP also led to a gradual decrease in factor VII clotting activity, which was not observed in OSA subjects not receiving CPAP therapy [73].

■ Carotid intima–media thickness

In 24 patients with severe OSA who were free of comorbidities and randomized to receive no treatment (control, n = 12) or CPAP (n = 12) for 4 months, it was observed that all measurements were similar in both groups at baseline. This did not change in the control group after 4 months. By contrast, a significant decrease between baseline and 4 months of CPAP therapy occurred in carotid intima–media thickness (707 ± 105 vs 645 ± 95 mm; p = 0.04). The changes in carotid intima–media thickness were correlated with changes in catecholamine (r = 0.41; p < 0.05) [62]. Likewise, in a group of 50 symptomatic patients newly diagnosed with severe OSA, a nonrandomized, prospective study has shown that CPAP treatment (n = 28) resulted in significant reduction in carotid artery intima–media thickness compared with those who had opted for conservative treatment (n = 22) over a study period of 12 months. Most of the reduction in carotid artery intima–media thickness, when comparing CPAP against conservative treatment, appeared to have occurred within the first 6 months of treatment [74].

Effect of CPAP on cardiovascular outcomes

As OSA is a potential risk factor of cardiovascular diseases, treatment of OSA may alleviate cardiovascular risk. This is supported by the aforementioned reversal of the pathophysiological mechanisms of OSA with CPAP therapy. A number of moderate-to-large scale nonrandomized clinical studies have demonstrated that CPAP therapy reduces the occurrence of cardiovascular events and mortality (Table 1). In addition, OSA patients who complied with the CPAP therapy (used more than 4 h per night) were found to have lower adverse events than those who did not comply.

Marin *et al.* observed that patients treated with CPAP were found to have reduced incidence of fatal and nonfatal cardiovascular events [10]. This is consistent with results from two other studies, independent of confounding factors [75,76]. An increased incidence of death from cardiovascular disease in untreated OSA patients compared with patients using CPAP therapy (14.8 vs 1.9%, respectively; p = 0.009) was also previously reported [77]. However, no significant difference in the occurrence of major adverse cardiac events was found between the treated and untreated OSA patients.

In a recent prospective, observational cohort study conducted in Spain, 1116 female patients were classified into three groups: non-OSA, CPAP-treated OSA (adherence ≥4 h per day) and untreated OSA (adherence <4 h per day or not prescribed). Compared with the non-OSA group, the adjusted hazard ratios for cardiovascular mortality were 3.50 for the untreated, severe OSA group; 0.55 for the CPAP-treated, severe OSA group; 1.60 for the untreated, mild-to-moderate OSA group; and 0.19 for the CPAP-treated, mild-to-moderate OSA group. It was concluded that adequate CPAP treatment may reduce the risk of cardiovascular death related to OSA [12]. A similar result was obtained in another Spanish trial [13].

A retrospective cohort study from the Mayo Clinic monitored the cardiovascular outcomes of 371 OSA patients who had undergone percutaneous coronary intervention [78]. The patients were stratified into two groups based on whether they had received treatment for OSA. At the 5 year follow-up, the group that had received OSA treatment showed a significantly decreased risk of cardiac deaths in comparison with the untreated group (3 vs 10%; p = 0.027). In addition, there was a trend towards lower risk of all-cause mortality (p = 0.058) favoring the treated group. Another study examined OSA treatment with CPAP on arterial restenosis rate after percutaneous transluminal coronary angiography [6]. This study demonstrated that CPAP therapy resulted in a marginally lower late lumen loss. However, this reduction was not statistically significant (0.57 ± 0.47 vs 0.99 ± 0.86 mm; p = 0.08).

Nevertheless, CPAP treatment appears to reduce the risk of CAD events in OSA patients. It is conceivable that the recommendation of CPAP treatment in OSA patients, especially those at high risk of CAD, may become a standard requirement in future.

Conclusion

Many published studies have explicitly demonstrated OSA to be demonstrative of worse cardiovascular outcomes in both healthy patients and patients with CAD. As such, screening for and treating OSA in CAD patients or patients at a high risk of CAD may prove to be an effective strategy to reduce the residual risks. Meanwhile, CPAP is the recommended treatment for symptomatic OSA. The exact role of CPAP therapy

Table 1. Summary of studies on effect of continuous positive airway pressure on cardiovascular outcomes.

Study (year)	Randomized trial	Total number of patients	Mean/median follow-up duration	Number of patients on CPAP	Main findings	Ref.
Peker *et al.* (2002)	No	182	7 years	15 treated, 37 incompletely treated	Efficient OSA treatment was associated with a significant risk reduction for cardiovascular disease incidence (OR: 0.1; 95% CI: 0–0.7) independent of age and blood pressure at baseline	[75]
Milleron *et al.* (2004)	No	54	86.5 ± 39 months	21	A significant ($p < 0.01$) greater number of patients without OSA treatment (17 out of 29 patients, 58%) reached the end point (cardiovascular death, ACS, hospitalization for heart failure or need for coronary revascularization) compared with patients receiving OSA treatment	[3]
Marin *et al.* (2005)	No	1651	10.1 years	372	A higher incidence of fatal cardiovascular events (1.06 per 100 person-years) and nonfatal cardiovascular events (2.13 per 100 person-years) in patients with severe, untreated OSA was observed in comparison to patients treated with CPAP (0.35 per 100 person-years; $p = 0.0008$ and 0.64 per 100 person-years; $p < 0.0001$)	[10]
Doherty *et al.* (2005)	No	168	7.5 years	107	The untreated group had significantly greater mortality from cardiovascular disease than the CPAP-treated group (14.8 vs 1.9%; $p = 0.009$), but there were no significant differences in the development of new cases of hypertension, cardiac disorder or stroke	[77]
Buchner *et al.* (2007)	No	449	72 months	364	OSA treatment was an independent predictor for fatal and nonfatal cardiovascular events (hazard ratio: 0.36; 95% CI: 0.21–0.62; $p < 0.001$)	[76]
Cassar *et al.* (2007)	No	371	5 years	175	There was a significantly decreased number of cardiac deaths in treated OSA patients, compared with untreated OSA patients, (3 vs 10% after 5 years; $p = 0.027$) and a trend toward decreased all-cause mortality ($p = 0.058$) No difference in the number of major adverse cardiovascular events or major adverse cardiovascular and cerebral events between the two groups was observed ($p = 0.91$ and $p = 0.96$, respectively)	[78]
Campos-Rodriguez *et al.* (2012)	No	1116	72 months	576	The non-OSA group had a lower cardiovascular mortality rate than the untreated groups with mild-to-moderate OSA ($p = 0.034$) or severe OSA ($p < 0.001$). Compared with the non-OSA group, the adjusted hazard ratios for cardiovascular mortality were 3.50 for the untreated, severe OSA group; 0.55 for the CPAP-treated, severe OSA group; 1.60 for the untreated, mild-to-moderate OSA group; and 0.19 for the CPAP-treated, mild-to-moderate OSA group	[12]

ACS: Acute coronary syndrome; CPAP: Continuous positive airway pressure; OR: Odds ratio; OSA: Obstructive sleep apnea.

in CAD patients with OSA remains to be demonstrated in randomized clinical trials.

Future perspective

Although OSA is prevalent in the CAD population, it remains underdiagnosed and undertreated. The increased occurrence of OSA in CAD patients appears to be significant enough that the possibility of OSA should be considered in any patient with CAD. However, there are several limitations to the conclusions that can be derived from current literature regarding the relationship between OSA and CAD. Limited long-term outcome studies beyond a decade in follow-up duration exist and most of the present published studies are small. A lack of a large-scale evaluation of OSA in the CAD population, especially in patients presented with ACS is present. Moreover, the impact of OSA and the comorbidity of cardiovascular risk factors has not been well studied. It remains unclear whether the influence of OSA on CAD is altered in the presence of existing cardiovascular risk factors. Although most trials of CPAP on OSA patients with stable ischemia had positive results, it is less apparent whether the beneficial effects of CPAP can also be extended to patients with ACS. Evidently, it will require multiple well-executed large-scale prospective pathophysiological and clinical studies to give us a clear understanding in this area.

More research is required to better define the potential role of CPAP in the treatment of CAD as well. There is currently no large-scale randomized clinical trial that demonstrates whether treatment of OSA would improve clinical outcomes of patients with myocardial infarction. Therefore, the precise relationships between OSA and myocardial infarction remain unclear. In the first American Heart Association/American College

Executive summary

Epidemiology studies

- Obstructive sleep apnea (OSA) has emerged as a potential risk factor for coronary artery disease (CAD).
- When looking specifically at ischemic heart disease, the prevalence of previously undiagnosed moderate/severe OSA (apnea–hypopnea index >15) was up to 66.4% in a group of acute coronary syndrome patients.

Pathophysiology of OSA on atherosclerosis & thrombosis

- At basic research and tissue levels, the pathophysiological components of OSA resulting in atherosclerosis and thrombosis can be attributed to sympathetic nervous system overactivity, endothelial dysfunction, inflammation, coagulopathy and platelet dysfunction as well as other factors.

Impact of OSA on CAD

- The main impacts of OSA on CAD, especially acute coronary syndrome, are on the following:
  - Time onset of myocardial ischemia;
  - Nocturnal myocardial ischemia, acute myocardial infarction and sudden cardiac death are correlated with peak time of apnea–hypopnea episodes and/or oxygen desaturation in OSA patients;
  - Mortality and restenosis rate;
  - Studies focused on acute coronary syndrome patients following percutaneous coronary intervention showed that the presence of OSA was an independent predictor of major adverse cardiac events, mortality, increased late lumen loss and restenosis;
  - Microvascular and macrovascular perfusion;
  - A significantly lower recovery of left ventricular ejection fraction, regional wall motion abnomalities and imparied myocardial perfusion have been evidenced in OSA patients. However, an intervention study found no relationship between OSA and impaired microvascular perfusion;
  - Future studies are required to elucidate the role of OSA in this context.

Effect of continuous positive airway pressure on aforementioned mechanisms

- Continuous positive airway pressure treatment appears to reverse the aforementioned pathophysiological mechanism of OSA.
- Many studies have documented improvements in the following components: endothelial dysfunction, inflammation, coagulopathy and platelet dysfunction and carotid intima–media thickness.

Effect of continuous positive airway pressure on cardiovascular outcomes

- Continuous positive airway pressure treatment in OSA patients were associated with reduced incidence of fatal and nonfatal cardiovascular events compared with untreated OSA patients in moderate-to-large scale nonrandomized clinical studies.

Conclusion

- The increased occurrence of OSA appears to be significant enough that the possibility of OSA should be considered in any patients with CAD.
- Multiple well-executed large-scale prospective pathophysiological and clinical studies are required to give us a clear understanding regarding OSA and CAD.
- The exact role of continuous positive airway pressure therapy in CAD patients with OSA remains to be demonstrated in randomized clinical trials.

of Cardiology Scientific Statement on Sleep Apnea and Cardiovascular Disease, it was emphasized that, "...although holding great promise, this general area is in need of a substantially expanded knowledge base" [2]. Furthermore, the management of asymptomatic OSA patients remains controversial and results regarding this are inconclusive. Although Barbé *et al.* found no significant reduction in cardiovascular events or incident hypertension in nonsleepy OSA patients using CPAP [79], preliminary results of a large randomized controlled trial found no baseline differences in prevalent CAD between symptomatic and asymptomatic OSA patients [80].

A large prospective randomized CPAP therapy trial in patients with ACS and OSA is currently being conducted (NCT01335087) [101]. This study will assess the impact of CPAP treatment on a composite end point of the rate of cardiovascular events (cardiovascular death, acute myocardial infarction, nonfatal stroke, hospital admission for heart failure and new hospitalizations) in patients with ACS and co-occurring sleep apnea. An increase in the number of such trials will help better elucidate the impact of OSA therapy on improvement of cardiovascular morbidities. Similarly, in Europe, a large prospective randomized CPAP intervention in 400 patients with CAD and OSA is currently underway (NCT00519597) [102]. This trial aims to assess the impact of CPAP treatment on a composite end point of new revascularization, myocardial infarction, stroke and cardiovascular mortality over a 3-year period in people with CAD and OSA. Future trials providing evidence to this end will guide the use of CPAP treatment for CAD in a rational, evidence-based manner.

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