

SLEEP APNEA AND CARDIOVASCULAR DISEASES

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Sleep Apnea and Cardiovascular Diseases

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Guest Editors: Rodolfo Álvarez-Sala, Francisco García-Río,
Félix Del Campo, Carlos Zamarrón, and Nikolaus C. Netzer



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Editorial

Sleep Apnea and Cardiovascular Diseases

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Obstructive sleep apnea (OSA) is a common respiratory disease characterized by abnormal collapse of the pharyngeal airway during sleep, causing repetitive arousals and falls in the oxygen saturation [1]. This disorder, when not correctly treated, has been associated with higher fatal and nonfatal cardiovascular events [2]. Also, OSA has been related to many cardiovascular diseases (CVD) such as heart failure [3], arrhythmias [4], pulmonary hypertension [5], and coronary artery disease (CAD) [6]. Moreover, in recent years OSA has emerged as a major public health problem due to its profound impact on patients' health. By this reason, we have proposed this special issue about the relationship between sleep disordered breathing (SDB) and CVD. We have suggested different topics such as potential mechanisms linking OSA to CVD, acute cardiovascular effects of OSA, impact of OSA on natural history of CVD, cardiovascular effects of continuous positive airway pressure (CPAP) treatment, and therapeutic cardiovascular efficacy of emerging treatment for OSA and central sleep apnea (CSA).

Several mechanisms are involved in the association between OSA and CVD. In fact, enhanced sympathetic activity, oxidative stress, systemic inflammation, and endothelial dysfunction contribute to this association and promote atherogenesis. Moreover, cyclic decreases in blood oxygen saturation during recurrent episodes of apnea produce chronic intermittent hypoxia and contribute to the development of atherosclerosis. Some hypoxia-induced transcription

factors as hypoxia-inducible factor-1 and nuclear factor- κ B are activated during intermittent hypoxia and contribute to the generation of inflammation and expression of proinflammatory cytokines such as tumor necrosis factor- α and interleukin-8.

It seems that these mechanisms could have an important impact in the occurrence of ischemic cardiac events. Hence, CAD in OSA patients probably precludes the activation of multiple mechanisms, such as atherosclerosis, hypertension, and endothelial dysfunction. Likewise, OSA may influence outcomes in patients with acute or chronic CAD, but this effect remains controversial as results obtained from studies have yielded discrepant data. In this way, Yumino et al. [7] observed a higher incident of cardiac death, reinfarction, or new revascularization in OSA patients with CAD and compared to subjects without OSA, after a mean follow-up period of 7 months. Nevertheless, Hagenah et al. [8] found that OSA did not increase the risk of mortality and cardiovascular complications in 50 patients with stable CAD after 10 years of follow-up period. Moreover, concerning treatment of OSA patients with CAD, CPAP may have beneficial effects in recurrence of ischemic cardiac disease and necessity of new revascularization procedures but higher-evidence studies are necessary to investigate the effect of CPAP in these subjects.

Regarding heart failure, a high prevalence of OSA and CSA in this disorder has been observed. Also, different therapeutic strategies such as oxygen therapy, CPAP, bilevel

positive airway pressure (BIPAP), and adaptive servoventilation (ASV) have been proposed to treat OSA in heart failure patients. In this way, in OSA heart failure subjects, CPAP may improve survival, left ventricular ejection fraction, and quality of life [9–11]. Nevertheless, in heart failure CSA patients, CPAP probably is not effective as ASV to abolish the apnea-hypopnea index to <15 events·h⁻¹ [12]. So far, it is evident that SDB treatment has showed consistent improvements in heart function, quality of life, and respiratory events in patients with heart failure. However, it is necessary to evaluate the impact of these respiratory treatments in randomized-controlled, long-term longitudinal studies.

Finally, respecting the association between atrial arrhythmia and OSA, it has been described that cardiac remodeling, sympathetic activity, and systemic inflammation may lead to the development of arrhythmias in these patients. Moreover, hypoxemia and hypercapnia have an important role in the pathogenesis of this association. However, it is necessary to investigate the effect of CPAP treatment in atrial arrhythmias of OSA patients.

In conclusion, sleep apnea is a high prevalence disease that has an important relationship with cardiovascular disease. In this special issue, we have tried to make an extensive review about mechanisms involved in the association between ischemic cardiac disease, heart failure, and arrhythmias with OSA. Nevertheless, we know that despite multiple reports about OSA and cardiovascular disease, it is yet necessary to perform higher grade evidence studies to explore mechanisms involved in this association and the impact of CPAP treatment in these subjects.

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References

- [1] P. Lloberes, J. Durán-Cantolla, M. Á. Martínez-García et al., “Diagnosis and treatment of sleep apnea-hypopnea syndrome. spanish society of pulmonology and thoracic surgery,” *Archivos De Bronconeumologia*, vol. 47, no. 3, pp. 143–156, 2011.
- [2] J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. N. Agustí, “Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study,” *Lancet*, vol. 365, no. 9464, pp. 1046–1053, 2005.
- [3] E. Shahar, C. W. Whitney, S. Redline et al., “Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the sleep heart health study,” *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 1, pp. 19–25, 2001.
- [4] S. Javaheri, T. J. Parker, J. D. Liming et al., “Sleep apnea in 81 ambulatory male patients with stable heart failure: types and their prevalences, consequences, and presentations,” *Circulation*, vol. 97, no. 21, pp. 2154–2159, 1998.
- [5] M. Alchanatis, G. Tourkohoriti, S. Kakouros, E. Kosmas, S. Podaras, and J. B. Jordanoglou, “Daytime pulmonary hypertension in patients with obstructive sleep apnea: the effect of continuous positive airway pressure on pulmonary hemodynamics,” *Respiration*, vol. 68, no. 6, pp. 566–572, 2001.
- [6] C.-H. Lee, S.-M. Khoo, B.-C. Tai et al., “Obstructive sleep apnea in patients admitted for acute myocardial infarction: prevalence, predictors, and effect on microvascular perfusion,” *Chest*, vol. 135, no. 6, pp. 1488–1495, 2009.
- [7] D. Yumino, Y. Tsurumi, A. Takagi, K. Suzuki, and H. Kasanuki, “Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome,” *American Journal of Cardiology*, vol. 99, no. 1, pp. 26–30, 2007.
- [8] G. C. Hagenah, E. Gueven, and S. Andreas, “Influence of obstructive sleep apnoea in coronary artery disease: a 10-year follow-up,” *Respiratory Medicine*, vol. 100, no. 1, pp. 180–182, 2006.
- [9] D. R. Mansfield, N. C. Gollogly, D. M. Kaye, M. Richardson, P. Bergin, and M. T. Naughton, “Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure,” *American Journal of Respiratory and Critical Care Medicine*, vol. 169, no. 3, pp. 361–366, 2004.
- [10] Y. Kaneko, J. S. Floras, K. Usui et al., “Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea,” *The New England Journal of Medicine*, vol. 348, no. 13, pp. 1233–1241, 2003.
- [11] H. Wang, J. D. Parker, G. E. Newton et al., “Influence of obstructive sleep apnea on mortality in patients with heart failure,” *Journal of the American College of Cardiology*, vol. 49, no. 15, pp. 1625–1631, 2007.
- [12] T. D. Bradley, A. G. Logan, R. J. Kimoff et al., “Continuous positive airway pressure for central sleep apnea and heart failure,” *The New England Journal of Medicine*, vol. 353, no. 19, pp. 2025–2033, 2005.

Review Article

Pathophysiologic Mechanisms of Cardiovascular Disease in Obstructive Sleep Apnea Syndrome

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Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep disorder, characterized by repeated disruptions of breathing during sleep. This disease has many potential consequences including excessive daytime sleepiness, neurocognitive deterioration, endocrinologic and metabolic effects, and decreased quality of life. Patients with OSAS experience repetitive episodes of hypoxia and reoxygenation during transient cessation of breathing that provoke systemic effects. Furthermore, there may be increased levels of biomarkers linked to endocrine-metabolic and cardiovascular alterations. Epidemiological studies have identified OSAS as an independent comorbid factor in cardiovascular and cerebrovascular diseases, and pathophysiological links may exist with onset and progression of heart failure. In addition, OSAS is associated with other disorders and comorbidities which worsen cardiovascular consequences, such as obesity, diabetes, and metabolic syndrome. Metabolic syndrome is an emerging public health problem that represents a constellation of cardiovascular risk factors. Both OSAS and metabolic syndrome may exert negative synergistic effects on the cardiovascular system through multiple mechanisms (e.g., hypoxemia, sleep disruption, activation of the sympathetic nervous system, and inflammatory activation). It has been found that CPAP therapy for OSAS provides an objective improvement in symptoms and cardiac function, decreases cardiovascular risk, improves insulin sensitivity, and normalises biomarkers. OSAS contributes to the pathogenesis of cardiovascular disease independently and by interaction with comorbidities. The present review focuses on indirect and direct evidence regarding mechanisms implicated in cardiovascular disease among OSAS patients.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder characterized by recurrent upper airway collapse during sleep [1]. This results in a reduction or complete cessation of airflow despite ongoing inspiratory efforts and leads to arousals, sleep fragmentation, and oxyhemoglobin desaturation [2].

A spectrum of sleep related obstructed breathing has been described in the literature [3]. This ranges from snoring [4], and upper airway resistance syndrome [5] to obesity hypoventilation syndrome [6]. The focus of the current review is OSAS, which lies in between these two extremes.

Though clinically recognized since the 1960s [7], general awareness of OSAS has been slow to develop. OSAS has

been associated with cardiovascular disease [8], automobile accidents [9], chronic obstructive pulmonary disease (COPD) [10], heart failure [11] and health related quality of life deterioration [12].

Another emerging public health problem is metabolic syndrome, which represents a constellation of cardiovascular risk factors. OSAS often coexists with obesity and has been shown to be independently associated with insulin resistance, which is an important component of metabolic syndrome [1, 13]. Given the current obesity epidemic, the prevalence of both metabolic syndrome and OSAS is on the rise.

The present review analyzes the relation between OSAS and cardiovascular disease and how it may be affected by OSAS-associated disorders and comorbidities.

TABLE 1: Prevalence studies on obstructive sleep apnea syndrome.

Study	Population	Age	Method	Criteria	SDB prevalence	OSAS
Durán et al. 2001 [14]	2148 subjects from the electoral census	30–70	(1) Questionnaire (2) Validated portable instrument in 442 subjects (3) PSG in 555 subjects	AHI ≥ 5	26.3% (M) and 28% (F)	
				AHI ≥ 10	19% (M) and 14.9% (F)	
				AHI ≥ 15	14.2% (M) and 8.6% (F)	
				AHI ≥ 20	9.6% (M) and 6% (F)	
				AHI ≥ 30	6.8% (M) and 4.3% (F)	
				OSAS = AHI ≥ 10 plus Symptoms		3.4% M 3% F
Udwadia et al., 2004 [15]	658 healthy urban Indian subjects	35–65	(1) Questionnaire (2) PSG on subgroup in 250 subjects	AHI ≥ 5	19.5%	7.5%
				AHI ≥ 10	11.1%	6.1%
				AHI ≥ 15	8.4%	5.4%
				OSAS = AHI plus Symptoms		
Sharma et al., 2006 [16]	2150 semiurban community in Delhi	30–60	(1) Questionnaire (2) PSG on subgroup in 150 subjects	AHI ≥ 5 OSAS = AHI ≥ 5 plus Symptoms	13.7%	3.6%
Plywaczewski et al., 2008 [17]	1503 from Warsaw electoral registers	Over 30 years of age	(1) Questionnaire (2) PSG on subgroup in 676 subjects	AHI ≥ 10 OSAS = AHI ≥ 10 plus Symptoms	14.3%	7.5%

Abbreviations: AHI: apnea hypopnea index; PSG: polysomnography; SDB: sleep disordered breathing; M: male; F: female.

2. OSAS Epidemiology

A variety of epidemiological studies have demonstrated the high prevalence of OSAS and its relation to cardiovascular risk factors (Table 1). Durán et al. in 2001, performed 555 complete polysomnographies and found sleep disordered breathing, defined as AHI > 5 , in 26.3% of men and 28% of women. AHI was associated with hypertension after adjusting for age, sex, BMI, neck circumference, alcohol use, and smoking habit [14]. In India, Udwadia et al. found a 19.5% prevalence of sleep disordered breathing, defined as AHI > 5 , and 7.5% prevalence of OSAS, defined as AHI > 5 with symptoms. BMI, neck circumference and diabetes mellitus were found to be associated with sleep disordered breathing [15]. Sharma et al. reported a 13.7% overall prevalence of sleep disordered breathing and 3.6% prevalence of OSAS. Multivariate analysis revealed that male gender, age, obesity, and waist/hip ratio were significant risk factors for OSAS [16].

Plywaczewski et al. found a 7.5% prevalence of OSAS. OSAS was found to be an independent predictor of coronary artery disease after adjusting for age, sex, BMI, neck circumference, and smoking habit [17].

As age advances, sleep breathing related difficulties become increasingly common. Several OSAS studies in older populations report little or no association of OSAS with sleepiness, hypertension, or decrements in cognitive function [18, 19].

3. OSAS and Cardiovascular Diseases Mechanisms

The mechanisms involved in the association between OSAS and vascular diseases are complex and diverse. Patients

with OSAS experience repetitive episodes of hypoxia and reoxygenation during transient cessation of breathing that may provoke systemic effects. These patients also present increased levels of biomarkers linked to endocrine-metabolic and cardiovascular alterations. The relation between OSAS and cardiovascular disease involves a number of mechanisms such as the following (Figure 1).

3.1. Sleep Fragmentation. The importance of sleep to health and cardiovascular disease has become increasingly apparent. Percentage time in slow wave sleep has been inversely associated with incident hypertension (regardless of sleep duration and fragmentation) and sleep-disordered breathing. In fact, selective deprivation of slow wave sleep may contribute to adverse blood pressure in older men [20]. Bekci et al. found that total antioxidant capacities were decreased in the higher arousal index, suggesting that patients with higher arousal index may be more prone to vascular events [21].

In OSAS, severe sleep fragmentation disturbs nocturnal renin and aldosterone secretion profiles and increases nighttime urine excretion. CPAP treatment has been reported to improve sleep, restore plasma renin activity and aldosterone oscillations, and lower nocturnal urine natriuresis and diuresis [22]. Møller et al. found that long-term CPAP (Continuous positive airway pressure) reduced blood pressure, which was correlated with reductions in plasma renin and angiotensin II levels [23].

Extreme sleep habits can affect health and have been associated with increased inflammation. Significant changes in habitual sleep duration can lead to chronic low-grade systemic inflammation [24] and activation of proinflammatory pathways may represent a mechanism. In a study involving

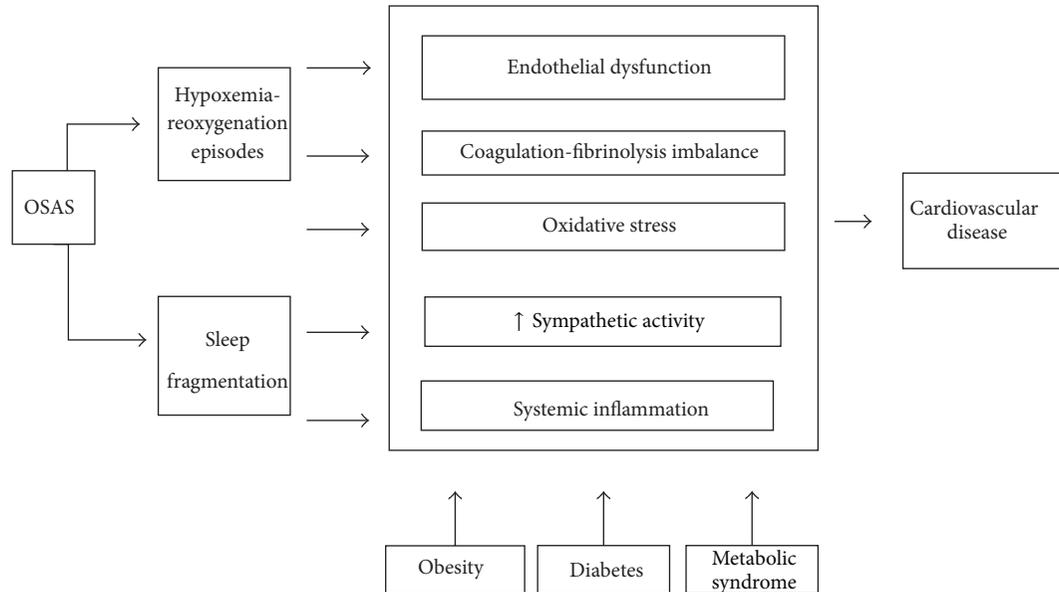


FIGURE 1: A schematic summary of the proposed sequence of events in obstructive sleep apnea syndrome starting from episodic hypoxia and sleep fragmentation.

pediatric OSAS patients, increased TNF- α levels were primarily driven by sleep fragmentation and BMI. These levels were closely associated with the degree of sleepiness. Surgical treatment of OSAS resulted in significant reductions in TNF- α levels and reduction in sleepiness [25].

3.2. Enhanced Sympathetic Traffic. In OSAS, there is enhanced sympathetic traffic through a tonic activation of chemoreflex activity that normalizes with CPAP treatment [26, 27]. OSAS-associated disturbances, especially chronic intermittent hypoxia and enhanced sympathetic activity, lead to upregulation of the renin-angiotensin system and downregulation of nitric oxide synthases [28]. When an obstructive apnea occurs, it is terminated by a sudden arousal, that is, lightening of sleep or awakening from sleep [29]. The cyclic intermittent hypoxia provides the causal link between upper airway obstruction during sleep and sympathetic activation during awakening. Cyclic intermittent hypoxia may lead to sympathoexcitation via two mechanisms: first, augmentation of peripheral chemoreflex sensitivity (hypoxic acclimatization) and, second, direct effects on sites of central sympathetic regulation.

In a study in healthy humans, intermittent hypoxia significantly increased sympathetic activity and daytime blood pressure after a single night of exposure. The baroreflex control of sympathetic outflow declined [30]. Surges in sympathetic nervous system activity associated with apneic events have also been related to antifibrinolytic activity reflected by elevations in PAI-1 [31].

Increased sympathetic activity and intermittent hypoxia associated with apneic episodes has been proposed as a possible mechanism behind the association between OSAS, systemic inflammation and cardiovascular disease. CPAP

reduces sympathetic nerve activity [32], increases arterial baroreflex sensitivity [33], and decreases vascular risk [34].

3.3. Oxidative Stress. In OSAS patients, increased production of superoxide by neutrophils [35], increased biomarkers of lipid peroxidation [36], and increased levels of 8-isoprostanes [37] have been observed. There is an emerging consensus that OSAS is an oxidative stress disorder.

Apnea produces a decline in oxygen levels followed by reoxygenation when breathing resumes. Cyclical episodes of hypoxia-reoxygenation, which are analogous to cardiac ischemia/reoxygenation injury, may cause ATP depletion and xanthine oxidase activation and increases the generation of oxygen-derived free radicals. CPAP therapy decreases the levels of oxidative stress in OSAS patients [38, 39].

In a study involving children with OSAS, Malakasioti et al. found increased hydrogen peroxide levels in exhaled breath condensate, which is an indirect index of altered redox status in the respiratory tract [40].

Oxidative stress can profoundly regulate the cellular transcriptome through activation of transcription factors, including specificity protein-1, hypoxia-inducible factor-1, c-jun, and possibly NF κ B. Activation of redox-sensitive gene expression is suggested by the increase in some protein products of these genes, including vascular endothelial growth factor [41], erythropoietin [42], and endothelin-1 [43]. Low oxygen tension is a trigger for activation of polymorphonuclear neutrophils, which adhere to the endothelium [44].

Increased oxidative stress has been associated with development of cardiovascular diseases and can be promoted by the chronic intermittent hypoxia characteristic of OSAS [45]. A variety of studies suggest that oxidative stress is present in OSAS at levels relevant to tissues such as the arterial wall [46, 47]. This process enhances lipid uptake into human

macrophages and may contribute to atherosclerosis in OSAS patients [48]. Furthermore, OSAS decreases blood antioxidant status in high-BMI subjects and may change the relationship between oxidative stress markers [49]. After CPAP, expression of eNOS and phosphorylated eNOS was found to be significantly increased, whereas expression of nitrotyrosine and nuclear factor-kappaB was significantly decreased [50]. However, other studies have shown that CPAP may not affect antioxidant defense [51]. Nair reported that oxidative stress is mediated, at least in part, by excessive NADPH oxidase activity. This author suggests that pharmacological agents targeting NADPH oxidase may provide a therapeutic strategy in OSAS [52].

3.4. Systemic Inflammation. In OSAS, intense local and systemic inflammations are present. Insofar as local inflammation, bronchial and nasal changes are especially relevant [53]. In a study by Carpagnano et al., OSAS patients showed a significant increase in IL-8 and ICAM concentrations in both plasma and exhaled condensate. In addition, they showed a higher neutrophil percentage in induced sputum. These findings were significantly and positively correlated to AHI [54]. In a recent study of 80 nonsmoking males, Cofta et al., found a progressive increase in the concentrations of three selectins with the severity of OSAS [55].

Adhesion of circulating leukocytes to the endothelial cells is considered one of the initial steps in the pathogenesis of atherosclerosis. The repetitive hypoxia-reoxygenation episodes associated with apneas and hypopneas in OSAS up-regulate the production of inflammatory mediators and the expression of adhesion molecules. Different studies have reported changes in circulating levels of adhesion molecules in OSAS patients [56, 57]. Dyugovskaya et al. analysed polymorphonuclear apoptosis and expression of adhesion molecules *in vitro* in patients with moderate to severe OSAS. Decreased apoptosis and increased expression of adhesion molecules were observed. Although adhesion molecules may facilitate increased polymorphonuclear-endothelium interactions, decreased apoptosis may further augment these interactions and facilitate free radical and proteolytic enzymes [58].

OSAS patients present increased levels of inflammatory mediators such as TNF α and IL-6 [59, 60] that decrease with CPAP treatment [61, 62].

Systemic inflammation is increasingly being recognized as a risk factor for a number of complications including atherosclerosis [63] and is a well-established factor in the pathogenesis of cardiovascular disease [64]. Serum amyloid A is a major acute-phase protein in humans that has been associated with cardiovascular disease [65]. Levels of this protein are chronically elevated in patients with OSAS [66] and improve with CPAP [67].

C-reactive protein is an important serum marker of inflammation with major implications for cardiovascular morbidity and atherogenesis [68]. C-reactive protein levels are increased in OSAS in accordance with disease severity [69–71] and are decreased after CPAP treatment [72, 73].

The mechanisms by which inflammation contributes to OSAS-induced vascular dysfunction are not known.

Reoxygenation after a brief period of hypoxia as experienced repetitively and systematically by OSAS patients may predispose to cell stress, possibly because of mitochondrial dysfunction. It has been suggested that such events favor the activation of a proinflammatory response as mediated through the transcription factor nuclear NF κ B, a master regulator of inflammatory gene expression. The downstream effects of this activation include increased expression of inflammatory cytokines which may contribute to endothelial dysfunction and subsequently cardiovascular complications [74].

Inflammation may be an important link between increased sympathetic nervous system activity and vascular dysfunction in OSAS. Chronically elevated sympathetic activity produced an inflammatory response in several organs and vascular beds [75].

Some authors point to the role of the T lymphocyte. This cell is known to play an important role in angiotensin II-induced hypertension and endothelial dysfunction via NADPH oxidase-induced superoxide production [76].

Increased expression of inflammatory cytokines may contribute to endothelial dysfunction and subsequent cardiovascular complications. Currently, some studies suggest that pentraxin 3, an acute phase response protein, is rapidly produced and released by several cell types, especially mononuclear phagocytes and endothelial cells in response to primary inflammatory signals. Pentraxin 3 may play a significant role in OSAS-associated vascular damage [77]. Arnaud et al. reported that some inhibition of molecules such as RANTES/CCL5, a cytokine that selectively attracts memory T lymphocytes and monocytes, may play a significant role in atherosclerosis remodeling and OSAS-associated vascular damage [78].

However, mesenchymal stem cells triggered an early anti-inflammatory response in rats subjected to recurrent obstructive apneas, suggesting that these stem cells could play a role in the physiological response to counterbalance inflammation in OSAS [79].

In healthy human males, Querido et al. analysed the effect over 10 days of nightly intermittent hypoxia in the following systemic inflammatory markers: serum granulocyte macrophage colony-stimulating factor, interferon- γ , interleukin 1 β , interleukin 6, interleukin 8, leptin, monocyte chemoattractant protein-1, vascular endothelial growth factor, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1. There was no significant change in any of the markers. These findings suggest that a more substantial or a different pattern of hypoxemia might be necessary to activate systemic inflammation, that the system may need to be primed before hypoxic exposure, or that increases in inflammatory markers in OSAS patients may be more related to other factors such as obesity or nocturnal arousal [80].

3.5. Hypercoagulability. Hypercoagulability resulting from increased coagulation or inhibited fibrinolysis is associated with an increased risk for cardiovascular disease [81, 82]. This is another factor implicated in its association with OSAS [83, 84].

A variety of findings support the existence of a relation between hypercoagulability, OSAS, and cardiovascular disease. Firstly, patients with OSAS present higher plasma levels of several procoagulant factors such as fibrinogen [85], activated clotting factor FVII (FVIIa), FXIIa, and thrombin/antithrombin III complexes [86], platelet activity [87], and the fibrinolysis-inhibiting enzyme plasminogen activator inhibitor (PAI-1) [88, 89]. Secondly, increased D-dimer levels in untreated OSAS have been correlated with severity of nocturnal hypoxemia, characteristic of OSAS [90]. Von Känel et al., found that OSAS patients showed lower mesor (mean) and amplitude (difference between maximum and minimum activity) of D-dimer. However, there were no significant differences in changes of periodic pattern and in day/night rhythm parameters of prothrombotic markers pre- to posttreatment between the CPAP and placebo condition [91].

Thirdly, sleep fragmentation and sleep efficiency data have been associated with increased levels of von Willebrand factor and soluble tissue factor, two markers of a prothrombotic state [92].

3.6. Endothelial Dysfunction. Endothelial dysfunction is an early marker of vascular abnormality preceding clinically overt cardiovascular disease [93–95]. It is known from years ago that endothelial dysfunction identified in the peripheral vasculature strongly predicts coronary disease [96].

The intact endothelium regulates vascular tone and repair capacity, maintaining proinflammatory, anti-inflammatory, and coagulation homeostasis. Alteration of these homeostatic pathways results in endothelial dysfunction before structural changes in the vasculature. The hypoxia, hypercapnia, and pressor surges accompanying obstructive apneic events may serve as potent stimuli for the release of vasoactive substances. Levels of nitric oxide, a major vasodilator substance released by the endothelium, have been found to be decreased in OSAS patients, and these levels normalize with CPAP therapy [97].

In OSAS, endothelial dysfunction could be caused by both hypoxia-reoxygenation cycles and chronic sleep fragmentation produced by repetitive arousals. A causal relationship between OSAS and endothelial dysfunction was demonstrated by a study in which flow-mediated dilation in the forearm was improved by CPAP treatment [98, 99]. Levels of nitric oxide, a major vasodilator substance released by the endothelium, have been found to be decreased in OSAS patients, and these levels normalize with CPAP therapy [100].

A number of studies involving OSAS patients indicate an associated endothelial dysfunction [101–103] that improves after CPAP [104, 105]. In addition to the fact that OSAS comorbidities (e.g., hypertension, diabetes, hyperlipidaemia, and smoking) may result in endothelial dysfunction, OSAS itself may be an independent risk factor.

Among the most important vasoconstrictive substances is endothelin-1, a peptide hormone secreted under the influence of hypoxia [106]. Several studies have reported higher endothelin-1 levels in OSAS patients [107, 108]; however, Grimpen et al. report conflicting findings [109]. This divergence might be explained by differences in study design. The groups studied by Phillips and Saarelainen had more severe

disease and, thus, underwent more severe oxygen desaturations that acted as a trigger for endothelin-1 secretion. Gjørup et al. showed that hypertensive OSAS patients had greater nocturnal and diurnal endothelin-1 plasma levels than healthy controls, suggesting that OSAS does not affect plasma endothelin-1 levels in the absence of coexistent cardiovascular diseases [110].

The inconsistency of the above endothelin-1 levels likely reflects the predominantly abluminal release of endothelin. Using rat models of arterial hypertension, several authors have reported elevated vascular production of endothelin-1, while circulating levels remained similar to controls [111, 112]. This demonstrates that circulating levels of endothelin-1 do not exclude elevated vascular production in OSAS.

In recent years, endothelial progenitor cells have gained a central role in vascular regeneration and endothelial repair capacity through angiogenesis and restoring endothelial function of injured blood vessels. Endothelial dysfunction is frequently present in OSAS [113] and may have a potential role in the pathogenesis of vascular diseases that is pertinent to OSAS [114].

Furthermore, It has been reported that microvascular endothelial function is affected by OSAS predominantly through increased oxidative stress, and treatment of OSAS may improve endothelial function mainly by reducing oxidative stress [115, 116].

3.7. Vibration Resulting from Snoring. Snoring associated vibration energy transmission from the upper airway to the carotid artery has been hypothesized as a potential atherosclerotic plaque initiating and rupturing event that may provide a pathogenic mechanism linking snoring and embolic stroke. The vibration produced by snoring could lead to vessel wall damage in the carotid arteries [117, 118].

In animals models, Howitt et al. demonstrated the transmission of oscillatory pressure waves from the upper airway lumen to the peripharyngeal tissues and across the carotid artery wall to the lumen [119]. Cho et al. found carotid arteries subjected to continuous pericarotid tissue vibration displayed endothelial dysfunction, suggesting a direct plausible mechanism linking heavy snoring to the development of carotid atherosclerosis [120]. Although intriguing, this concept requires further study.

4. Obesity

OSAS often coexists with obesity and many epidemiological studies have demonstrated the existence of an association. Significant OSAS is present in approximately 40% of obese individuals, and about 70% of OSAS patients are obese [121]. Young et al. estimated that the majority of severe OSAS cases (58%) were due to obesity [122]. In fact, obesity parameters such as BMI, neck circumference, and visceral fat accumulation have been identified as the most important predictors of OSAS [123, 124].

Obesity is one of the major cardiovascular risk factors associated with OSAS. The OSAS-obesity association may have an influence on other disorders, such as cardiovascular

diseases. Vgontzas et al. found a strong independent association between OSAS, visceral obesity, and insulin resistance. This author demonstrated that male obese patients with OSAS had a greater amount of computerised tomography-determined visceral adipose tissue in the abdomen than a group of BMI-matched men without OSAS [125]. Moreover, increased abdominal fat accumulation has been singled out as an independent risk factor for cardiovascular diseases [126]. It has been suggested that upper abdominal obesity is more insulin resistant and releases metabolically active products into the portal circulation.

The mechanism by which obesity can favor the onset of OSAS is not well known, but it could be that central obesity precipitates or exacerbates OSAS because fat deposits in the upper airway affect distensibility [127]. The increased volume of abdominal fat could predispose to hypoventilation during sleep and/or reduce the oxygen reserve, favoring oxygen desaturation during sleep [128]. In recent years, much attention has been focused on the interaction between OSAS and products released by adipose tissue such as leptin, adiponectin, resistin, and ghrelin [129].

4.1. Leptin. Leptin is an adipocyte-derived hormone that regulates body weight through control of appetite and energy expenditure [130]. Furthermore, leptin is a cytokine and is therefore also involved in the inflammatory process. Several studies have shown increased levels of leptin in OSAS suggesting its role in the disease [131–133]. The mechanisms underlying the relation between leptin and OSAS are very diverse and may involve overnight changes in apnea levels [134, 135], sleep hypoxemia [136], and hypercapnia [137].

A direct relationship between OSAS and leptin is supported by the fact that effective OSAS treatment with CPAP also influences leptin levels [138, 139]. Although the precise mechanism explaining the effect of CPAP has not yet been elucidated, it can be inferred that reduction in sympathetic activity [140] and improvement in insulin sensitivity play a role [141].

Leptin levels have been proposed as a prognostic marker for OSAS [142, 143] and have been implicated in the pathogenesis of OSAS and related cardiovascular disease [132, 144, 145]. Leptin's role had been recently extended into that of participant to oxidative stress, although its exact role in this process is yet to be defined. Elevated leptin levels correlate significantly with several indices of OSAS disease severity such as nocturnal hypoxemia. Leptin may be a counteractive mechanism against chronic intermittent hypoxia-related oxidative stress and may also be a marker for atherosclerosis risk [146].

4.2. Adiponectin. Adiponectin is an adipocyte-derived cytokine with regulatory functions in glucose and lipid metabolism. It also has profound anti-inflammatory and antiatherogenic effects. Levels of plasma adiponectin are decreased in obesity and metabolic syndrome [147, 148]. OSAS has independently been associated with reduced levels of adiponectin [149, 150] which may favour cardiovascular disease development. The recurrent hypoxia-reoxygenation

attacks in OSAS patients may activate oxidative stress and lead to low levels of adiponectin [151].

Some authors have observed that serum adiponectin levels may be independent of the degree of OSAS [132]. Decreased adiponectin may result from increased sympathetic activity [152] and higher levels of cytokines such as IL-6 and TNF α [153]. In fact, there are conflicting reports as to whether CPAP treatment of OSAS effectively normalizes adiponectin levels [154, 155].

Obesity has been implicated in the relation between OSAS and adiponectin [156]. In a study involving media under hypoxic conditions in an ex vivo mouse model, adiponectin secretion was measured. In obese mice, hypoxic stress reduced adiponectin in the supernatant of mesenteric fat tissue but not subcutaneous fat tissue. These findings suggest that abdominal obesity, representing abundant mesenteric fat tissue susceptible to hypoxic stress, partly explains adiponectin levels in OSAS patients, and that reduction of visceral fat accumulation may combat OSAS-related atherosclerotic cardiovascular diseases in abdominal obesity [157].

4.3. Resistin. Resistin is a white adipose tissue hormone whose function has yet to be established. Evidence suggests that resistin is involved in pathological processes leading to cardiovascular disease including inflammation, endothelial dysfunction, thrombosis, angiogenesis, and smooth muscle cell dysfunction [158]. In a study of 20 obese OSAS patients, Harsch et al. found that CPAP treatment of OSAS had no significant influence on resistin levels [159]. In OSAS patients, hypoxic stress during sleep may enhance resistin production, possibly mediating systemic inflammatory processes. Through its effect on OSAS, CPAP therapy may help control resistin production [160].

4.4. Ghrelin. Ghrelin is a hormone that influences appetite and fat accumulation and its physiological effects are opposite to those of leptin. Current experimental evidence suggests that ghrelin may act centrally to decrease sympathetic nervous system activity through peripheral afferent nerve [161]. Thus, administration of ghrelin might become a unique new therapy for cardiovascular diseases [162].

In a study of 30 obese OSAS patients, Harsch et al. found that plasma ghrelin levels were significantly higher in OSAS patients than in controls. These elevated ghrelin levels could not be explained by obesity alone, since they rapidly decreased with CPAP therapy [163]. In a study of 55 consecutive OSAS patients, the study group presented significantly higher serum ghrelin levels than controls. No significant difference was noted in the levels of leptin, adiponectin, and resistin. There was a significant positive correlation between ghrelin and AHI [164].

Increased ghrelin levels have been found to support the presence of increased appetite and caloric intake in obese patients with OSAS, which in turn may further promote the severity of the underlying conditions [165]. In obese children, OSAS is associated with daytime sleepiness, elevation of proinflammatory cytokines, increased leptin, and decreased adiponectin [166]. However, in a recent study, OSAS patients

with excessive daytime sleepiness were associated with increased circulating hypocretin-1 and decreased circulating ghrelin levels. This relationship is independent of AHI and obesity [167].

5. OSAS and Insulin Resistance

Dysglycemia and diabetes also increase the risk of developing cardiovascular disease [168]. With respect to OSAS, Mondini and Guilleminault found increased frequency of abnormal breathing during sleep in both lean and obese diabetics [169]. Elmasry et al. studied 116 hypertensive men and found a 36% prevalence of severe OSAS in diabetes patients compared to 15% in controls [170]. West et al. involving men with type 2 diabetes also reported a very high prevalence of OSAS (23%) [171, 172]. Several studies have reported that diabetic subjects with autonomic neuropathy, regardless of severity, had a relatively high prevalence of OSAS (26% and 30%) [153, 173].

OSAS might be a manifestation of an endocrine/metabolic abnormality with a strong role played by insulin resistance [174–176]. A variety of studies based on animal models have shown that hypoxia can alter glucose homeostasis [177, 178]. Polotsky et al. described that long-term exposure to intermittent hypoxia increased levels of insulin and glucose intolerance in obese, leptin-deficient mice [179]. Humans exposed to hypoxia present worsened glucose tolerance [180].

Most studies involving OSAS and insulin resistance have demonstrated an association between these two diseases, regardless of obesity [181, 182]. In a large population-based study involving normoglycemic hypertensive men, Resnick et al. found that the severity of OSAS was associated with increased insulin resistance [183]. Insulin resistance is associated with states of inflammation. Monocyte chemoattractant protein-1 levels are elevated in OSAS and may be involved in the pathogenesis of insulin resistance in these patients [184, 185].

6. Metabolic Syndrome and OSAS

Metabolic syndrome is an emerging public health problem that represents a constellation of cardiovascular risk factors [186]. The association of metabolic syndrome with cardiovascular disease was already observed more than 40 years ago [187]. In addition, Reaven confirmed that metabolic syndrome was a well-established risk factor for cardiovascular disease [188].

The diagnosis of metabolic syndrome is based on a variety of criteria. According to the National Cholesterol Education Program (NCEP) guidelines, a diagnosis of metabolic syndrome requires three or more of the following risk factors: waist circumference 102 cm, triglycerides 1.7 mmol/L, HDL cholesterol < 1.04 mmol/L, blood pressure 130/85 mmHg, and fasting glucose 6.1 mmol/L [189].

The prevalence of metabolic syndrome is markedly higher among OSAS patients. Ambrosetti et al. studied 89 consecutive OSAS patients and found metabolic syndrome in 53% of them [190]. Obese OSAS patients may have an increased

rate of metabolic syndrome and higher levels of serum lipids, fasting glucose, leptin, and fibrinogen than obese subjects without OSAS. Thus, clinicians should be encouraged to systematically evaluate the presence of metabolic abnormalities in OSAS and vice versa [191] (Figure 2).

A number of previous epidemiological studies have found links between OSAS and metabolic syndrome. Vgontzas et al. reported that fasting glucose and insulin levels were significantly higher in OSAS patients compared to weight-matched control subjects. They also found that OSAS led to systemic inflammation and metabolic syndrome [192]. Gruber et al. prospectively studied 38 subjects with OSAS and 41 controls. After adjusting for age, BMI, and smoking, OSAS patients were found to be nearly six times more likely to have metabolic syndrome than control group [193]. In a 255-subject study by Lam et al. a similar likelihood was reported [194]. Shina et al. reported that C-reactive protein was higher in patients with both OSAS and metabolic syndrome [195]. Bonsignore et al. conclude that the metabolic syndrome occurs in about half of OSAS patients, irrespective of daytime sleepiness, and is a reliable marker of insulin resistance [196].

Both OSAS and metabolic syndrome may exert negative synergistic effects on the cardiovascular system through multiple mechanisms [197, 198]. In a study by Su et al., metabolic factors such as a higher BMI and fasting blood glucose and a lower HDL-cholesterol level were more strongly associated with elevated cardiovascular disease than with OSAS severity, suggesting that metabolic parameters are important contributors to cardiovascular diseases and should be corrected in patients with OSAS [199]. In a double-blind, placebo-controlled trial in OSAS patients, 3 months of CPAP therapy lowers blood pressure and partially reverses metabolic abnormalities [200].

7. OSAS and COPD

COPD is a systemic disease with multiple effects on end-organs including organs in the cardiovascular system [201]. Patients with diagnosed and treated COPD are at increased risk for hospitalizations and deaths due to cardiovascular diseases [202, 203]. Several studies have focused on the relation between endothelial dysfunction and COPD [204–206].

Systemic inflammation is the main atherothrombotic abnormality in COPD, but hypoxia-related platelet activation, procoagulant status, and oxidative stress may play a role [207, 208]. Mills et al. showed that patients with COPD have increased arterial stiffness and blood pressure in comparison with controls matched for age and smoking status [209]. Furthermore, there is evidence that COPD patients have a perturbed neurohumoral regulatory system leading to sympathovagal imbalance [210, 211]. This process may be related to chronic respiratory or metabolic conditions that manifest hypoxia, hypercapnia, and acidosis and elicit a maladaptive autonomic and inflammatory response [212].

OSAS may coexist with COPD and this combination has been the focus of extensive study. Flenley referred to it as “overlap syndrome” [213]. Overlap patients present more nocturnal desaturation than patients with either OSAS or

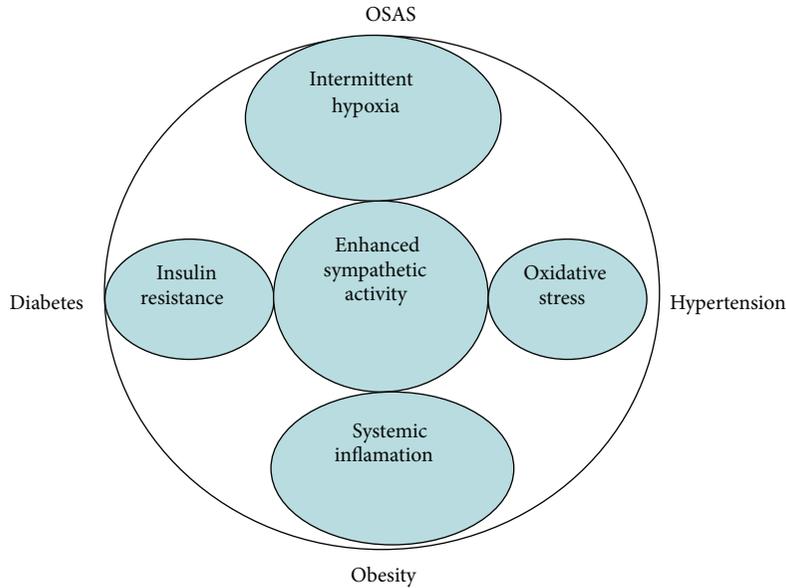


FIGURE 2: Obstructive sleep apnea syndrome and metabolic syndrome. Current perspective.

COPD alone [214]. Individuals with overlap syndrome are at greater risk for pulmonary hypertension, right heart failure, and hypercapnia than patients who have either COPD or OSAS alone [215].

As inflammatory diseases, both OSAS and COPD are associated with higher cardiovascular risk. The mechanisms that may be involved include vascular inflammation, endothelial dysfunction, and tonic elevation of sympathetic neural activity. In sum, OSAS is one of the most frequent COPD comorbidities and may bring on increased inflammation [216–218]. The overlap syndrome is associated with an increased risk of death and hospitalization because of COPD exacerbation. CPAP treatment was associated with improved survival and decreased hospitalizations in patients with overlap syndrome [219]. Treatment consists of CPAP or noninvasive positive pressure ventilation, with or without associated O₂, for correction of the upper airway obstructive episodes and hypoxemia during sleep [220, 221].

8. Conclusions

OSAS and intermittent hypoxia are associated with early vascular changes. Animal and clinical data support a specific role for intermittent hypoxia in promoting cellular changes at the vascular wall level thus triggering atherosclerosis. Independently, OSAS impairs endothelial function by altering regulation of endothelial vasomotor tone and repair capacity while promoting vascular inflammation and oxidative stress.

There is increasing evidence of a causal relationship between OSAS and metabolic dysfunction. OSAS, by intermittent hypoxia, may induce or exacerbate various aspects of metabolic syndrome. Clinical studies show that OSAS can affect glucose metabolism, cholesterol, and inflammatory markers. Identification of OSAS as a potential causative factor in metabolic syndrome would have significant clinical impact

and could improve the management and understanding of both disorders.

The association of OSAS with endocrine-metabolic and cardiovascular alterations indicates that, more than a local abnormality, OSAS should be considered a systemic disease. A vicious cycle may also appear involving hypoxemia-reoxygenation cycles, oxidative stress, and elaboration of proinflammatory cytokines promoting a more generalized inflammatory state.

Sleep apnea research is an intriguing field providing considerable contributions to the cardiovascular literature with exciting insights for clinicians, basic scientists, and epidemiologists.

Abbreviations

OSAS:	Obstructive sleep apnea syndrome
CPAP:	Continuous positive airway pressure
COPD:	Chronic obstructive pulmonary disease
AHI:	Apnea hypopnea index
BMI:	Body mass index
PAI:	Plasminogen activator inhibitor
ATP:	Adenosine triphosphate
eNOS:	Endothelial nitric oxide synthase
NF κ B:	Nuclear factor-kappaB
NADPH:	Nicotinamide adenine dinucleotide phosphate
IL-8:	Interleukin 8
IL-6:	Interleukin 6
ICAM:	Intercellular adhesion molecule-1
RANTES:	Regulated and normal T cell expressed and secreted
CCL5:	Chemokine (C-C motif) ligand 5
TNF α :	Tumor necrosis factor alpha
HDL:	High-density lipoprotein.

References

- [1] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, "The occurrence of sleep-disordered breathing among middle-aged adults," *The New England Journal of Medicine*, vol. 328, no. 17, pp. 1230–1235, 1993.
- [2] J. E. Remmers, W. J. DeGroot, E. K. Sauerland, and A. M. Anch, "Pathogenesis of upper airway occlusion during sleep," *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, vol. 44, no. 6, pp. 931–938, 1978.
- [3] M. Anstead and B. Phillips, "The spectrum of sleep-disordered breathing," *Respiratory Care Clinics of North America*, vol. 5, no. 3, pp. 363–377, 1999.
- [4] E. Lugaresi and G. Plazzi, "Heavy snorer disease: from snoring to the sleep apnea syndrome—an overview," *Respiration*, vol. 64, no. 1, pp. 11–21, 1997.
- [5] C. Guilleminault, R. Stoohs, T. Shiomi, C. Kushida, and I. Schnittger, "Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension," *Chest*, vol. 109, no. 4, pp. 901–908, 1996.
- [6] K. I. Berger, I. Ayappa, B. Chatr-Amorntri et al., "Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep," *Chest*, vol. 120, no. 4, pp. 1231–1238, 2001.
- [7] H. Gastaut, C. A. Tassinari, and B. Duron, "Polygraphic study of diurnal and nocturnal (hypnic and respiratory) episodic manifestations of Pickwick syndrome," *Revue Neurologique*, vol. 112, no. 6, pp. 568–579, 1965.
- [8] J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. N. Agustí, "Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study," *The Lancet*, vol. 365, no. 9464, pp. 1046–1053, 2005.
- [9] J. Terán-Santos, A. Jiménez-Gómez, and J. Cordero-Guevara, "The association between sleep apnea and the risk of traffic accidents," *The New England Journal of Medicine*, vol. 340, no. 11, pp. 847–851, 1999.
- [10] A. Chaouat, E. Weitzenblum, J. Krieger, T. Ifoundza, M. Oswald, and R. Kessler, "Association of chronic obstructive pulmonary disease and sleep apnea syndrome," *The American Journal of Respiratory and Critical Care Medicine*, vol. 151, no. 1, pp. 82–86, 1995.
- [11] O. Oldenburg, B. Lamp, L. Faber, H. Teschler, D. Horstkotte, and V. Töpfer, "Sleep-disordered breathing in patients with symptomatic heart failure. A contemporary study of prevalence in and characteristics of 700 patients," *European Journal of Heart Failure*, vol. 9, no. 3, pp. 251–257, 2007.
- [12] F. Pichel, C. Zamarrón, F. Magán, F. del Campo, R. Alvarez-Sala, and J. R. Rodríguez Suarez, "Health-related quality of life in patients with obstructive sleep apnea: effects of long-term positive airway pressure treatment," *Respiratory Medicine*, vol. 98, no. 10, pp. 968–976, 2004.
- [13] S. R. Coughlin, L. Mawdsley, J. A. Mugarza, P. M. A. Calverley, and J. P. H. Wilding, "Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome," *European Heart Journal*, vol. 25, no. 9, pp. 735–741, 2004.
- [14] J. Durán, S. Esnaola, R. Rubio, and Á. Iztueta, "Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr," *The American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 3, part 1, pp. 685–689, 2001.
- [15] Z. F. Udawadia, A. V. Doshi, S. G. Lonkar, and C. I. Singh, "Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men," *The American Journal of Respiratory and Critical Care Medicine*, vol. 169, no. 2, pp. 168–173, 2004.
- [16] S. K. Sharma, S. Kumpawat, A. Banga, and A. Goel, "Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India," *Chest*, vol. 130, no. 1, pp. 149–156, 2006.
- [17] R. Plywaczewski, M. Bednarek, L. Jonczak, and J. Zieliński, "Sleep-disordered breathing in a middle-aged and older Polish urban population," *Journal of Sleep Research*, vol. 17, no. 1, pp. 73–81, 2008.
- [18] S. Ancoli-Israel and T. Coy, "Are breathing disturbances in elderly equivalent to sleep apnea syndrome?" *Sleep*, vol. 17, no. 1, pp. 77–83, 1994.
- [19] T. Young, "Sleep-disordered breathing in older adults: is it a condition distinct from that in middle-aged adults?" *Sleep*, vol. 19, no. 7, pp. 529–530, 1996.
- [20] M. M. Fung, K. Peters, S. Redline et al., "Decreased slow wave sleep increases risk of developing hypertension in elderly men," *Hypertension*, vol. 58, no. 4, pp. 596–603, 2011.
- [21] T. T. Bekci, M. Kayrak, A. Kiyici et al., "The association among lipoprotein-associated phospholipase A2 levels, total antioxidant capacity and arousal in male patients with OSA," *International Journal of Medical Sciences*, vol. 8, no. 5, pp. 369–376, 2011.
- [22] M. Follenius, J. Krieger, M. O. Krauth, F. Sforza, and G. Brandenberger, "Obstructive sleep apnea treatment: peripheral and central effects on plasma renin activity and aldosterone," *Sleep*, vol. 14, no. 3, pp. 211–217, 1991.
- [23] D. S. Møller, P. Lind, B. Strunge, and E. B. Pedersen, "Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea," *The American Journal of Hypertension*, vol. 16, no. 4, pp. 274–280, 2003.
- [24] S. R. Patel, X. Zhu, A. Storfer-Isser et al., "Sleep duration and biomarkers of inflammation," *Sleep*, vol. 32, no. 2, pp. 200–204, 2009.
- [25] D. Gozal, L. D. Serpero, L. Kheirandish-Gozal, O. S. Capdevila, A. Khalyfa, and R. Tauman, "Sleep measures and morning plasma TNF- α levels in children with sleep-disordered breathing," *Sleep*, vol. 33, no. 3, pp. 319–325, 2010.
- [26] V. K. Somers, A. L. Mark, and F. M. Abboud, "Sympathetic activation by hypoxia and hypercapnia—implications for sleep apnea," *Clinical and Experimental Hypertension A*, vol. 10, no. 1, pp. 413–422, 1988.
- [27] V. A. Imadojemu, Z. Mawji, A. Kunselman, K. S. Gray, C. S. Hogeman, and U. A. Leuenberger, "Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy," *Chest*, vol. 131, no. 5, pp. 1406–1413, 2007.
- [28] N. R. Prabhakar, R. D. Fields, T. Baker, and E. C. Fletcher, "Intermittent hypoxia: cell to system," *The American Journal of Physiology*, vol. 281, no. 3, pp. L524–L528, 2001.
- [29] V. K. Somers, M. E. Dyken, M. P. Clary, and F. M. Abboud, "Sympathetic neural mechanisms in obstructive sleep apnea," *Journal of Clinical Investigation*, vol. 96, no. 4, pp. 1897–1904, 1995.
- [30] R. Tamisier, J. L. Pépin, J. Rémy et al., "14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans," *European Respiratory Journal*, vol. 37, no. 1, pp. 119–128, 2011.

- [31] R. Von Känel and J. E. Dimsdale, "Hemostatic alterations in patients with obstructive sleep apnea and the implications for cardiovascular disease," *Chest*, vol. 124, no. 5, pp. 1956–1967, 2003.
- [32] R. E. Maser, M. J. Lenhard, A. A. Rizzo, and A. A. Vasile, "Continuous positive airway pressure therapy improves cardiovascular autonomic function for persons with sleep-disordered breathing," *Chest*, vol. 133, no. 1, pp. 86–91, 2008.
- [33] O. Marrone, A. Salvaggio, A. L. Bue et al., "Blood pressure changes after automatic and fixed CPAP in obstructive sleep apnea: relationship with nocturnal sympathetic activity," *Clinical and Experimental Hypertension*, vol. 33, no. 6, pp. 373–380, 2011.
- [34] G. V. Robinson, J. C. T. Pepperell, H. C. Segal, R. J. O. Davies, and J. R. Stradling, "Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials," *Thorax*, vol. 59, no. 9, pp. 777–782, 2004.
- [35] R. Schulz, S. Mahmoudi, K. Hattar et al., "Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea: impact of continuous positive airway pressure therapy," *The American Journal of Respiratory and Critical Care Medicine*, vol. 162, no. 2, part 1, pp. 566–570, 2000.
- [36] L. Lavie, A. Vishnevsky, and P. Lavie, "Evidence for lipid peroxidation in obstructive sleep apnea," *Sleep*, vol. 27, no. 1, pp. 123–128, 2004.
- [37] G. E. Carpagnano, S. A. Kharitonov, O. Resta, M. P. Foschino-Barbaro, E. Gramiccioni, and P. J. Barnes, "8-isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy," *Chest*, vol. 124, no. 4, pp. 1386–1392, 2003.
- [38] A. Alonso-Fernández, F. García-Río, M. A. Arias et al., "Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: a randomised trial," *Thorax*, vol. 64, no. 7, pp. 581–586, 2009.
- [39] P. Celec, J. Hodosy, M. Behuliak et al., "Oxidative and carbonyl stress in patients with obstructive sleep apnea treated with continuous positive airway pressure," *Sleep and Breathing*, vol. 16, no. 2, pp. 393–398, 2012.
- [40] G. Malakasioti, E. Alexopoulos, C. Befani et al., "Oxidative stress and inflammatory markers in the exhaled breath condensate of children with OSA," *Sleep and Breathing*, vol. 16, no. 3, pp. 703–708, 2012.
- [41] S. Teramoto, H. Kume, H. Yamamoto et al., "Effects of oxygen administration on the circulating vascular endothelial growth factor (VEGF) levels in patients with obstructive sleep apnea syndrome," *Internal Medicine*, vol. 42, no. 8, pp. 681–685, 2003.
- [42] O. Marrone, A. Salvaggio, M. Gioia et al., "Reticulocytes in untreated obstructive sleep apnoea," *Monaldi Archives for Chest Disease*, vol. 69, no. 3, pp. 107–113, 2008.
- [43] E. Belaidi, M. Joyeux-Faure, C. Ribuot, S. H. Launois, P. Levy, and D. Godin-Ribuot, "Major role for hypoxia inducible factor-1 and the endothelin system in promoting myocardial infarction and hypertension in an animal model of obstructive sleep apnea," *Journal of the American College of Cardiology*, vol. 53, no. 15, pp. 1309–1317, 2009.
- [44] L. Dyugovskaya, P. Lavie, and L. Lavie, "Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients," *The American Journal of Respiratory and Critical Care Medicine*, vol. 165, no. 7, pp. 934–939, 2002.
- [45] A. Park, H. Nagase, S. V. Kumar, and Y. J. Suzuki, "Effects of intermittent hypoxia on the heart," *Antioxidants and Redox Signaling*, vol. 9, no. 6, pp. 723–729, 2007.
- [46] A. Barceló, F. Barbé, M. de la Peña et al., "Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment," *European Respiratory Journal*, vol. 27, no. 4, pp. 756–760, 2006.
- [47] M. Grebe, H. J. Eisele, N. Weissmann et al., "Antioxidant vitamin C improves endothelial function in obstructive sleep apnea," *The American Journal of Respiratory and Critical Care Medicine*, vol. 173, no. 8, pp. 897–901, 2006.
- [48] J. L. Lattimore, I. Wilcox, S. Nakhla, M. Langenfeld, W. Jessup, and D. S. Celermajer, "Repetitive hypoxia increases lipid loading in human macrophages—a potentially atherogenic effect," *Atherosclerosis*, vol. 179, no. 2, pp. 255–259, 2005.
- [49] E. Wysocka, S. Cofta, M. Cymerys, J. Gozdzik, L. Torlinski, and H. Batura-Gabryel, "The impact of the sleep apnea syndrome on oxidant-antioxidant balance in the blood of overweight and obese patients," *Journal of Physiology and Pharmacology*, vol. 59, supplement 6, pp. 761–769, 2008.
- [50] S. Jelic, D. J. Lederer, T. Adams et al., "Vascular inflammation in obesity and sleep apnea," *Circulation*, vol. 121, no. 8, pp. 1014–1021, 2010.
- [51] M. A. Alzoughaibi and A. S. BaHamman, "The effect of one night of continuous positive airway pressure therapy on oxidative stress and antioxidant defense in hypertensive patients with severe obstructive sleep apnea," *Sleep and Breathing*, vol. 16, no. 2, pp. 499–504, 2012.
- [52] D. Nair, E. A. Dayyat, S. X. Zhang, Y. Wang, and D. Gozal, "Intermittent hypoxia-induced cognitive deficits are mediated by NADPH oxidase activity in a murine model of sleep apnea," *PLoS ONE*, vol. 6, no. 5, Article ID e19847, 2011.
- [53] G. Devouassoux, P. Lévy, E. Rossini et al., "Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure-induced airway hyperresponsiveness," *Journal of Allergy and Clinical Immunology*, vol. 119, no. 3, pp. 597–603, 2007.
- [54] G. E. Carpagnano, A. Spanevello, R. Sabato et al., "Systemic and airway inflammation in sleep apnea and obesity: the role of ICAM-1 and IL-8," *Translational Research*, vol. 155, no. 1, pp. 35–43, 2010.
- [55] S. Cofta, E. Wysocka, S. Dziegielewska-Gesiak et al., "Plasma selectins in patients with obstructive sleep apnea," *Advances in Experimental Medicine and Biology*, vol. 756, pp. 113–119, 2013.
- [56] A. A. El-Solh, M. J. Mador, P. Sikka, R. S. Dhillon, D. Amsterdam, and B. J. B. Grant, "Adhesion molecules in patients with coronary artery disease and moderate-to-severe obstructive sleep apnea," *Chest*, vol. 121, no. 5, pp. 1541–1547, 2002.
- [57] C. Zamarrón-Sanz, J. Ricoy-Galbaldon, F. Gude-Sampedro, and A. Riveiro-Riveiro, "Plasma levels of vascular endothelial markers in obstructive sleep apnea," *Archives of Medical Research*, vol. 37, no. 4, pp. 552–555, 2006.
- [58] L. Dyugovskaya, A. Polyakov, P. Lavie, and L. Lavie, "Delayed neutrophil apoptosis in patients with sleep apnea," *The American Journal of Respiratory and Critical Care Medicine*, vol. 177, no. 5, pp. 544–554, 2008.
- [59] S. Imagawa, Y. Yamaguchi, K. Ogawa et al., "Interleukin-6 and tumor necrosis factor- α in patients with obstructive sleep apnea-hypopnea syndrome," *Respiration*, vol. 71, no. 1, pp. 24–29, 2004.
- [60] M. de la Peña Bravo, L. D. Serpero, A. Barceló, F. Barbé, A. Agustí, and D. Gozal, "Inflammatory proteins in patients with

- obstructive sleep apnea with and without daytime sleepiness," *Sleep and Breathing*, vol. 11, no. 3, pp. 177–185, 2007.
- [61] P. Steiropoulos, I. Kotsianidis, E. Nena et al., "Long-term effect of continuous positive airway pressure therapy on inflammation markers of patients with obstructive sleep apnea syndrome," *Sleep*, vol. 32, no. 4, pp. 537–543, 2009.
- [62] M. A. Arias, F. García-Río, A. Alonso-Fernández et al., "CPAP decreases plasma levels of soluble tumour necrosis factor- α receptor 1 in obstructive sleep apnoea," *European Respiratory Journal*, vol. 32, no. 4, pp. 1009–1015, 2008.
- [63] R. Ross, "Atherosclerosis—an inflammatory disease," *The New England Journal of Medicine*, vol. 340, no. 2, pp. 115–126, 1999.
- [64] G. K. Hansson, "Mechanisms of disease: inflammation, atherosclerosis, and coronary artery disease," *The New England Journal of Medicine*, vol. 352, no. 16, pp. 1685–1695, 2005.
- [65] J. R. Delanghe, M. R. Langlois, D. de Bacquer et al., "Discriminative value of serum amyloid A and other acute-phase proteins for coronary heart disease," *Atherosclerosis*, vol. 160, no. 2, pp. 471–476, 2002.
- [66] A. Svatikova, R. Wolk, A. S. Shamsuzzaman, T. Kara, E. J. Olson, and V. K. Somers, "Serum amyloid a in obstructive sleep apnea," *Circulation*, vol. 108, no. 12, pp. 1451–1454, 2003.
- [67] E. Kuramoto, S. Kinami, Y. Ishida, H. Shiotani, and Y. Nishimura, "Continuous positive nasal airway pressure decreases levels of serum amyloid A and improves autonomic function in obstructive sleep apnea syndrome," *International Journal of Cardiology*, vol. 135, no. 3, pp. 338–345, 2009.
- [68] M. K. Rutter, J. B. Meigs, L. M. Sullivan, R. B. D'Agostino Sr., and P. W. F. Wilson, "C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham offspring study," *Circulation*, vol. 110, no. 4, pp. 380–385, 2004.
- [69] A. S. M. Shamsuzzaman, M. Winnicki, P. Lanfranchi et al., "Elevated C-reactive protein in patients with obstructive sleep apnea," *Circulation*, vol. 105, no. 21, pp. 2462–2464, 2002.
- [70] O. Kokturk, T. U. Ciftci, E. Mollarecep, and B. Ciftci, "Elevated C-reactive protein levels and increased cardiovascular risk in patients with obstructive sleep apnea syndrome," *International Heart Journal*, vol. 46, no. 5, pp. 801–809, 2005.
- [71] S. Taheri, D. Austin, L. Lin, F. J. Nieto, T. Young, and E. Mignot, "Correlates of serum C-reactive protein (CRP)—no association with sleep duration or sleep disordered breathing," *Sleep*, vol. 30, no. 8, pp. 991–996, 2007.
- [72] T. Yokoe, K. Minoguchi, H. Matsuo et al., "Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure," *Circulation*, vol. 107, no. 8, pp. 1129–1134, 2003.
- [73] S. E. Schiza, C. Mermigkis, P. Panagiotis et al., "C-reactive protein evolution in obstructive sleep apnoea patients under CPAP therapy," *European Journal of Clinical Investigation*, vol. 40, no. 11, pp. 968–975, 2010.
- [74] S. Ryan, C. T. Taylor, and W. T. McNicholas, "Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome," *Circulation*, vol. 112, no. 17, pp. 2660–2667, 2005.
- [75] H. J. Yu, B. R. Lin, H. S. Lee et al., "Sympathetic vesicovascular reflex induced by acute urinary retention evokes proinflammatory and proapoptotic injury in rat liver," *The American Journal of Physiology*, vol. 288, no. 5, pp. F1005–F1014, 2005.
- [76] T. J. Guzik, N. E. Hoch, K. A. Brown et al., "Role of the T cell in the genesis of angiotensin II-induced hypertension and vascular dysfunction," *Journal of Experimental Medicine*, vol. 204, no. 10, pp. 2449–2460, 2007.
- [77] T. Kasai, K. Inoue, T. Kumagai et al., "Plasma pentraxin3 and arterial stiffness in men with obstructive sleep apnea," *The American Journal of Hypertension*, vol. 24, no. 4, pp. 401–407, 2011.
- [78] C. Arnaud, P. C. Beguin, S. Lantuejoul et al., "The inflammatory preatherosclerotic remodeling induced by intermittent hypoxia is attenuated by RANTES/CCL5 inhibition," *The American Journal of Respiratory and Critical Care Medicine*, vol. 184, no. 6, pp. 724–731, 2011.
- [79] A. Carreras, I. Almendros, J. M. Montserrat, D. Navajas, and R. Farré, "Mesenchymal stem cells reduce inflammation in a rat model of obstructive sleep apnea," *Respiratory Physiology and Neurobiology*, vol. 172, no. 3, pp. 210–212, 2010.
- [80] J. S. Querido, A. W. Sheel, R. Cheema, S. van Eeden, A. T. Mulgrew, and N. T. Ayas, "Effects of 10 days of modest intermittent hypoxia on circulating measures of inflammation in healthy humans," *Sleep and Breathing*, vol. 16, no. 3, pp. 657–662, 2012.
- [81] K. Zouaoui Boudjeltia, M. Guillaume, C. Henuzet et al., "Fibrinolysis and cardiovascular risk factors: association with fibrinogen, lipids, and monocyte count," *European Journal of Internal Medicine*, vol. 17, no. 2, pp. 102–108, 2006.
- [82] V. Bratseth, A. A. Pettersen, T. B. Opstad, H. Arnesen, and I. Seljeflot, "Markers of hypercoagulability in CAD patients. Effects of single aspirin and clopidogrel treatment," *Thrombosis Journal*, vol. 10, article 12, 2012.
- [83] N. Peled, M. Kassirer, M. R. Kramer et al., "Increased erythrocyte adhesiveness and aggregation in obstructive sleep apnea syndrome," *Thrombosis Research*, vol. 121, no. 5, pp. 631–636, 2008.
- [84] M. Othman, S. P. Gordon, and S. Iscoe, "Repeated inspiratory occlusions in anesthetized rats acutely increase blood coagulability as assessed by thromboelastography," *Respiratory Physiology and Neurobiology*, vol. 171, no. 1, pp. 61–66, 2010.
- [85] W. H. Reinhart, J. Oswald, R. Walter, and M. Kuhn, "Blood viscosity and platelet function in patients with obstructive sleep apnea syndrome treated with nasal continuous positive airway pressure," *Clinical Hemorheology and Microcirculation*, vol. 27, no. 3–4, pp. 201–207, 2002.
- [86] R. von Känel, J. S. Loredó, F. L. Powell, K. A. Adler, and J. E. Dimsdale, "Short-term isocapnic hypoxia and coagulation activation in patients with sleep apnea," *Clinical Hemorheology and Microcirculation*, vol. 33, no. 4, pp. 369–377, 2005.
- [87] M. E. Akinnusi, L. L. Paasch, K. R. Szarpa, P. K. Wallace, and A. A. El Solh, "Impact of nasal continuous positive airway pressure therapy on markers of platelet activation in patients with obstructive sleep apnea," *Respiration*, vol. 77, no. 1, pp. 25–31, 2009.
- [88] R. von Känel, J. S. Loredó, S. Ancoli-Israel, and J. E. Dimsdale, "Association between sleep apnea severity and blood coagulability: treatment effects of nasal continuous positive airway pressure," *Sleep and Breathing*, vol. 10, no. 3, pp. 139–146, 2006.
- [89] C. Zamarrón, J. Ricoy, A. Riveiro, and F. Gude, "Plasminogen activator inhibitor-1 in obstructive sleep apnea patients with and without hypertension," *Lung*, vol. 186, no. 3, pp. 151–156, 2008.
- [90] D. Shritit, N. Peled, A. B. Shritit et al., "An association between oxygen desaturation and D-dimer in patients with obstructive sleep apnea syndrome," *Thrombosis and Haemostasis*, vol. 94, no. 3, pp. 544–547, 2005.

- [91] K. R. von Känel, L. Natarajan, S. Ancoli-Israel et al., "Effect of continuous positive airway pressure on day/night rhythm of prothrombotic markers in obstructive sleep apnea," *Sleep Medicine*, vol. 14, no. 1, pp. 58–65, 2013.
- [92] R. von Känel, J. S. Loredó, S. Ancoli-Israel, P. J. Mills, L. Natarajan, and J. E. Dimsdale, "Association between polysomnographic measures of disrupted sleep and prothrombotic factors," *Chest*, vol. 131, no. 3, pp. 733–739, 2007.
- [93] S. J. Cleland, N. Sattar, J. R. Petrie, N. G. Forouhi, H. L. Elliott, and J. M. C. Connell, "Endothelial dysfunction as a possible link between C-reactive protein levels and cardiovascular disease," *Clinical Science*, vol. 98, no. 5, pp. 531–535, 2000.
- [94] H. A. R. Hadi and J. A. Al Suwaidi, "Endothelial dysfunction in diabetes mellitus," *Vascular Health and Risk Management*, vol. 3, no. 6, pp. 853–876, 2007.
- [95] J. P. J. Halcox, A. E. Donald, E. Ellins et al., "Endothelial function predicts progression of carotid intima-media thickness," *Circulation*, vol. 119, no. 7, pp. 1005–1012, 2009.
- [96] T. J. Anderson, A. Uehata, M. D. Gerhard et al., "Close relation of endothelial function in the human coronary and peripheral circulations," *Journal of the American College of Cardiology*, vol. 26, no. 5, pp. 1235–1241, 1995.
- [97] J. Oyama, H. Yamamoto, T. Maeda, A. Ito, K. Node, and N. Makino, "Continuous positive airway pressure therapy improves vascular dysfunction and decreases oxidative stress in patients with the metabolic syndrome and obstructive sleep apnea syndrome," *Clinical Cardiology*, vol. 35, no. 4, pp. 231–236, 2012.
- [98] M. S. M. Ip, H. Tse, B. Lam, K. W. T. Tsang, and W. Lam, "Endothelial function in obstructive sleep apnea and response to treatment," *The American Journal of Respiratory and Critical Care Medicine*, vol. 169, no. 3, pp. 348–353, 2004.
- [99] W. Trzepizur, F. Gagnadoux, P. Abraham et al., "Microvascular endothelial function in obstructive sleep apnea: impact of continuous positive airway pressure and mandibular advancement," *Sleep Medicine*, vol. 10, no. 7, pp. 746–752, 2009.
- [100] J. S. J. Haight and P. G. Djupesland, "Nitric oxide (NO) and obstructive sleep apnea (OSA)," *Sleep and Breathing*, vol. 7, no. 2, pp. 53–62, 2003.
- [101] F. J. Nieto, D. M. Herrington, S. Redline, E. J. Benjamin, and J. A. Robbins, "Sleep apnea and markers of vascular endothelial function in a large community sample of older adults," *The American Journal of Respiratory and Critical Care Medicine*, vol. 169, no. 3, pp. 354–360, 2004.
- [102] M. Kohler, S. Craig, D. Nicoll, P. Leeson, R. J. O. Davies, and J. R. Stradling, "Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea," *The American Journal of Respiratory and Critical Care Medicine*, vol. 178, no. 9, pp. 984–988, 2008.
- [103] M. de la Peña, A. Barceló, F. Barbe et al., "Endothelial function and circulating endothelial progenitor cells in patients with sleep apnea syndrome," *Respiration*, vol. 76, no. 1, pp. 28–32, 2008.
- [104] M. Kohler, A. Stoewhas, L. Ayers et al., "Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial," *The American Journal of Respiratory and Critical Care Medicine*, vol. 184, no. 10, pp. 1192–1199, 2011.
- [105] M. M. Ciccone, S. Favale, P. Scicchitano et al., "Reversibility of the endothelial dysfunction after CPAP therapy in OSAS patients," *International Journal of Cardiology*, vol. 158, no. 3, pp. 383–386, 2012.
- [106] N. L. Kanagy, B. R. Walker, and L. D. Nelin, "Role of endothelin in intermittent hypoxia-induced hypertension," *Hypertension*, vol. 37, no. 2, pp. 511–515, 2001.
- [107] B. G. Phillips, K. Narkiewicz, C. A. Pesek, W. G. Haynes, M. E. Dyken, and V. K. Somers, "Effects of obstructive sleep apnea on endothelin-1 and blood pressure," *Journal of Hypertension*, vol. 17, no. 1, pp. 61–66, 1999.
- [108] S. Saarelainen and J. Hasan, "Circulating endothelin-1 and obstructive sleep apnoea," *European Respiratory Journal*, vol. 16, no. 4, pp. 794–795, 2000.
- [109] F. Grimpen, P. Kanne, E. Schulz, G. Hagenah, G. Hasenfuß, and S. Andreas, "Endothelin-1 plasma levels are not elevated in patients with obstructive sleep apnoea," *European Respiratory Journal*, vol. 15, no. 2, pp. 320–325, 2000.
- [110] P. H. Gjørup, L. Sadauskienė, J. Wessels, O. Nyvad, B. Strunge, and E. B. Pedersen, "Abnormally increased endothelin-1 in plasma during the night in obstructive sleep apnea: relation to blood pressure and severity of disease," *The American Journal of Hypertension*, vol. 20, no. 1, pp. 44–52, 2007.
- [111] G. P. Rossi and G. Pitter, "Genetic variation in the endothelin system: do polymorphisms affect the therapeutic strategies?" *Annals of the New York Academy of Sciences*, vol. 1069, pp. 34–50, 2006.
- [112] U. Pohl and R. Busse, "Differential vascular sensitivity to lumenally and adventitially applied endothelin-1," *Journal of Cardiovascular Pharmacology*, vol. 13, supplement 5, pp. S188–S190, 1989.
- [113] L. Kheirandish-Gozal, R. Bhattacharjee, J. Kim, H. B. Clair, and D. Gozal, "Endothelial progenitor cells and vascular dysfunction in children with obstructive sleep apnea," *The American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 1, pp. 92–97, 2010.
- [114] S. Berger and L. Lavie, "Endothelial progenitor cells in cardiovascular disease and hypoxia—potential implications to obstructive sleep apnea," *Translational Research*, vol. 158, no. 1, pp. 1–13, 2011.
- [115] B. T. Patt, D. Jarjoura, D. N. Haddad et al., "Endothelial dysfunction in the microcirculation of patients with obstructive sleep apnea," *The American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 12, pp. 1540–1545, 2010.
- [116] N. J. Büchner, I. Quack, M. Woznowski, C. Stähle, U. Wenzel, and L. C. Rump, "Microvascular endothelial dysfunction in obstructive sleep apnea is caused by oxidative stress and improved by continuous positive airway pressure therapy," *Respiration*, vol. 82, no. 5, pp. 409–417, 2011.
- [117] S. A. Lee, T. C. Amis, K. Byth et al., "Heavy snoring as a cause of carotid artery atherosclerosis," *Sleep*, vol. 31, no. 9, pp. 1207–1213, 2008.
- [118] J. Amatoury, L. Howitt, J. R. Wheatley, A. P. Avolio, and T. C. Amis, "Snoring-related energy transmission to the carotid artery in rabbits," *Journal of Applied Physiology*, vol. 100, no. 5, pp. 1547–1553, 2006.
- [119] L. Howitt, K. Kairaitis, J. P. Kirkness et al., "Oscillatory pressure wave transmission from the upper airway to the carotid artery," *Journal of Applied Physiology*, vol. 103, no. 5, pp. 1622–1627, 2007.
- [120] J. Cho, P. K. Witting, M. Verma et al., "Tissue vibration induces carotid artery endothelial dysfunction: a mechanism linking snoring and carotid atherosclerosis?" *Sleep*, vol. 34, no. 6, pp. 751–757, 2011.
- [121] R. Wolk, A. S. M. Shamsuzzaman, and V. K. Somers, "Obesity, sleep apnea, and hypertension," *Hypertension*, vol. 42, no. 6, pp. 1067–1074, 2003.

- [122] T. Young, P. E. Peppard, and S. Taheri, "Excess weight and sleep-disordered breathing," *Journal of Applied Physiology*, vol. 99, no. 4, pp. 1592–1599, 2005.
- [123] H. Schäfer, D. Pauleit, T. Sudhop, I. Gouni-Berthold, S. Ewig, and H. K. Berthold, "Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea," *Chest*, vol. 122, no. 3, pp. 829–839, 2002.
- [124] C. A. Canapari, A. G. Hoppin, T. B. Kinane, B. J. Thomas, M. Torriani, and E. S. Katz, "Relationship between sleep apnea, fat distribution, and insulin resistance in obese children," *Journal of Clinical Sleep Medicine*, vol. 7, no. 3, pp. 268–273, 2011.
- [125] A. N. Vgontzas, D. A. Papanicolaou, E. O. Bixler et al., "Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 3, pp. 1151–1158, 2000.
- [126] H. Nagaretani, T. Nakamura, T. Funahashi et al., "Visceral fat is a major contributor for multiple risk factor clustering in Japanese men with impaired glucose tolerance," *Diabetes Care*, vol. 24, no. 12, pp. 2127–2133, 2001.
- [127] S. Isono, "Obstructive sleep apnea of obese adults: pathophysiology and perioperative airway management," *Anesthesiology*, vol. 110, no. 4, pp. 908–921, 2009.
- [128] A. R. Schwartz, S. P. Patil, A. M. Laffan, V. Polotsky, H. Schneider, and P. L. Smith, "Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches," *Proceedings of the American Thoracic Society*, vol. 5, no. 2, pp. 185–192, 2008.
- [129] T. Ronti, G. Lupattelli, and E. Mannarino, "The endocrine function of adipose tissue: an update," *Clinical Endocrinology*, vol. 64, no. 4, pp. 355–365, 2006.
- [130] K. Proulx, D. Richard, and C. Walker, "Leptin regulates appetite-related neuropeptides in the hypothalamus of developing rats without affecting food intake," *Endocrinology*, vol. 143, no. 12, pp. 4683–4692, 2002.
- [131] B. G. Phillips, M. Kato, K. Narkiewicz, I. Choe, and V. K. Somers, "Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea," *The American Journal of Physiology*, vol. 279, no. 1, pp. H234–H237, 2000.
- [132] F. Tokuda, Y. Sando, H. Matsui, H. Koike, and T. Yokoyama, "Serum levels of adipocytokines, adiponectin and leptin, in patients with obstructive sleep apnea syndrome," *Internal Medicine*, vol. 47, no. 21, pp. 1843–1849, 2008.
- [133] M. S. M. Ip, K. S. L. Lam, C. Ho, K. W. T. Tsang, and W. Lam, "Serum leptin and vascular risk factors in obstructive sleep apnea," *Chest*, vol. 118, no. 3, pp. 580–586, 2000.
- [134] B. M. Sanner, P. Kollhoser, N. Buechner, W. Zidek, and M. Tepel, "Influence of treatment on leptin levels in patients with obstructive sleep apnoea," *European Respiratory Journal*, vol. 23, no. 4, pp. 601–604, 2004.
- [135] S. R. Patel, L. J. Palmer, E. K. Larkin, N. S. Jenny, D. P. White, and S. Redline, "Relationship between obstructive sleep apnea and diurnal leptin rhythms," *Sleep*, vol. 27, no. 2, pp. 235–239, 2004.
- [136] K. Tatsumi, J. Kasahara, K. Kurosu, N. Tanabe, Y. Takiguchi, and T. Kuriyama, "Sleep oxygen desaturation and circulating leptin in obstructive sleep apnea-hypopnea syndrome," *Chest*, vol. 127, no. 3, pp. 716–721, 2005.
- [137] R. Shimura, K. Tatsumi, A. Nakamura et al., "Fat accumulation, leptin, and hypercapnia in obstructive sleep apnea-hypopnea syndrome," *Chest*, vol. 127, no. 2, pp. 543–549, 2005.
- [138] K. Shimizu, T. Nakamura, A. Niimi et al., "Plasma leptin levels and cardiac sympathetic function in patients with obstructive sleep apnoea-hypopnoea syndrome," *Thorax*, vol. 57, no. 5, pp. 429–434, 2002.
- [139] C. Çuhadaroğlu, A. Utkusavaş, L. Öztürk, S. Salman, and T. Ece, "Effects of nasal CPAP treatment on insulin resistance, lipid profile, and plasma leptin in sleep apnea," *Lung*, vol. 187, no. 2, pp. 75–81, 2009.
- [140] S. Snitker, R. E. Pratley, M. Nicolson, P. A. Tataranni, and E. Ravussin, "Relationship between muscle sympathetic nerve activity and plasma leptin concentration," *Obesity Research*, vol. 5, no. 4, pp. 338–340, 1997.
- [141] B. Brooks, P. A. Cistulli, M. Borkman et al., "Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness," *Journal of Clinical Endocrinology and Metabolism*, vol. 79, no. 6, pp. 1681–1685, 1994.
- [142] L. Öztürk, M. Ünal, L. Tamer, and F. Çelikoğlu, "The association of the severity of obstructive sleep apnea with plasma leptin levels," *Archives of Otolaryngology—Head and Neck Surgery*, vol. 129, no. 5, pp. 538–540, 2003.
- [143] S. Zirlik, T. Hauck, F. S. Fuchs, M. F. Neurath, P. C. Konturek, and I. A. Harsch, "Leptin, obestatin and apelin levels in patients with obstructive sleep apnoea syndrome," *Medical Science Monitor*, vol. 17, no. 3, pp. CR159–CR164, 2011.
- [144] N. Al Lawati, A. Mulgrew, R. Cheema et al., "Pro-atherogenic cytokine profile of patients with suspected obstructive sleep apnea," *Sleep and Breathing*, vol. 13, no. 4, pp. 391–395, 2009.
- [145] F. Kapsimalis, G. Varouchakis, A. Manousaki et al., "Association of sleep apnea severity and obesity with insulin resistance, C-reactive protein, and leptin levels in male patients with obstructive sleep apnea," *Lung*, vol. 186, no. 4, pp. 209–217, 2008.
- [146] M. Macrea, T. Martin, L. Zagrean, Z. Jia, and H. Misra, "Role of leptin as antioxidant in obstructive sleep apnea: an in vitro study using electron paramagnetic resonance method," *Sleep and Breathing*, vol. 17, no. 1, pp. 105–110, 2013.
- [147] D. K. Oh, T. Ciaraldi, and R. R. Henry, "Adiponectin in health and disease," *Diabetes, Obesity and Metabolism*, vol. 9, no. 3, pp. 282–289, 2007.
- [148] N. Ouchi and K. Walsh, "Adiponectin as an anti-inflammatory factor," *Clinica Chimica Acta*, vol. 380, no. 1–2, pp. 24–30, 2007.
- [149] X. L. Zhang, K. S. Yin, H. Wang, and S. Su, "Serum adiponectin levels in adult male patients with obstructive sleep apnea hypopnea syndrome," *Respiration*, vol. 73, no. 1, pp. 73–77, 2006.
- [150] B. Masserini, P. S. Morpurgo, F. Donadio, C. Baldessari, P. Beck-Peccoz, and E. Orsi, "Reduced levels of adiponectin in sleep apnea syndrome," *Journal of Endocrinological Investigation*, vol. 29, no. 8, pp. 700–705, 2006.
- [151] E. Vatanserver, E. Surmen-Gur, A. Ursavas, and M. Karadag, "Obstructive sleep apnea causes oxidative damage to plasma lipids and proteins and decreases adiponectin levels," *Sleep and Breathing*, vol. 15, no. 3, pp. 275–282, 2011.
- [152] M. Fasshauer, S. Kralisch, M. Klier et al., "Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes," *Biochemical and Biophysical Research Communications*, vol. 301, no. 4, pp. 1045–1050, 2003.
- [153] W. T. McNicholas and M. R. Bonsignore, "Sleep apnoea as an independent risk for cardiovascular disease: current evidence, basic mechanisms and research priorities," *European Respiratory Journal*, vol. 29, no. 1, pp. 156–178, 2007.

- [154] G. Carneiro, S. M. Togeiro, F. F. Ribeiro-Filho et al., "Continuous positive airway pressure therapy improves hypoadiponectinemia in severe obese men with obstructive sleep apnea without changes in insulin resistance," *Metabolic Syndrome and Related Disorders*, vol. 7, no. 6, pp. 537–542, 2009.
- [155] A. M. J. de Lima, C. M. R. Franco, C. M. M. B. de Castro, A. D. A. Bezerra, L. Ataíde Jr., and A. Halpern, "Effects of nasal continuous positive airway pressure treatment on oxidative stress and adiponectin levels in obese patients with obstructive sleep apnea," *Respiration*, vol. 79, no. 5, pp. 370–376, 2010.
- [156] S. Makino, H. Handa, K. Suzukawa et al., "Obstructive sleep apnoea syndrome, plasma adiponectin levels, and insulin resistance," *Clinical Endocrinology*, vol. 64, no. 1, pp. 12–19, 2006.
- [157] Y. Nakagawa, K. Kishida, S. Kihara, R. Yoshida, T. Funahashi, and I. Shimomura, "Nocturnal falls of adiponectin levels in sleep apnea with abdominal obesity and impact of hypoxia-induced dysregulated adiponectin production in obese murine mesenteric adipose tissue," *Journal of Atherosclerosis and Thrombosis*, vol. 18, no. 3, pp. 240–247, 2011.
- [158] M. S. Jamaluddin, S. M. Weakley, Q. Yao, and C. Chen, "Resistin: functional roles and therapeutic considerations for cardiovascular disease," *The British Journal of Pharmacology*, vol. 165, no. 3, pp. 622–632, 2012.
- [159] I. A. Harsch, C. Koebnick, H. Wallaschofski et al., "Resistin levels in patients with obstructive sleep apnoea syndrome—the link to subclinical inflammation?" *Medical Science Monitor*, vol. 10, no. 9, pp. CR510–CR515, 2004.
- [160] Y. Yamamoto, S. Fujiuchi, M. Hiramatsu et al., "Resistin is closely related to systemic inflammation in obstructive sleep apnea," *Respiration*, vol. 76, no. 4, pp. 377–385, 2008.
- [161] A. F. Krapalis, J. Reiter, F. Machleidt et al., "Ghrelin modulates baroreflex-regulation of sympathetic vasomotor tone in healthy humans," *The American Journal of Physiology*, vol. 302, no. 11, pp. R1305–R1312, 2012.
- [162] I. Kishimoto, T. Tokudome, H. Hosoda, M. Miyazato, and K. Kangawa, "Ghrelin and cardiovascular diseases," *Journal of Cardiology*, vol. 59, no. 1, pp. 8–13, 2012.
- [163] I. A. Harsch, P. C. Konturek, C. Koebnick et al., "Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment," *European Respiratory Journal*, vol. 22, no. 2, pp. 251–257, 2003.
- [164] A. M. Li, C. Ng, S. K. Ng et al., "Adipokines in children with obstructive sleep apnea and the effects of treatment," *Chest*, vol. 137, no. 3, pp. 529–535, 2010.
- [165] K. Spruyt, O. S. Capdevila, L. D. Serpero, L. Kheirandish-Gozal, and D. Gozal, "Dietary and physical activity patterns in children with obstructive sleep apnea," *Journal of Pediatrics*, vol. 156, no. 5, pp. 724.e3–730.e3, 2010.
- [166] M. Tsaoussoglou, E. O. Bixler, S. Calhoun, G. P. Chrousos, K. Sauder, and A. N. Vgontzas, "Sleep-disordered breathing in obese children is associated with prevalent excessive daytime sleepiness, inflammation, and metabolic abnormalities," *Journal of Clinical Endocrinology and Metabolism*, vol. 95, no. 1, pp. 143–150, 2010.
- [167] M. Sánchez-De-La-Torre, A. Barceló, J. Piérola et al., "Plasma levels of neuropeptides and metabolic hormones, and sleepiness in obstructive sleep apnea," *Respiratory Medicine*, vol. 105, no. 12, pp. 1954–1960, 2011.
- [168] C. Prugger, J. Wellmann, J. Heidrich, S. Brand-Herrmann, and U. Keil, "Cardiovascular risk factors and mortality in patients with coronary heart disease," *European Journal of Epidemiology*, vol. 23, no. 11, pp. 731–737, 2008.
- [169] S. Mondini and C. Guilleminault, "Abnormal breathing patterns during sleep in diabetes," *Annals of Neurology*, vol. 17, no. 4, pp. 391–395, 1985.
- [170] A. Elmasry, E. Lindberg, C. Berne et al., "Sleep-disordered breathing and glucose metabolism in hypertensive men: a population-based study," *Journal of Internal Medicine*, vol. 249, no. 2, pp. 153–161, 2001.
- [171] S. D. West, D. J. Nicoll, and J. R. Stradling, "Prevalence of obstructive sleep apnoea in men with type 2 diabetes," *Thorax*, vol. 61, no. 11, pp. 945–950, 2006.
- [172] J. H. Ficker, S. H. Dertinger, W. Siegfried et al., "Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy," *European Respiratory Journal*, vol. 11, no. 1, pp. 14–19, 1998.
- [173] P. Bottini, M. L. Dottorini, M. C. Cordoni, G. Casucci, and C. Tantucci, "Sleep-disordered breathing in nonobese diabetic subjects with autonomic neuropathy," *European Respiratory Journal*, vol. 22, no. 4, pp. 654–660, 2003.
- [174] L. K. Brown, "A waist is a terrible thing to mind: central obesity, the metabolic syndrome, and sleep apnea hypopnea syndrome," *Chest*, vol. 122, no. 3, pp. 774–778, 2002.
- [175] A. N. Vgontzas, E. O. Bixler, and G. P. Chrousos, "Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance," *Journal of Internal Medicine*, vol. 254, no. 1, pp. 32–44, 2003.
- [176] F. Tassone, F. Lanfranco, L. Gianotti et al., "Obstructive sleep apnoea syndrome impairs insulin sensitivity independently of anthropometric variables," *Clinical Endocrinology*, vol. 59, no. 3, pp. 374–379, 2003.
- [177] N. Cheng, W. Cai, M. Jiang, and S. Wu, "Effect of hypoxia on blood glucose, hormones, and insulin receptor functions in newborn calves," *Pediatric Research*, vol. 41, no. 6, pp. 852–856, 1997.
- [178] J. Li, M. Bosch-Marce, A. Nanayakkara et al., "Altered metabolic responses to intermittent hypoxia in mice with partial deficiency of hypoxia-inducible factor-1 α ," *Physiological Genomics*, vol. 25, no. 3, pp. 450–457, 2006.
- [179] V. Y. Polotsky, J. Li, N. M. Punjabi et al., "Intermittent hypoxia increases insulin resistance in genetically obese mice," *Journal of Physiology*, vol. 552, no. 1, pp. 253–264, 2003.
- [180] B. Braun, P. B. Rock, S. Zamudio et al., "Women at altitude: short-term exposure to hypoxia and/or α 1-adrenergic blockade reduces insulin sensitivity," *Journal of Applied Physiology*, vol. 91, no. 2, pp. 623–631, 2001.
- [181] M. Gasa, N. Salord, A. M. Fortuna et al., "Obstructive sleep apnoea and metabolic impairment in severe obesity," *European Respiratory Journal*, vol. 38, no. 5, pp. 1089–1097, 2011.
- [182] N. McArdle, D. Hillman, L. Beilin, and G. Watts, "Metabolic risk factors for vascular disease in obstructive sleep apnea: a matched controlled study," *The American Journal of Respiratory and Critical Care Medicine*, vol. 175, no. 2, pp. 190–195, 2007.
- [183] H. E. Resnick, K. Jones, G. Ruotolo et al., "Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: the strong heart study," *Diabetes Care*, vol. 26, no. 3, pp. 861–867, 2003.
- [184] L. Piemonti, G. Calori, A. Mercalli et al., "Fasting plasma leptin, tumor necrosis factor- α receptor 2, and monocyte chemoattracting protein 1 concentration in a population of glucose-tolerant and glucose-intolerant women impact on cardiovascular mortality," *Diabetes Care*, vol. 26, no. 10, pp. 2883–2889, 2003.

- [185] M. Hayashi, K. Fujimoto, K. Urushibata, A. Takamizawa, O. Kinoshita, and K. Kubo, "Hypoxia-sensitive molecules may modulate the development of atherosclerosis in sleep apnoea syndrome," *Respirology*, vol. 11, no. 1, pp. 24–31, 2006.
- [186] J. A. Batsis, R. E. Nieto-Martinez, and F. Lopez-Jimenez, "Metabolic syndrome: from global epidemiology to individualized medicine," *Clinical Pharmacology and Therapeutics*, vol. 82, no. 5, pp. 509–524, 2007.
- [187] T. A. Welborn, A. Breckenridge, A. H. Rubinstein, C. T. Dollery, and T. R. Fraser, "Serum-insulin in essential hypertension and in peripheral vascular disease," *The Lancet*, vol. 1, no. 7451, pp. 1336–1337, 1966.
- [188] G. Reaven, "Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease," *Circulation*, vol. 106, no. 3, pp. 286–288, 2002.
- [189] S. M. Grundy, H. B. Brewer Jr., J. I. Cleeman, S. C. Smith Jr., and C. Lenfant, "Definition of metabolic syndrome: report of the national heart, lung, and blood institute/American heart association conference on scientific issues related to definition," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 24, no. 2, pp. e13–e18, 2004.
- [190] M. Ambrosetti, A. M. Lucioni, S. Conti, R. F. Pedretti, and M. Neri, "Metabolic syndrome in obstructive sleep apnea and related cardiovascular risk," *Journal of Cardiovascular Medicine*, vol. 7, no. 11, pp. 826–829, 2006.
- [191] O. K. Basoglu, F. Sarac, S. Sarac, H. Uluer, and C. Yilmaz, "Metabolic syndrome, insulin resistance, fibrinogen, homocysteine, leptin, and C-reactive protein in obese patients with obstructive sleep apnea syndrome," *Annals of Thoracic Medicine*, vol. 6, no. 3, pp. 120–125, 2011.
- [192] A. N. Vgontzas, E. O. Bixler, and G. P. Chrousos, "Sleep apnea is a manifestation of the metabolic syndrome," *Sleep Medicine Reviews*, vol. 9, no. 3, pp. 211–224, 2005.
- [193] A. Gruber, F. Horwood, J. Sithole, N. J. Ali, and I. Idris, "Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state," *Cardiovascular Diabetology*, vol. 5, article 22, 2006.
- [194] J. C. M. Lam, B. Lam, C. Lam et al., "Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong," *Respiratory Medicine*, vol. 100, no. 6, pp. 980–987, 2006.
- [195] K. Shina, H. Tomiyama, Y. Takata et al., "Concurrent presence of metabolic syndrome in obstructive sleep apnea syndrome exacerbates the cardiovascular risk: a sleep clinic cohort study," *Hypertension Research*, vol. 29, no. 6, pp. 433–441, 2006.
- [196] M. R. Bonsignore, C. Esquinas, A. Barcelo et al., "Metabolic syndrome, insulin resistance and sleepiness in real-life obstructive sleep apnoea," *European Respiratory Journal*, vol. 39, no. 5, pp. 1136–1143, 2012.
- [197] M. R. Bonsignore and A. Zito, "Metabolic effects of the obstructive sleep apnea syndrome and cardiovascular risk," *Archives of Physiology and Biochemistry*, vol. 114, no. 4, pp. 255–260, 2008.
- [198] P. Lévy, J. Pépin, C. Arnaud, J. Baguet, M. Dematteis, and F. Mach, "Obstructive sleep apnea and atherosclerosis," *Progress in Cardiovascular Diseases*, vol. 51, no. 5, pp. 400–410, 2009.
- [199] M. C. Su, Y. C. Chen, K. T. Huang, C. C. Wang, M. C. Lin, and H. C. Lin, "Association of metabolic factors with high-sensitivity C-reactive protein in patients with sleep-disordered breathing," *European Archives of Oto-Rhino-Laryngology*, pp. 749–754, 2013.
- [200] S. K. Sharma, S. Agrawal, D. Damodaran et al., "CPAP for the metabolic syndrome in patients with obstructive sleep apnea," *The New England Journal of Medicine*, vol. 365, no. 24, pp. 2277–2286, 2011.
- [201] A. G. Agustí, "Systemic effects of chronic obstructive pulmonary disease," *Proceedings of the American Thoracic Society*, vol. 2, no. 4, pp. 367–370, 2005.
- [202] P. de Lucas-Ramos, J. L. Izquierdo-Alonso, J. M. Rodriguez-Gonzalez Moro, J. F. Frances, P. V. Lozano, and J. M. Belloncino, "Chronic obstructive pulmonary disease as a cardiovascular risk factor. Results of a case-control study (CONSISTE study)," *International Journal of Chronic Obstructive Pulmonary Disease*, pp. 679–686, 2012.
- [203] J. D. Maclay, D. A. McAllister, S. Johnston et al., "Increased platelet activation in patients with stable and acute exacerbation of COPD," *Thorax*, vol. 66, no. 9, pp. 769–774, 2011.
- [204] G. Cella, A. Sbarai, G. Mazzaro et al., "Plasma markers of endothelial dysfunction in chronic obstructive pulmonary disease," *Clinical and Applied Thrombosis/Hemostasis*, vol. 7, no. 3, pp. 205–208, 2001.
- [205] L. Moro, C. Pedone, S. Scarlata, V. Malafarina, F. Fimognari, and R. Antonelli-Incalzi, "Endothelial dysfunction in chronic obstructive pulmonary disease," *Angiology*, vol. 59, no. 3, pp. 357–364, 2008.
- [206] K. Nakanishi, Y. Takeda, S. Tetsumoto et al., "Involvement of endothelial apoptosis underlying chronic obstructive pulmonary disease-like phenotype in adiponectin-null mice: implications for therapy," *The American Journal of Respiratory and Critical Care Medicine*, vol. 183, no. 9, pp. 1164–1175, 2011.
- [207] C. Minet, I. Vivodtzev, R. Tamisier et al., "Reduced six-minute walking distance, high fat-free-mass index and hypercapnia are associated with endothelial dysfunction in COPD," *Respiratory Physiology and Neurobiology*, vol. 183, no. 2, pp. 128–134, 2012.
- [208] N. Takabatake, H. Nakamura, S. Abe et al., "The relationship between chronic hypoxemia and activation of the tumor necrosis factor- α system in patients with chronic obstructive pulmonary disease," *The American Journal of Respiratory and Critical Care Medicine*, vol. 161, no. 4 I, pp. 1179–1184, 2000.
- [209] N. L. Mills, J. J. Miller, A. Anand et al., "Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk," *Thorax*, vol. 63, no. 4, pp. 306–311, 2008.
- [210] S. Andreas, S. D. Anker, P. D. Scanlon, and V. K. Somers, "Neurohumoral activation as a link to systemic manifestations of chronic lung disease," *Chest*, vol. 128, no. 5, pp. 3618–3624, 2005.
- [211] T. Raupach, F. Bahr, P. Herrmann et al., "Slow breathing reduces sympathoexcitation in COPD," *European Respiratory Journal*, vol. 32, no. 2, pp. 387–392, 2008.
- [212] S. Heindl, M. Lehnert, C. Crieé, G. Hasenfuss, and S. Andreas, "Marked sympathetic activation in patients with chronic respiratory failure," *The American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 4, pp. 597–601, 2001.
- [213] D. C. Flenley, "Sleep in chronic obstructive lung disease," *Clinics in Chest Medicine*, vol. 6, no. 4, pp. 651–661, 1985.
- [214] A. Chaouat, E. Weitzenblum, J. Krieger, M. Oswald, and R. Kessler, "Pulmonary hemodynamics in the obstructive sleep apnea syndrome results in 220 consecutive patients," *Chest*, vol. 109, no. 2, pp. 380–386, 1996.
- [215] I. Hawrylkiewicz, P. Sliwinski, D. Gorecka, R. Plywaczewski, and J. Zielinski, "Pulmonary haemodynamics in patients with OSAS or an overlap syndrome," *Monaldi Archives for Chest Disease*, vol. 61, pp. 148–152, 2004.

- [216] W. MacNee, J. Maclay, and D. McAllister, "Cardiovascular injury and repair in chronic obstructive pulmonary disease," *Proceedings of the American Thoracic Society*, vol. 5, no. 8, pp. 824–833, 2008.
- [217] G. S. Gilmartin, R. Tamisier, M. Curley, and J. W. Weiss, "Ventilatory, hemodynamic, sympathetic nervous system, and vascular reactivity changes after recurrent nocturnal sustained hypoxia in humans," *The American Journal of Physiology*, vol. 295, no. 2, pp. H778–H785, 2008.
- [218] K. Shiina, H. Tomiyama, Y. Takata et al., "Overlap syndrome: additive effects of COPD on the cardiovascular damages in patients with OSA," *Respiratory Medicine*, vol. 106, no. 9, pp. 1335–1341, 2012.
- [219] J. M. Marin, J. B. Soriano, S. J. Carrizo, A. Boldova, and B. R. Celli, "Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome," *The American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 3, pp. 325–331, 2010.
- [220] C. Pronzato, "Chronic obstructive pulmonary disease and obstructive sleep apnea. Association, consequences and treatment," *Monaldi Archives for Chest Disease*, vol. 73, no. 4, pp. 155–161, 2010.
- [221] S. Nural, E. Gunay, B. Halici, S. Celik, and M. Unlu, "Inflammatory processes and effects of continuous positive airway pressure (CPAP) in overlap syndrome," *Inflammation*, vol. 36, no. 1, pp. 66–74, 2013.

Review Article

Epidemiological and Pathogenic Relationship between Sleep Apnea and Ischemic Heart Disease

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Obstructive sleep apnea is recognized as having high prevalence and causing remarkable cardiovascular risk. Coronary artery disease has been associated with obstructive sleep apnea in many reports. The pathophysiology of coronary artery disease in obstructive sleep apnea patients probably includes the activation of multiple mechanisms, as the sympathetic activity, endothelial dysfunction, atherosclerosis, and systemic hypertension. Moreover, chronic intermittent hypoxia and oxidative stress have an important role in the pathogenesis of coronary disease and are also fundamental to the development of atherosclerosis and other comorbidities present in coronary artery diseases such as lipid metabolic disorders. Interestingly, the prognosis of patients with coronary artery disease has been associated with obstructive sleep apnea and the severity of sleep disordered breathing may have a direct relationship with the morbidity and mortality of patients with coronary diseases. Nevertheless, treatment with CPAP may have important effects, and recent reports have described the benefits of obstructive sleep apnea treatment on the recurrence of acute heart ischaemic events in patients with coronary artery disease.

1. Introduction

Obstructive sleep apnea (OSA) is a common medical condition characterized by abnormal collapse of the pharyngeal airway during sleep, causing repetitive arousals, and drops in the oxygen saturation. It is highly prevalent in the general population [1] and it acts as an independent risk factor for hypertension (HT) [2, 3]. In addition, several studies have suggested that OSA is associated with other cardiovascular diseases such as heart failure [4], arrhythmias [5], pulmonary hypertension [6], and coronary artery disease (CAD).

Although mortality from CAD has fallen since 1975, it is still a major cause of death and disability in developed countries. The high prevalence of cardiovascular risk factors in the general population (diabetes mellitus, cigarette smoking, obesity, hypertension, and lack of regular physical activity) facilitates the development of atherosclerosis in coronary arteries and, subsequently, the presence of CAD. Although clinical guidelines for the management of CAD still do not consider OSA as a specific risk factor, results from the Sleep Heart Health Study have shown that OSA may increase

the risk of CAD in middle-aged men with an apnea-hypopnea index (AHI) $\geq 30 \text{ h}^{-1}$ [7].

2. Association between Obstructive Sleep Apnea and Coronary Artery Disease

Several cross-sectional and epidemiological studies have evaluated the association between OSA and CAD. In a case-control study, Moore et al. [8] selected 102 women with CAD and 50 age-matched controls and reported that CAD patients had a higher prevalence of sleep breathing disorders than the control group (AHI $\geq 5 \text{ h}^{-1}$: 54% versus 20%, $P < 0.0001$; AHI $\geq 10 \text{ h}^{-1}$: 31% versus 18%, $P < 0.05$, resp.). These findings were also described in men, where authors observed that 37% of patients with CAD had an AHI $\geq 10 \text{ h}^{-1}$ [9]. Despite their interesting findings, these studies had several limitations. For instance, important cardiovascular risk factors, such as cholesterol levels, were not included in the analysis. Also, in the manual score of the sleep study, authors did not discriminate between central and obstructive

apneas. And finally, a questionnaire was only used about coronary symptoms to exclude CAD in the control subjects. A similar association had been found in a population cross-sectional study. Shahar et al. [10], analyzed the association between OSA and self-reported cardiovascular disease in 6,424 individuals who underwent overnight polysomnography from the Sleep Heart Health Study. They showed that subjects with the highest quartile of AHI (AHI > 11 events h^{-1}) had an adjusted ratio of 1.27 for self-reported CAD. Recently, Gottlieb et al. [7] have found a significant association between severe OSA and coronary heart disease in middle-aged men from the Sleep Heart Health Study, and they reported a significant association between severe OSA and coronary heart disease in middle-aged men.

There is some evidence suggesting that the prevalence and the severity of OSA are modified along the CAD evolution. Moruzzi et al. [11] performed overnight polysomnographic studies in three groups of CAD patients: immediately after an acute myocardial infarction (AMI) (group 1), after clinical stabilization of unstable angina (group 2), and with stable angina (group 3). They observed a significantly higher AHI in groups 1 and 2 compared with group 3 ($11.1 \pm 19.4 h^{-1}$, $14.7 \pm 5.20 h^{-1}$, and $2.8 \pm 6.4 h^{-1}$, resp.; $P < 0.01$). However, studies from Moore et al. [8] and Moruzzi et al. [11] did not adjust properly for confounding factors. So Peker et al. [12] performed a case-control study adjusted for several cardiovascular risk factors that included hypertension, hypercholesterolemia, diabetes, and smoking, and compared the results of sleep recording studies of 62 patients admitted in the coronary care unit due to acute CAD and 62-age-, sex-, and BMI-matched control subjects without history or signs of heart disease. OSA (AHI $\geq 10 h^{-1}$) was present in 19 CAD patients but only in 8 control subjects ($P = 0.017$). In the multiple logistic regression analysis, current smoking (odds ratio [OR] 9.8, 95% CI 2.6–36.5), diabetes (OR 4.2, 95% CI 1.1–17.1), and OSA (OR 3.1, 95% CI 1.2–8.3) were independently associated with coronary disease. However, this study also had several limitations as the high prevalence of hypercholesterolemia in both groups (>80% of patients), the sleep diagnostic procedure used, and the substantial delay between the cardiac event and the sleep study (4–21 months). Supporting the relationship between OSA and CAD, Lee et al. [13] and Nakashima et al. [14] have also found similar results and they have observed a moderate-severe OSAS (AHI $\geq 15 h^{-1}$) in 43% and 65.7% of subjects with CAD, respectively. Despite the high prevalence of OSA reported in patients with CAD, it is frequently underdiagnosed. One study demonstrated that OSA was initially suspected in only 12% of patients admitted with myocardial infarction (MI) whereas, after an overnight polysomnography, 70% of patients presented an AHI $\geq 5 h^{-1}$ and 41% an AHI $\geq 15 h^{-1}$ [15].

There are several explanations for the difference in the OSA prevalence among the aforementioned studies. The definition of the ideal timing for OSA screening after an acute cardiovascular event remains unresolved. Skinner et al. [16] performed two overnight sleep studies in patients with CAD (MI, unstable angina or congestive heart failure): at the time

of acute presentation in the Coronary Care Unit and at least six weeks after hospital discharge. They identified an AHI $\geq 15 h^{-1}$ in 13 of 26 patients (50%) in the first sleep study but in only 5 of 18 patients (28%) during the second study. In fact, it has been reported that the AHI obtained by overnight polysomnography significantly decreases in the CAD chronic phase (day 14) with respect to the acute phase (days 3–5) (6.97 ± 5.67 versus 13.26 ± 11.30 , resp.) [17]. Moreover, it seems that alterations in sleep architecture in CAD subjects tend to decrease over time. In accordance with this line, Schiza et al. [18] performed a full-night polysomnography in 22 patients with acute coronary syndrome (ACS) within 3 days of the first episode and 1 and 6 months later. They found a progressive increase in the total sleep time, sleep efficiency, slow wave sleep, and rapid eye movement (REM) sleep. Despite this, an early identification of OSA in subjects admitted with ACS does not affect the odds of hospital readmission in the next six months [19]. Possible reasons that explain why patients in the acute phase of CAD have higher OSA diagnosis rate have been reported and they are related to the supine position of patients in the Coronary Care Unit, the fragmented sleep with reduced rapid eye movement stage in the first night and finally, the sleep breathing disorders that produce coronary ischemic diseases by itself (central apneas).

Not all studies have an adequate assessment of conditions that may increase the prevalence of sleep-disordered breathing, such as sedation or narcotics use, COPD, alcoholism, level of consciousness, and stroke. Additionally, the sleep diagnostic tests differ in several studies, and although attended polysomnography is considered standard practice in patients with related medical comorbid conditions [13, 17], many studies have used nonattended sleep studies [14, 15]. Moreover, definitions of respiratory events have not been homogeneous. For example, Lee et al. [13], consider a 3% decrease in oxygen saturation to define hypopneas, while Nakashima et al. [14] considered them when the drop of oxygen saturation was equal or greater than 4%.

3. Mechanisms of Coronary Artery Disease in Obstructive Sleep Apnea

Systemic hypertension is a risk factor for the development of CAD and guidelines for the management of hypertension consider that OSA contributes directly to the pathogenesis of hypertension [3, 20]. OSA is characterized by recurrent episodes of upper airway collapse during sleep, which is accompanied by cycles of hypoxia-reoxygenation leading chronic intermittent hypoxia (CIH). In animal models, it has been shown that intermittent hypoxia could be associated with the development of hypertension [21]. Moreover, CIH may affect the plasma renin-angiotensin activity, the production of endothelin, and the function of peripheral chemoreceptors, increasing the sympathetic activity [22]. OSA patients have higher plasma and urinary catecholamine levels than control subjects [23–25] and the disbalance between sympathetic and parasympathetic systems may increase systemic vascular resistance and blood pressure [26]. Furthermore, evidence from animal models supports that

CIH contributes to vascular remodeling [27] and Drager et al. [28] reported that an increased carotid intima-media thickness is associated to sympathetic activity and atherosclerosis.

OSA patients present systemic inflammation related to endothelial dysfunction. CIH has been associated with endothelial dysfunction independently of other risk factors for atherosclerosis such as obesity, dyslipidemia, diabetes, or smoking [29]. Moreover, patients with OSA have an increased number of apoptotic endothelial cells and fewer circulating progenitor cells [30, 31]. Finally, endothelial dysfunction has been also associated with a reduced availability of nitric oxide in subjects with OSA [29, 32].

The third mechanism involved in the pathogenesis of CAD in patients with OSA is due to the development of atherosclerotic plaques through metabolic, oxidative, and inflammatory pathways. Recurrent episodes of hypoxia are associated with adipose tissue dysfunction and production of different adipokines. Increased leptin levels observed in OSA are related to endothelial dysfunction, production of cytokines, platelet aggregation, and oxidative stress [33, 34]. Moreover, obstructive apneas downregulate adiponectin levels, which are closely associated with endothelial dysfunction and atherosclerosis [35]. Furthermore, dyslipidemia is present in many OSA subjects and it is characterized by an increased synthesis and secretion of very LDL-cholesterol and triglycerides and a reduced secretion of HDL-cholesterol, promoting atherogenesis [36, 37].

Production of some proinflammatory mediators such as TNF- α , IL-1, IL-8, and adhesion molecules are promoted by lipid peroxidation and endothelial dysfunction, resulting in an environment of systemic inflammation. This facilitates the recruitment and accumulation of macrophages and fat cells that further activates lipid peroxidation and promotes endothelial cell damage and atherosclerosis [38, 39]. C-reactive protein (CRP), another inflammatory biomarker, has been associated with ACS. Higher CRP levels have been reported in OSA patients, but it is difficult to tease out the independent contribution of obesity on the CRP levels [40, 41] (Figure 1).

This inflammatory process associated to CIH, endothelial dysfunction and atherosclerosis, is induced and regulated by several transcription factors, such as kappa-B nuclear factor (NF- κ B) and hypoxia inducible factor (HIF)-1 α [42, 43]. They have a key role in the regulation of the innate immunity and participate actively in inflammatory pathway. Also, in animal models, they have been implicated in hypertension and in components of the metabolic syndrome. However, the potential role of these and other transcription factors in the pathogenesis of CAD should be further investigated in the future, and thereby, combining with individual gene analysis and personalized medicine, may provide new treatment strategies for cardiovascular protection.

4. Influence of Sleep-Disordered Breathing on the CAD Prognosis

There has been growing evidence associating OSA with prognosis of CAD, both in stable and unstable patients.

Peker et al. [44] observed, during a follow-up period of 5 years, the cardiovascular mortality of 62 consecutive CAD stable patients with and without OSA. They found 6 cardiovascular deaths in OSA patients (37.5%) and 4 in the non-OSA group (9.3%) ($P = 0.018$). Additionally, in the Cox multiple conditional regression model, respiratory disturbance index (RDI) was found to be an independent predictor of cardiovascular mortality (hazard ratio [HR] = 1.13; 95% CI 1.05–1.21, $P < 0.001$). Main limitations of this study concern aspects that could affect the prevalence of OSA, as the type of sleep studies and the timing of OSA screening (4–21 months after admission).

Moreover, OSA appeared to affect clinical and angiographic outcomes after percutaneous coronary intervention (PCI) in patients with ACS. In fact, Yumino et al. [45] performed a sleep study in 89 patients with ACS and, after a follow-up mean period of 227 days, they observed a higher incidence of major adverse cardiac events (cardiac death, reinfarction, and target vessel revascularization) in patients with OSA (AHI $> 10 \text{ h}^{-1}$) (23.5% versus 5.3%, $P = 0.022$). Furthermore, OSA was an independent predictor for major adverse cardiac events (HR 11.62, 95% CI 2.17–62.24; $P = 0.004$) and of subsequent angiographic binary restenosis (HR 7.69, 95% CI 1.74–34.05; $P = 0.007$). Evidence linking sleep-disordered breathing to increased mortality and cardiovascular morbidity has been conflicting and inconclusive in patients with established CAD. On one hand, Moee et al. [46] in a prospective cohort of 408 patients with chronic CAD followed during a median period of 5.1 years found that there was a 70% and a 62% relative increase in the primary end point (composite of death, cerebrovascular events, and myocardial infarction) in patients with a desaturation index (DI) $\geq 5 \text{ h}^{-1}$ and an AHI $\geq 10 \text{ h}^{-1}$, respectively. On the other hand, Hagenah et al. [47] evaluated the prognostic influence of OSA in 50 patients with stable CAD. After 10 years of follow-up, they observed that OSA did not increase the risk of mortality and cardiovascular complications. However, both groups were not fully comparable, having non-OSA patients with a tendency to more severe coronary lesions.

Myocardial tissue perfusion after primary PCI plays a pivotal role in recovery of left ventricular function and patient prognosis in the clinical setting of ACS [48]. Nakashima et al. [49] used systolic retrograde flow (SRF) and ST-segment resolution (STR) $< 50\%$ to measure myocardial tissue perfusion immediately after the PCI in 100 patients with ACS. They performed overnight polysomnography at 14 days of admission in all patients and they found in the multiple logistic regression analysis that OSA induced more severe microvascular injury related to ischemia-reperfusion (SRF: OR = 4.46, $P = 0.044$; STR: OR = 3.79, $P = 0.010$). However, Lee et al. [13] did not find similar results. To measure impaired microvascular perfusion after primary PCI, these authors used ST-segment resolution of $< 70\%$, myocardial blush grade 0 or 1, or a corrected Thrombolysis in Myocardial Infarction (TIMI) frame count > 28 . A sleep study was performed and completed in 105 patients and OSA was not found associated with impaired microvascular perfusion after primary PCI. These differences could be related to the different technique

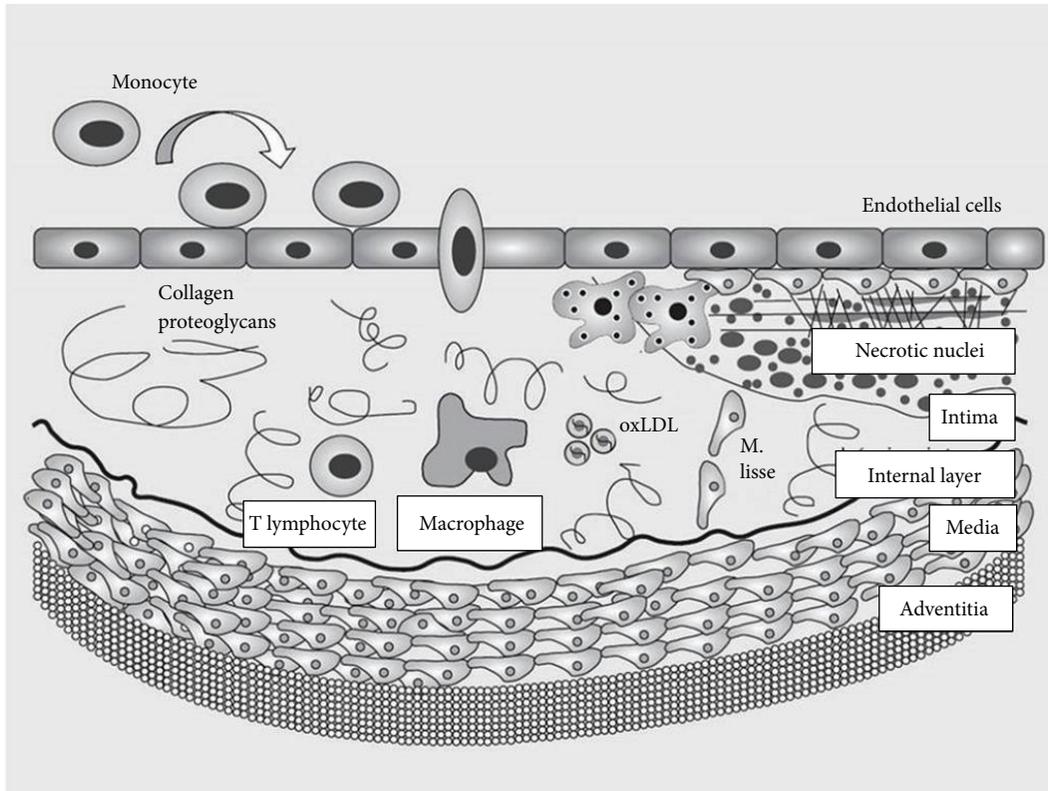


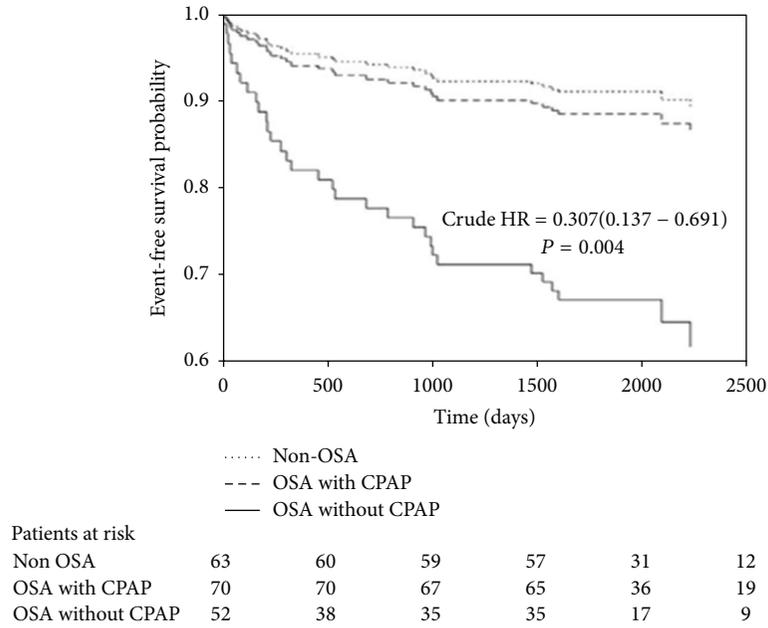
FIGURE 1: Development of atherosclerotic plaques in obstructive sleep apnea patients, modified from Náchér et al. [39].

used to measure myocardial perfusion in both studies. Moreover, differences in the timing of sleep studies (Lee et al. [13] performed the sleep study 14 to 21 days after hospital admission, whereas Nakashima et al. [49] did it 2 to 5 days after hospital admission) could affect the prevalence of OSA in CAD subjects.

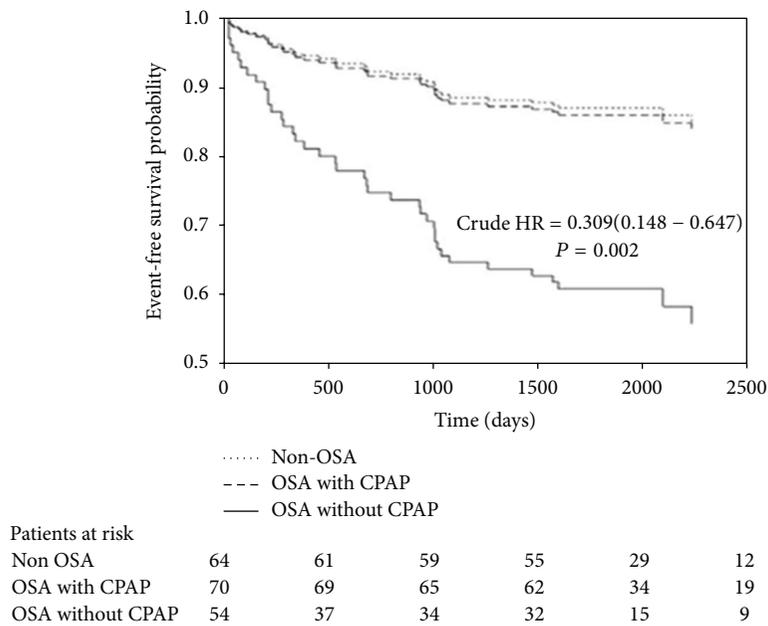
5. CPAP Effect on the Prognosis of Ischemic Cardiac Disease

Several observational studies have reported that CPAP may reduce cardiovascular mortality in OSA patients. One study showed that the incidence of fatal and nonfatal cardiovascular events during 10 years of follow-up was higher in untreated severe OSA patients than in patients treated with CPAP or in healthy subjects [50]. Furthermore, Buchner et al. [51] reported that treatment of OSA decreases the risk of fatal and nonfatal cardiovascular events (myocardial infarction, stroke, and ACS requiring revascularization procedures) in patients with mild-moderate OSA (HR 0.36, 95% CI 0.21–0.62, $P = 0.001$) after 72-month follow-up. However, in this study, the mean duration of follow-up was significantly different between untreated and treated patients (50.0 ± 49.4 versus 77.0 ± 55.0 months; $P = 0.001$). Moreover, both Marín et al. and Buchner et al. studies did not have a controlled, randomized design, so their findings could not be used to make causal inferences.

Few studies have assessed the effects of CPAP on the morbidity and mortality of CAD patients with OSA, but some recent reports confirm the possible positive impact of OSA treatment on the prognosis of CAD. An early report compared the occurrence of a composite endpoint (cardiovascular death, ACS, hospitalization for heart failure, or need for coronary revascularization) between OSA patient who accepted (CPAP = 11 patients, upper airway surgery = 4 patients) and declined OSA treatment (29 patients). At the end of follow-up (86.5 ± 39 months), the endpoint was reached in 6 (24%) and 17 (58%) patients with and without OSA treatment, respectively ($P < 0.01$). Moreover, OSA treatment reduced in 62% the risk of occurrence of the composite endpoint (HR 0.24; 95% CI: 0.09–0.62; $P < 0.01$) [52]. Cassar et al. [53] added further information to the study of Milleron et al. [52]. They designed a retrospective cohort study of 371 patients diagnosed with OSA ($AHI \geq 15 h^{-1}$) who subsequently underwent a PCI and evaluated cardiac death, general mortality, major adverse cardiac events (MACE) (severe angina, myocardial infarction, PCI, coronary artery bypass grafting, or death), and major adverse cardiac or cerebrovascular events (MACCE). They observed that patients treated for OSA had a statistically significant decreased number of cardiac deaths on 5-year follow-up when compared with untreated OSA patients (3% versus 10%, $P = 0.027$), as well as a trend toward decreased all-cause mortality (11% versus 17%, $P = 0.058$). However, there was



(a)



(b)

FIGURE 2: Time until first recurrent myocardial infarction (a) or revascularization procedure (b) in the three groups of MI patients. Crude hazard ratio (HR) of treated versus untreated OSA is presented, reproduced from Garcia-Rio et al. [55].

no difference in the number of MACE or MACCE between the 2 groups.

Two recent studies performed in Spain have analyzed the efficacy of CPAP treatment in cardiovascular diseases. Barbé et al. [54], in a multicenter, parallel, randomized controlled trial, assigned in a 1:1 ratio to receive CPAP treatment or no active intervention in 723 nonsleepy OSA patients. They compared the incidence of either systemic hypertension or cardiovascular events (nonfatal myocardial

infarction, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, heart failure, or cardiovascular death). At the end of follow-up (4 years), there were no differences in the hypertension or cardiovascular event incidence density rate (IDR) between CPAP and control groups. However, in the post hoc analysis, patients with CPAP adherence of ≥ 4 hours per night had a lower incidence of hypertension or cardiovascular events than control group (IDR: 0.69, 95% IC 0.50–0.94, $P = 0.02$).

Recently, we have analyzed the evolution of 192 patients diagnosed with MI and 96 control subjects after a follow-up period of 6.5 years. OSA was an independent predictor of AMI (OR 4.9, IC 95% 2.9–8.3, $P = 0.017$), with directly proportional relationship. Furthermore, we have observed that treated OSA patients had a lower risk of recurrent AMI (HR 0.16, IC 95% 0.03–0.76, $P = 0.021$) and revascularization (HR 0.15, IC 95% 0.03–0.79, $P = 0.025$) than untreated OSA patients, but a similar risk to non-OSA patients [55] (Figure 2).

6. Conclusions

OSA is a common condition that is associated with several cardiovascular complications such as CAD. The CAD pathogenesis in OSA is complex and probably related to increased sympathetic activity, endothelial dysfunction, and atherosclerosis. In addition, abnormal lipid metabolism related to OSA could also participate in the pathogenesis of CAD. Several studies have reported an association between OSA and CAD in stable and unstable patients. Furthermore, the prognosis of subjects with coronary disease could be affected by the presence and the severity of OSA. Finally, there is evidence that OSA treatment with CPAP reduces the mortality and morbidity of CAD patients, but there is still a need for long-term data to confirm the benefit of CPAP treatment.

References

- [1] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, "The occurrence of sleep-disordered breathing among middle-aged adults," *New England Journal of Medicine*, vol. 328, no. 17, pp. 1230–1235, 1993.
- [2] P. E. Peppard, T. Young, M. Palta, and J. Skatrud, "Prospective study of the association between sleep-disordered breathing and hypertension," *New England Journal of Medicine*, vol. 342, no. 19, pp. 1378–1384, 2000.
- [3] G. Mancia, G. De Backer, A. Dominiczak, R. Cifkova, R. Fagard, and G. Germano, "2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)," *Journal of Hypertension*, vol. 25, no. 6, pp. 1105–1187, 2007.
- [4] R. Schulz, A. Blau, J. Borgel et al., "Sleep apnoea in heart failure: results of a German survey," *European Respiratory Journal*, vol. 29, no. 6, pp. 1201–1205, 2007.
- [5] A. S. Gami, G. Pressman, S. M. Caples et al., "Association of atrial fibrillation and obstructive sleep apnea," *Circulation*, vol. 110, no. 4, pp. 364–367, 2004.
- [6] M. A. Arias, F. García-Río, A. Alonso-Fernández, I. Martínez, and J. Villamor, "Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study," *European Heart Journal*, vol. 27, no. 9, pp. 1106–1113, 2006.
- [7] D. J. Gottlieb, G. Yenokyan, A. B. Newman et al., "Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study," *Circulation*, vol. 122, no. 4, pp. 352–360, 2010.
- [8] T. Moore, T. Rabben, U. Wiklund, K. A. Franklin, and P. Eriksson, "Sleep-disordered breathing in women: occurrence and association with coronary artery disease," *American Journal of Medicine*, vol. 101, no. 3, pp. 251–256, 1996.
- [9] T. Moore, T. Rabben, U. Wiklund, K. A. Franklin, and P. Eriksson, "Sleep-disordered breathing in men with coronary artery disease," *Chest*, vol. 109, no. 3, pp. 659–663, 1996.
- [10] E. Shahar, C. W. Whitney, S. Redline et al., "Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the sleep heart health study," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 1, pp. 19–25, 2001.
- [11] P. Moruzzi, S. Sarzi-Braga, M. Rossi, and M. Contini, "Sleep apnoea in ischaemic heart disease: differences between acute and chronic coronary syndromes," *Heart*, vol. 82, no. 3, pp. 343–347, 1999.
- [12] Y. Peker, H. Kraiczi, J. Hedner, S. Löth, A. Johansson, and M. Bende, "An independent association between obstructive sleep apnoea and coronary artery disease," *European Respiratory Journal*, vol. 14, no. 1, pp. 179–184, 1999.
- [13] C.-H. Lee, S.-M. Khoo, B.-C. Tai et al., "Obstructive sleep apnea in patients admitted for acute myocardial infarction: prevalence, predictors, and effect on microvascular perfusion," *Chest*, vol. 135, no. 6, pp. 1488–1495, 2009.
- [14] H. Nakashima, T. Katayama, C. Takagi et al., "Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction," *European Heart Journal*, vol. 27, no. 19, pp. 2317–2322, 2006.
- [15] T. Konecny, F. H. Sert Kuniyoshi, M. Orban et al., "Underdiagnosis of sleep apnea in patients after acute myocardial infarction," *Journal of the American College of Cardiology*, vol. 56, no. 9, pp. 742–743, 2010.
- [16] M. A. Skinner, M. S. Choudhury, S. D. R. Homan, J. O. Cowan, G. T. Wilkins, and D. R. Taylor, "Accuracy of monitoring for sleep-related breathing disorders in the coronary care unit," *Chest*, vol. 127, no. 1, pp. 66–71, 2005.
- [17] K. Tsukamoto and A. Ohara, "Temporal worsening of sleep-disordered breathing in the acute phase of myocardial infarction," *Circulation Journal*, vol. 70, no. 12, pp. 1553–1556, 2006.
- [18] S. E. Schiza, E. Simantirakis, I. Bouloukaki et al., "Sleep patterns in patients with acute coronary syndromes," *Sleep Medicine*, vol. 11, no. 2, pp. 149–153, 2010.
- [19] R. Mehra, K. Principe-Rodriguez, H. L. Kirchner, and K. P. Strohl, "Sleep apnea in acute coronary syndrome: high prevalence but low impact on 6-month outcome," *Sleep Medicine*, vol. 7, no. 6, pp. 521–528, 2006.
- [20] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report," *Journal of the American Medical Association*, vol. 289, no. 19, pp. 2560–2572, 2003.
- [21] D. Brooks, R. L. Horner, L. F. Kozar, C. L. Render-Teixeira, and E. A. Phillipson, "Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model," *Journal of Clinical Investigation*, vol. 99, no. 1, pp. 106–109, 1997.
- [22] V. K. Somers, M. E. Dyken, M. P. Clary, and F. M. Abboud, "Sympathetic neural mechanisms in obstructive sleep apnea," *Journal of Clinical Investigation*, vol. 96, no. 4, pp. 1897–1904, 1995.
- [23] J. T. Carlson, J. Hedner, M. Elam, H. Ejjnell, J. Sellgren, and B. G. Wallin, "Augmented resting sympathetic activity in awake patients with obstructive sleep apnea," *Chest*, vol. 103, no. 6, pp. 1763–1768, 1993.

- [24] P. Jennum, G. Wildschiodtz, N. J. Christensen, and T. Schwartz, "Blood pressure, catecholamines, and pancreatic polypeptide in obstructive sleep apnea with and without nasal continuous positive airway pressure (nCPAP) treatment," *American Journal of Hypertension*, vol. 2, no. 11 I, pp. 847–852, 1989.
- [25] O. Marrone, L. Riccobono, A. Salvaggio, A. Mirabella, A. Bonanno, and M. R. Bonsignore, "Catecholamines and blood pressure in obstructive sleep apnea syndrome," *Chest*, vol. 103, no. 3, pp. 722–727, 1993.
- [26] F. García-Río, M. A. Racionero, J. M. Pino et al., "Sleep apnea and hypertension," *Chest*, vol. 117, no. 5, pp. 1417–1425, 2000.
- [27] M. Dematteis, C. Julien, C. Guillermet et al., "Intermittent hypoxia induces early functional cardiovascular remodeling in mice," *American Journal of Respiratory and Critical Care Medicine*, vol. 177, no. 2, pp. 227–235, 2008.
- [28] L. F. Drager, L. A. Bortolotto, A. C. Figueiredo, E. M. Krieger, and G. Lorenzi-Filho, "Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 176, no. 7, pp. 706–712, 2007.
- [29] M. Kato, P. Roberts-Thomson, B. G. Phillips et al., "Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea," *Circulation*, vol. 102, no. 21, pp. 2607–2610, 2000.
- [30] A. A. El-Solh, M. J. Mador, P. Sikka, R. S. Dhillon, D. Amsterdam, and B. J. B. Grant, "Adhesion molecules in patients with coronary artery disease and moderate-to-severe obstructive sleep apnea," *Chest*, vol. 121, no. 5, pp. 1541–1547, 2002.
- [31] S. Jelic, M. Padeletti, S. M. Kawut et al., "Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea," *Circulation*, vol. 117, no. 17, pp. 2270–2278, 2008.
- [32] M. B. Grisham, D. N. Granger, and D. J. Lefer, "Modulation of leukocyte-endothelial interactions by reactive metabolites of oxygen and nitrogen: relevance to ischemic heart disease," *Free Radical Biology and Medicine*, vol. 25, no. 4–5, pp. 404–433, 1998.
- [33] L. Dubey and Z. Hesong, "Role of leptin in atherogenesis," *Experimental and Clinical Cardiology*, vol. 11, no. 4, pp. 269–275, 2006.
- [34] J. Beltowski, "Leptin and atherosclerosis," *Atherosclerosis*, vol. 189, no. 1, pp. 47–60, 2006.
- [35] X.-L. Zhang, K.-S. Yin, H. Wang, and S. Su, "Serum adiponectin levels in adult male patients with obstructive sleep apnea hypopnea syndrome," *Respiration*, vol. 73, no. 1, pp. 73–77, 2006.
- [36] G. V. Robinson, J. C. T. Pepperell, H. C. Segal, R. J. O. Davies, and J. R. Stradling, "Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials," *Thorax*, vol. 59, no. 9, pp. 777–782, 2004.
- [37] J. Li, V. Savransky, A. Nanayakkara, P. L. Smith, C. P. O'Donnell, and V. Y. Polotsky, "Hyperlipidemia and lipid peroxidation are dependent on the severity of chronic intermittent hypoxia," *Journal of Applied Physiology*, vol. 102, no. 2, pp. 557–563, 2007.
- [38] S. Ryan, C. T. Taylor, and W. T. McNicholas, "Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome," *Circulation*, vol. 112, no. 17, pp. 2660–2667, 2005.
- [39] M. Nacher, A. Serrano-Mollar, and J. M. Montserrat, "Nuevos aspectos patogénicos en el síndrome de apneas e hipopneas durante el sueño (SAHS)," *Archivos de Bronconeumología*, vol. 43, no. 2, supplement, pp. 40–47, 2007.
- [40] M. Yao, N. Tachibana, M. Okura et al., "The relationship between sleep-disordered breathing and high-sensitivity C-reactive protein in Japanese men," *Sleep*, vol. 29, no. 5, pp. 661–665, 2006.
- [41] S. Taheri, D. Austin, L. Lin, F. J. Nieto, T. Young, and E. Mignot, "Correlates of serum C-Reactive Protein (CRP)—no association with sleep duration or sleep disordered breathing," *Sleep*, vol. 30, no. 8, pp. 991–996, 2007.
- [42] M. Yamauchi, S. Tamaki, K. Tomoda et al., "Evidence for activation of nuclear factor kappaB in obstructive sleep apnea," *Sleep and Breathing*, vol. 10, no. 4, pp. 189–193, 2006.
- [43] Y.-J. Peng, G. Yuan, D. Ramakrishnan et al., "Heterozygous HIF-1 α deficiency impairs carotid body-mediated systemic responses and reactive oxygen species generation in mice exposed to intermittent hypoxia," *Journal of Physiology*, vol. 577, no. 2, pp. 705–716, 2006.
- [44] Y. Peker, J. Hedner, H. Kraiczki, and S. Löth, "Respiratory disturbance index: an independent predictor of mortality in coronary artery disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 162, no. 1, pp. 81–86, 2000.
- [45] D. Yumino, Y. Tsurumi, A. Takagi, K. Suzuki, and H. Kasanuki, "Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome," *American Journal of Cardiology*, vol. 99, no. 1, pp. 26–30, 2007.
- [46] T. Mooe, K. A. Franklin, K. Holmström, T. Rabben, and U. Wiklund, "Sleep-disordered breathing and coronary artery disease: long-term prognosis," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 10 I, pp. 1910–1913, 2001.
- [47] G. C. Hagenah, E. Gueven, and S. Andreas, "Influence of obstructive sleep apnoea in coronary artery disease: a 10-year follow-up," *Respiratory Medicine*, vol. 100, no. 1, pp. 180–182, 2006.
- [48] A. Poli, R. Fèveau, P. Vandoni et al., "Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty: real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function," *Circulation*, vol. 106, no. 3, pp. 313–318, 2002.
- [49] H. Nakashima, S. Muto, K. Amenomori, Y. Shiraishi, T. Nunohiro, and S. Suzuki, "Impact of obstructive sleep apnea on myocardial tissue perfusion in patients with ST-segment elevation myocardial infarction," *Circulation Journal*, vol. 75, no. 4, pp. 890–896, 2011.
- [50] J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. N. Agustí, "Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study," *Lancet*, vol. 365, no. 9464, pp. 1046–1053, 2005.
- [51] N. J. Buchner, B. M. Sanner, J. Borgel, and L. C. Rump, "Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk," *American Journal of Respiratory and Critical Care Medicine*, vol. 176, no. 12, pp. 1274–1280, 2007.
- [52] O. Milleron, R. Pillière, A. Foucher et al., "Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study," *European Heart Journal*, vol. 25, no. 9, pp. 728–734, 2004.
- [53] A. Cassar, T. I. Morgenthaler, R. J. Lennon, C. S. Rihal, and A. Lerman, "Treatment of obstructive sleep apnea is associated with decreased cardiac death after percutaneous coronary intervention," *Journal of the American College of Cardiology*, vol. 50, no. 14, pp. 1310–1314, 2007.

- [54] F. Barbé, J. Durán-Cantolla, M. Sánchez-de-la-Torre et al., “Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial,” *Journal of the American Medical Association*, vol. 307, no. 20, pp. 2161–2168, 2012.
- [55] F. Garcia-Rio F, A. Alonso-Fernández, E. Armada et al., “CPAP effect on recurrent episodes in patients with sleep apnea and myocardial infarction,” *International Journal of Cardiology*, 2013.

Review Article

Obstructive Sleep Apnea and Coronary Artery Disease: From Pathophysiology to Clinical Implications

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Coronary artery disease (CAD) and obstructive sleep apnea (OSA) are both complex and significant clinical problems. The pathophysiological mechanisms that link OSA with CAD are complex and can influence the broad spectrum of conditions caused by CAD, from subclinical atherosclerosis to myocardial infarction. OSA remains a significant clinical problem among patients with CAD, and evidence suggesting its role as a risk factor for CAD is growing. Furthermore, increasing data support that CAD prognosis may be influenced by OSA and its treatment by continuous positive airway pressure (CPAP) therapy. However, stronger evidence is needed to definitely answer these questions. This paper focuses on the relationship between OSA and CAD from the pathophysiological effects of OSA in CAD, to the clinical implications of OSA and its treatment in CAD patients.

1. Introduction

Coronary artery disease (CAD) is a major health issue in developed countries and constitutes a significant cause of death and disability. The clinical spectrum of CAD ranges from stable angina pectoris to acute coronary syndromes (ACSs), a term which includes unstable angina (UA), non-ST elevation (non-Q wave) myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI) [1]. The primary pathologic process causing CAD is coronary atherosclerosis, which causes progressive coronary stenosis, provoking myocardial ischemia when myocardial oxygen demand exceeds oxygen supply, leading to angina pectoris. On the contrary, acute coronary syndromes are caused by the loss of integrity of the protective covering of some atherosclerotic plaques, leading to thrombus formation and subsequent vessel obstruction [2].

Despite the reduction in mortality rates that occurred in the past decades, it still affects 6.4% of adults in any of its forms and constitutes the cause of death of nearly 17% of adult population in the United States [3]. According to data from the Framingham Heart Study, a population-based

longitudinal study, nearly one-half of males and one-third of females over 40 years of age will develop some manifestation of CAD [4].

OSA is a common disorder which has become an important public health problem, as it affects 2 to 7% of adults in the general population [5]. OSA is characterized by repetitive interruption of ventilation during sleep due to total collapse or narrowing of the pharyngeal airway despite breathing effort, resulting in a fall in oxygen saturation and arousal from sleep [6]. Repeated hypoxemia and arousals can lead to deleterious effects, ranging from daytime symptoms of disrupted sleep such as sleepiness, fatigue, or poor neurocognitive performance [7] to severe medical disorders [8]. A growing body of evidence links OSA with the development and progression of certain cardiovascular conditions such as systemic hypertension, pulmonary hypertension, CAD and myocardial ischemia, stroke, congestive heart failure, and cardiac arrhythmias [9].

This paper focuses on the relationship between OSA and CAD, from the pathophysiological effects of OSA in CAD, to the clinical implications of OSA and its treatment in CAD patients.

2. Pathophysiological Effects of OSA in CAD

The pathophysiological relation between OSA and CAD is complex, as many pathological changes induced by OSA in the cardiovascular system are involved and may interact to facilitate the development and/or progression of the pathological substrates of the different clinical conditions in the spectrum of CAD.

2.1. OSA and Coronary Atherosclerosis. The mechanisms leading to the formation and progression of atherosclerotic plaques involve a complex interaction between multiple factors, including oxidative stress, endothelial dysfunction, and inflammatory and immunologic factors [10].

Oxidative stress is enhanced in atherosclerosis, leading to endothelial damage and to oxidative modification of lipoproteins and other molecules [11]. This oxidized particles perpetuate endothelial damage [12] and promote accelerated accumulation of cholesterol in the atherosclerotic plaque [13]. In OSA patients, repeated hypoxia and reoxygenation during sleep can increase oxidative stress [10, 14–16], leading to vascular damage, and CPAP treatment reversion of these changes has been reported [17]. Enhanced lipid peroxidation resulting from this enhanced oxidative stress has also been observed in OSA patients [18], and in a murine model of chronic intermittent hypoxia combined with a high-cholesterol diet Savransky et al. [19] reported increased lipid peroxidation and development of atherosclerotic lesions.

Endothelial dysfunction with loss of endothelium-derived nitric oxide production leads to impairment of the endothelium-dependent relaxation in the vasculature, and is an initial step in atherosclerosis [13]. This endothelium-dependent relaxation in other vascular beds is impaired in OSA patients [20–23] and CPAP treatment may improve these abnormalities [24].

Endothelial dysfunction in OSA patients is independent from obesity and other traditional risk factors, as Namtvedt et al. have recently published [25]. A specific coronary endothelial function has been scarcely studied in patients with OSA. Kadohira et al. [26] reported a significant correlation between coronary endothelial dysfunction measured by vasoreactivity response to acetylcholine infusion and the severity of OSA.

Inflammation plays also a major role in the development and progression of atherosclerosis. It has been repeatedly reported that OSA patients have increased serum levels of inflammatory substances [27–33] and adhesion molecules [14, 34, 35] and that chronic hypoxemia in OSA patients can activate specific inflammatory pathways [36, 37] that could facilitate the atherosclerotic process [38, 39]. CPAP treatment may also influence reversibility of these findings [40].

All these mechanisms facilitate the onset and progression of atherosclerosis, accelerating the process of arterial damage. Numerous studies have found a higher prevalence of atherosclerosis in vascular beds other than the coronary arteries, such as the carotid arteries [41, 42]. Similarly, Drager et al. found signs of atherosclerosis in large arteries of OSA patients without other risk factors for CAD, and the severity of the signs of atherosclerosis was correlated to the severity of OSA [43]. In another study by the same group, these signs

of early atherosclerosis in OSA patients were responsive to CPAP treatment, supporting the concept that OSA may be an independent risk factor for atherosclerosis [44].

However, the evidence of more severe atherosclerosis specifically in the coronary vessels in OSA patients is scarcer. Recently Turmel et al. [45] studied 19 OSA patients with stable CAD who underwent three-dimensional intravascular ultrasound plaque evaluation and showed a higher atherosclerotic plaque volume in those patients with a more severe OSA. Similarly, Sharma et al. [46] found that the frequency of noncalcified or mixed plaques is much higher in patients with OSA than in non-OSA patients.

2.2. OSA and Thrombosis and Coagulation. The final pathogenic mechanism of an ACS is coronary artery thrombosis as a result of the loss of integrity of the covering of an atherosclerotic plaque, due to rupture or erosion, and subsequent platelet adhesion, activation, aggregation and thrombus formation [2].

Several studies have reported increased platelet activity in OSA patients [47], associated with oxygen desaturation [48] and reduced fibrinogen concentrations and fibrinolytic activity in OSA patients [49], among other abnormalities in the coagulation system [50]. These alterations have also been found to be reduced after CPAP treatment [51–53].

2.3. OSA and Myocardial Ischemia. Myocardial ischemia is the result of an imbalance between oxygen supply and demand in the myocardium. Some OSA-induced pathophysiological changes may have an influence in this equilibrium and provoke myocardial ischemia in some specific stressful situations.

Airway obstruction during OSA can lead to recurrent high negative intrathoracic pressure that increases transmural gradients across the ventricles and thus myocardial afterload, leading to a rise in myocardial oxygen demand during the apneas, a fact that combined with the diminished oxygen supply can cause myocardial ischemia in some patients, such as patients with preexisting CAD [54]. Additionally, OSA leads to an increased sympathetic activity [55] due to hypoxia and hypercapnia, resulting in an increase in blood pressure and resting heart rate [56] that may induce myocardial ischemia [57].

Clinical evidence of myocardial ischemia induced by OSA has been addressed in several studies. Symptoms in some forms of ACS, such as nocturnal angina, can be triggered by OSA [58]. Similarly, nocturnal ST-segment depression is observed among patients with known CAD and OSA [59] but is also reported in patients with OSA without known CAD [60, 61]. CPAP is able to improve these abnormalities [54].

However, whether severe OSA is a trigger of nocturnal myocardial injury in patients with CAD is under discussion. In a prospective study of 15 patients with known CAD and moderate-to-severe OSA (apnea/hypopnea index (AHI) > 30), Gami et al. [62] reported no evidence of myocardial injury assessed by a third-generation troponin T assay during sleep. However, in a more recent study by Randby et al. [63] in a community-based sample of patients without known

CAD, high-sensitivity cardiac troponin T levels were elevated in 53% of patients with OSA. This high prevalence lost significance after adjusting for other significant risk factor resulting in absence of association between high-sensitivity cardiac troponin T levels and OSA severity. The high-sensitivity cardiac troponin T detection among those patients may have been probably related to the higher prevalence and grouping of cardiovascular risk factors among patients with OSA, rather than to a nocturnal pattern of myocardial injury in patients without CAD.

In patients with an ACS, acute ischemia of a region of the myocardium is caused by the complete or partial cessation of coronary blood flow by a thrombotic occlusion of a coronary vessel, leading to a wide range of clinical manifestations, from unstable chest pain to sudden cardiac arrest. OSA may influence the onset of acute ischemic events, as ACS [64] and sudden cardiac death [65] are more frequent during nighttime in OSA patients, contrarily to the usual diurnal pattern, although there is not enough evidence to conclude that OSA can be a definite trigger of ACS, even in those occurring at night.

However, some authors state that intermittent hypoxia that occurs at night in OSA patients may play a role in the development of ischemic preconditioning in the myocardium and is thus protective against myocardial ischemic insults by the regulation of critical transcription factors that play important roles in coronary endothelium [66]. Mechanisms underlying ischemic preconditioning are under active research, and clinical translation of the growing body of basic research is still to come [67]. In a recent observational study by Shah et al. [68], infarct size measured by peak troponin levels was assessed in 136 patients after an AMI who were screened for OSA. Troponin levels after an acute nonfatal AMI were significantly lower in patients with a more severe SAHS, after adjusting for other cardiovascular risk factors. This may be due to ischemic preconditioning in the myocardium, although more studies are needed to confirm this hypothesis and to better understand the mechanisms responsible for this response. Recently, a study by Berger et al. in patients presenting with AMI showed that those patients with sleep disordered breathing showed a greater mobilization of endothelial progenitor cells and increased vascular endothelial growth factor expression compared to patients with normal breathing [69].

Similarly, another possible adaptive mechanism of coronary circulation to chronic intermittent ischemia of OSA patients is the development of coronary collaterals. Coronary collateral formation from healthy vessels to an ischemic region of the myocardium is a well-known phenomenon in patients with chronic ischemic heart disease, present in 50% of patients with severe obstructive coronary lesions or totally occluded coronary arteries that can provide a perfusion reserve in case of increased myocardial oxygen demand in the affected territory. Mechanisms and factors associated with the development of these collaterals are not totally understood, and chronic intermittent hypoxia in OSA patients may play a role in this scenario, via the upregulation of critical vascular growth factors involved in vessel proliferation [70, 71]. In fact, Steiner et al. [72] reported a significantly higher coronary

collateral vessel development in patients of totally occluded coronary arteries and OSA compared to those patients without OSA, suggesting that chronic intermittent hypoxia of patients with OSA may be a significant factor affecting growth of CCVs as a compensatory mechanism to chronic myocardial ischemia. However, more studies are needed to better understand the underlying mechanisms of the adaptive responses of coronary circulation to chronic intermittent hypoxia and the clinical implications of these responses in OSA patients.

3. Clinical Implications of OSA in Patients with CAD

3.1. Epidemiology. The prevalence of OSA in patients with CAD is higher as in normal population, as numerous studies state [73–80]. Moore et al. [73] reported a prevalence of OSA (AHI > 10) of 37% in 142 patients with stable angina pectoris and angiographically confirmed CAD, and Peker et al. [74] reported a prevalence of OSA of 30% in those patients admitted with an ACS. A more recent report from Konecny et al. [75] highlights the underrecognition of OSA among patients admitted for an ACS, with a prevalence of OSA of 69% and severe OSA (AHI > 30) of 34%.

Other studies reported a wide range of prevalence, ranging from 26% to 66% [76–80], partially explained by the different value of AHI used to establish the diagnosis of OSA in the different studies.

However, despite the high prevalence described in some of these studies, the current guidelines of practice guidelines for the management of STEMI [81] and NSTEMI and UA [82] do not state any recommendation for screening OSA in patients presenting with an ACS.

3.2. OSA as a Risk Factor for CAD. There is a growing body of literature addressing the role of OSA as an independent risk factor of CAD [83]. As both disorders share common risk factors, such as obesity, male sex, age, and smoking, overlapping without a causal relationship may be possible [7, 84, 85]. Moreover, several of well-established risk factors for CAD have been associated with OSA in multiple studies, specially systemic hypertension [28, 86, 87], but also diabetes mellitus [88, 89], dyslipidemia [90], and metabolic syndrome [91]. Therefore, proving that OSA can independently cause CAD remains a difficult issue.

OSA is independently associated with subclinical coronary atherosclerosis measured by coronary calcification in computed tomography [92], and there is also a higher prevalence of noncalcified obstructive atherosclerotic plaques in OSA patients, as stated above. Several clinic-based longitudinal studies have found an association between OSA and the development of CAD, after adjusting for other risk factors, mainly in untreated individuals referred to CPAP treatment [93–97]. Data of more than 6000 patients from the community-based Sleep Heart Health Study found an association between OSA and incident CAD in those patients with the most severe OSA [98], but a more recent analysis of the same cohort, with longitudinal data after a 8.7-year followup, found no association of OSA with incident CAD,

after adjusting for other risk factors, except in patients younger than 70 years of age, in which the risk of CAD was slightly increased and was also slightly higher in patients with the most severe OSA [99]. On the contrary, in an other recent observational study of >1000 patients, Shah et al. [100] found a significant association between OSA and incident coronary events or cardiac death after adjusting for other traditional risk factors. Similarly, García-Río et al. [80] reported significant association between OSA and acute myocardial infarction. Although most of these observational data suggest a strong association, data are not conclusive and evidence is still insufficient to establish a causative role of OSA in the development of CAD.

3.3. OSA and Outcomes of CAD. OSA may also influence outcomes when present in patients with CAD [101, 102], but its effect remains a controversial issue as studies have yielded discrepant data. In a prospective cohort study of >400 patients with stable angina pectoris and CAD confirmed by coronary angiography, with a followup of >5 years, OSA was associated with a higher rate of death, myocardial infarction, and stroke [103]. More recent long-term follow-up data from the same group [104] show a significant association of OSA and stroke among stable CAD patients. Similarly to chronic CAD patients, patients who present with an ACS as the first manifestation of CAD also show worse outcomes. Yumino et al. [105], in a prospective cohort study of 89 patients with ACS who underwent polysomnography found OSA in 57% of patients. After a mean followup of >7 months, the incidence of cardiac death, reinfarction or new revascularization was higher in patients with OSA compared to those without OSA. Similarly, a more recent study by Lee et al. [78] showed a higher incidence of major adverse events patients with severe OSA after a STEMI. Non-STEMI patients with OSA have also been reported to have poorer in-hospital outcomes [106]. Recovery of the left ventricle systolic function after an acute myocardial infarction is one of the strongest long-term prognostic factors. There are data that suggest that OSA may inhibit the recovery of the left ventricular systolic function after an acute myocardial infarction [107]. However, other studies did not find an association between OSA and recurrent cardiovascular events in CAD patients [108].

Data suggest that OSA may worsen prognosis in all the spectrum of CAD patients, but more research is necessary in order to determine whether diagnosing and treating OSA may influence the prognosis of patients with CAD.

3.4. Treatment of OSA and CAD. CPAP continues to be the primary therapy for patients with symptomatic OSA. Most studies report that the treatment of OSA with CPAP results in a favorable clinical effect on various factors associated with the structure and function of the cardiovascular system, like reduction of sympathetic activity, improved vasodilatatory capacity of the endothelium, hypercoagulability and systemic inflammation, increased intrathoracic pressure, and other effects that lead to a reduction in myocardial oxygen demand and increased coronary flow [17, 24, 40, 51–54].

Treatment of OSA with CPAP in symptomatic patients without known CAD has been associated with a reduction

in cardiovascular events [96, 97, 109]. However, the question whether CPAP treatment in nonsleepy OSA patients aiming at a decrease in cardiovascular events still remains unclear. CPAP treatment did not significantly reduce the incidence of cardiovascular events compared to no intervention in general population, as data from a recent multicenter randomized controlled clinical trial show [110]. However, adherence to treatment had a significant impact in the results of this trial, as when patients who were adherent to CPAP treatment more than 4 hours per day were analyzed a statistically significant reduction in the incidence of CV events was found. This is consistent with other observational studies [111, 112] that support the hypothesis of a protective effect of CPAP treatment in OSA patients regardless of sleepiness symptoms.

However, information regarding this question in the specific population of patients with CAD is more scarce and derived only from observational studies, and thus, the impact of the OSA treatment as a secondary prevention measure for CAD patients intended to reduce cardiovascular events in the long term remains unclear, mainly due to the lack of a placebo-controlled, randomized treatment trials in patients with OSA and CAD.

In 54 patients with chronic stable CAD and severe OSA, an observational study by Milleron et al. [95] with a median followup of 86 months reported a beneficial effect of CPAP treatment, in terms of a reduction and a later occurrence of recurrent cardiovascular events. However, Cassar et al. [113] reported fewer cardiac deaths but not fewer cardiovascular events in CPAP-treated OSA patients undergoing percutaneous coronary intervention for stable angina. In a recent observational study by García-Río et al. [80], acute myocardial infarction patients with untreated OSA had a higher rate of recurrent myocardial infarction and necessity of new revascularization compared to treated OSA patients and non-OSA patients. In this scenario, adherence to CPAP treatment in patients without daytime sleepiness may be a concern, as patients with CAD, especially after an ACS, have shown a very low adherence to behavioral or lifestyle preventive measures, in contrast to a high adherence to pharmacological preventive measures [114]. However, a study by Sampol et al. [115] has shown that adherence to CPAP treatment in patients with CAD is not influenced by the absence of sleepiness symptoms.

However, although the above data suggest a possible benefit of CPAP treatment in this population, they come from observational studies, and randomized clinical trials are needed to establish whether CPAP treatment should be recommended to chronic or acute CAD patients without daytime sleepiness. This issue is addressed by three ongoing randomized clinical trials from which results are strongly awaited. The first randomized trial (Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease—SAVE Trial, NCT00738179) aims to test whether long-term use of CPAP can reduce the incidence of cardiovascular events (cardiovascular death, nonfatal AMI, nonfatal stroke, hospital admission for heart failure, and new hospitalization for unstable angina or transient ischemic attack) in 5000 patients with evidence of established coronary or cerebrovascular disease over a mean

follow-up period of 4 years. The second trial (The Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea—RICCADSA Trial, NCT0051959) addresses this issue in stable CAD patients. This randomized trial that is expected to complete recruitment by December 2012 aims to include more than 500 patients with CAD undergoing planned percutaneous or surgical revascularization, and address if CPAP treatment reduces the combined rate of new revascularization, myocardial infarction, stroke, and cardiovascular mortality over a mean follow-up period of 3 years in CAD patients with OSA and without daytime sleepiness [116]. The third trial (Continuous Positive Airway Pressure in Patients With Acute Coronary Syndrome and Obstructive Sleep Apnea—ISAACC trial, NCT 01335087) addresses this issue in the setting of the acute coronary syndromes. This randomized trial will include more than 1800 patients with a recent ACS and will assess whether CPAP treatment will reduce the rate of major cardiovascular events (cardiovascular death, nonfatal AMI, nonfatal stroke, hospital admission for heart failure, and new hospitalizations for unstable angina or transient ischemic attack) in patients with non-ST elevation or ST elevation ACS admitted in a coronary care unit and co-occurring with OSA. These trials will probably be the pivotal trials which will definitely answer the question of whether CPAP treatment influences prognosis of CAD patients with OSA both in the acute and in the chronic settings.

4. Summary

CAD is a complex disease with a wide range of clinical manifestations. OSA is as well a condition with numerous systemic implications, which can influence CAD in numerous phases and pathological processes. Moreover, despite that CAD and OSA share risk factors and that systemic conditions influenced by OSA have a role as well in the pathogenesis of CAD, evidence is lacking to address OSA as a risk factor of CAD, as a prognostic factor of CAD. Similarly, more evidence is needed to address CPAP treatment as a useful therapy for patients with CAD and nonsymptomatic OSA. However, research in this field is growing rapidly, and data answering some of these questions may soon, be available.

References

- [1] K. Thygesen, J. S. Alpert, A. S. Jaffe, M. L. Simoons, B. R. Chaitman, and H. D. White, "Third universal definition of myocardial infarction," *European Heart Journal*, vol. 33, no. 20, pp. 2551–2567, 2012.
- [2] P. Libby, "Current concepts of the pathogenesis of the acute coronary syndromes," *Circulation*, vol. 104, no. 3, pp. 365–372, 2001.
- [3] A. S. Go, D. Mozaffarian, V. L. Roger et al., "Heart disease and stroke statistics—2013 update a report from the American Heart Association," *Circulation*, vol. 127, pp. e6–e245, 2013.
- [4] D. M. Lloyd-Jones, M. G. Larson, A. Beiser, and D. Levy, "Lifetime risk of developing coronary heart disease," *The Lancet*, vol. 353, no. 9147, pp. 89–92, 1999.
- [5] N. M. Punjabi, "The epidemiology of adult obstructive sleep apnea," *Proceedings of the American Thoracic Society*, vol. 5, no. 2, pp. 136–143, 2008.
- [6] L. J. Epstein, D. Kristo, P. J. Strollo et al., "Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults," *Journal of Clinical Sleep Medicine*, vol. 5, no. 3, pp. 263–276, 2009.
- [7] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, "The occurrence of sleep-disordered breathing among middle-aged adults," *The New England Journal of Medicine*, vol. 328, no. 17, pp. 1230–1235, 1993.
- [8] V. K. Vijayan, "Morbidities associated with obstructive sleep apnea," *Expert Review of Respiratory Medicine*, vol. 6, no. 5, pp. 557–566, 2012.
- [9] T. Kasai, J. S. Floras, and T. D. Bradley, "Sleep apnea and cardiovascular disease: a bidirectional relationship," *Circulation*, vol. 126, no. 12, pp. 1495–1510, 2012.
- [10] M. M.-S. Lui and M. Sau-Man, "OSA and atherosclerosis," *Journal of Thoracic Disease*, vol. 4, no. 2, pp. 164–172, 2012.
- [11] U. Singh and I. Jialal, "Oxidative stress and atherosclerosis," *Pathophysiology*, vol. 13, no. 3, pp. 129–142, 2006.
- [12] H. Vink, A. A. Constantinescu, and J. A. E. Spaan, "Oxidized lipoproteins degrade the endothelial surface layer: implications for platelet-endothelial cell adhesion," *Circulation*, vol. 101, no. 13, pp. 1500–1502, 2000.
- [13] J. Davignon and P. Ganz, "Role of endothelial dysfunction in atherosclerosis," *Circulation*, vol. 109, no. 23, pp. III27–III32, 2004.
- [14] E. Ohga, T. Tomita, H. Wada, H. Yamamoto, T. Nagase, and Y. Ouchi, "Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1," *Journal of Applied Physiology*, vol. 94, no. 1, pp. 179–184, 2003.
- [15] M. Yamauchi, H. Nakano, J. Maekawa et al., "Oxidative stress in obstructive sleep apnea," *Chest*, vol. 127, no. 5, pp. 1674–1679, 2005.
- [16] M. Yamauchi and H. Kimura, "Oxidative stress in obstructive sleep apnea: putative pathways to the cardiovascular complications," *Antioxidants and Redox Signaling*, vol. 10, no. 4, pp. 755–768, 2008.
- [17] A. Alonso-Fernández, F. García-Río, M. A. Arias et al., "Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: a randomised trial," *Thorax*, vol. 64, no. 7, pp. 581–586, 2009.
- [18] A. Barceló, C. Miralles, F. Barbé, M. Vila, S. Pons, and A. G. Agustí, "Abnormal lipid peroxidation in patients with sleep apnoea," *The European Respiratory Journal*, vol. 16, no. 4, pp. 644–647, 2000.
- [19] V. Savransky, A. Nanayakkara, J. Li et al., "Chronic intermittent hypoxia induces atherosclerosis," *American Journal of Respiratory and Critical Care Medicine*, vol. 175, no. 12, pp. 1290–1297, 2007.
- [20] M. S. M. Ip, H. F. Tse, B. Lam, K. W. T. Tsang, and W. K. Lam, "Endothelial function in obstructive sleep apnea and response to treatment," *American Journal of Respiratory and Critical Care Medicine*, vol. 169, no. 3, pp. 348–353, 2004.
- [21] S. Itzhaki, L. Lavie, G. Pillar, G. Tal, and P. Lavie, "Endothelial dysfunction in obstructive sleep apnea measured by peripheral arterial tone response in the finger to reactive hyperemia," *Sleep*, vol. 28, no. 5, pp. 594–600, 2005.
- [22] A. Lurie, "Endothelial dysfunction in adults with obstructive sleep apnea," *Advances in Cardiology*, vol. 46, pp. 139–170, 2011.

- [23] B. T. Patt, D. Jarjoura, D. N. Haddad et al., "Endothelial dysfunction in the microcirculation of patients with obstructive sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 12, pp. 1540–1545, 2010.
- [24] R. Schulz, D. Schmidt, A. Blum et al., "Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy," *Thorax*, vol. 55, no. 12, pp. 1046–1051, 2000.
- [25] S. K. Namtvedt, J. Hisdal, A. Randby et al., "Impaired endothelial function in persons with obstructive sleep apnoea: impact of obesity," *Heart*, vol. 99, no. 1, pp. 30–34, 2013.
- [26] T. Kadohira, Y. Kobayashi, Y. Iwata, H. Kitahara, and I. Komuro, "Coronary artery endothelial dysfunction associated with sleep apnea," *Angiology*, vol. 62, no. 5, pp. 397–400, 2011.
- [27] A. N. Vgontzas, D. A. Papanicolaou, E. O. Bixler, A. Kales, K. Tyson, and G. P. Chrousos, "Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 82, no. 5, pp. 1313–1316, 1997.
- [28] F. Javier Nieto, T. B. Young, B. K. Lind et al., "Association of sleep-disordered breathing sleep apnea, and hypertension in a large community-based study," *Journal of the American Medical Association*, vol. 283, no. 14, pp. 1829–1836, 2000.
- [29] A. S. M. Shamsuzzaman, M. Winnicki, P. Lanfranchi et al., "Elevated C-reactive protein in patients with obstructive sleep apnea," *Circulation*, vol. 105, no. 21, pp. 2462–2464, 2002.
- [30] E. K. Larkin, C. L. Rosen, H. L. Kirchner et al., "Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration," *Circulation*, vol. 111, no. 15, pp. 1978–1984, 2005.
- [31] N. M. Punjabi and B. A. Beamer, "C-reactive protein is associated with sleep disordered breathing independent of adiposity," *Sleep*, vol. 30, no. 1, pp. 29–34, 2007.
- [32] C. Guilleminault, C. Kirisoglu, and M. M. Ohayon, "C-reactive protein and sleep-disordered breathing," *Sleep*, vol. 27, no. 8, pp. 1507–1511, 2004.
- [33] H. K. Meier-Ewert, P. M. Ridker, N. Rifai et al., "Effect of sleep loss on C-Reactive protein, an inflammatory marker of cardiovascular risk," *Journal of the American College of Cardiology*, vol. 43, no. 4, pp. 678–683, 2004.
- [34] L. Dyugovskaya, P. Lavie, and L. Lavie, "Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients," *American Journal of Respiratory and Critical Care Medicine*, vol. 165, no. 7, pp. 934–939, 2002.
- [35] L. Dyugovskaya, P. Lavie, and L. Lavie, "Lymphocyte activation as a possible measure of atherosclerotic risk in patients with sleep apnea," *Annals of the New York Academy of Sciences*, vol. 1051, pp. 340–350, 2005.
- [36] S. Ryan, C. T. Taylor, and W. T. McNicholas, "Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome," *Circulation*, vol. 112, no. 17, pp. 2660–2667, 2005.
- [37] L. F. Drager, V. Y. Polotsky, and G. Lorenzi-Filho, "Obstructive sleep apnea: an emerging risk factor for atherosclerosis," *Chest*, vol. 140, no. 2, pp. 534–542, 2011.
- [38] K. Minoguchi, T. Yokoe, T. Tazaki et al., "Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 172, no. 5, pp. 625–630, 2005.
- [39] S. Jelic, M. Padeletti, S. M. Kawut et al., "Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea," *Circulation*, vol. 117, no. 17, pp. 2270–2278, 2008.
- [40] T. Yokoe, K. Minoguchi, H. Matsuo et al., "Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure," *Circulation*, vol. 107, no. 8, pp. 1129–1134, 2003.
- [41] R. Altin, H. Özdemir, K. Mahmutyazicioğlu et al., "Evaluation of carotid artery wall thickness with high-resolution sonography in obstructive sleep apnea syndrome," *Journal of Clinical Ultrasound*, vol. 33, no. 2, pp. 80–86, 2005.
- [42] M. M. Ciccone, P. Scicchitano, G. Mitacchione et al., "Is there a correlation between OSAS duration/severity and carotid intima-media thickness?" *Respiratory Medicine*, vol. 106, no. 5, pp. 740–746, 2012.
- [43] L. F. Drager, L. A. Bortolotto, M. C. Lorenzi, A. C. Figueiredo, E. M. Krieger, and G. Lorenzi-Filho, "Early signs of atherosclerosis in obstructive sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 172, no. 5, pp. 613–618, 2005.
- [44] L. F. Drager, L. A. Bortolotto, A. C. Figueiredo, E. M. Krieger, and G. Lorenzi-Filho, "Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 176, no. 7, pp. 706–712, 2007.
- [45] J. Turmel, F. Sériès, L. P. Boulet et al., "Relationship between atherosclerosis and the sleep apnea syndrome: an intravascular ultrasound study," *International Journal of Cardiology*, vol. 132, no. 2, pp. 203–209, 2009.
- [46] S. Sharma, M. Gebregziabher, A. T. Parker, J. A. Abro, A. M. Armstrong, and U. J. Schoepf, "Independent association between obstructive sleep apnea and noncalcified coronary plaque demonstrated by noninvasive coronary computed tomography angiography," *Clinical Cardiology*, vol. 35, no. 10, pp. 641–645, 2012.
- [47] G. Bokinsky, M. Miller, K. Ault, P. Husband, and J. Mitchell, "Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure: a preliminary investigation," *Chest*, vol. 108, no. 3, pp. 625–630, 1995.
- [48] S. Rahangdale, S. Y. Yeh, V. Novack et al., "The influence of intermittent hypoxemia on platelet activation in obese patients with obstructive sleep apnea," *Journal of Clinical Sleep Medicine*, vol. 7, no. 2, pp. 172–178, 2011.
- [49] R. Von Känel and J. E. Dimsdale, "Hemostatic alterations in patients with obstructive sleep apnea and the implications for cardiovascular disease," *Chest*, vol. 124, no. 5, pp. 1956–1967, 2003.
- [50] C. Liak and M. Fitzpatrick, "Coagulability in obstructive sleep apnea," *Canadian Respiratory Journal*, vol. 18, no. 6, pp. 338–348, 2011.
- [51] D. S. Hui, F. W. Ko, J. P. Fok et al., "The effects of nasal continuous positive airway pressure on platelet activation in obstructive sleep apnea syndrome," *Chest*, vol. 125, no. 5, pp. 1768–1775, 2004.
- [52] K. Chin, M. Ohi, H. Kita et al., "Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 153, no. 6, pp. 1972–1976, 1996.
- [53] R. von Känel, J. S. Lored, S. Ancoli-Israel, and J. E. Dimsdale, "Association between sleep apnea severity and blood coagulability: treatment effects of nasal continuous positive airway pressure," *Sleep and Breathing*, vol. 10, no. 3, pp. 139–146, 2006.

- [54] T. D. Bradley and J. S. Floras, "Obstructive sleep apnoea and its cardiovascular consequences," *The Lancet*, vol. 373, no. 9657, pp. 82–93, 2009.
- [55] J. T. Carlson, J. Hedner, M. Elam, H. Ejnell, J. Sellgren, and B. G. Wallin, "Augmented resting sympathetic activity in awake patients with obstructive sleep apnea," *Chest*, vol. 103, no. 6, pp. 1763–1768, 1993.
- [56] J. Wolf, J. Lewicka, and K. Narkiewicz, "Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 17, no. 3, pp. 233–240, 2007.
- [57] J. Nauman, I. Janszky, L. J. Vatten, and U. Wisløff, "Temporal changes in resting heart rate and deaths from ischemic heart disease," *The Journal of The American Medical Association*, vol. 306, no. 23, pp. 2579–2587, 2011.
- [58] K. A. Franklin, J. B. Nilsson, C. Sahlin, and U. Naslund, "Sleep apnoea and nocturnal angina," *The Lancet*, vol. 345, no. 8957, pp. 1085–1087, 1995.
- [59] N. Peled, E. G. Abinader, G. Pillar, D. Sharif, and P. Lavie, "Nocturnal ischemic events in patients with obstructive sleep apnea syndrome and ischemic heart disease: effects of continuous positive air pressure treatment," *Journal of the American College of Cardiology*, vol. 34, no. 6, pp. 1744–1749, 1999.
- [60] P. Hanly, Z. Sasson, N. Zuberi, and K. Lunn, "ST-segment depression during sleep in obstructive sleep apnea," *American Journal of Cardiology*, vol. 71, no. 15, pp. 1341–1345, 1993.
- [61] P. Philip and C. Guilleminault, "Letter to the editor: ST segment abnormality, angina during sleep and obstructive sleep apnea," *Sleep*, vol. 16, no. 6, pp. 558–559, 1993.
- [62] A. S. Gami, A. Svatikova, R. Wolk et al., "Cardiac troponin T in obstructive sleep apnea," *Chest*, vol. 125, no. 6, pp. 2097–2100, 2004.
- [63] A. Randby, S. K. Namtvedt, G. Einvik et al., "Obstructive sleep apnea is associated with increased high-sensitivity cardiac troponin T levels," *Chest*, vol. 142, no. 3, pp. 639–646, 2012.
- [64] F. H. Sert Kuniyoshi, A. Garcia-Touchard, A. S. Gami et al., "Day-night variation of acute myocardial infarction in obstructive sleep apnea," *Journal of the American College of Cardiology*, vol. 52, no. 5, pp. 343–346, 2008.
- [65] A. S. Gami, D. E. Howard, E. J. Olson, and V. K. Somers, "Day-night pattern of sudden death in obstructive sleep apnea," *The New England Journal of Medicine*, vol. 352, no. 12, pp. 1206–1214, 2005.
- [66] L. Lavie and P. Lavie, "Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea," *Medical Hypotheses*, vol. 66, no. 6, pp. 1069–1073, 2006.
- [67] H. K. Eltzschig and T. Eckle, "Ischemia and reperfusion—from mechanism to translation," *Nature Medicine*, vol. 17, no. 11, pp. 1391–1401, 2011.
- [68] N. Shah, S. Redline, H. K. Yaggi et al., "Obstructive sleep apnea and acute myocardial infarction severity: ischemic preconditioning?" *Sleep and Breathing*. In press.
- [69] S. Berger, D. Aronson, P. Lavie, and L. Lavie, "Endothelial progenitor cells in acute myocardial infarction and sleep-disordered breathing," *American Journal of Respiratory and Critical Care Medicine*, vol. 187, no. 1, pp. 90–98, 2013.
- [70] J. R. Resar, A. Roguin, J. Voner et al., "Hypoxia-inducible factor 1 α polymorphism and coronary collaterals in patients with ischemic heart disease," *Chest*, vol. 128, no. 2, pp. 787–791, 2005.
- [71] A. Schultz, L. Lavie, I. Hochberg et al., "Interindividual heterogeneity in the hypoxic regulation of VEGF: significance for the development of the coronary artery collateral circulation," *Circulation*, vol. 100, no. 5, pp. 547–552, 1999.
- [72] S. Steiner, P. O. Schueller, V. Schulze, and B. E. Strauer, "Occurrence of coronary collateral vessels in patients with sleep apnea and total coronary occlusion," *Chest*, vol. 137, no. 3, pp. 516–520, 2010.
- [73] T. Moore, T. Rabben, U. Wiklund, K. A. Franklin, and P. Eriksson, "Sleep-disordered breathing in men with coronary artery disease," *Chest*, vol. 109, no. 3, pp. 659–663, 1996.
- [74] Y. Peker, H. Kraiczi, J. Hedner, S. Löth, A. Johansson, and M. Bende, "An independent association between obstructive sleep apnoea and coronary artery disease," *European Respiratory Journal*, vol. 14, no. 1, pp. 179–184, 1999.
- [75] T. Konecny, F. H. Sert Kuniyoshi, M. Orban et al., "Under-diagnosis of sleep apnea in patients after acute myocardial infarction," *Journal of the American College of Cardiology*, vol. 56, no. 9, pp. 742–743, 2010.
- [76] B. M. Sanner, M. Konermann, C. Doberauer, T. Weiss, and W. Zidek, "Sleep-disordered breathing in patients referred for angina evaluation—association with left ventricular dysfunction," *Clinical Cardiology*, vol. 24, no. 2, pp. 146–150, 2001.
- [77] C. H. Lee, S. M. Khoo, B. C. Tai et al., "Obstructive sleep apnea in patients admitted for acute myocardial infarction: prevalence, predictors, and effect on microvascular perfusion," *Chest*, vol. 135, no. 6, pp. 1488–1495, 2009.
- [78] C. Lee, S. Khoo, M. Y. Chan et al., "Severe obstructive sleep apnea and outcomes following myocardial infarction," *Journal of Clinical Sleep Medicine*, vol. 7, no. 6, pp. 616–621, 2011.
- [79] V. Areias, J. Romero, K. Cunha et al., "Sleep apnea-hypopnea syndrome and acute coronary syndrome—an association not to forget," *Revista Portuguesa De Pneumologia*, vol. 18, no. 1, pp. 22–28, 2012.
- [80] F. Garcia-Rio, A. Alonso-Fernández, E. Armada et al., "CPAP effect on recurrent episodes in patients with sleep apnea and myocardial infarction," *International Journal of Cardiology*. In press.
- [81] P. G. Steg, S. K. James, D. Atar et al., "ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation," *European Heart Journal*, vol. 33, no. 20, pp. 2569–2619, 2012.
- [82] C. W. Hamm, J. Bassand, S. Agewall et al., "ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)," *European Heart Journal*, vol. 32, no. 23, pp. 2999–3054, 2011.
- [83] K. Monahan and S. Redline, "Role of obstructive sleep apnea in cardiovascular disease," *Current Opinion in Cardiology*, vol. 26, no. 6, pp. 541–547, 2011.
- [84] T. Young, E. Shahar, F. J. Nieto et al., "Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study," *Archives of Internal Medicine*, vol. 162, no. 8, pp. 893–900, 2002.
- [85] Y. Lin, Q. Li, and X. Zhang, "Interaction between smoking and obstructive sleep apnea: not just participants," *Chinese Medical Journal*, vol. 125, no. 17, pp. 3150–3156, 2012.
- [86] P. E. Peppard, T. Young, M. Palta, and J. Skatrud, "Prospective study of the association between sleep-disordered breathing and hypertension," *The New England Journal of Medicine*, vol. 342, no. 19, pp. 1378–1384, 2000.

- [87] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report," *Journal of the American Medical Association*, vol. 289, no. 19, pp. 2560–2572, 2003.
- [88] K. J. Reichmuth, D. Austin, J. B. Skatrud, and T. Young, "Association of sleep apnea and type II diabetes: a population-based study," *American Journal of Respiratory and Critical Care Medicine*, vol. 172, no. 12, pp. 1590–1595, 2005.
- [89] E. Tasali, B. Mokhlesi, and E. Van Cauter, "Obstructive sleep apnea and type 2 diabetes: interacting epidemics," *Chest*, vol. 133, no. 2, pp. 496–506, 2008.
- [90] A. M. Adedayo, O. Olafiranye, D. Smith et al., "Obstructive sleep apnea and dyslipidemia: evidence and underlying mechanism," *Sleep and Breathing*. In press.
- [91] J. C. Lam, J. C. Mak, and M. S. Ip, "Obesity, obstructive sleep apnoea and metabolic syndrome," *Respirology*, vol. 17, no. 2, pp. 223–236, 2012.
- [92] D. Sorajja, A. S. Gami, V. K. Somers, T. R. Behrenbeck, A. Garcia-Touchard, and F. Lopez-Jimenez, "Independent association between obstructive sleep apnea and subclinical coronary artery disease," *Chest*, vol. 133, no. 4, pp. 927–933, 2008.
- [93] H. Schäfer, U. Koehler, S. Ewig, E. Hasper, S. Tasci, and B. Lüderitz, "Obstructive sleep apnea as a risk marker in coronary artery disease," *Cardiology*, vol. 92, no. 2, pp. 79–84, 1999.
- [94] Y. Peker, J. Hedner, J. Norum, H. Kraiczi, and J. Carlson, "Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up," *American Journal of Respiratory and Critical Care Medicine*, vol. 166, no. 2, pp. 159–165, 2002.
- [95] O. Milleron, R. Pillière, A. Foucher et al., "Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study," *European Heart Journal*, vol. 25, no. 9, pp. 728–734, 2004.
- [96] L. S. Doherty, J. L. Kiely, V. Swan, and W. T. McNicholas, "Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome," *Chest*, vol. 127, no. 6, pp. 2076–2084, 2005.
- [97] J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. N. Agustí, "Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study," *The Lancet*, vol. 365, no. 9464, pp. 1046–1053, 2005.
- [98] E. Shahar, C. W. Whitney, S. Redline et al., "Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the sleep heart health study," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 1, pp. 19–25, 2001.
- [99] D. J. Gottlieb, G. Yenokyan, A. B. Newman et al., "Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study," *Circulation*, vol. 122, no. 4, pp. 352–360, 2010.
- [100] N. A. Shah, H. K. Yaggi, J. Concato, and V. Mohsenin, "Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death," *Sleep & Breathing = Schlaf & Atmung*, vol. 14, no. 2, pp. 131–136, 2010.
- [101] J. M. Marin, S. J. Carrizo, and I. Kogan, "Obstructive sleep apnea and acute myocardial infarction: clinical implications of the association," *Sleep*, vol. 21, no. 8, pp. 809–815, 1998.
- [102] Y. Peker, J. Hedner, H. Kraiczi, and S. Löth, "Respiratory disturbance index: an independent predictor of mortality in coronary artery disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 162, no. 1, pp. 81–86, 2000.
- [103] T. Moøe, K. A. Franklin, K. Holmström, T. Rabben, and U. Wiklund, "Sleep-disordered breathing and coronary artery disease: long-term prognosis," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 10, pp. 1910–1913, 2001.
- [104] F. Valham, T. Moøe, T. Rabben, H. Stenlund, U. Wiklund, and K. A. Franklin, "Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10-year follow-up," *Circulation*, vol. 118, no. 9, pp. 955–960, 2008.
- [105] D. Yumino, Y. Tsurumi, A. Takagi, K. Suzuki, and H. Kasanuki, "Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome," *American Journal of Cardiology*, vol. 99, no. 1, pp. 26–30, 2007.
- [106] L. C. Correia, A. C. Souza, G. Garcia et al., "Obstructive sleep apnea affects hospital outcomes of patients with non-ST-elevation acute coronary syndromes," *Sleep*, vol. 35, no. 9, pp. 1241A–125A, 2012.
- [107] H. Nakashima, T. Katayama, C. Takagi et al., "Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction," *European Heart Journal*, vol. 27, no. 19, pp. 2317–2322, 2006.
- [108] G. C. Hagenah, E. Gueven, and S. Andreas, "Influence of obstructive sleep apnoea in coronary artery disease: a 10-year follow-up," *Respiratory Medicine*, vol. 100, no. 1, pp. 180–182, 2006.
- [109] N. J. Buchner, B. M. Sanner, J. Borgel, and L. C. Rump, "Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk," *American Journal of Respiratory and Critical Care Medicine*, vol. 176, no. 12, pp. 1274–1280, 2007.
- [110] F. Barbé, J. Durán-Cantolla, M. Sánchez-de-la-Torre et al., "Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial," *The Journal of The American Medical Association*, vol. 307, no. 20, pp. 2161–2168, 2012.
- [111] F. Campos-Rodríguez, M. A. Martínez-García, I. de La Cruz-Moron, C. Almeida-Gonzalez, P. Catalan-Serra, and J. M. Montserrat, "Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study," *Annals of Internal Medicine*, vol. 156, no. 2, pp. 115–122, 2012.
- [112] M. Martínez-García, F. Campos-Rodríguez, P. Catalán-Serra et al., "Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study," *American Journal of Respiratory and Critical Care Medicine*, vol. 186, no. 9, pp. 909–916, 2012.
- [113] A. Cassar, T. I. Morgenthaler, R. J. Lennon, C. S. Rihal, and A. Lerman, "Treatment of obstructive sleep apnea is associated with decreased cardiac death after percutaneous coronary intervention," *Journal of the American College of Cardiology*, vol. 50, no. 14, pp. 1310–1314, 2007.
- [114] C. K. Chow, S. Jolly, P. Rao-Melacini, K. A. A. Fox, S. S. Anand, and S. Yusuf, "Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes," *Circulation*, vol. 121, no. 6, pp. 750–758, 2010.
- [115] G. Sampol, G. Rodés, O. Romero, M. J. Jurado, and P. Lloberes, "Adherence to nCPAP in patients with coronary disease and sleep apnea without sleepiness," *Respiratory Medicine*, vol. 101, no. 3, pp. 461–466, 2007.

- [116] Y. Peker, H. Glantz, E. Thunström, A. Kallryd, J. Herlitz, and J. Ejdebäck, "Rationale and design of the randomized intervention with CPAP in coronary artery disease and sleep apnoea—RICCADSA trial," *Scandinavian Cardiovascular Journal*, vol. 43, no. 1, pp. 24–31, 2009.

Review Article

Atrial Arrhythmias in Obstructive Sleep Apnea: Underlying Mechanisms and Implications in the Clinical Setting

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Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive interruption of ventilation during sleep caused by recurrent upper airway collapse, which leads to intermittent hypoxia. The disorder is commonly undiagnosed despite its relationship with substantial cardiovascular morbidity and mortality. Moreover, the effects of the disorder appear to be particularly dangerous in young subjects. In the last decade, substantial clinical evidence has identified OSA as independent risk factor for both bradyarrhythmias and tachyarrhythmias. To date the mechanisms leading to such arrhythmias have not been completely understood. However, recent data from animal models and new molecular analyses have increased our knowledge of the field, which might lead to future improvement in current therapeutic strategies mainly based on continuous positive airway pressure. This paper aims at providing readers a brief and specific revision of current knowledge about the mechanisms underlying atrial arrhythmias in OSA and their clinical and therapeutic implications.

1. Introduction

Obstructive sleep apnea (OSA) is a relevant health problem because of its high prevalence and concomitant severe effects in the general population [1]. Although the disorder is mainly present in obese men, other clinical characteristics such as age 65 years or older, smoking, and alcohol consumption are also common [1]. OSA is characterized by repetitive interruption of ventilation during sleep caused by recurrent upper airway collapse, which is associated with increasing respiratory efforts and intermittent arterial oxygen desaturation. Nocturnal arousals, loud intermittent snoring, and increased daytime sleepiness are the main symptoms [2]. Obstructive apneas and hypopneas are considered significant if they last for more than 10 seconds. Such episodes can be recorded and quantified by a polysomnography study, which

remains the standard technique for the diagnosis. Currently, international guidelines consider the diagnosis of OSA in the presence of an apnea-hypopnea index ≥ 5 and persistent respiratory effort during the episodes [2].

Cardiovascular morbidity and mortality significantly increase in patients with untreated severe OSA [3]. Moreover, the effects of the disorder appear to be particularly dangerous in young subjects [3, 4]. Substantial evidence supports the association between OSA and cardiovascular diseases, among which atrial arrhythmias and conduction disorders are of particular interest [5, 6]. Abnormalities such as hypoxia or sympathovagal imbalance are consistently present in OSA and have been associated with atrial arrhythmias [7, 8]. Moreover, under continuous positive airway pressure (CPAP) treatment, it has been shown the disappearance of both atrial fibrillation (AF) and heart block in patients with severe OSA

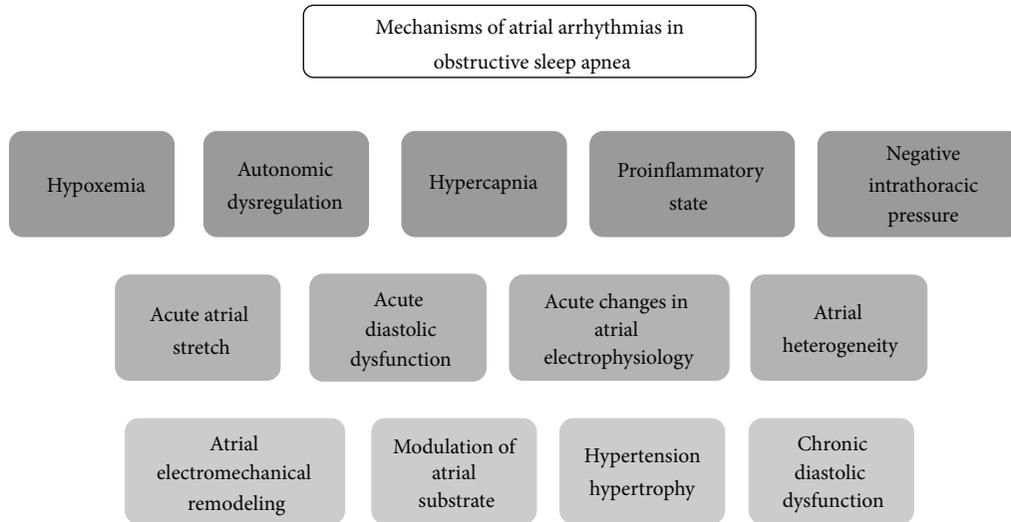


FIGURE 1: Diagram of mechanisms involved in atrial arrhythmias in patients with obstructive sleep apnea.

[8, 9]. In this work we aim at reviewing the current knowledge about the mechanisms underlying atrial disorders in OSA and their implications in clinical practice, in such a way that clinicians will be able to establish a mechanistic link from molecular basis to animal models and clinical setting.

2. Mechanisms of Increased Risk of Atrial Arrhythmias in OSA

Different abnormalities have been involved in the pathogenesis of atrial arrhythmias and increased cardiovascular risk in patients with OSA [2]. Significantly relevant is the strong association between tachyarrhythmias, especially AF and OSA [5]. Thus hypoxia, hypercapnia, negative intrathoracic pressure, autonomic alterations, inflammation, increase in intravascular volume, and left ventricular diastolic dysfunction are likely implicated in a multifactorial process leading to functional and structural changes prompt to atrial arrhythmias (Figure 1).

Hypoxemia significantly impairs relaxation of left and right ventricles in healthy humans rendered hypoxic by breathing a variable nitrogen/oxygen mixture [10]. Similarly, intermittent apnea-induced hypoxemia documented during a polysomnographic study has been associated with significant hemodynamic changes in left and right ventricular functions [11, 12]. Thus, the severity of apnea-related hypoxemia is associated with a gradual deterioration of left ventricular filling, which may explain the presence of left ventricular hypertrophy in patients with OSA and no history of hypertension [13, 14]. Experimental evidence from animal models has yielded some clues about the molecular mechanisms leading to diastolic dysfunction. Thus, intermittent hypoxia seems to increase both oxidative stress and susceptibility of the heart to such a stress [15, 16]. In addition, myocyte hypertrophy, apoptosis, and multifocal infarcts have been also associated with left ventricular dysfunction [17]. Interestingly, hypoxia-induced deterioration of left ventricular filling is

significantly correlated with acute atrial changes. In a rat model of obesity and acute OSA, increases in left ventricular end diastolic pressure during obstructive apnea correlated with significant left atrial enlargement monitored by echocardiography [18]. Moreover, in the same study Iwasaki et al. tried to elucidate the main mechanism leading to reproducibly inducible AF in those animals. To do so, they tested four different interventions consisting of pharmacologic autonomic blockade, ventilatory muscle paralysis, balloon occlusion of the inferior vena cava, and saline injection as control. Autonomic blockade partially decreased AF inducibility compared with control. However, only prevention of left atrial dilatation by balloon occlusion of the inferior vena cava was associated with significant suppression of AF inducibility [18]. The latter suggests that acute atrial dilatation due to apnea-related increase in left ventricular end diastolic pressure may prompt the atria to AF.

The results are especially relevant since acute atrial stretch has been traditionally associated with increased vulnerability to AF. Moreover, resumption of sinus rhythm is consistently achieved after releasing the atrial stretch [19]. The latter has important clinical implications in spite of the fact that mechanisms underlying stretch-induced AF are highly complex and not completely understood [20]. Therefore, AF might be terminated or prevented by correcting apnea-induced acute hemodynamic changes in the left atrium.

In addition, hypoxia may affect atrial electrophysiology by modifying conduction velocity and atrial refractoriness. However, data from different animal models have yielded divergent results, which preclude identifying conclusive effects [21, 22]. High levels of hypercapnia may also affect atrial electrophysiology by slowing atrial conduction and increasing atrial refractoriness. Upon returning to normocapnia, refractoriness rapidly returns to baseline levels while conduction slowing still persists. Although it is difficult to reproduce *in vivo* responses to acute hypoxemia and hypercapnia, hypercapnia-related electrophysiology changes have been associated with AF in the sheep intact heart [23].

Autonomic neural inputs to ganglionated plexi occurring during apnea may initiate AF. However, the exact mechanisms leading to AF are extremely difficult to elucidate because of the anatomic and physiological complexity of the sympathetic and parasympathetic innervation of the heart [24]. Ganglionated plexi neural activity progressively increases before the onset of AF, which associates with shortening of the atrial refractory period [25]. The latter allows nonconducted premature stimuli at baseline to activate the atrium and probably generate heterogeneity [26], which leads to reentry and AF. Moreover, either the blockade of both arms of the autonomic nervous system or ablation of pericardiac fat pad containing ganglionated plexi inhibits the occurrence of apnea-induced AF, similar to the previously mentioned effect of releasing atrial stretch [25]. However, acute effects of autonomic blockade may not last in the long term, rendering AF reinducible after several weeks of ablation-based autonomic denervation [27]. It is difficult to determine whether autonomic inputs or atrial stretch plays the main role in initiating and sustaining AF. Model-based differences on the presence or absence of negative intrathoracic pressure during apnea might be responsible for more stretch-dependent or autonomic deregulation-dependent AF [18, 25].

Negative intrathoracic pressure occurs during OSA due to ineffective inspiratory efforts against the occluded upper airway. Animal models simulating clinical OSA incorporate negative intrathoracic pressure during tracheal occlusion, which leads to shortening of the atrial effective refractory period and action potential duration [18, 28]. Such electrophysiological changes increase AF susceptibility, which seems to be partially mediated by vagal activation. The latter is further supported by a high rate of AF prevention upon atropine or vagotomy [28]. Concomitant changes in sympathetic activity and atrial pressure have been also documented [18, 29], which may increase atrial susceptibility to AF in the presence of vagal activation. Acetylcholine-mediated AF is facilitated by isoproterenol, which decreases the threshold of acetylcholine concentration for AF induction and increases AF duration [30]. Similarly, increases in left atrial pressure and atrial dilatation decrease the conduction velocity and increase the degree of spatial heterogeneities in conduction, which facilitates reentry and AF [31]. Both phenomena, along with vagal activation may generate an optimal substrate to initiate and sustain AF. Additionally, in the presence of hypoxia it might be expected a significant role of the ATP-sensitive K^+ current (I_{K-ATP}). However, its role seems to be much less prominent and probably overcome by the vagal-mediated activity [28].

Inflammation may facilitate AF in patients with atrial substrate suitable to develop the arrhythmia. It is also possible a direct effect of inflammatory markers on ionic channels and signaling pathways involved in the development of atrial fibrosis, both leading to AF [32]. Interestingly, as inflammatory cytokines rise the risk of AF concomitantly increases [33]. Intermittent hypoxia and hypercapnia in animal models result in systemic inflammation and increases in interleukin-6 (IL-6) [34]. The mechanism by which IL-6 may be produced in hypoxic conditions is the upregulation

of transcription factors NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and NF-IL6 (nuclear factor for IL-6 expression) [35]. In addition, increases in IL-6 precede increases in C-reactive protein (CRP), which is an inflammatory mediator involved in releasing new proinflammatory cytokines. Patients with OSA show markedly elevated monocyte and neutrophil NF- κ B activity [36]. Therefore, a proinflammatory state may lead to higher susceptibility to AF in OSA patients. Moreover, inflammation is common in OSA patients, including elevated levels of proinflammatory cytokines. Tumor necrosis factor- α (TNF- α) and IL-6 levels are elevated in OSA independent of obesity [37, 38]. However, the initial trigger driving the elevation of proinflammatory cytokines in OSA patients has not been completely elucidated. Some evidence supports the role of both sides of the autonomic nervous system and hypoxia as the main initiation mechanisms [39].

Some of the mechanisms involved in tachyarrhythmias have been also associated with bradyarrhythmias or asystole in patients with severe OSA. In fact, bradycardia, significant pauses (>3 s) and some degree of conduction block are highly prevalent in OSA patients [40]. The occurrence and degree of bradycardia during apnea depends on the degree of hypoxemia resulting from these apneas. Furthermore, increased vagal efferent activity appears to cause the bradycardia, which can be prevented by intravenous atropine [41]. Paroxysmal parasympathetic discharges are more pronounced during rapid eye movement (REM) sleep, which even in healthy young subjects have been associated with marked bradycardia and prolonged asystolic pauses [42]. In patients with OSA marked bradycardia may occur particularly in REM state, during which longer breathing pauses and greater degrees of oxyhemoglobin desaturation occur. In addition, in OSA there is lack of normal lung expansion during ventilation, which prevents attenuation of parasympathetic discharges by vagolytic properties of normal lung expansion [43]. The influence of parasympathetic tone is further supported by clinical electrophysiological studies revealing no evidence for advanced sinus node disease or atrioventricular conduction system dysfunction, which suggest that prolonged ventricular asystole during OSA is not due to fixed or anatomic disease of the sinus node or the atrioventricular conduction system [44]. Animal models aimed at studying AF in OSA have also shown slowing of the heart rate concurrent with increased blood pressure after the initiation of apnea [25, 28]. The effects are compatible with simultaneous increases in cardiac parasympathetic and vasoconstricting sympathetic tone, similar to the diving reflex seen in mammals, during which the body responds to apnea by increasing sympathetic tone to the peripheral vasculature and parasympathetic tone to the heart [45].

3. Clinical Significance of Atrial Arrhythmias in OSA Patients

In the early 80's a potential relationship between OSA and AF emerged from an observational, uncontrolled study by Guilleminault et al., in which the use of 24-hour holter

electrocardiography identified a prevalence of nocturnal paroxysms of AF of $\approx 3\%$ in OSA patients compared with the general population prevalence of 0.4 to 1% [46]. The same study reported sinus arrest lasting for more than 2.5 seconds and second-degree atrioventricular conduction block in 10% and 7% of OSA patients, respectively.

In a large cohort of 3542 patients who underwent their first diagnostic polysomnogram study and further average follows up of 4.7 years, obesity and OSA were independent risk factors for incident AF in individuals <65 years of age [47]. Moreover, the magnitude of nocturnal oxygen desaturation is consistently present in several studies as independently predictive of AF [47–49]. The latter provides further support to hypoxemia-related pathophysiological changes in AF onset.

OSA and AF have been linked in different clinical settings. Thus, an apnea-hypopnea index (AHI) ≥ 5 was associated with significant higher risk of postcoronary artery bypass surgery AF compared with lower values of AHI [49]. Recurrence of AF was also associated with untreated OSA in a prospective cohort of patients who underwent electrical cardioversion and one-year follow up [48]. More recently, data from several observational studies have supported the assertion that OSA patients diagnosed using polysomnography have significantly greater AF recurrence rates after pulmonary vein isolation compared with controls [50]. Such a higher risk of recurrences might be explained by significant differences in atrial remodeling compared with patients who underwent catheter ablation of AF and an AHI ≤ 15 . In fact, OSA is associated with significant larger atrial enlargement, lower atrial voltage, and more site-specific and widespread conduction abnormalities [51].

OSA is also an independent risk factor for stroke. Therefore it would be particularly relevant to determine a potential increased risk of stroke in AF patients with OSA. Although such data is not available to date, some clues indicate that OSA may have a role in stroke risk stratification scores in patients with AF. Thus, OSA is strongly associated with AF and most of the relative risks included in current stroke risk stratification scores are very similar between AF and OSA patients [52, 53]. In addition, OSA is associated with other risk factors in AF such as hypertension and diabetes mellitus [54].

Bradyarrhythmia and sinus pauses are commonly described in patients with OSA. However, there is a huge variability between trials, which show incidences ranging from 5% to 50% [6, 40, 46]. Even no differences in conduction delay disturbances between severe sleep-disordered breathing and controls have been reported using retrospective ECG data recorded during the sleep period [55]. Noncomparable study designs, methods, and populations may explain such differences. The large intraindividual variability reported by Simantirakis et al. in a cohort of patients with moderate to severe OSA who underwent continuous monitoring by implantable loop recorder [40], demonstrates the incapability of 24-hour and 48-hour holter monitoring to accurately determine the incidence of atrial arrhythmias. Therefore, assuming that continuous ECG monitoring is the most reliable tool to determine the

incidence of cardiac arrhythmias, approximately half of OSA patients evidence severe cardiac rhythm disturbances [40]. Moreover, the frequency and severity of apnea-related nocturnal bradyarrhythmias correlate with body mass index, AHI, and desaturation level during the sleep study [6, 40, 56].

Other ECG parameters such as QT interval are affected by the severity of the sleep apnea. Thus, QT corrected interval is increased in patients with moderate to severe OSA [57]. Moreover, QT corrected interval dispersion, defined as the difference between the maximum and minimum QT intervals, shows a strong positive correlation with the AHI [58]. Nocturnal prolonged cycle lengths can facilitate the occurrence of early afterdepolarizations and ventricular arrhythmias including torsades de pointes. Both increased QT interval and QT corrected interval dispersion are of interest in OSA individuals particularly sensitive to nocturnal heart rate pauses and QT prolongation such as patients treated with class III antiarrhythmic agents or with diuretics, along with subsets of patients with the long QT syndrome. Although several factors are involved, serious and potentially fatal arrhythmias may occur during sleep in patients with OSA, which is especially relevant between 10 p.m. and 6 a.m [59] (see Table 1 with supplementary information about risk of atrial arrhythmias in OSA).

4. Clinical Implications of Appropriate Treatment in OSA Patients with Atrial Arrhythmias

From the foregoing, we have discussed and provided substantial scientific support about the mechanisms and clinical impact of atrial arrhythmias in OSA patients. However, to date it is still difficult to determine the exact role of OSA treatment in preventing atrial arrhythmias. Current clinical consensus recommends that OSA should be treated with continuous positive airway pressure (CPAP) for ventilatory support as well as a tool for secondary prevention of cardiac problems [60]. It is not clear either whether other modes of ventilatory support such as bilevel pressure support (BPAP) offer any advantages over the conventional CPAP. Nowadays, BPAP should be reserved for patients with ventilatory failure [60].

Direct evidence of long-lasting apneic events (≈ 48 s) preceding AF onset has been rarely reported [9]. However, it suggests a causal association between OSA and AF. Furthermore, a period without apneas leads to spontaneous resumption to sinus rhythm. Appropriate CPAP therapy in OSA patients with AF who underwent electrical cardioversion significantly reduced AF recurrences after 12-month followup. AF recurred in only 42% of OSA patients effectively treated with CPAP, compared to 82% in untreated patients. Interestingly, recurrence rates were also significantly lower than in randomly selected controls without previous history of polysomnography, which suggests the presence of undiagnosed OSA among controls [48]. Recently, a large series by Abe et al. has shown that treatment with CPAP therapy significantly prevents OSA-associated paroxysmal AF in patients with moderate to severe nocturnal apneas

TABLE 1: Risk of atrial arrhythmias in obstructive sleep apnea.

Author, year	Design	Study population	Diagnostic method	N of patients	Cardiac monitoring	Results
Guilleminault et al., 1983 [46]	Uncontrolled	Severe OSA	PSG	400	24 h holter ECG	Nocturnal paroxysms of AF in $\approx 3\%$ of OSA patients Sinus arrest and AV block in 10% and 7% of OSA patients
Gami et al., 2007 [47]	Observational retrospective	Adults underwent a 1st PSG study. No AF at baseline	PSG	3542	N/A. Medical index diagnostic codes for AF	Obesity and OSA were independent risk factors for incident AF
Moore et al., 1996 [49]	Observational prospective	Patients underwent CABG surgery	PSG	121	Prospective monitoring until discharge	AHI ≥ 5 was associated with significant higher risk of postsurgical AF
Ng et al., 2011 [50]	Meta-analysis (observational studies)	Patients underwent PVI	PSG/Berlin questionnaire	3995	24/48 h holter ECG Event monitor/recorder Telephone follow-up ECG	OSA led to greater AF recurrence rates after PVI
Simantirakis et al., 2004 [40]	Observational prospective	Moderate-severe OSA	PSG	23	Implantable loop recorder	Cardiac pauses >3 s and bradycardic episodes <40 bpm in 47% of patients
Becker, 1998 [6]	Observational prospective	Unselected OSA	PSG	239	24 h holter ECG	2nd- and 3rd-degree AV block and/or sinus arrest in $\approx 7.5\%$ of OSA patients
Hoffstein and Mateika, 1994 [56]	Observational prospective	Patients underwent PSG study	PSG	458	Single lead ECG during PSG	58% prevalence of arrhythmias in OSA patients

AF: atrial fibrillation; AHI: apnea/hypopnea index; AV block: atrioventricular block; CABG: coronary artery bypass graft; OSA: obstructive sleep apnea; PSG: polysomnography; PVI: pulmonary vein isolation.

[61]. Similar to previous series and considering the above-mentioned limitation of limited electrocardiographic recording period during polysomnography [46], CPAP therapy significantly eliminates sinus bradycardia and sinus pauses. Only a trend to significant differences before and after CPAP therapy was also present in episodes of second- and third-degree atrioventricular block [61]. The latter may be explained by the limited monitoring period and very low rate of second- and third-degree atrioventricular block, which precludes reaching statistical significance.

Untreated OSA patients have higher recurrence rates after catheter ablation of AF. Such higher recurrence rates are also associated with the presence of more prevalent nonpulmonary veins triggers [62]. More recently Naruse et al. have suggested that an AHI of more than 10 has predictive value of AF recurrences after AF ablation. Moreover, CPAP therapy reduces the risk of recurrent AF after pulmonary vein isolation in patients with an AHI >5 [63]. AF recurrences were also reduced in the followup of patients with atrial flutter who underwent radiofrequency ablation of cavotricuspid isthmus (CTI) and proper CPAP therapy [64]. However, CPAP was only protective from AF recurrences when AF was not present prior to CTI ablation.

The exact mechanisms for preventing AF recurrences by CPAP therapy are not understood. Beyond preventing upper airway obstruction, correcting hypoxemia, and decreasing

the AHI, CPAP therapy seems to attenuate oxidative stress and systemic inflammation [65], which has been associated with both incident AF and AF recurrences after catheter ablation [66, 67].

The effects of CPAP therapy have been also studied in patients with OSA and bradyarrhythmia. Cornerstone series by Guilleminault et al. in the early 80's initially suggested that preventing upper airway obstruction by tracheostomy completely abolished conduction disturbances at 6 months of followup [46]. Case reports have also documented complete reversion of second-degree atrioventricular block after initiation of CPAP treatment [68]. During polysomnography the vast majority of the apnea-associated bradyarrhythmias occur during rapid eye movement sleep and significant desaturation of at least 4%. Both CPAP and BPAP drastically decrease the AHI and bradyarrhythmias [69]. More accurate followup using implantable loop recorders shows that the initiation of CPAP therapy tends to reduce the total number of the recorded episodes in the short term while in the long term bradycardia episodes are completely abolished [40]. CPAP therapy also has the capability to decrease the QT corrected interval dispersion present at baseline in patients with moderate to severe OSA [58]. The latter might have implications in preventing bradycardia-related early afterdepolarizations and ventricular arrhythmias leading to nocturnal sudden death (see Table 2 with supplementary information about effects

TABLE 2: Effects of CPAP therapy on atrial arrhythmia outcomes in OSA patients.

Author, year	Design	Study population	Diagnostic method	N of patients	Cardiac monitoring	Results
Kanagala et al., 2003 [48]	Observational prospective	Patients underwent AF/AFL DC shock	PSG	121	Hospital records Phone interviews ECG Medical visits	AF recurrences in 42% of OSA treated with CPAP AF recurrences in 82% of untreated patients
Abe et al., 2010 [61]	Nonrandomized prospective	Adults underwent PSG study	PSG	1456	ECG monitoring during PSG	CPAP prevented AF, sinus bradycardia/pauses in patients with moderate to severe OSA
Naruse et al., 2013 [63]	Nonrandomized prospective	Patients underwent PVI isolation	PSG	153	12-lead ECG 24 h holter ECG Portable ECG monitoring	Untreated OSA showed higher recurrence of AF after ablation
Koehler et al., 1998 [69]	Nonrandomized prospective	OSA patients with bradyarrhythmia	PSG	16	ECG monitoring during PSG	CPAP and BPAP drastically decreased bradyarrhythmias
Simantirakis et al., 2004 [40]	Observational prospective	Moderate-severe OSA	PSG	23	Implantable loop recorder	Long-term CPAP therapy completely abolished bradycardia episodes

AF: atrial fibrillation; AFL: atrial flutter; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnea; PSG: polysomnography; PVI: pulmonary vein isolation.

of CPAP therapy on atrial arrhythmia outcomes in OSA patients).

However, one important limitation of CPAP therapy is the poor long-term acceptance of treatment. Approximately 40% of patients are no longer compliant with the treatment after 3 years [70]. However, it seems that patients with the most severe sleep apnea are more likely to be compliant. The most common reason for discontinuing is intolerance of the mask [71]. Moreover, mask leak is a major independent predictor of CPAP compliance; therefore reducing mask leak predicts good compliance with CPAP therapy [72].

Finally, based on the benefits of CPAP therapy and such a frequent undiagnosed disorder in the general population, screening for OSA in patients with both AF and atrial flutter appears to be a reasonable clinical strategy if either a clinical or catheter-based rhythm control strategy is pursued. It seems also reasonable to identify patients with apnea-related bradyarrhythmias, since appropriate treatment may completely abolish its presence.

5. Conclusions and Future Directions

Atrial arrhythmias are highly prevalent in patients with moderate to severe obstructive sleep apnea, which has been identified as independent risk factor for both bradyarrhythmias and tachyarrhythmias. Hypoxia, hypercapnia, autonomic dysfunction, acute atrial stretch, negative intrathoracic pressure, and inflammation are some of the mechanisms leading to arrhythmia. However, complete understanding of such mechanisms is still ongoing and further research based on animal models is needed. CPAP therapy has demonstrated significant improvement in preventing and even abolishing atrial arrhythmias. However, it is necessary to improve and develop alternatives to conventional CPAP, which help to

prevent current high rates of treatment discontinuation in the long-term.

References

- [1] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, "The occurrence of sleep-disordered breathing among middle-aged adults," *The New England Journal of Medicine*, vol. 328, no. 17, pp. 1230–1235, 1993.
- [2] G. Parati, C. Lombardi, J. Hedner et al. et al., "Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea," *Journal of Hypertension*, vol. 30, no. 4, pp. 633–646, 2012.
- [3] J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. N. Agusti, "Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study," *The Lancet*, vol. 365, no. 9464, pp. 1046–1053, 2005.
- [4] P. Lavie, L. Lavie, and P. Herer, "All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age," *European Respiratory Journal*, vol. 25, no. 3, pp. 514–520, 2005.
- [5] A. S. Gami, G. Pressman, S. M. Caples et al., "Association of atrial fibrillation and obstructive sleep apnea," *Circulation*, vol. 110, no. 4, pp. 364–367, 2004.
- [6] H. F. Becker, "Heart block in patients with sleep apnoea," *Thorax*, vol. 53, no. 3, pp. S29–S32, 1998.
- [7] R. Tkacova, F. Rankin, F. S. Fitzgerald, J. S. Floras, and T. D. Bradley, "Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure," *Circulation*, vol. 98, no. 21, pp. 2269–2275, 1998.

- [8] F. Roche, A. N. T. Xuong, I. Court-Fortune et al., "Relationship among the severity of sleep apnea syndrome, cardiac arrhythmias, and autonomic imbalance," *Pacing and Clinical Electrophysiology*, vol. 26, no. 3, pp. 669–677, 2003.
- [9] R. Schulz, H. J. Eisele, and W. Seeger, "Nocturnal atrial fibrillation in a patient with obstructive sleep apnoea," *Thorax*, vol. 60, no. 2, article 174, 2005.
- [10] R. I. Cargill, D. G. Kiely, and B. J. Lipworth, "Adverse effects of hypoxaemia on diastolic filling in humans," *Clinical Science*, vol. 89, no. 2, pp. 165–169, 1995.
- [11] S. Q. Yang, L. L. Han, X. L. Dong et al., "Mal-effects of obstructive sleep apnea on the heart," *Sleep Breath*, vol. 16, no. 3, pp. 717–722, 2012.
- [12] H. Kraiczi, K. Caidahl, A. Samuelsson, Y. Peker, and J. Hedner, "Impairment of vascular endothelial function and left ventricular filling: association with the severity of apnea-induced hypoxemia during sleep," *Chest*, vol. 119, no. 4, pp. 1085–1091, 2001.
- [13] J. Hedner, H. Ejnell, and K. Caidahl, "Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea," *Journal of Hypertension*, vol. 8, no. 10, pp. 941–946, 1990.
- [14] M. A. Arias, F. García-Río, A. Alonso-Fernández, O. Mediano, I. Martínez, and J. Villamor, "Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men," *Circulation*, vol. 112, no. 3, pp. 375–383, 2005.
- [15] A. M. Park and Y. J. Suzuki, "Effects of intermittent hypoxia on oxidative stress-induced myocardial damage in mice," *Journal of Applied Physiology*, vol. 102, no. 5, pp. 1806–1814, 2007.
- [16] T. Hayashi, C. Yamashita, C. Matsumoto et al., "Role of gp91phox-containing NADPH oxidase in left ventricular remodeling induced by intermittent hypoxic stress," *American Journal of Physiology*, vol. 294, no. 5, pp. H2197–H2203, 2008.
- [17] R. Farré, J. M. Montserrat, and D. Navajas, "Morbidity due to obstructive sleep apnea: insights from animal models," *Current Opinion in Pulmonary Medicine*, vol. 14, no. 6, pp. 530–536, 2008.
- [18] Y. K. Iwasaki, Y. Shi, B. Benito et al., "Determinants of atrial fibrillation in an animal model of obesity and acute obstructive sleep apnea," *Heart Rhythm*, vol. 9, no. 9, pp. 1409.e1–1416.e1, 2012.
- [19] F. Ravelli and M. Allesie, "Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart," *Circulation*, vol. 96, no. 5, pp. 1686–1695, 1997.
- [20] D. Filgueiras-Rama, R. P. Martins, S. Mironov et al. et al., "Chloroquine terminates stretch-induced atrial fibrillation more effectively than flecainide in the sheep heart," *Circulation*, vol. 5, no. 3, pp. 561–570, 2012.
- [21] P. C. Krause, H. Inoue, and D. P. Zipes, "Electrophysiologic alterations produced by hypoxia in the canine heart," *American Heart Journal*, vol. 117, no. 3, pp. 550–561, 1989.
- [22] W. J. E. P. Lammers, C. Kirchhof, F. I. M. Bonke, and M. A. Allesie, "Vulnerability of rabbit atrium to reentry by hypoxia. Role of inhomogeneity in conduction and wavelength," *American Journal of Physiology*, vol. 262, no. 1, pp. H47–H55, 1992.
- [23] I. H. Stevenson, K. C. Roberts-Thomson, P. M. Kistler et al., "Atrial electrophysiology is altered by acute hypercapnia but not hypoxemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea," *Heart Rhythm*, vol. 7, no. 9, pp. 1263–1270, 2010.
- [24] A. Puodziukynas, T. Kazakevicius, R. Vaitkevicius et al. et al., "Radiofrequency catheter ablation of pulmonary vein roots results in axonal degeneration of distal epicardial nerves," *Autonomic Neuroscience*, vol. 167, pp. 61–65, 2012.
- [25] M. Ghias, B. J. Scherlag, Z. Lu et al., "The role of ganglionated plexi in Apnea-related atrial fibrillation," *Journal of the American College of Cardiology*, vol. 54, no. 22, pp. 2075–2083, 2009.
- [26] G. K. Moe, W. C. Rheinboldt, and J. A. Abildskov, "A computer model of atrial fibrillation," *American Heart Journal*, vol. 67, no. 2, pp. 200–220, 1964.
- [27] S. Oh, Y. Zhang, S. Bibeviski, N. F. Marrouche, A. Natale, and T. N. Mazgalev, "Vagal denervation and atrial fibrillation inducibility: epicardial fat pad ablation does not have long-term effects," *Heart Rhythm*, vol. 3, no. 6, pp. 701–708, 2006.
- [28] D. Linz, U. Schotten, H. R. Neuberger, M. Böhm, and K. Wirth, "Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation," *Heart Rhythm*, no. 9, pp. 1436–1443, 2011.
- [29] D. Linz, F. Mahfoud, U. Schotten et al., "Renal sympathetic denervation suppresses postapneic blood pressure rises and atrial fibrillation in a model for sleep apnea," *Hypertension*, vol. 60, no. 1, pp. 172–178, 2012.
- [30] O. F. Sharifov, V. V. Fedorov, G. G. Beloshapko, A. V. Glukhov, A. V. Yushmanova, and L. V. Rosenshtraukh, "Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs," *Journal of the American College of Cardiology*, vol. 43, no. 3, pp. 483–490, 2004.
- [31] S. C. M. Eijsbouts, R. P. M. Houben, Y. Blaauw, U. Schotten, and M. A. Allesie, "Synergistic action of atrial dilation and sodium channel blockade on conduction in rabbit atria," *Journal of Cardiovascular Electrophysiology*, vol. 15, no. 12, pp. 1453–1461, 2004.
- [32] R. Ramos-Mondragón, A. V. Vega, and G. Avila, "Long-term modulation of Na⁺ and K⁺ channels by TGF- β 1 in neonatal rat cardiac myocytes," *Pflugers Archiv European Journal of Physiology*, vol. 461, no. 2, pp. 235–247, 2011.
- [33] B. Richter, M. Gwechenberger, A. Socas et al., "Markers of oxidative stress after ablation of atrial fibrillation are associated with inflammation, delivered radiofrequency energy and early recurrence of atrial fibrillation," *Clinical Research in Cardiology*, vol. 101, no. 3, pp. 217–225, 2012.
- [34] C. S. Tam, M. Wong, K. Tam, L. Aouad, and K. A. Waters, "The effect of acute intermittent hypercapnic hypoxia treatment on IL-6, TNF- α , and CRP levels in piglets," *Sleep*, vol. 30, no. 6, pp. 723–727, 2007.
- [35] H. Matsui, Y. Ihara, Y. Fujio et al., "Induction of interleukin (IL)-6 by hypoxia is mediated by nuclear factor (NF)- κ B and NF-IL6 in cardiac myocytes," *Cardiovascular Research*, vol. 42, no. 1, pp. 104–112, 1999.
- [36] A. K. Htoo, H. Greenberg, S. Tongia et al., "Activation of nuclear factor κ B in obstructive sleep apnea: a pathway leading to systemic inflammation," *Sleep and Breathing*, vol. 10, no. 1, pp. 43–50, 2006.
- [37] M. A. Arias, F. García-Río, A. Alonso-Fernández et al., "CPAP decreases plasma levels of soluble tumour necrosis factor- α receptor 1 in obstructive sleep apnoea," *European Respiratory Journal*, vol. 32, no. 4, pp. 1009–1015, 2008.
- [38] A. N. Vgontzas, D. A. Papanicolaou, E. O. Bixler, A. Kales, K. Tyson, and G. P. Chrousos, "Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 82, no. 5, pp. 1313–1316, 1997.

- [39] P. J. Mills and J. E. Dimsdale, "Sleep apnea: a model for studying cytokines, sleep, and sleep disruption," *Brain, Behavior, and Immunity*, vol. 18, no. 4, pp. 298–303, 2004.
- [40] E. N. Simantirakis, S. I. Schiza, M. E. Marketou et al., "Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder," *European Heart Journal*, vol. 25, no. 12, pp. 1070–1076, 2004.
- [41] C. Zwillich, T. Devlin, and D. White, "Bradycardia during sleep apnea. Characteristics and mechanism," *Journal of Clinical Investigation*, vol. 69, no. 6, pp. 1286–1292, 1982.
- [42] C. Guilleminault, P. Pool, J. Motta, and A. M. Gillis, "Sinus arrest during REM sleep in young adults," *The New England Journal of Medicine*, vol. 311, no. 16, pp. 1006–1010, 1984.
- [43] V. K. Somers, M. E. Dyken, and J. L. Skinner, "Autonomic and hemodynamic responses and interactions during the Mueller maneuver in humans," *Journal of the Autonomic Nervous System*, vol. 44, no. 2-3, pp. 253–259, 1993.
- [44] W. Grimm, J. Hoffmann, V. Menz et al., "Electrophysiologic evaluation of sinus node function and atrioventricular conduction in patients with prolonged ventricular asystole during obstructive sleep apnea," *American Journal of Cardiology*, vol. 77, no. 15, pp. 1310–1314, 1996.
- [45] J. Fagius and G. Sundlof, "The diving response in man: effects on sympathetic activity in muscle and skin nerve fascicles," *Journal of Physiology*, vol. 377, pp. 429–443, 1986.
- [46] C. Guilleminault, S. J. Connolly, and R. A. Winkle, "Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome," *American Journal of Cardiology*, vol. 52, no. 5, pp. 490–494, 1983.
- [47] A. S. Gami, D. O. Hodge, R. M. Herges et al., "Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation," *Journal of the American College of Cardiology*, vol. 49, no. 5, pp. 565–571, 2007.
- [48] R. Kanagala, N. S. Murali, P. A. Friedman et al., "Obstructive sleep apnea and the recurrence of atrial fibrillation," *Circulation*, vol. 107, no. 20, pp. 2589–2594, 2003.
- [49] T. Mooe, S. Gullsbj, T. Rabben, and P. Eriksson, "Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery," *Coronary Artery Disease*, vol. 7, no. 6, pp. 475–478, 1996.
- [50] C. Y. Ng, T. Liu, M. Shehata, S. Stevens, S. S. Chugh, and X. Wang, "Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation," *American Journal of Cardiology*, vol. 108, no. 1, pp. 47–51, 2011.
- [51] H. Dimitri, M. Ng, A. G. Brooks et al. et al., "Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation," *Heart Rhythm*, vol. 9, no. 3, pp. 321–327, 2012.
- [52] R. G. Hart, L. A. Pearce, G. W. Albers et al., "Independent predictors of stroke in patients with atrial fibrillation: a systematic review," *Neurology*, vol. 69, no. 6, pp. 546–554, 2007.
- [53] F. Valham, T. Mooe, T. Rabben, H. Stenlund, U. Wiklund, and K. A. Franklin, "Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10-year follow-up," *Circulation*, vol. 118, no. 9, pp. 955–960, 2008.
- [54] W. T. McNicholas and M. R. Bonsignore, "Sleep apnoea as an independent risk for cardiovascular disease: current evidence, basic mechanisms and research priorities," *European Respiratory Journal*, vol. 29, no. 1, pp. 156–178, 2007.
- [55] R. Mehra, E. J. Benjamin, E. Shahar et al., "Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study," *American Journal of Respiratory and Critical Care Medicine*, vol. 173, no. 8, pp. 910–916, 2006.
- [56] V. Hoffstein and S. Mateika, "Cardiac arrhythmias, snoring, and sleep apnea," *Chest*, vol. 106, no. 2, pp. 466–471, 1994.
- [57] D. Cicek, H. Lakadamyali, S. Gokay, I. Sapmaz, and H. Muderrisoglu, "Effect of obstructive sleep apnea on heart rate, heart rate recovery and QTc and P-wave dispersion in newly diagnosed untreated patients," *American Journal of the Medical Sciences*, vol. 344, no. 3, pp. 180–185, 2012.
- [58] D. Dursunoglu and N. Dursunoglu, "Effect of CPAP on QT interval dispersion in obstructive sleep apnea patients without hypertension," *Sleep Medicine*, vol. 8, no. 5, pp. 478–483, 2007.
- [59] A. S. Gami, D. E. Howard, E. J. Olson, and V. K. Somers, "Day-night pattern of sudden death in obstructive sleep apnea," *The New England Journal of Medicine*, vol. 352, no. 12, pp. 1206–1214, 2005.
- [60] J. Fleetham, N. Ayas, D. Bradley et al., "Canadian Thoracic Society 2011 guideline update: diagnosis and treatment of sleep disordered breathing," *Canadian Respiratory Journal*, vol. 18, no. 1, pp. 25–47, 2011.
- [61] H. Abe, M. Takahashi, H. Yaegashi et al., "Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients," *Heart and Vessels*, vol. 25, no. 1, pp. 63–69, 2010.
- [62] D. Patel, P. Mohanty, L. Di Biase et al., "Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure," *Circulation*, vol. 3, no. 5, pp. 445–451, 2010.
- [63] Y. Naruse, H. Tada, M. Satoh et al. et al., "Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy," *Heart Rhythm*, vol. 10, no. 3, pp. 331–337, 2013.
- [64] V. Bazan, N. Grau, E. Valles et al. et al., "Obstructive sleep apnea in patients with typical atrial flutter: prevalence and impact on arrhythmia control outcome," *Chest*. In press.
- [65] M. Murri, J. Alcázar-Ramírez, L. Garrido-Sánchez et al., "Oxidative stress and metabolic changes after continuous positive airway pressure treatment according to previous metabolic disorders in sleep apnea-hypopnea syndrome patients," *Translational Research*, vol. 154, no. 3, pp. 111–121, 2009.
- [66] K. Ishida, F. Kimura, M. Imamaki et al., "Relation of inflammatory cytokines to atrial fibrillation after off-pump coronary artery bypass grafting," *European Journal of Cardio-Thoracic Surgery*, vol. 29, no. 4, pp. 501–505, 2006.
- [67] S. Deftereos, G. Giannopoulos, C. Kossyvakis et al. et al., "Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study," *Journal of the American College of Cardiology*, vol. 60, no. 18, pp. 1790–1796, 2012.
- [68] R. Dziewas, T. Imai, R. Dittrich et al., "Night-time bradyarrhythmia in a patient with mild obstructive sleep apnea syndrome is reversed with CPAP treatment," *Journal of Clinical Sleep Medicine*, vol. 2, no. 4, pp. 454–457, 2006.
- [69] U. Koehler, E. Fus, W. Grimm et al., "Heart block in patients with obstructive sleep apnoea: pathogenetic factors and effects of treatment," *European Respiratory Journal*, vol. 11, no. 2, pp. 434–439, 1998.
- [70] A. Abdelghani, S. Slama, A. Hayouni et al., "Acceptance and long-term compliance to continuous positive airway pressure in obstructive sleep apnea. A prospective study on 72 patients treated between 2004 and 2007," *Revue de Pneumologie Clinique*, vol. 65, no. 3, pp. 147–152, 2009.

- [71] I. Rolfe, L. G. Olson, and N. A. Saunders, "Long-term acceptance of continuous positive airway pressure in obstructive sleep apnea," *American Review of Respiratory Disease*, vol. 144, no. 5, pp. 1130–1133, 1991.
- [72] Z. Sopkova, Z. Dorkova, and R. Tkacova, "Predictors of compliance with continuous positive airway pressure treatment in patients with obstructive sleep apnea and metabolic syndrome," *Wiener Klinische Wochenschrift*, vol. 121, no. 11-12, pp. 398–404, 2009.

Review Article

The Relationship between Obstructive Sleep Apnea and Atrial Fibrillation: A Complex Interplay

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In recent years, growing evidence suggests an association between obstructive sleep apnea (OSA), a common sleep breathing disorder which is increasing in prevalence as the obesity epidemic surges, and atrial fibrillation (AF), the most common cardiac arrhythmia. AF is a costly public health problem increasing a patient's risk of stroke, heart failure, and all-cause mortality. It remains unclear whether the association is based on mutual risk factors, such as obesity and hypertension, or whether OSA is an independent risk factor and causative in nature. This paper explores the pathophysiology of OSA which may predispose to AF, clinical implications of stroke risk in this cohort who display overlapping disease processes, and targeted treatment strategies such as continuous positive airway pressure and AF ablation.

1. Introduction

Obstructive sleep apnea, a common breathing disorder, is characterized by recurrent episodes of airway collapse resulting in occlusion of airflow during sleep. These episodes of hypopnea and apnea can manifest as transient or prolonged hypoxemia, sleep arousals, and sympathetic nervous system activation, resulting in symptoms such as snoring, headaches, daytime sleepiness, and impaired alertness [1]. Approximately 3–7% percent of the adult population in the United States is affected by OSA, and that number is likely an underestimate as it goes undiagnosed in many cases [2–4]. Another condition which is also prevalent as well as undiagnosed in many circumstances is atrial fibrillation (AF). It is predicted that by 2050, more than 10 million Americans will have AF and possibly up to 16 million if the increase in incidence continues on the same trajectory [5]. The question has been posed, on more than one occasion, how these two common entities of OSA and AF impact one another. Although the relationship between sleep-disordered breathing and arrhythmias was proposed a few decades ago [6], only recently has it been recognized that OSA seems to be correlated with AF (see Table 1) [7–15].

The studies in Table 1 suggest the increased risk of AF in OSA patients, but the quality of the data is limited [7–15]. Known risk factors for AF include age, male gender, smoking, obesity, hypertension, diabetes mellitus, myocardial infarction, congestive heart failure, and cardiac surgery [15]. Of the six studies evaluated in Table 1, only two adjusted for male gender [8, 11], one for hypertension [9], and none controlled for diabetes mellitus, or heart failure [8, 16]. In the Sleep Heart Health Study, Mehra et al. demonstrated that the risk of AF among patients with OSA is about four times than of those with no sleep-disordered breathing (adjusted OR 4.02; 95% CI 1.03–15.74) [8].

It is important to note that the MrOS Study and the Sleep Heart Health Study compared the incidence of nocturnal arrhythmias in subjects with and without sleep-disordered breathing, suggesting that sleep disordered breathing directly affects heart rhythm [8, 10]. Furthermore, Gami et al. showed that for patients with OSA under age 65, the hazard ratio of developing any type of AF over the course of approximately 5 years was 3.29 (95% CI 1.35–8.04) [11]. These studies suggest that OSA predisposes patients to develop AF, but it is not clear whether the relationship is independent of hypertension, diabetes mellitus, or other confounding factors. A study by

TABLE 1: Risk of AF in OSA patients.

Investigator	Number of patients	Methods of diagnosis for OSA	Control group	Risk factor adjustments	Results
Guilleminault et al. (1983) [6]	400	PSG	No	N/A	Cardiac arrhythmias observed in 48% of patients with OSA
Moore et al. (1996) [14]	121	PSG	Yes	Age.	Risk of AF after CABG in OSA patients, OR 2.8 (1.2–6.8)
Mehra et al. (2006) [8]	566	PSG	Yes	Age, gender, BMI, coronary heart disease.	Risk of AF in OSA patients, adjusted OR 4.02 (1.03–15.74)
Tanigawa et al. (2006) [9]	1763	Pulse oximeter during sleep	Yes	Age, BMI, alcohol intake, blood pressure, hypertension, and antihypertensives.	Risk of AF for severe OSA, adjusted OR 5.66 (1.75–18.34)
Gami et al. (2007) [11]	3542	PSG	Yes	Age, gender, coronary artery disease, BMI.	Incident AF in OSA for patients age <65, HR 3.29 (1.35–8.04)
Monahan et al. (2009) [10]	2816	PSG	Yes	Subjects serve as their own controls during event-free periods.	Risk of AF after a respiratory disturbance compared to normal breathing, OR 17.9 (2.2–144.2)
Mehra et al. (2009) [15]	2911	PSG	Yes	Age, race, BMI, HTN, DM, CAD, pacemaker, cholesterol.	Increasing OSA quartile associated with CVE ($P = 0.01$) but not AF.

PSG: polysomnogram; CABG: coronary artery bypass graft; BMI: body mass index; HTN: hypertension; DM: diabetes mellitus; CAD: cardiac disease; OR: odds ratio; HR: hazard ratio; CVE: complex ventricular ectopy.

Mehra et al. in 2009 (MrOS Study) demonstrated that AF was associated with central sleep apnea but not obstructive sleep apnea after adjusting for confounding factors [15]. A prospective randomized trial is needed to confirm the association between OSA and AF.

Conversely, it has been shown that patients with AF appear to be more likely to have OSA compared to the general population [7, 12, 13]. In a landmark study in 2004, Gami et al. showed that after adjusting for body mass index, neck circumference, hypertension, and diabetes mellitus, approximately half of patients with AF were likely to have OSA (adjusted OR 2.19, 95% CI 1.40–3.42, $P = 0.0006$) [7]. However, conflicting data does exist, as one study did not show any difference in the prevalence of OSA among patients with AF compared to gender-, age-, and cardiovascular morbidity-matched community controls [17].

The question remains whether the association of OSA and AF is based on mutual risk factors, such as obesity and hypertension, or whether OSA independently, directly, and definitively leads to AF. This paper will delineate the underlying pathophysiologic mechanisms that support the plausibility of this interplay. In addition, we will describe the clinical implications of stroke risk and discuss treatment strategies such as continuous positive airway pressure (CPAP) and AF ablation.

2. Methods

This is a comprehensive review based on a literature search of the Ovid Medline database (1946 to September 2012) and Cochrane Database of Systematic Reviews. The following searches were conducted: (1) “sleep apnea” or “obstructive sleep apnea” AND “atrial fibrillation” (2) “sleep apnea” AND “catheter ablation” (3) “sleep apnea” AND “pulmonary

vein isolation” (4) “CPAP” AND “atrial fibrillation” and (5) “obstructive sleep apnea” AND “stroke.” The paper intends to address the underlying pathophysiology of obstructive sleep apnea leading to atrial fibrillation. We will discuss the impact of OSA treatment on AF and the correlation between OSA and stroke.

3. Pathophysiology of Obstructive Sleep Apnea

The upper airspace in the pharyngeal region is a combination of muscles and soft tissue, differing from the cartilaginous trachea and bronchi in that the airspace can collapse [18]. Sleep naturally causes a loss of tone in the muscles surrounding the pharynx, reducing the pharyngeal airspace and increasing resistance to airflow [18]. Obesity is the main risk factor for obstructive sleep apnea, as the fat accumulates and narrows the lumen of the pharynx [19]. In individuals with narrowed and compliant airways at baseline, the reduction of muscle tone leads to occlusion of the pharynx, resulting in hypopneas, complete obstruction of airflow, hypoxia, and hypercapnia. Unsuccessful inspiratory efforts against an occluded airway lead to a precipitous drop in intrathoracic pressure with a subsequent increase in afterload [20], enhancement of venous return, leading to distention of the right ventricle and shifting of the interventricular septum. The combination of interventricular septal shift, impeding left ventricular filling, and an increased afterload leads to a decrease in left ventricular stroke volume and thus a temporary fall in cardiac output [19].

3.1. Sympathetic Activation. During apneic episodes, the sympathetic nervous system is activated by pulmonary stretch receptors normally quiescent during sleep [19]. Hypoxia and hypercapnia increase sympathetic nervous

system activation by stimulating peripheral and central chemoreceptors [21, 22]. The resulting sympathetic stimulation causes vasoconstriction and results in a significant increase in blood pressure [21]. Immediately after the apneic period resolves, there is a significant elevation in heart rate and blood pressure [19]. These surges can occur hundreds of times per night in someone with severe OSA, leading to large variability in heart rate and blood pressure. Sleep apnea has been strongly correlated with hypertension in several studies [23–26]. Nevertheless, more recent studies suggest that the relationship between OSA and hypertension may not be causal and may be confounded by obesity [27, 28]. Normotensive patients newly diagnosed with OSA have faster resting heart rates [29], increased blood pressure variability [30] and are predisposed to developing hypertension [31] and end-organ damage [32].

3.2. Systemic Vascular Responses and Inflammation. Inflammatory mediators such as cytokines and adhesion molecules appear to be increased in OSA [33, 34]. C-reactive protein (CRP), a marker of systemic inflammation, is also increased in OSA [35, 36]. Oxidative stress on neutrophils and monocytes results in higher levels of oxygen radicals in patients with OSA [37]. Patients with OSA have higher plasma CRP concentrations that increased corresponding to the severity of their apnea-hypopnea index score [35]. CRP and interleukin-6 (IL-6) levels were significantly higher in patients with OSA compared to obese control subjects (CRP $P < 0.001$, IL-6 $P < 0.05$) [36]. In turn, Yokoe et al. also showed that CPAP significantly alleviated the effect of OSA on CRP and IL-6 levels [36]. Treatment of OSA with CPAP downregulates the expression of adhesion molecules and decreases the formation of reactive oxygen species [34, 37].

4. Diagnosis of Obstructive Sleep Apnea

The gold standard of diagnosis is a polysomnographic study which records sleep and breathing in a sleep laboratory overnight. A hypopneic episode is defined to fit one of the following criteria: greater than 50% reduction in airflow or tidal volume for at least 10 seconds, moderate reduction in airflow (less than 50%) with arterial oxygen desaturation greater than 3%, or moderate reduction in airflow with electroencephalographic evidence of arousal from sleep [38]. Arousal from sleep is defined as transient awakening for less than 10 seconds [19]. The severity of OSA is measured by the apnea-hypopnea index (AHI), the frequency of apneas and hypopneas per hour of sleep. An apnea-hypopnea index ≥ 5 is considered mild, while AHI ≥ 15 is moderate-to-severe OSA [39, 40].

Albuquerque et al. recently showed that daytime sleepiness symptoms did not correlate with the presence of sleep-disordered breathing in patients with AF [41]. Patients may be asymptomatic and thus unaware of their sleep-disordered breathing, raising the question of not only how to manage these patients but also how to screen for them.

TABLE 2: Pathophysiologic mechanisms.

Mechanisms of AF development in obstructive sleep apnea
Negative intrathoracic pressure
Hypoxemia
Hypercapnia
Autonomic nervous system activation
Inflammation
Arterial stiffening
Hypertension
Left ventricular hypertrophy
Diastolic dysfunction
Interventricular septal wall thickening
Left atrial enlargement
Atrial electromechanical remodeling

4.1. Risk Factors. Risk factors for developing OSA include obesity, neck circumference, male gender, increasing age, alcohol use, smoking, menopausal status, and black race [38, 42]. Obesity is the most important risk factor, as approximately 70% of patients with OSA are obese [38]. As obesity is at epidemic proportions, the number of people affected by OSA is likely to increase accordingly. The relationship between OSA and AF is complicated by the fact that obesity is also an independent predictor of AF. Furthermore, in patients with OSA who are under 50 years of age, there has been evidence to show that they are more likely to suffer hypertension, AF, and all-cause mortality [11, 43, 44].

5. Pathophysiologic Mechanisms of Obstructive Sleep Apnea Influencing Atrial Fibrillation

Multiple pathophysiologic mechanisms have been proposed to explain the association between OSA and AF, and it is likely that the interplay among them, rather than one factor, predisposes OSA patients to AF (Table 2). Data suggests that OSA may induce cardiac remodeling [45–48], increase sympathetic activity [21, 49, 50], and cause systemic inflammation [33–36].

5.1. Structural and Functional. Recent studies have examined atrial remodeling of structural and electrical components in patients with OSA to account for predisposition to AF [45–48, 51–54]. Sudden negative intrathoracic pressures may lead to repetitive atrial stretch and gradually lead to left atrial enlargement [55]. As a result of left atrial enlargement, there may be remodeling at the pulmonary vein ostia, a site known to initiate and propagate AF [56]. Patients with severe OSA (AHI > 15) undergoing catheter ablation had significantly larger left atria indexed to body surface area compared to those patients those with an AHI < 15 ($P = 0.009$) [46], confirming the results found in other studies [55, 57]. Since an enlarged left atrium is a risk factor for AF [58], a plausible mechanism for OSA leading to a predisposition to AF is structural remodeling.

Severe OSA patients were also shown to have extensive areas of low voltage or electrical silence, and conduction abnormalities as indicated by prolonged P-wave durations, slower atrial conduction velocity and sinus node recovery times [46]. A study of Japanese males with OSA found that the atrial electromechanical activation time (EMAT) was significantly longer than control subjects [59]. Yagmur et al. showed that interatrial and intra-atrial electromechanical delay were significantly prolonged in patients with moderate-to-severe OSA compared to controls ($P < 0.0001$) [60]. These electrical abnormalities may underlie a predisposition of OSA patients to AF.

In addition to causing left atrial enlargement and atrial conduction abnormalities, OSA also appears to induce left ventricular hypertrophy (LVH). An observational study of 51 males with OSA showed that LVH and right ventricular hypertrophy were more prevalent in men with severe OSA compared to those with mild OSA [61]. All the patients with LVH had hypertension. Several studies have established that OSA is significantly associated with hypertension, especially in patients younger than 65 years [23–25, 43, 57, 62, 63]. However, there is conflicting data from the Sleep Heart Study that suggests this association was accounted for by obesity and not statistically significant after correcting for body mass index [28].

Drager et al. looked at arterial stiffness by measuring pulse wave velocity and heart structure in OSA patients with and without hypertension [57]. They demonstrated that patients with untreated OSA had increased left atrial diameter, septal wall thickness, left ventricular (LV) posterior wall thickness, LV mass index, and LVH, even controlling for cardiovascular risk factors [57]. These indicators showed additive effects of hypertension and OSA.

These studies support the concept that OSA leads to cardiac remodeling in order to compensate for the repeated stress of an occluded airway. On the contrary, other studies did not show any difference in LV mass between obese patients with and without OSA [52, 55, 64].

The Müller maneuver, occluded inspiration, can generate negative intrathoracic pressure of -60 to -80 mm Hg [65], to simulate OSA [66, 67]. Orban et al. showed that when healthy individuals performed the Müller maneuver without confounding hypoxia and comorbidities, there was a decrease in LV ejection fraction and left atrial volume [66]. Immediately after release of the maneuver, there was a compensatory increase in cardiac output above baseline. Koshino et al. showed that during the Müller maneuver ventricular longitudinal deformation, as measured by strain and strain rate, was significantly reduced [67]. These variations in left atrial size and cardiac output as well as impairment of ventricular mechanics may result in long-term compensation, potentially increasing the risk of AF and heart failure in OSA patients.

There are a number of animal models that further detail these structural changes. In a pig model, tracheal occlusions increased AF susceptibility [68]. A recent study evaluating AF inducibility in rats showed that the likelihood of AF induction in obese rats was greater than in lean rats (85.7% versus 27.8%, $P < 0.001$) [69]. Their animal model suggests that obesity

and OSA interrelate to promote AF by promoting left atrial dilation and LV dysfunction.

Studies have suggested that OSA is associated with diastolic dysfunction [55, 70, 71]. Fung et al. showed a correlation between the severity of OSA and the degree of left ventricular diastolic dysfunction in an uncontrolled study [71]. Kraiczki et al. showed that nocturnal oxygen desaturations were found to be associated with left ventricular diastolic dysfunction [70]. Otto et al. confirmed these findings, showing that 82% of patients with OSA had indicators of early diastolic dysfunction compared to 26% of obese control patients without OSA ($P = 0.001$) [55]. Cardiac structural and functional changes leading to reduced diastolic function may predispose OSA patients to AF.

5.2. Hypoxemia. Hypoxemia and hypercapnia affect sympathetic nerve activity, causing vasoconstriction and, as a result, hypertension [21] which, in turn, is a risk factor for AF. Studies suggest that the severity of OSA as measured by nocturnal oxygen desaturations correlates to the prevalence of AF [9, 11]. In a study of Japanese men, Tanigawa et al. looked at 3% oxygen desaturation indices to measure apneic events during sleep [9]. Patients with more desaturation events had a trend toward an increased risk of AF; the multivariate adjusted OR was 2.47 (95% CI 0.91–6.69) and 5.66 (95% CI 1.74–18.34), for mild and severe OSA, respectively ($P = 0.02$) [9]. In a retrospective cohort study, mean followup of 4.7 years, risk factors for AF in individuals ≤ 65 years included male gender (HR 2.66, 95% CI 1.33–5.30), age (HR 2.04, 95% CI 1.48–2.80), coronary artery disease (HR 2.66, 95% CI 1.46–4.83), body mass index (HR 1.07, 95% CI 1.05–1.10), and nocturnal oxygen saturation (HR 3.29, 95% CI 1.35–8.04) [11]. Of interest, the magnitude of nocturnal oxygen desaturation was a risk factor for AF, independent of a diagnosis of OSA. The study by Gami et al. was novel in that it demonstrated the degree of nocturnal desaturations predicts AF within approximately 5 years of diagnosis of OSA [11]. Their findings implicate hypoxemia as a potential important mediator of AF.

In a prospective study, patients with greater falls in nocturnal oxygen saturation had a higher recurrence rate of AF after cardioversion [72]. In the untreated OSA patients, the AF recurrence rate exceeded 80%, compared to 42% in the treated OSA group and 53% in the control patients [72]. The higher recurrence rate among controls compared to treated OSA patients suggests that some of the controls may have had undiagnosed OSA.

5.3. Autonomic Tone. Frequent episodes of desaturation can lead to sympathetic activation and contribute to cyclical increases in blood pressure. The pulmonary vein ostia are innervated by adrenergic and vagal nerves, which have been implicated in the development of AF and targeted by ablation [73]. Noda et al. showed that in patients with OSA, nocturnal plasma norepinephrine levels were correlated with the duration of oxygen desaturation [61].

Animal studies have been performed to attempt to elucidate the autonomic mechanisms that affect OSA and AF. Using a canine model, Ghias et al. demonstrated that they

were able to induce AF during acute apnea episodes, and significantly repress AF inducibility after either autonomic blockade or neural ablation of the right pulmonary artery ganglionic plexus [74].

Linz et al. showed that atrial effective refractive period (AERP) was shortened with applied negative tracheal pressure in a swine model, resulting in greater AF inducibility [68]. They further showed that negative tracheal pressure-induced AF inducibility was completely inhibited by atropine and bilateral vagotomy. Based on these results, they concluded that negative tracheal pressure-triggered AF was mediated by vagal activation alone because it was inhibited by atropine or vagotomy.

Their group also used a swine model to demonstrate that blocking early and late potassium currents, with an early activated potassium current blocker (AVE0118), amiodarone, and sotalol, did not affect the negative tracheal pressure-induced AERP shortening [75]. From this data, they concluded that it is difficult to inhibit arrhythmias caused by negative tracheal pressure (simulating OSA) with class III antiarrhythmic drugs. Nevertheless, they did find that an early and a late activated potassium current in combination could reduce negative tracheal pressure-induced AERP shortening and thus AF inducibility [75].

In a more recent animal study, Linz et al. revealed that renal denervation reduced AF inducibility during applied negative tracheal pressure. Postapneic hypertension was inhibited by renal denervation but not changed by atenolol [79]. Thus, they concluded that renal denervation had antiarrhythmic effects and reduced blood pressure elevations following obstructive apneic episodes.

The pathophysiologic mechanisms of cardiac remodeling, structural changes such as left atrial dilation and electrical remodeling, hypoxemia, and autonomic dysregulation have been implicated as predisposing factors in OSA patients to AF. Animal studies as well as human data are beginning to illustrate these mechanistic links.

6. Treatment of Atrial Fibrillation in Obstructive Sleep Apnea Patients

Continuous positive airway pressure is the treatment of choice for OSA [80]. Tkacova et al. showed that CPAP reduced LV afterload and heart rate during sleep in patients with OSA and congestive heart failure [81]. Pepperell et al. demonstrated that nasal CPAP treatment lowered blood pressure and improved symptoms of daytime sleepiness and quality of life [26, 82–84]. CPAP also helps alleviate brady-arrhythmias associated with OSA [85]. Although these studies have not shown a direct impact on AF specifically, they influence the mechanisms which may lead to AF.

There have only been a few studies which have examined the impact of CPAP therapy on AF in OSA patients (please see Table 3) [72, 76–78]. None of the four studies were randomized. A Japanese group looked at the effect of CPAP on nocturnal arrhythmias and found that CPAP significantly decreased the occurrence of paroxysmal AF ($P < 0.001$) [77]. As previously noted, Kanagala et al.

demonstrated that patients treated appropriately with CPAP had a lower recurrence of AF after cardioversion [72]. Anter et al. and Patel et al. also demonstrated that among patients who underwent pulmonary vein isolation for AF, there was a significant decrease in AF recurrence in CPAP-treated patients compared to untreated patients [76, 78]. While these studies suggest that CPAP may alleviate the obstructive mechanisms leading to AF, a randomized trial looking at the effectiveness of CPAP to decrease the incidence of AF has not been performed. One trial, recently completed in May 2012, aimed to determine the effect of CPAP on the rate of recurrence of AF after cardioversion therapy [99]. There is an ongoing trial currently recruiting participants aimed to determine the incidence of new onset atrial fibrillation among patients with severe OSA using an implantable loop recorder [100]. The study will also examine the effect of CPAP on the incidence of AF and is estimated to complete in 2014. These trials should help determine if CPAP affects the onset of new or recurrent AF.

Given the increased risk of cardiac death at night in OSA patients (RR 2.57, 95% CI 1.87–3.52) [101], and the evidence suggesting that CPAP therapy protects against death secondary to cardiovascular causes in patients with OSA [102], it would be prudent to evaluate the effectiveness of CPAP as it relates to incidence of arrhythmias. If CPAP therapy is found to be effective for arrhythmia prevention, it could be considered as upstream therapy prior to or in conjunction with antiarrhythmic medication, pacemaker placement for bradyarrhythmias, or catheter ablation for AF. Early intervention with CPAP, a noninvasive therapy, is a reasonable consideration as patients with severe OSA are less likely to respond to antiarrhythmic drug therapy [103].

7. Catheter Ablation of Atrial Fibrillation in OSA Patients

Although pulmonary vein isolation (PVI) has been established as an effective treatment for AF [56, 104–106], some patients experience conduction recurrence across a previously disconnected pulmonary vein. Sauer et al. characterized this group and concluded that acute return of pulmonary vein conduction is more likely after successful PVI in patients who are elderly, hypertensive, with nonparoxysmal AF, a large left atrium, and sleep apnea [107].

A recent meta-analysis by Ng et al. determined that OSA patients have a 25% greater AF recurrence rate after PVI (RR 1.25, 95% CI 1.08–1.45, $P = 0.003$) [86]. The meta-analysis looked at six studies published between 2008 and 2010 and included 3,995 patients [78, 87–91]. These studies are summarized in Table 4. Subgroup analysis demonstrated that patients diagnosed with OSA using the Berlin Questionnaire (BQ) did not have a greater risk of AF recurrence after catheter ablation, but patients diagnosed using polysomnography were at increased risk. The BQ, a popular diagnostic tool due to its relative ease and cost-effectiveness, may overestimate the number of OSA patients, leading to a greater false-positive rate [89]. According to Jongnarangsin et al., after multivariate analysis, OSA was the strongest predictor

TABLE 3: Does CPAP improve AF outcomes?

Investigator	Number of patients	Follow-up period (months)	Methods	Results
Anter et al. (2012) [76]	426	26 ± 18	Prospective consecutive patients	After PVI, 72% of the CPAP patients and 62% of the non-CPAP patients were free of AF ($P = 0.005$)
Abe et al. (2010) [77]	1394	N/A	Prospective trial	CPAP significantly reduced the occurrences of paroxysmal AF ($P < 0.001$)
Patel et al. (2010) [78]	640 OSA patients, 2360 controls	32 ± 14	Prospective consecutive patients	After PVI, 79% of CPAP users compared to 68% of non-CPAP users were free of AF ($P = 0.003$)
Kanagala et al. (2003) [72]	39 OSA patients, 79 controls	12	Prospective trial	Recurrence on CPAP was 42% versus 82% in non-CPAP group ($P = 0.013$); and 53% in controls ($P = 0.009$)

CPAP: continuous positive airway pressure; PVI: pulmonary vein isolation.

TABLE 4: Risk of AF recurrence after catheter ablation.

Investigator	Number of patients	Ablation strategy	Diagnosis of OSA	Results: recurrence of AF in patients with OSA versus no OSA [86]
Patel et al. (2010) [78]	3000	PVI plus left atrial linear ablation	PSG	RR 1.23 [1.06, 1.43]
Matiello et al. (2010) [87]	174	PVI plus left atrial linear ablation	PSG	RR 1.53 [1.21, 1.92]
Chilukuri et al. (2010) [88]	109	PVI	BQ	RR 0.97 [0.75, 1.26]
Tang et al. (2009) [89]	178	PVI	BQ	RR 1.03 [0.61, 1.73]
Chilukuri et al. (2009) [90]	210	PVI	BQ	RR 1.18 [0.93, 1.49]
Jongnarangsin et al. (2008) [91]	324	PVI plus CAFE ablation	PSG	RR 1.61 [1.16, 2.22]

PVI: pulmonary vein isolation; PSG: polysomnogram; RR: risk ratio; BQ: Berlin Questionnaire; CAFE: complex fractionated atrial electrograms. Adapted from Ng et al. 2011 [86].

of recurrent AF after catheter ablation, associated with a threefold increase in the probability of recurrence (OR = 3.04, 95% CI 1.11–8.32, $P = 0.03$) [91]. A recent study showed that moderate-to-severe sleep-disordered breathing (AHI ≥ 15) was an independent predictor of AF recurrence after PVI with cryoballoon technique (HR 2.95, $P = 0.04$) [108].

As previously noted, treatment with CPAP was shown by Patel et al. to improve PVI success rate [78]. Patients not treated with CPAP had a higher prevalence of nonpulmonary vein triggers, which is likely a reflection of electrical and structural remodeling of the atria, and they were 8 times more likely to fail the procedure [78]. Patients with OSA should be given special consideration when they are being evaluated for catheter-based AF ablation, and OSA treatment should be maximized to improve ablation results.

8. OSA and Stroke Risk

Obstructive sleep apnea also increases the risk of stroke and death [94, 95, 109]. It remains unclear if this increased risk of stroke is related to the increased risk of paroxysmal AF, or if this is an independent factor. According to a meta-analysis by Loke et al. of 8345 participants, OSA more than doubled the risk of stroke (OR 2.24, 95% CI 1.57–3.19, $I^2 = 7\%$), but only three of the five studies recorded the presence of AF [110].

Studies examining the relationship between OSA and stroke risk are summarized in Table 5.

There are three ongoing trials examining whether CPAP treatment reduces the rate of cardiovascular events and stroke. The RICCADSA Trial at Skaraborg Hospital aims to determine if CPAP reduces the rate of revascularization, MI, stroke, and cardiovascular mortality in 400 patients over a mean of 3 years followup in coronary artery disease patients without daytime sleepiness [111]. There are two other multicenter randomized clinical trials estimated to complete in 2014 and 2015 which also aim to determine if CPAP will reduce cardiovascular death and nonfatal events such as MI, stroke, and heart failure [112, 113]. While these studies are not looking directly at the relationship between stroke and AF, they may shed some light on whether CPAP lowers the risk of stroke in OSA patients.

The Framingham Study defined AF as a risk factor for stroke [114]. In 2001, the CHADS₂ score was developed to aid the decision to prophylactically anticoagulate a patient to decrease the risk of stroke [115]. This scoring system awards one point for the risk factors congestive heart failure, hypertension, age ≥ 75 , and diabetes mellitus, and two points for previous stroke or transient ischemic attack. A score of two or higher implies the patient should be anti-coagulated with warfarin or another appropriate anticoagulant than

TABLE 5: OSA and stroke risk.

Investigator	Number of patients	Primary endpoints	Mean followup (yrs)	Control for AF	Risk factor adjustments	Results for stroke
Boden-Albala et al. (2012) [92]	2088	Ischemic stroke, MI, death	5.1	Yes	Age, sex, race, education, WC, systolic and diastolic BP, fasting glucose, HDL, alcohol, smoking, physical activity, PVD, CAD, total cholesterol/HDL level, depression, and medication usage.	HR for ischemic stroke in patients with significant dozing was 2.74 (1.38–5.43); HR for all stroke, 3.00 (1.57–5.73)
Redline et al. (2010) [93]	5422	Ischemic stroke	8.7	No	Age, race, BMI, smoking, BP, antihypertensives, DM.	Adjusted HR for stroke in men with severe OSA was 2.86 (1.10–7.39)
Munoz et al. (2006) [94]	394	Stroke	4.5	Yes	Sex.	Adjusted HR for stroke in OSA patients was 2.52 (1.04–6.10)
Yaggi et al. (2005) [95]	1022	Stroke or death	3.4	Yes	Age, race, sex, smoking, alcohol consumption, BMI, AF, HTN, and lipids.	Unadjusted RR for stroke in OSA was 3.02 (1.27–7.21), death adjusted RR, 1.70 (0.92–3.16)
Arzt et al. (2005) [45]	1189	Stroke	4	No	Age, sex, and BMI.	Fully adjusted OR for stroke in severe OSA was 3.08 (0.74–12.81)
Marin et al. (2005) [96]	1010	Fatal MI, stroke	10.1	No	Age, CV disease, DM, HTN, lipid disorders, smoking, alcohol use, BP, glucose, lipid levels, and CV drugs.	OR for fatal MI or stroke in untreated severe OSA was 2.87 (1.17–7.51)
Moore et al. (2001) [97]	408	Death, cerebrovascular events, MI	5.1	No	Age, sex, BMI, HTN, DM, left ventricular function, and coronary intervention.	OR for stroke in moderate OSA patients was 2.62 (1.26–5.46), in severe OSA patients, 2.98 (1.43–6.20)
Hu et al. (2000) [98]	71,779 women	Stroke, coronary heart disease, fatal cardiovascular events	8	No	Age, BMI, cigarette smoking, DM, hypercholesterolemia, menopausal status, family history of MI before age 60, alcohol consumption, multivitamin and vitamin E use, physical activity, number of hours sleeping, and sleep position.	Age-adjusted total stroke RR for occasional snorers, 1.60 (1.21–2.12); for regular snorers 1.88 (1.29–2.74). Multivariate adjusted RR for occasional snorers, 1.42 (1.07–1.89); for regular snorers RR 1.35 (0.91–1.99)

MI: myocardial infarction; WC: waist circumference; BP: blood pressure; HDL: high density lipoprotein; PVD: peripheral vascular disease; CAD: coronary artery disease; BMI: body mass index; HR: hazard ratio; DM: diabetes mellitus; HTN: hypertension; RR: relative risk; OR: odds ratio; CV: cardiovascular.

aspirin or clopidogrel if there are no contraindications. The CHADS₂ score was developed before OSA was recognized to increase the risk of stroke, and it has recently been debated whether OSA should be added to the CHADS₂ score [116]. The relative risks for hypertension, age, diabetes, and prior stroke/TIA are similar to that of OSA [116]. Obstructive sleep apnea is often associated with significant cardiac risk factors such as hypertension, diabetes, and obesity, further increasing the risk of stroke [117]. A large prospective trial is needed to determine if the CHADS₂ score should be the CHADSS₂ score, adding one more “s” for sleep apnea.

9. Conclusion

In obstructive sleep apnea, left atrial remodeling, diastolic dysfunction, increased autonomic tone, inflammatory mediators, and hypertension are potential factors which coalesce to amplify the risk of AF. OSA also increases the risk of stroke,

and it remains unclear whether this is related to paroxysmal AF or an independent risk factor. Patients with OSA and AF are prone to recurrent AF after cardioversion or catheter ablation. CPAP is the treatment of choice for OSA, and it may have some antiarrhythmic effects. However, a prospective randomized control trial is needed to determine the effect of CPAP on AF prevention. General internists and electrophysiologists alike should screen patients for OSA when considering possible interventions for atrial fibrillation.

References

- [1] S. F. Quan, B. V. Howard, C. Iber et al., “The Sleep Heart Health Study: design, rationale, and methods,” *Sleep*, vol. 20, no. 12, pp. 1077–1085, 1997.
- [2] N. M. Punjabi, “The epidemiology of adult obstructive sleep apnea,” *Proceedings of the American Thoracic Society*, vol. 5, no. 2, pp. 136–143, 2008.

- [3] J. R. Stradling and R. J. O. Davies, "Sleep · 1: obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history," *Thorax*, vol. 59, no. 1, pp. 73–78, 2004.
- [4] M. Partinen and H. Palomaki, "Snoring and cerebral infarction," *The Lancet*, vol. 2, no. 8468, pp. 1325–1326, 1985.
- [5] Y. Miyasaka, M. E. Barnes, B. J. Gersh et al., "Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence," *Circulation*, vol. 114, no. 2, pp. 119–125, 2006.
- [6] C. Guilleminault, S. J. Connolly, and R. A. Winkle, "Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome," *The American Journal of Cardiology*, vol. 52, no. 5, pp. 490–494, 1983.
- [7] A. S. Gami, G. Pressman, S. M. Caples et al., "Association of atrial fibrillation and obstructive sleep apnea," *Circulation*, vol. 110, no. 4, pp. 364–367, 2004.
- [8] R. Mehra, E. J. Benjamin, E. Shahar et al., "Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study," *American Journal of Respiratory and Critical Care Medicine*, vol. 173, no. 8, pp. 910–916, 2006.
- [9] T. Tanigawa, K. Yamagishi, S. Sakurai et al., "Arterial oxygen desaturation during sleep and atrial fibrillation," *Heart*, vol. 92, no. 12, pp. 1854–1855, 2006.
- [10] K. Monahan, A. Storfer-Isser, R. Mehra et al., "Triggering of nocturnal arrhythmias by sleep-disordered breathing events," *Journal of the American College of Cardiology*, vol. 54, no. 19, pp. 1797–1804, 2009.
- [11] A. S. Gami, D. O. Hodge, R. M. Herges et al., "Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation," *Journal of the American College of Cardiology*, vol. 49, no. 5, pp. 565–571, 2007.
- [12] I. H. Stevenson, H. Teichtahl, D. Cunnington, S. Ciavarella, I. Gordon, and J. M. Kalman, "Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function," *European Heart Journal*, vol. 29, no. 13, pp. 1662–1669, 2008.
- [13] B. Braga, D. Poyares, F. Cintra et al., "Sleep-disordered breathing and chronic atrial fibrillation," *Sleep Medicine*, vol. 10, no. 2, pp. 212–216, 2009.
- [14] T. Mooe, S. Gullsbj, T. Rabben, and P. Eriksson, "Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery," *Coronary Artery Disease*, vol. 7, no. 6, pp. 475–478, 1996.
- [15] R. Mehra, K. L. Stone, P. D. Varosy et al., "Nocturnal arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study," *Archives of Internal Medicine*, vol. 169, no. 12, pp. 1147–1155, 2009.
- [16] P. Kirchhof, G. Y. Lip, I. C. Van Gelder et al., "Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options—a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference," *Europace*, vol. 14, no. 1, pp. 8–27, 2012.
- [17] K. M. Porthan, J. H. Melin, J. T. Kupila, K. K. K. Venho, and M. M. Partinen, "Prevalence of sleep apnea syndrome in lone atrial fibrillation: a case-control study," *Chest*, vol. 125, no. 3, pp. 879–885, 2004.
- [18] R. L. Horner, "Pathophysiology of obstructive sleep apnea," *Journal of Cardiopulmonary Rehabilitation and Prevention*, vol. 28, no. 5, pp. 289–298, 2008.
- [19] T. D. Bradley and J. S. Floras, "Sleep apnea and heart failure, part I: obstructive sleep apnea," *Circulation*, vol. 107, no. 12, pp. 1671–1678, 2003.
- [20] T. D. Bradley, M. J. Hall, S. I. Ando, and J. S. Floras, "Hemodynamic effects of simulated obstructive apneas in humans with and without heart failure," *Chest*, vol. 119, no. 6, pp. 1827–1835, 2001.
- [21] V. K. Somers, A. L. Mark, D. C. Zavala, and F. M. Abboud, "Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans," *Journal of Applied Physiology*, vol. 67, no. 5, pp. 2101–2106, 1989.
- [22] D. A. Spriggs, J. M. French, J. M. Murdy, R. H. Curless, D. Bates, and O. F. W. James, "Snoring increases the risk of stroke and adversely affects prognosis," *Quarterly Journal of Medicine*, vol. 83, no. 303, pp. 555–562, 1992.
- [23] P. E. Peppard, T. Young, M. Palta, and J. Skatrud, "Prospective study of the association between sleep-disordered breathing and hypertension," *The New England Journal of Medicine*, vol. 342, no. 19, pp. 1378–1384, 2000.
- [24] F. J. Nieto, T. B. Young, B. K. Lind et al., "Association of sleep-disordered breathing sleep apnea, and hypertension in a large community-based study," *Journal of the American Medical Association*, vol. 283, no. 14, pp. 1829–1836, 2000.
- [25] C. W. H. Davies, J. H. Crosby, R. L. Mullins, C. Barbour, R. J. O. Davies, and J. R. Stradling, "Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects," *Thorax*, vol. 55, no. 9, pp. 736–740, 2000.
- [26] J. C. T. Pepperell, S. Ramdassingh-Dow, N. Crosthwaite et al., "Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial," *The Lancet*, vol. 359, no. 9302, pp. 204–210, 2002.
- [27] I. Cano-Pumarega, J. Duran-Cantolla, F. Aizpuru et al., "Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population: the Vitoria Sleep Cohort," *American Journal of Respiratory and Critical Care Medicine*, vol. 184, no. 11, pp. 1299–1304, 2011.
- [28] G. T. O'Connor, B. Caffo, A. B. Newman et al., "Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study," *American Journal of Respiratory and Critical Care Medicine*, vol. 179, no. 12, pp. 1159–1164, 2009.
- [29] H. Palomaki, "Snoring and the risk of ischemic brain infarction," *Stroke*, vol. 22, no. 8, pp. 1021–1025, 1991.
- [30] S. Smirne, S. Palazzi, M. Zucconi, S. Chierchia, and L. Ferini-Strambi, "Habitual snoring as a risk factor for acute vascular disease," *European Respiratory Journal*, vol. 6, no. 9, pp. 1357–1361, 1993.
- [31] J. P. Neau, J. C. Meurice, J. Paquereau, J. J. Chavagnat, P. Ingrand, and R. Gil, "Habitual snoring as a risk factor for brain infarction," *Acta Neurologica Scandinavica*, vol. 92, no. 1, pp. 63–68, 1995.
- [32] G. Parati and P. Lantelme, "Blood pressure variability, target organ damage and cardiovascular events," *Journal of Hypertension*, vol. 20, no. 9, pp. 1725–1729, 2002.
- [33] E. Ohga, T. Tomita, H. Wada, H. Yamamoto, T. Nagase, and Y. Ouchi, "Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1," *Journal of Applied Physiology*, vol. 94, no. 1, pp. 179–184, 2003.
- [34] L. Dyugovskaya, P. Lavie, and L. Lavie, "Increased adhesion molecules expression and production of reactive oxygen species

- in leukocytes of sleep apnea patients," *American Journal of Respiratory and Critical Care Medicine*, vol. 165, no. 7, pp. 934–939, 2002.
- [35] A. S. M. Shamsuzzaman, M. Winnicki, P. Lanfranchi et al., "Elevated C-reactive protein in patients with obstructive sleep apnea," *Circulation*, vol. 105, no. 21, pp. 2462–2464, 2002.
- [36] T. Yokoe, K. Minoguchi, H. Matsuo et al., "Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure," *Circulation*, vol. 107, no. 8, pp. 1129–1134, 2003.
- [37] R. Schulz, S. Mahmoudi, K. Hattar et al., "Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea: impact of continuous positive airway pressure therapy," *American Journal of Respiratory and Critical Care Medicine*, vol. 162, no. 2 I, pp. 566–570, 2000.
- [38] A. Malhotra and D. P. White, "Obstructive sleep apnoea," *The Lancet*, vol. 360, no. 9328, pp. 237–245, 2002.
- [39] V. K. Somers, D. P. White, R. Amin et al., "Sleep apnea and cardiovascular disease. An American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing in Collaboration with the National Heart, Lung," *Journal of the American College of Cardiology*, vol. 52, no. 8, pp. 686–717, 2008.
- [40] W. T. McNicholas, "Diagnosis of obstructive sleep apnea in adults," *Proceedings of the American Thoracic Society*, vol. 5, no. 2, pp. 154–160, 2008.
- [41] F. N. Albuquerque, A. D. Calvin, F. H. S. Kuniyoshi et al., "Sleep-disordered breathing and excessive daytime sleepiness in patients with atrial fibrillation," *Chest*, vol. 141, no. 4, pp. 967–973, 2012.
- [42] R. J. O. Davies, N. J. Ali, and J. R. Stradling, "Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome," *Thorax*, vol. 47, no. 2, pp. 101–105, 1992.
- [43] D. C. Haas, G. L. Foster, F. J. Nieto et al., "Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study," *Circulation*, vol. 111, no. 5, pp. 614–621, 2005.
- [44] P. Lavie, L. Lavie, and P. Herer, "All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age," *European Respiratory Journal*, vol. 25, no. 3, pp. 514–520, 2005.
- [45] M. Arzt, T. Young, L. Finn, J. B. Skatrud, and T. D. Bradley, "Association of sleep-disordered breathing and the occurrence of stroke," *American Journal of Respiratory and Critical Care Medicine*, vol. 172, no. 11, pp. 1447–1451, 2005.
- [46] H. Dimitri, M. Ng, A. G. Brooks et al., "Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation," *Heart Rhythm*, vol. 9, no. 3, pp. 321–327, 2012.
- [47] D. H. Lau, L. MacKenzie, D. J. Kelly et al., "Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model," *Heart Rhythm*, vol. 7, no. 9, pp. 1282–1290, 2010.
- [48] M. K. Stiles, B. John, C. X. Wong et al., "Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the 'second factor,'" *Journal of the American College of Cardiology*, vol. 53, no. 14, pp. 1182–1191, 2009.
- [49] V. K. Somers, M. E. Dyken, M. P. Clary, and F. M. Abboud, "Sympathetic neural mechanisms in obstructive sleep apnea," *Journal of Clinical Investigation*, vol. 96, no. 4, pp. 1897–1904, 1995.
- [50] V. K. Somers, A. L. Mark, D. C. Zavala, and F. M. Abboud, "Influence of ventilation and hypocapnia on sympathetic nerve responses to hypoxia in normal humans," *Journal of Applied Physiology*, vol. 67, no. 5, pp. 2095–2100, 1989.
- [51] B. John, M. K. Stiles, P. Kuklik et al., "Electrical remodeling of the left and right atria due to rheumatic mitral stenosis," *European Heart Journal*, vol. 29, no. 18, pp. 2234–2243, 2008.
- [52] E. Varol, S. Akcay, M. Ozaydin, O. Ozturk, S. S. Cerci, and U. Sahin, "Influence of obstructive sleep apnea on left ventricular mass and global function: sleep apnea and myocardial performance index," *Heart and Vessels*, vol. 25, no. 5, pp. 400–404, 2010.
- [53] P. Sanders, J. B. Morton, P. M. Kistler et al., "Electrophysiological and electroanatomic characterization of the atria in sinus node disease: evidence of diffuse atrial remodeling," *Circulation*, vol. 109, no. 12, pp. 1514–1522, 2004.
- [54] P. Sanders, J. B. Morton, N. C. Davidson et al., "Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans," *Circulation*, vol. 108, no. 12, pp. 1461–1468, 2003.
- [55] M. E. Otto, M. Belohlavek, A. Romero-Corral et al., "Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea," *The American Journal of Cardiology*, vol. 99, no. 9, pp. 1298–1302, 2007.
- [56] M. Haïssaguerre, P. Jaïs, D. C. Shah et al., "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins," *The New England Journal of Medicine*, vol. 339, no. 10, pp. 659–666, 1998.
- [57] L. F. Drager, L. A. Bortolotto, A. C. Figueiredo, B. C. Silva, E. M. Krieger, and G. Lorenzi-Filho, "Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling," *Chest*, vol. 131, no. 5, pp. 1379–1386, 2007.
- [58] R. Parkash, M. S. Green, C. R. Kerr et al., "The association of left atrial size and occurrence of atrial fibrillation: a prospective cohort study from the Canadian Registry of Atrial Fibrillation," *American Heart Journal*, vol. 148, no. 4, pp. 649–654, 2004.
- [59] H. E. Lim, Y. H. Kim, S. H. Kim et al., "Impact of obstructive sleep apnea on the atrial electromechanical activation time," *Circulation Journal*, vol. 73, no. 2, pp. 249–255, 2009.
- [60] J. Yagmur, O. Yetkin, M. Cansel et al., "Assessment of atrial electromechanical delay and influential factors in patients with obstructive sleep apnea," *Sleep and Breathing*, vol. 16, no. 1, pp. 83–88, 2012.
- [61] A. Noda, T. Okada, F. Yasuma, N. Nakashima, and M. Yokota, "Cardiac hypertrophy in obstructive sleep apnea syndrome," *Chest*, vol. 107, no. 6, pp. 1538–1544, 1995.
- [62] K. M. Hla, T. B. Young, T. Bidwell, M. Palta, J. B. Skatrud, and J. Dempsey, "Sleep apnea and hypertension: a population-based study," *Annals of Internal Medicine*, vol. 120, no. 5, pp. 382–388, 1994.
- [63] T. Young, P. Peppard, M. Palta et al., "Population-based study of sleep-disordered breathing as a risk factor for hypertension," *Archives of Internal Medicine*, vol. 157, no. 15, pp. 1746–1752, 1997.

- [64] M. Niroumand, R. Kuperstein, Z. Sasson, and P. J. Hanly, "Impact of obstructive sleep apnea on left ventricular mass and diastolic function," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 7, pp. 1632–1636, 2001.
- [65] A. J. Buda, M. R. Pinsky, N. B. Ingels Jr., G. T. Daughters II, E. B. Stinson, and E. L. Alderman, "Effect of intrathoracic pressure on left ventricular performance," *The New England Journal of Medicine*, vol. 301, no. 9, pp. 453–459, 1979.
- [66] M. Orban, C. J. Bruce, G. S. Pressman et al., "Dynamic changes of left ventricular performance and left atrial volume induced by the mueller maneuver in healthy young adults and implications for obstructive sleep apnea, atrial fibrillation, and heart failure," *The American Journal of Cardiology*, vol. 102, no. 11, pp. 1557–1561, 2008.
- [67] Y. Koshino, H. R. Villarraga, M. Orban et al., "Changes in left and right ventricular mechanics during the Mueller maneuver in healthy Adults a possible mechanism for abnormal cardiac function in patients with obstructive sleep apnea," *Circulation*, vol. 3, no. 3, pp. 282–289, 2010.
- [68] D. Linz, U. Schotten, H. R. Neuberger, M. Böhm, and K. Wirth, "Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation," *Heart Rhythm*, vol. 8, no. 9, pp. 1436–1443, 2011.
- [69] Y. K. Iwasaki, Y. Shi, B. Benito et al., "Determinants of atrial fibrillation in an animal model of obesity and acute obstructive sleep apnea," *Heart Rhythm*, vol. 9, no. 9, pp. 1409.e1–1416.e1, 2012.
- [70] H. Kraiczi, K. Caidahl, A. Samuelsson, Y. Peker, and J. Hedner, "Impairment of vascular endothelial function and left ventricular filling: association with the severity of apnea-induced hypoxemia during sleep," *Chest*, vol. 119, no. 4, pp. 1085–1091, 2001.
- [71] J. W. H. Fung, T. S. T. Li, D. K. L. Choy et al., "Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction," *Chest*, vol. 121, no. 2, pp. 422–429, 2002.
- [72] R. Kanagala, N. S. Murali, P. A. Friedman et al., "Obstructive sleep apnea and the recurrence of atrial fibrillation," *Circulation*, vol. 107, no. 20, pp. 2589–2594, 2003.
- [73] A. Y. Tan, P. S. Chen, L. S. Chen, and M. C. Fishbein, "Autonomic nerves in pulmonary veins," *Heart Rhythm*, vol. 4, supplement 3, pp. S57–S60, 2007.
- [74] M. Ghias, B. J. Scherlag, Z. Lu et al., "The role of ganglionated plexi in apnea-related atrial fibrillation," *Journal of the American College of Cardiology*, vol. 54, no. 22, pp. 2075–2083, 2009.
- [75] D. Linz, U. Schotten, H. R. Neuberger, M. Bohm, and K. Wirth, "Combined blockade of early and late activated atrial potassium currents suppresses atrial fibrillation in a pig model of obstructive apnea," *Heart Rhythm*, vol. 8, no. 12, pp. 1933–1939, 2011.
- [76] E. Anter, P. Zimetbaum, and M. Josephson, "Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence following catheter ablation," *Journal of the American College of Cardiology*, vol. 59, no. 13, supplement 1, pp. E612–E612, 2012.
- [77] H. Abe, M. Takahashi, H. Yaegashi et al., "Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients," *Heart and vessels*, vol. 25, no. 1, pp. 63–69, 2010.
- [78] D. Patel, P. Mohanty, L. di Biase et al., "Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure," *Circulation*, vol. 3, no. 5, pp. 445–451, 2010.
- [79] D. Linz, F. Mahfoud, U. Schotten et al., "Renal sympathetic denervation suppresses postapneic blood pressure rises and atrial fibrillation in a model for sleep apnea," *Hypertension*, vol. 60, no. 1, pp. 172–178, 2012.
- [80] R. C. Basner, "Continuous positive airway pressure for obstructive sleep apnea," *The New England Journal of Medicine*, vol. 356, no. 17, pp. 1751–1758, 2007.
- [81] R. Tkacova, F. Rankin, F. S. Fitzgerald, J. S. Floras, and T. D. Bradley, "Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure," *Circulation*, vol. 98, no. 21, pp. 2269–2275, 1998.
- [82] F. Barbe, J. Duran-Cantolla, M. Sanchez-de-la-Torre et al., "Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial," *Journal of the American Medical Association*, vol. 307, no. 20, pp. 2161–2168, 2012.
- [83] P. Haentjens, A. van Meerhaeghe, A. Moscariello et al., "The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials," *Archives of Internal Medicine*, vol. 167, no. 8, pp. 757–764, 2007.
- [84] K. Monahan and S. Redline, "Role of obstructive sleep apnea in cardiovascular disease," *Current Opinion in Cardiology*, vol. 26, no. 6, pp. 541–547, 2011.
- [85] U. Koehler, E. Fus, W. Grimm et al., "Heart block in patients with obstructive sleep apnoea: pathogenetic factors and effects of treatment," *European Respiratory Journal*, vol. 11, no. 2, pp. 434–439, 1998.
- [86] C. Y. Ng, T. Liu, M. Shehata, S. Stevens, S. S. Chugh, and X. Wang, "Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation," *The American Journal of Cardiology*, vol. 108, no. 1, pp. 47–51, 2011.
- [87] M. Matiello, M. Nadal, D. Tamborero et al., "Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients," *Europace*, vol. 12, no. 8, pp. 1084–1089, 2010.
- [88] K. Chilukuri, D. Dalal, S. Gadrey et al., "A prospective study evaluating the role of obesity and obstructive sleep apnea for outcomes after catheter ablation of atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 21, no. 5, pp. 521–525, 2010.
- [89] R. B. Tang, J. Z. Dong, X. P. Liu et al., "Obstructive sleep apnoea risk profile and the risk of recurrence of atrial fibrillation after catheter ablation," *Europace*, vol. 11, no. 1, pp. 100–105, 2009.
- [90] K. Chilukuri, D. Dalal, J. E. Marine et al., "Predictive value of obstructive sleep apnoea assessed by the Berlin Questionnaire for outcomes after the catheter ablation of atrial fibrillation," *Europace*, vol. 11, no. 7, pp. 896–901, 2009.
- [91] K. Jongnarangsin, A. Chugh, E. Good et al., "Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 19, no. 7, pp. 668–672, 2008.
- [92] B. Boden-Albala, E. T. Roberts, C. Bazil et al., "Daytime sleepiness and risk of stroke and vascular disease: findings from the Northern Manhattan Study (NOMAS)," *Circulation*, vol. 5, no. 4, pp. 500–507, 2012.
- [93] S. Redline, G. Yenokyan, D. J. Gottlieb et al., "Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health Study," *American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 2, pp. 269–277, 2010.

- [94] R. Munoz, J. Duran-Cantolla, E. Martínez-Vila et al., "Severe sleep apnea and risk of ischemic stroke in the elderly," *Stroke*, vol. 37, no. 9, pp. 2317–2321, 2006.
- [95] H. K. Yaggi, J. Concato, W. N. Kernan, J. H. Lichtman, L. M. Brass, and V. Mohsenin, "Obstructive sleep apnea as a risk factor for stroke and death," *The New England Journal of Medicine*, vol. 353, no. 19, pp. 2034–2041, 2005.
- [96] J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. N. Agustí, "Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study," *The Lancet*, vol. 365, no. 9464, pp. 1046–1053, 2005.
- [97] T. Moos, K. A. Franklin, K. Holmström, T. Rabben, and U. Wiklund, "Sleep-disordered breathing and coronary artery disease: long-term prognosis," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 10 I, pp. 1910–1913, 2001.
- [98] F. B. Hu, W. C. Willett, J. E. Manson et al., "Snoring and risk of cardiovascular disease in women," *Journal of the American College of Cardiology*, vol. 35, no. 2, pp. 308–313, 2000.
- [99] S. M. Caples, *A Randomized Trial of Positive Airway Pressure Therapy in Atrial Fibrillation Recurrence in Sleep Apnea*, National Library of Medicine, Bethesda, Md, USA, 2009.
- [100] A. Baranchuk, *Incidence of New Onset Atrial Fibrillation in Patients with Severe Obstructive Sleep Apnea: The Reveal XT-SA Study*, National Library of Medicine, Bethesda, Md, USA, 2010.
- [101] A. S. Gami, D. E. Howard, E. J. Olson, and V. K. Somers, "Day-night pattern of sudden death in obstructive sleep apnea," *The New England Journal of Medicine*, vol. 352, no. 12, pp. 1206–1214, 2005.
- [102] L. S. Doherty, J. L. Kiely, V. Swan, and W. T. McNicholas, "Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome," *Chest*, vol. 127, no. 6, pp. 2076–2084, 2005.
- [103] K. Monahan, J. Brewster, L. Wang et al., "Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter," *The American Journal of Cardiology*, vol. 110, no. 3, pp. 369–372, 2012.
- [104] C. Pappone, S. Rosanio, G. Oreto et al., "Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation," *Circulation*, vol. 102, no. 21, pp. 2619–2628, 2000.
- [105] H. Oral, C. Scharf, A. Chugh et al., "Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation," *Circulation*, vol. 108, no. 19, pp. 2355–2360, 2003.
- [106] F. E. Marchlinski, D. Callans, S. Dixit et al., "Efficacy and safety of targeted focal ablation versus PV isolation assisted by magnetic electroanatomic mapping," *Journal of Cardiovascular Electrophysiology*, vol. 14, no. 4, pp. 358–365, 2003.
- [107] W. H. Sauer, M. L. McKernan, D. Lin, E. P. Gerstenfeld, D. J. Callans, and F. E. Marchlinski, "Clinical predictors and outcomes associated with acute return of pulmonary vein conduction during pulmonary vein isolation for treatment of atrial fibrillation," *Heart Rhythm*, vol. 3, no. 9, pp. 1024–1028, 2006.
- [108] T. Bitter, G. Nolker, J. Vogt, C. Prinz, D. Horstkotte, and O. Oldenburg, "Predictors of recurrence in patients undergoing cryoballoon ablation for treatment of atrial fibrillation: the independent role of sleep-disordered breathing," *Journal of Cardiovascular Electrophysiology*, vol. 23, no. 1, pp. 18–25, 2012.
- [109] E. Shahar, C. W. Whitney, S. Redline et al., "Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 1, pp. 19–25, 2001.
- [110] Y. K. Loke, J. W. Brown, C. S. Kwok, A. Niruban, and P. K. Myint, "Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis," *Circulation*, vol. 125, no. 5, pp. 720–728, 2012.
- [111] Y. Peker, H. Glantz, E. Thunström, A. Kallryd, J. Herlitz, and J. Ejdebäck, "Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea—RICCADSA trial," *Scandinavian Cardiovascular Journal*, vol. 43, no. 1, pp. 24–31, 2009.
- [112] Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome. Effect of Intervention with Continuous Positive Airway Pressure (CPAP). A Prospective Randomized Study: iSAACC Study, <http://clinicaltrials.gov/show/NCT01335087>.
- [113] Sleep Apnea cardiovascular Endpoints Study—Investigating the Effectiveness of Treatment with CPAP versus Standard Care in Reducing CV Morbidity and Mortality in Patients With Co-existing CV Disease and Moderate-severe Obstructive Sleep Apnea, <http://clinicaltrials.gov/show/NCT00738179>.
- [114] P. A. Wolf, R. D. Abbott, and W. B. Kannel, "Atrial fibrillation as an independent risk factor for stroke: the Framingham Study," *Stroke*, vol. 22, no. 8, pp. 983–988, 1991.
- [115] B. F. Gage, A. D. Waterman, W. Shannon, M. Boechler, M. W. Rich, and M. J. Radford, "Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation," *Journal of the American Medical Association*, vol. 285, no. 22, pp. 2864–2870, 2001.
- [116] P. Yazdan-Ashoori and A. Baranchuk, "Obstructive sleep apnea may increase the risk of stroke in AF patients: refining the CHADS₂ score," *International Journal of Cardiology*, vol. 146, no. 2, pp. 131–133, 2011.
- [117] M. Butt, G. Dwivedi, O. Khair, and G. Y. H. Lip, "Obstructive sleep apnea and cardiovascular disease," *International Journal of Cardiology*, vol. 139, no. 1, pp. 7–16, 2010.

Review Article

Therapeutic Strategies for Sleep Apnea in Hypertension and Heart Failure

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Sleep-disordered breathing (SDB) causes hypoxemia, negative intrathoracic pressure, and frequent arousal, contributing to increased cardiovascular disease mortality and morbidity. Obstructive sleep apnea syndrome (OSAS) is linked to hypertension, ischemic heart disease, and cardiac arrhythmias. Successful continuous positive airway pressure (CPAP) treatment has a beneficial effect on hypertension and improves the survival rate of patients with cardiovascular disease. Thus, long-term compliance with CPAP treatment may result in substantial blood pressure reduction in patients with resistant hypertension suffering from OSAS. Central sleep apnea and Cheyne-Stokes respiration occur in 30–50% of patients with heart failure (HF). Intermittent hypoxemia, nocturnal surges in sympathetic activity, and increased left ventricular preload and afterload due to negative intrathoracic pressure all lead to impaired cardiac function and poor life prognosis. SDB-related HF has been considered the potential therapeutic target. CPAP, nocturnal O₂ therapy, and adaptive servoventilation minimize the effects of sleep apnea, thereby improving cardiac function, prognosis, and quality of life. Early diagnosis and treatment of SDB will yield better therapeutic outcomes for hypertension and HF.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of sleep apnea accompanied by hypoxia, fluctuations in heart rate and blood pressure (BP), frequent arousal, and consequent sleep fragmentation, resulting in an activation of the sympathetic nervous system [1–7]. The most common neuropsychiatric manifestation of OSAS is excessive daytime sleepiness that is secondary to sleep fragmentation and the lack of slow-wave sleep; other major, long-term manifestations of OSAS include disorders of the cardiovascular system [2].

The Sleep Heart Health Study [8] and Wisconsin Sleep Cohort Study [9] reported that OSAS is an independent risk factor for the development of essential hypertension. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, OSAS is one of the identifiable causes of hypertension [10].

Central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR) occur in 30–50% of patients with left ventricular (LV) dysfunction and heart failure (HF) caused by hypertension,

cardiomyopathy, and ischemic heart disease [11]. Treatment of sleep apnea with nocturnal continuous positive airway pressure (CPAP) in individuals with congestive HF not only treats sleep-disordered breathing (SDB), but also results in improved LV function, alleviated HF symptoms, and reduced sympathetic activation due to decreased norepinephrine secretion [12]. Although CPAP reportedly improves LV function and survival rate in patients with HF [12, 13], outcomes of long-term compliance with CPAP treatment in these patients remain unknown. Moreover, guidelines for CPAP treatment have yet to be established.

2. Hypertension

OSAS and hypertension are often comorbid; approximately 50% of patients with OSAS are hypertensive, whereas 30–40% of patients with hypertension are estimated to suffer from OSAS [14]. The Sleep Heart Health Study in 2000, a cross-sectional study, reported that the prevalence of hypertension was independently associated with apnea-hypopnea index (AHI), after adjusting for obesity, alcohol intake, smoking

habit, neck circumference, and waist-to-hip ratio [8]. The incidence of hypertension during a 4-year follow-up of the Wisconsin Sleep Cohort Study [9] rose with increasing OSAS severity.

Patients with severe OSAS exhibit attenuated nocturnal BP dipping (nondipping pattern), as well as marked and rapid BP elevation in the morning shortly after waking (morning BP surge) [4, 6, 15]. Mounting evidence suggests that morning BP surge is significantly associated with cardiac, cerebral, renal, and vascular damage [16]. Cross-sectional studies have demonstrated consistent results that moderate-to-severe OSAS (AHI >15 events/h) increases the risk of developing hypertension [17]. Thus, the diagnosis of OSAS and the proper treatment of BP are of particular importance for patients with hypertension.

We previously reported that repeated episodes of end-apneic arousal or hypoxia and consequent sleep fragmentation were associated with an increase in nocturnal BP, possibly leading to sustained hypertension and LV hypertrophy [4–6]. Both hypertension and LV hypertrophy are strong cardiovascular risk factors [18] and are linked to poor prognoses in patients with OSAS [19]. Yet, the mechanisms of how recurrent nocturnal BP surges and sympathetic activity lead to cardiovascular disease (CVD) or abnormal autonomic control of heart rate during the daytime in OSAS patients remains unclear. We also reported that nocturnal oxygen desaturation, sleep fragmentation, and increased sympathetic activity impaired daytime baroreflex sensitivity and nitric oxide (NO) production in patients with moderate-to-severe OSAS [20, 21]. Alterations in cardiac autonomic nervous function and endothelial dysfunction likely contribute to an increased risk of cardiovascular morbidity and mortality in OSAS patients.

Arousals that occur to terminate apneic events split the sleep pattern in patients with OSAS. Hypoxemia, CO₂ retention, and respiratory acidosis caused by repeated apnea/hypopnea disrupt the normal cardiovascular system [3]. Hypoxemia, negative intrathoracic pressure, and increased sympathetic activity that accompany arousal are important factors in the development of hypertension in patients with OSAS [7]. Negative intrathoracic pressure during apnea increases LV afterload and elevates myocardial oxygen demand. OSAS also reduces parasympathetic activity and the baroreceptor reflex. Moreover, repetitive hypoxemia and reoxygenation induce oxidative stress. Endothelial dysfunction, augmentation of central aortic pressure and increased central pulse pressure, enhanced renin-angiotensin system (RAS) activity, and insulin resistance have been reported in patients with OSAS [20, 21]. The prevalence of metabolic syndrome in patients with OSAS is about twice that of those without OSAS [22]. Hypoxemia, sympathetic activation, chemoreceptor stimulation, and enhanced RAS in OSAS are possible mechanisms underlying the development of hypertension and target-organ damage.

CPAP treatment significantly reduces apnea/hypopnea, improves hypoxemia, decreases arousal, and normalizes sleep architecture. Severe OSAS significantly increases the risk of fatal and nonfatal cardiovascular events, and CPAP treatment reduces this risk [19]. These positive effects are observed

from the first night of CPAP treatment in patients with OSAS; in a previous study, the 24-hour urinary excretion of norepinephrine was significantly reduced, and the plasma concentration of NO significantly increased, one night after CPAP treatment in patients with OSAS [21]. Successful CPAP treatment also ameliorates daytime excessive sleepiness, nocturnal arousal, and headache after waking. Furthermore, CPAP treatment reduces cyclic changes in heart beat and BP accompanied by apnea, increases arterial blood gas during waking, decreases brachial-ankle pulse wave velocity and the baroreceptor reflex, and decreases BP [5, 21]. Hence, CPAP not only treats SDB, but also improves the quality of life (QOL) by eliminating complications of OSAS and normalizing sleep architecture.

The effects of CPAP on BP reduction are observed both during daytime and sleep in patients with OSAS. Patients with resistant hypertension and OSAS showed a greater reduction in daytime diastolic BP, 24-hour systolic BP, and 24-hour diastolic BP after a 3-month CPAP treatment (>5.8 hours/night) [23]. Thus, 24-hour BP monitoring would be beneficial when starting CPAP treatment in patients undergoing antihypertensive therapy. Resistant hypertension increases cardiovascular risk, and thus it is an important public health problem. OSAS should be considered a major underlying factor that contributes to resistant hypertension [24–27].

OSAS is involved in CVD death; however, successful CPAP treatment reduces this risk [28, 29]. A cohort study in Japan reported that the prognosis in the middle-aged population might be affected by complications of hypertension or severity of oxygen desaturation related to OSAS [25]. The effects of CPAP treatment on systolic and diastolic BPs are related to daytime sleepiness and CPAP compliance [30, 31]. Appropriate treatment of OSAS should therefore be targeted to the prevention of hypertension, which causes CVD, as well as the early detection of atherosclerosis.

3. Heart Failure

Patients with HF have a high prevalence of CSA/CSR, which is characterized by the oscillation of tidal volumes, resulting in PaCO₂ levels below the apneic threshold. The overall mechanisms underlying CSA/CSR are complex, involving chemoreflexes by hypoxemia, prolonged circulation time by reduced cardiac output, upper airway resistance by congestion, and edema and arousals by hyperventilation and low PaCO₂ [32–34]. Important risk factors of CSA/CSR include sex (male), age (>60 years old), PaCO₂ (<38 mmHg), and a history of atrial fibrillation [35–39]. Poor survival rates among patients with HF are proportional to the frequency of central apneic events [40]. Along with CSA, low diastolic BP and severe right ventricular dysfunction are also variables predicting survival [41]. Given the high prevalence of SDB in men presenting with mild symptoms of HF, routine screening for SDB should be performed, as CPAP is a well-established treatment for such individuals.

CPAP treatment is effective in alleviating CSA/CSR in patients with HF [42–44]. Although the underlying

mechanisms are unclear, the decrease in LV preload and afterload and increase in PaCO₂ are possible contributing factors. CPAP treatment reduces cardiac output in patients with a pulmonary artery wedge pressure of <12 mmHg or normal cardiac output and stroke volume. In these patients, CPAP treatment should be carefully handled and followed up. In a randomized, controlled trial of 66 patients with CHF (29 with and 37 without CSR/CSA) under the age of 75 years, patients with CSR/CSA had a significantly increased mortality and cardiac transplantation rate compared with those without CSR/CSA [43]. Bradley et al. [12] found that CPAP resulted in attenuated CSA, improved nocturnal oxygenation, increased LV ejection fraction, lowered norepinephrine levels, and extended distance walked in six minutes; however, it did not affect patient survival. On the other hand, the Canadian CPAP for Patients with CSA and Heart Failure Trial (CANPAP) showed that CPAP might improve both LV ejection fraction and heart transplant-free survival if CSA is suppressed soon after its initiation [13]. Two studies have also assessed the role of CPAP in the prognosis of patients with OSAS and HF [45, 46].

Bilevel positive airway pressure (BIPAP) can set the inspiratory and expiratory pressure levels separately, and thus there is less patient discomfort in BIPAP than with CPAP treatment. Moreover, BIPAP treatment improves lung compliance and ventilation-perfusion ratio. In our cohort study of 52 patients with idiopathic dilated cardiomyopathy and CSA, LV ejection fraction, deceleration time of the peak early LV filling velocity, and specific activity scale were significantly increased, and the LV end-systolic internal dimension, heart rate, systolic and diastolic BPs, and plasma BNP levels were all significantly decreased in 10 patients after a 3-month BIPAP treatment. There were no significant changes in any of the measured parameters in patients with AHI >20 events/h and drug treatment during the 3-month period. Moreover, four patients in this group died from worsening HF [47]. BIPAP treatment could be effective in patients with cardiac dysfunction/HF complicated with SDB [47–49] and should be considered a nonpharmacologic adjunct to conventional drug therapy.

Adaptive servoventilation (ASV) is a new approach to treating CSA/CSR and involves providing patients a small but varying amount of ventilatory support. One night of ASV suppresses CSA/CSR in patients with HF and improves sleep quality better than CPAP or 2 L/min of oxygen supplementation [50]. Given the lack of consensus on what constitutes the optimal therapy, further studies will be needed to establish the standard treatment strategy for CSA/CSR in patients with HF.

Nocturnal oxygen supplementation reportedly diminishes CSR in patients with stable chronic HF [51]. Patients with HF, CSR, and hypoxemia related to CSA are considered candidates for nocturnal oxygen therapy; it is indicated for cases where CPAP treatment cannot achieve SpO₂ >90%, and oxygen increases until SpO₂ reaches >90%. Nocturnal oxygen therapy prevents hypoxemia during apnea, lessens the direct adverse effects on the cardiovascular system, inhibits central chemoreceptor sensitivity to CO₂, decreases sleep apnea by correcting hyperventilation during daytime,

and inhibits sympathetic activity. Therefore, patient QOL ameliorates along with improvements in sleep architecture, shortness of breath and fatigue during daytime, and cognitive function [52]. Nocturnal oxygen therapy might also have long-term efficacy, as sympathetic activity is decreased in patients with chronic HF and CSA [53].

Angiotensin-converting enzyme inhibition can improve AHI and nocturnal oxygen desaturation in patients with mild-to-moderate HF [54]. Diuresis with a reduction in LV filling pressure has also been shown to lower the severity of CSA [55]. β -adrenergic blockade, which counters excess sympathetic activation and may modulate ventilatory responses in HF, was shown to decrease AHI in patients with CSA [56].

The evaluation of SDB in patients with CVD is critical in cardiovascular medicine. CSA/CSR may play an important role in HF progression, morbidity, and mortality. Although advances in medicine have increased the survival rates of patients with CVD, the recent increase in the number of patients with HF is a major concern. The development of therapeutic strategies for SDB-related HF will continue to be a challenging issue in clinical medicine.

References

- [1] E. A. Phillipson, "Sleep apnea," in *Harrison's Principles of Internal Medicine*, E. Braunwald, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo, and J. L. Jameson, Eds., pp. 1520–1523, McGraw-Hill, New York, NY, USA, 15th edition, 2001.
- [2] T. D. Bradley and J. S. Floras, "Sleep apnea and heart failure: part I: obstructive sleep apnea," *Circulation*, vol. 107, no. 12, pp. 1671–1678, 2003.
- [3] R. S. T. Leung and T. D. Bradley, "Sleep apnea and cardiovascular disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 12, pp. 2147–2165, 2001.
- [4] A. Noda, T. Okada, F. Yasuma, N. Nakashima, and M. Yokota, "Cardiac hypertrophy in obstructive sleep apnea syndrome," *Chest*, vol. 107, no. 6, pp. 1538–1544, 1995.
- [5] A. Noda, F. Yasuma, T. Okada, and M. Yokota, "Circadian rhythm of autonomic activity in patients with obstructive sleep apnea syndrome," *Clinical Cardiology*, vol. 21, no. 4, pp. 271–276, 1998.
- [6] A. Noda, F. Yasuma, T. Okada, and M. Yokota, "Influence of movement arousal on circadian rhythm of blood pressure in obstructive sleep apnea syndrome," *Journal of Hypertension*, vol. 18, no. 5, pp. 539–544, 2000.
- [7] V. K. Somers, M. E. Dyken, M. P. Clary, and F. M. Abboud, "Sympathetic neural mechanisms in obstructive sleep apnea," *Journal of Clinical Investigation*, vol. 96, no. 4, pp. 1897–1904, 1995.
- [8] F. J. Nieto, T. B. Young, B. K. Lind et al., "Association of sleep-disordered breathing sleep apnea, and hypertension in a large community-based study," *Journal of the American Medical Association*, vol. 283, no. 14, pp. 1829–1836, 2000.
- [9] P. E. Peppard, T. Young, M. Palta, and J. Skatrud, "Prospective study of the association between sleep-disordered breathing and hypertension," *The New England Journal of Medicine*, vol. 342, no. 19, pp. 1378–1384, 2000.
- [10] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report," *Journal of the American Medical Association*, vol. 289, no. 19, pp. 2560–2571, 2003.

- [11] T. D. Bradley and J. S. Floras, "Sleep apnea and heart failure—part II: central sleep apnea," *Circulation*, vol. 107, no. 13, pp. 1822–1826, 2003.
- [12] T. D. Bradley, A. G. Logan, R. J. Kimoff et al., "Continuous positive airway pressure for central sleep apnea and heart failure," *The New England Journal of Medicine*, vol. 353, no. 19, pp. 2025–2033, 2005.
- [13] M. Arzt, J. S. Floras, A. G. Logan et al., "Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP)," *Circulation*, vol. 115, no. 25, pp. 3173–3180, 2007.
- [14] V. K. Somers, D. P. White, R. A. William et al., "Sleep apnea and cardiovascular disease: an American heart association college of cardiology foundation scientific statement from the American heart association council for high blood pressure reserch professional education committee, coucil on clinical cardiology, stroke council, and council on cardiovascular nursing in collaboration with the national heart lung, and blood institute national center on sleep disorders research(National Institutes of Health)," *Circulation*, vol. 118, no. 10, pp. 1080–1111, 2008.
- [15] A. Noda, T. Okada, H. Hayashi, F. Yasuma, and M. Yokota, "24-hour ambulatory blood pressure variability in obstructive sleep apnea syndrome," *Chest*, vol. 103, no. 5, pp. 1343–1347, 1993.
- [16] K. Kario, "Morning surge in blood pressure and cardiovascular risk: evidence and perspectives," *Hypertension*, vol. 56, no. 5, pp. 765–773, 2010.
- [17] C. J. Worsnop, M. T. Naughton, C. E. Barter, T. O. Morgan, A. I. Anderson, and R. J. Pierce, "The prevalence of obstructive sleep apnea in hypertensives," *American Journal of Respiratory and Critical Care Medicine*, vol. 157, no. 1, pp. 111–115, 1998.
- [18] D. Levy, R. J. Garrison, D. D. Savage, W. B. Kannel, and W. P. Castelli, "Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study," *The New England Journal of Medicine*, vol. 322, no. 22, pp. 1561–1566, 1990.
- [19] A. Noda, T. Okada, F. Yasuma, T. Sobue, N. Nakashima, and M. Yokota, "Prognosis of the middle-aged and aged patients with obstructive sleep apnea syndrome," *Psychiatry and Clinical Neurosciences*, vol. 52, no. 1, pp. 79–85, 1998.
- [20] A. Noda, S. Nakata, H. Fukatsu et al., "Aortic Pressure augmentation as a marker of cardiovascular risk in obstructive sleep apnea syndrome," *Hypertension Research*, vol. 31, no. 6, pp. 1109–1114, 2008.
- [21] A. Noda, S. Nakata, Y. Koike et al., "Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome," *Hypertension Research*, vol. 30, no. 8, pp. 669–676, 2007.
- [22] S. K. Sharma, E. V. Reddy, A. Sharma et al., "Prevalence and risk factors of syndrome Z in urban Indians," *Sleep Medicine*, vol. 11, no. 6, pp. 562–568, 2010.
- [23] L. Lozano, J. L. Tovar, G. Sampol et al., "Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial," *Journal of Hypertension*, vol. 28, no. 10, pp. 2161–2168, 2010.
- [24] P. Lavie and V. Hoffstein, "Sleep apnea syndrome: a possible contributing factor to resistant," *Sleep*, vol. 24, no. 6, pp. 721–725, 2001.
- [25] J. Ribstein, G. Du Cailar, and A. Mimran, "Glucose tolerance and age-associated decline in renal function of hypertensive patients," *Journal of Hypertension*, vol. 19, no. 12, pp. 2257–2264, 2001.
- [26] S. C. Gonçalves, D. Martinez, M. Gus et al., "Obstructive sleep apnea and resistant hypertension: a case-control study," *Chest*, vol. 132, no. 6, pp. 1858–1862, 2007.
- [27] M. A. Martínez-García, R. Gómez-Aldaraví, J. J. Soler-Cataluña, T. G. Martínez, B. Bernácer-Alpera, and P. Román-Sánchez, "Positive effect of CPAP treatment on the control of difficult-to-treat hypertension," *European Respiratory Journal*, vol. 29, no. 5, pp. 951–957, 2007.
- [28] F. Campos-Rodriguez, M. A. Martínez-García, I. de la Cruz-Moron, C. Almeida-Gonzalez, P. Catalan-Serra, and J. M. Montserrat, "Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatmenta cohort study," *Annals of Internal Medicine*, vol. 156, no. 2, pp. 115–122, 2012.
- [29] J. M. Marin, S. J. Carrizo, E. Vicente, and A. G. N. Agusti, "Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study," *The Lancet*, vol. 365, no. 9464, pp. 1046–1053, 2005.
- [30] F. Barbé, J. Durán-Cantolla, F. Capote et al., "Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 181, no. 7, pp. 718–726, 2010.
- [31] F. Barbé, J. Durán-Cantolla, M. Sánchez-de-la-Torre et al., "Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial," *Journal of the American Medical Association*, vol. 307, no. 20, pp. 2161–2168, 2012.
- [32] J. W. Crowell, A. C. Guyton, and J. W. Moore, "Basic oscillating mechanism of Cheyne-Stokes breathing," *The American Journal of Physiology*, vol. 187, no. 2, pp. 395–398, 1956.
- [33] D. P. Francis, K. Willson, L. C. Davies, A. J. S. Coats, and M. Piepoli, "Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications," *Circulation*, vol. 102, no. 18, pp. 2214–2221, 2000.
- [34] S. Javaheri, "Central sleep apnea in congestive heart failure: prevalence, mechanisms, impact, and therapeutic options," *Seminars in Respiratory and Critical Care Medicine*, vol. 26, no. 1, pp. 44–55, 2005.
- [35] D. D. Sin, F. Fitzgerald, J. D. Parker, G. Newton, J. S. Floras, and T. D. Bradley, "Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 160, no. 4, pp. 1101–1106, 1999.
- [36] K. Ferrier, A. Campbell, B. Yee et al., "Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure," *Chest*, vol. 128, no. 4, pp. 2116–2122, 2005.
- [37] S. Javaheri, "Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report," *International Journal of Cardiology*, vol. 106, no. 1, pp. 21–28, 2006.
- [38] A. Vazir, P. C. Hastings, M. Dayer et al., "A high prevalence of sleep disordered breathing in men with mild symptomatic chronic heart failure due to left ventricular systolic dysfunction," *European Journal of Heart Failure*, vol. 9, no. 3, pp. 243–250, 2007.
- [39] D. Yumino, H. Wang, J. S. Floras et al., "Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction," *Journal of Cardiac Failure*, vol. 15, no. 4, pp. 279–285, 2009.
- [40] T. Brack, I. Thüer, C. F. Clarenbach et al., "Daytime Cheyne-Stokes respiration in ambulatory patients with severe congestive

- heart failure is associated with increased mortality,” *Chest*, vol. 132, no. 5, pp. 1463–1471, 2007.
- [41] S. Javaheri, R. Shukla, H. Zeigler, and L. Wexler, “Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure,” *Journal of the American College of Cardiology*, vol. 49, no. 20, pp. 2028–2034, 2007.
- [42] M. T. Naughton, P. P. Liu, D. C. Benard, R. S. Goldstein, and T. D. Bradley, “Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure,” *American Journal of Respiratory and Critical Care Medicine*, vol. 151, no. 1, pp. 92–97, 1995.
- [43] D. D. Sin, A. G. Logan, F. S. Fitzgerald, P. P. Liu, and T. D. Bradley, “Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration,” *Circulation*, vol. 102, no. 1, pp. 61–66, 2000.
- [44] Y. Takasaki, D. Orr, J. Popkin, R. Rutherford, P. Liu, and T. D. Bradley, “Effect of nasal continuous positive airway pressure on sleep apnea in congestive heart failure,” *American Review of Respiratory Disease*, vol. 140, no. 6, pp. 1578–1584, 1989.
- [45] H. Wang, J. D. Parker, G. E. Newton et al., “Influence of obstructive sleep apnea on mortality in patients with heart failure,” *Journal of the American College of Cardiology*, vol. 49, no. 15, pp. 1625–1631, 2007.
- [46] T. Kasai, K. Narui, T. Dohi et al., “Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure,” *Chest*, vol. 133, no. 3, pp. 690–696, 2008.
- [47] A. Noda, H. Izawa, H. Asano et al., “Beneficial effect of bilevel positive airway pressure on left ventricular function in ambulatory patients with idiopathic dilated cardiomyopathy and central sleep apnea-hypopnea: a preliminary study,” *Chest*, vol. 131, no. 6, pp. 1694–1701, 2007.
- [48] T. Dohi, T. Kasai, K. Narui et al., “Bi-level positive airway pressure ventilation for treating heart failure with central sleep apnea that is unresponsive to continuous positive airway pressure,” *Circulation Journal*, vol. 72, no. 7, pp. 1100–1105, 2008.
- [49] T. Kasai, K. Narui, T. Dohi et al., “Efficacy of nasal bi-level positive airway pressure in congestive heart failure patients with Cheyne-Stokes respiration and central sleep apnea,” *Circulation Journal*, vol. 69, no. 8, pp. 913–921, 2005.
- [50] H. Teschler, J. Döhring, Y. M. Wang, and M. Berthon-Jones, “Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure,” *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 4, pp. 614–619, 2001.
- [51] S. Sasayama, T. Izumi, Y. Seino, K. Ueshima, and H. Asanoi, “Effects of nocturnal oxygen therapy on outcome measures in patients with chronic heart failure and Cheyne-Stokes respiration,” *Circulation Journal*, vol. 70, no. 1, pp. 1–7, 2006.
- [52] S. Sasayama, T. Izumi, M. Matsuzaki et al., “Improvement of quality of life with nocturnal oxygen therapy in heart failure patients with central sleep apnea,” *Circulation Journal*, vol. 73, no. 7, pp. 1255–1262, 2009.
- [53] T. Toyama, R. Seki, S. Kasama et al., “Effectiveness of nocturnal home oxygen therapy to improve exercise capacity, cardiac function and cardiac sympathetic nerve activity in patients with chronic heart failure and central sleep apnea,” *Circulation Journal*, vol. 73, no. 2, pp. 299–304, 2009.
- [54] J. T. Walsh, R. Andrews, R. Starling, A. J. Cowley, I. D. A. Johnston, and W. J. Kinnear, “Effects of captopril and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure,” *British Heart Journal*, vol. 73, no. 3, pp. 237–241, 1995.
- [55] P. Solin, P. Bergin, M. Richardson, D. M. Kaye, E. H. Walters, and M. T. Naughton, “Influence of pulmonary capillary wedge pressure on central apnea in heart failure,” *Circulation*, vol. 99, no. 12, pp. 1574–1579, 1999.
- [56] A. Tamura, Y. Kawano, S. Naono, M. Kotoku, and J. I. Kadota, “Relationship between β -blocker treatment and the severity of central sleep apnea in chronic heart failure,” *Chest*, vol. 131, no. 1, pp. 130–135, 2007.