Obstructive Sleep Apnea and its Relationship to Cardiac Arrhythmias

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OSA and Cardiac Arrhythmias. Obstructive sleep apnea (OSA) affects approximately 4% of middle-aged men and 2% of middle-aged women. Cardiac arrhythmias are common problems in patients with OSA, even though the true prevalence and clinical relevance of cardiac arrhythmias remains to be determined. The presence and complexity of both tachyarrhythmias and bradyarrhythmias may influence morbidity, mortality, and the quality of life for OSA patients. Although the exact mechanisms underlying the link between OSA and cardiac arrhythmias are not well established, they could be partially the same proposed mechanisms relating OSA to different cardiovascular diseases. OSA is characterized by repetitive pharyngeal collapse during sleep that leads to markedly reduced or absent airflow, followed by oxyhemoglobin desaturation, persistent inspiratory efforts against an occluded airway, and termination by arousal from sleep. These mechanisms elicit a variety of autonomic, hemodynamic, humoral, and neuroendocrine responses that by themselves evoke acute and chronic changes in cardiovascular function. These effects may lead to the development of cardiac arrhythmias and any other form of cardiovascular disease linked to OSA.

The aims of this review are to describe the essential cardiovascular pathophysiological aspects of OSA, to outline the relationship between OSA and both tachyarrhythmias and bradyarrhythmias and their possible influence in the natural history of OSA patients, and to assess the effects of OSA treatment on the presence of cardiac arrhythmias. (J Cardiovasc Electrophysiol, Vol. 18, pp. 1006-1014, September 2007)

Introduction

Obstructive sleep apnea (OSA) is a condition characterized by repetitive pharyngeal collapse during sleep that leads to markedly reduced (hypopnea) or absent (apnea) airflow, followed by oxyhemoglobin desaturation, persistent inspiratory efforts against an occluded airway, and termination by arousal from sleep. Snoring and daytime sleepiness are frequently associated with OSA. Severity of OSA is determined by the apnea-hypopnea index (AHI) measured during polysomnography, which represents the number of obstructive respiratory events per hour of sleep. However, the degree of oxygen desaturation associated with each apneic event, an important factor in the pathophysiology of OSA, is not considered by the AHI. An AHI of less than 10 is considered normal. An AHI of 10–20 is mild, 20–30 is moderate, and more than 30 events per hour characterizes severe OSA.

It has been estimated that OSA affects 4% of middle-aged men and 2% of middle-aged women,† and is strongly linked to obesity. Others major risk factors for OSA are male gender, abnormalities in craniofacial morphology, and increasing age. Apneas and hypopneas exert significant acute and chronic effects on the cardiovascular system, and there is increasing evidence that OSA increases cardiovascular morbidity and mortality.2 Nevertheless, many risk factors for OSA (including male gender, advanced age, and obesity) are the same for cardiovascular disease, which makes it difficult to recognize the role of OSA as an independent risk factor. Cardiovascular diseases related to OSA include systemic hypertension, heart failure, stroke, coronary heart disease, and pulmonary hypertension.3-6

In healthy subjects, sleep is associated with the frequent presence of various types of cardiac rhythm disturbances (sinus bradycardia, sinus pause, first degree, and Mobitz I second-degree AV block). These disturbances are considered physiologic and are related to normal changes in autonomic nervous system activity typical of the different sleep stages. Such a finding generally does not warrant further investigation and treatment. However, for subjects with risk factors for OSA, such as middle-aged male, obesity, habitual snoring, or diurnal sleepiness, the presence of cardiac arrhythmias during sleep must indicate the possibility of OSA, which would most likely be of at least moderate severity. In fact, various kinds of cardiac arrhythmias have been reported to be related to OSA (especially for moderate and severe forms of the disease), which may contribute to cardiovascular morbidity and probably to cardiac mortality in patients with OSA.2-16

Here, we will review data reported on the relationship...
between OSA and cardiac arrhythmias, with special attention to both the possible pathophysiologic mechanisms explaining the high incidence of cardiac arrhythmias in OSA patients and the appropriate management for this patient population. We have already summarized the primary acute and chronic effects of OSA on the cardiovascular system that obviously are also directly or indirectly involved in the pathophysiology of cardiac arrhythmias. The significance of each effect in the development of specific cardiac diseases remains to be determined and is of critical importance.

**Cardiovascular Effects of OSA**

Normal sleep is classified into two categories: nonrapid eye movement (NREM) and rapid eye movement (REM). In NREM sleep, parasympathetic tone increases and sympathetic tone decreases. As a result, a reduction in heart rate, blood pressure, systemic vascular resistance, and cardiac output and an increase in cardiac electrical stability are observed. This state of parasympathetic dominance is cyclically interrupted during the transition from NREM to REM sleep, in which sympathetic tone predominates and heart rate, blood pressure, systemic vascular resistance, cardiac output, and both supraventricular and ventricular arrhythmogenicity increase, similar to levels during wakefulness. Sleep is considered a period of cardiovascular quiescence since NREM sleep accounts for about 75–85% of the sleep time in normal healthy adults.

Cardiovascular consequences of OSA begin with OSA onset and the first apneic event, although patients are usually diagnosed later, usually at middle age when they become symptomatic. Recurrent episodes of cessation of breathing during sleep with futile inspiratory efforts against an occluded upper airway lead to important autonomic, hemodynamic, and neuroendocrine effects owing to repeated arousals and sleep fragmentation, abrupt generation of excessively negative intrathoracic pressure, and decreases in oxygen saturation with subsequent systemic hypoxemia.

**Acute effects of OSA**

The acute effects of OSA occur in association with each individual apneic event during sleep. Systemic hypoxemia and hypercapnia, generation of exaggerated negative intrathoracic pressure, and arousals from sleep are the predominant pathophysiological mechanisms underlying the acute effects of OSA on the cardiovascular system.

1. **Systemic hypoxemia**: Cessation of airflow during apnea results in systemic hypoxemia that leads to progressive chemoreflex-mediated increase in sympathetic activity. This sympathoexcitatory effect of hypoxemia is also amplified by CO₂ retention, which also activates the chemoreflexes. As a consequence of the increased sympathetic nervous system activity, there is an increase in peripheral vascular resistance and chronotropic effects with surges in systemic blood pressure and heart rate, especially during the postapneic ventilatory phase once resumption of breathing occurs. Moreover, hypoxemia may depress both cardiac contractility and cardiac performance, due to repeated acute increases in pulmonary artery pressure and to directly reduced cardiac contractility-related hypoxemia.

2. **Negative intrathoracic pressure**: Ongoing respiratory effort during pharyngeal collapse results in negative intrathoracic pressures reaching even −80 cm H₂O. The intrathoracic pressure determines fluctuations in intrathoracic hemodynamic affecting cardiac preload and afterload. Left-ventricular after load increases as a result of this increase in left-ventricular transmural pressure and venous return to the right heart increases due to a fall of central venous pressure, impairing the left-ventricular filling that reduces left-ventricular preload. Stroke volume and cardiac output are reduced as a result of the combination of increased left-ventricular after load and reduced left-ventricular preload. Such a reduction in cardiac performance is directly related to magnitude of the intrathoracic pressure decrease.

3. **Arousals from sleep**: Arousals terminate apnea through activation of upper airway dilator muscles, which restores airway patency. Arousals are triggered by the effects of hypoxemia, increased ventilatory effort, and hypercapnia, playing an important role against the consequences of extended apneas. Arousals are associated with high levels of cardiac and respiratory activity and may contribute to the development of postapneic surges in blood pressure and heart rate as well as sleep fragmentation, a key factor for the presence of daytime sleepiness, the cardinal symptom of OSA.

**Chronic effects of OSA**

The exact mechanisms underlying cardiovascular complications in OSA patients are still weakly understood. What is known is that OSA exerts a wide variety of chronic neural, vascular, humoral, and inflammatory effects that affect the cardiovascular system.

1. **Autonomic dysregulation**: Patients with OSA have increased heart rates, blunted heart rate variability, and increased blood pressure variability during sleep and even during daytime when awake, as compared with healthy subjects. There is also convincing evidence linking OSA to chronic systemic arterial hypertension. Sympathetic overactivity likely plays an important role in the origin of such findings, although impaired baroreflex, endothelial dysfunction, increased endothelin, and decreased nitric oxide constitute other potential contributing mechanisms in the development of arterial hypertension. Sympathetic nervous system activity is elevated during apneic events and peaks at apnea termination in relation with arousal from sleep. Moreover, untreated OSA patients have higher sympathetic nervous system activity when awake, and continuous positive airway pressure (CPAP) application (the treatment of choice for OSA) attenuates the increase in such activity. Intermittent apnea-related hypoxemia initiates sympathetic activation that might persist after removal of the hypoxic stimulus, and it could be a factor explaining the sympathoexcitatory activity during wakefulness. Additionally, sustained sympathetic hyperactivity could be a key factor for the development of a great variety of inflammatory and metabolic disturbances observed in OSA.

2. **Inflammation**: OSA seems to induce an inflammatory state. Elevations in C-reactive protein, serum amyloid A, tumor necrosis factor-α, interleukin-6, and interleukin-8 plasma levels have been reported and may be reduced by
CPAP therapy. This state may be an important component in the development of cardiovascular diseases in OSA.

3. Vascular endothelial dysfunction: Endothelial dysfunction has been associated with increased risk of cardiovascular disorders. In OSA, the occurrence of recurrent hypoxemia, hypercapnia, and pressure surges following apneic events may result in both endothelial dysfunction and enhanced sustained vascular vasoconstriction by increasing the release of vasoactive substances, such as endothelin-1 that may be decreased by CPAP treatment. The occurrence of impaired endothelial function and other vascular abnormalities may be a predisposing factor to the development of systemic hypertension and other forms of cardiovascular diseases. There are several mechanisms that increase the risk of atherosclerosis in OSA, including sympathetic activation, oxidative stress, vascular endothelial dysfunction, and inflammation. An increased prevalence of markers of systemic atherosclerosis has been reported in patients with OSA including calcified carotid arteries, atheroma, and increased carotid wall thickness.

4. Metabolic abnormalities: OSA may lead to the development of both insulin resistance and to individual components of the metabolic syndrome independently of obesity. Furthermore, metabolic abnormalities associated with the metabolic syndrome and insulin resistance may potentially aggravate OSA. The aforementioned metabolic disturbances may conceivably lead to diabetes mellitus, a chronic effect of untreated OSA. The development of such metabolic abnormalities in OSA might be exacerbated by obesity. OSA patients may be predisposed to weight gain and obesity. One plausible mechanism of this effect is leptin resistance and hyperleptinemia, as observed in OSA. The converse also seems true in that obesity may lead to OSA. It may be related to changes in upper airway muscle tone, effects of fat deposition on upper airway anatomic structures, and changes in central mechanisms of breathing control. As a result, OSA and obesity establish a vicious cycle that contributes to the rise in cardiovascular risk of OSA patients partially by leading to obesity-induced metabolic abnormalities.

5. Oxidative stress: OSA may promote oxidative stress by intermittent hypoxia, which resembles the event of ischemia/reperfusion injury. Several studies have demonstrated increased lipid peroxidation and primed reactive oxygen species generation by blood cells. However, the occurrence of oxidative stress in OSA remains controversial due in part to techniques utilized to measure oxidative stress markers in different studies. Oxidative stress might raise the risk for atherosclerosis in OSA.

6. Procoagulation state: OSA may be causally related to increased coagulation, as suggested by enhanced platelet aggregability, increased hematocrit, blood viscosity, and total serum fibrinogen levels, and reduced fibrinolytic activity, with alleviation of the majority of such abnormalities after adequate CPAP treatment. This procoagulation state is enhanced during sleeping hours and might be a contributing factor in the increased rate of cardiovascular events during such hours in OSA patients.

Potential Mechanisms Linking OSA To Cardiac Arrhythmias

There appear to be multiple mechanisms that might explain the relationship between OSA and cardiac arrhythmias. The presence of OSA alone and the coexistent occurrence of comorbid conditions, which in many patients could be caused or aggravated by OSA, such as obesity, amyloidosis, left-ventricular hypertrophy, heart failure, hypertension, or myocardial ischemia are plausible factors contributing to the development of cardiac arrhythmias (Fig. 1).

Obesity

It has been estimated that OSA is present in approximately 50% of obese subjects, and more than 50% of OSA...
subjects are obese. Prevalence of OSA may be rising as a consequence of increasing obesity, as obesity is the most important modifiable risk factor for OSA. Alternatively, OSA may be related to changes in upper airway muscle tone, effects of fat deposition on upper airway anatomic structures, and changes in central mechanisms of breathing control. Obesity and OSA share multiple cardiovascular pathophysiological mechanisms, such as endothelial dysfunction, insulin resistance, hyperleptinemia, systemic inflammation, and impaired baroreflex or sympathetic overactivity; and it is conceivable that the association of OSA and obesity in the same patient probably increase the rate of cardiovascular events, including cardiac arrhythmias. On the other hand, it is well established that obese subjects have an increased risk of cardiac arrhythmias and sudden cardiac death. Prolonged corrected QT (QTc) interval, increased vasomotor tone and ventricular instability by reducing nitric oxide availability, development of dilated cardiomyopathy, and impairment in autonomic nervous system cardiac modulation are possible mechanisms explaining the development of cardiac arrhythmias in obese subjects.

**Amyloidosis and Inflammation**

Serum levels of amyloid A appear to be increased in patients with moderate to severe OSA and may be pathophysiologically linked to intermittent hypoxemia or sleep deprivation. Although cardiac involvement in amyloidosis is more frequent and severe in primary amyloidosis, it is possible that some OSA patients can develop secondary amyloidosis with cardiac involvement. The myocardial dysfunction from amyloidosis results from the replacement of functional myocardial tissue with amyloid protein, leading to impaired systolic and diastolic function. Infiltration of the His-Purkinje system leads to infra-His conduction system alterations. Amyloid deposited in the atria disturbs myocyte contractility and conduction, enhancing the susceptibility for atrial fibrillation.

There is growing evidence to support the influence of inflammation in the pathogenesis of atrial fibrillation. Historical studies have demonstrated inflammatory infiltrates in atrial fibrillation patients. As mentioned earlier, certain markers of systemic inflammation are elevated in OSA patients and decreased with CPAP therapy. Consequently, the generation of a local inflammatory state in the atria could be involved in the pathophysiology of atrial fibrillation and other atrial arrhythmias in subjects with OSA.

**Systemic Hypertension and Cardiac Hypertrophy**

A direct relationship exists between OSA and both systemic arterial hypertension and left-ventricular hypertrophy. Moreover, treatment of OSA lowers blood pressure and reduces left-ventricular hypertrophy in OSA patients. Approximately 70% of OSA patients are hypertensive, and OSA is now considered an identifiable cause of systemic arterial hypertension. Generally, hypertensive patients suffer from an increased risk of atrial and ventricular arrhythmias, and hypertension is an independent risk factor for systolic and diastolic heart failure. The main arrhythmogenic mechanisms in hypertension are triggered activity with early or delayed afterdepolarizations and reentry. These mechanisms are associated with myocardial ischemia, myocardial fibrosis, increased wall stress, and acute changes of arterial pressure. In hypertension and left-ventricular hypertrophy, the presence of fibrotic areas surrounded by normal tissue leads to nonuniform prolongation of the action potential that may increase dispersion of repolarization or refractoriness favoring reentry. The prevalence of atrial fibrillation is also increased in patients with arterial hypertension; and the development of left-ventricular diastolic dysfunction, either secondary to left-ventricular hypertrophy or due to OSA independently increases the risk for atrial arrhythmias. In addition, the presence of left-ventricular hypertrophy is a strong independent risk factor for future cardiac events, and all cause mortality in the general population; the risk for sudden cardiac death is increased in subjects with left-ventricular hypertrophy, regardless of the cause.

**Systolic and Diastolic Heart Failure**

OSA is more common in patients with heart failure (systolic and/or diastolic) than in subjects with normal cardiac function and may contribute to its origin and progression. This hypothesis is reinforced by the improvement in systolic and diastolic ventricular function observed in OSA patients correctly treated with CPAP. Intermittent arterial blood gas abnormalities, arousals from sleep with increased sympathetic nervous system activity and decreased parasympathetic activity, and large negative swings in intrathoracic pressure are the main pathophysiological mechanism that may potentially affect cardiac function. Cardiac arrhythmias and sudden death are an important source of morbidity and mortality for patients with heart failure. The presence of structural and hemodynamic abnormalities, myocardial ischemia, neurohormonal activation and enhanced sympathetic activation, electrolyte abnormalities, and electrophysiologic changes, such as action potential prolongation, altered calcium handling, and altered potassium currents are the primary mechanisms explaining the occurrence of cardiac arrhythmias in patients with heart failure. The prevalence of cardiac arrhythmias parallels heart failure severity. In light of the added presence of OSA in heart failure patients promoting the progression of heart failure, it is conceivable that treating OSA might reduce the incidence of cardiac arrhythmias in such patient populations. The same could be true for those patients in which OSA may constitute the causal agent of cardiac dysfunction.

**Myocardial Ischemia**

Secondary to each apneic event in OSA, intermittent hypoxemia, sympathetic hyperactivity, and increased left-ventricular after load increases myocardial oxygen demand and can cause myocardial ischemia. This deleterious effect may be stressed if the patient has coronary artery atherosclerosis, a disease that could be promoted by OSA. Intermittent myocardial ischemia, with transient diastolic dysfunction, may lead to myocardial scarring and systolic left-ventricular dysfunction, and also promote potentially malignant ventricular arrhythmias. Atrial ischemia may also contribute to the increased risk for atrial fibrillation. As a result, some cardiac arrhythmias in OSA patients are probably secondary to myocardial ischemia, and the occurrence of ventricular arrhythmias might account for the peak levels of sudden cardiac death during sleeping hours observed in OSA patients.
Mechanical Effects of Apneas

An increase in left-ventricular wall stress caused by abrupt reductions in intrathoracic pressure following each apneic event with subsequent increase in ventricular after load stimulates myocyte hypertrophy, collagen formation, and fibroblasts with an increase in fibrous tissue. These changes will subsequently reduce left-ventricular compliance, leading to diastolic dysfunction and increased left atrial size that may predict incident atrial fibrillation. Atrial stretch secondary to futile inspiratory efforts against the occluded pharynx during apnea also leads to an increase in the left atrial size and predisposes to atrial arrhythmias. In many patients, repeated increases in sympathetic tone and ventricular afterload leads to left-ventricular hypertrophy with potential arrhythmogenesis, as previously detailed.

Hypoxemia and Sympathetic Hyperactivity

Activation of the diving reflex by simultaneous hypoxemia and apnea, with reflex cardiac vagal activation, may induce severe nocturnal bradyarrhythmias (especially during REM sleep\(^{23,24}\)) in the absence of any conduction system disease, which resolve on treatment of the sleep apnea. The diving reflex is a reduction in heart rate due to an increase in cardiac parasympathetic nerve activity, peripheral vasoconstriction on the arterial vascular tree, and an increase in sympathetic activity triggered in response to the cessation of respiration.

On the other hand, enhanced sympathetic nervous system activity related to repetitive hypoxemia and arousals from sleep may play a critical role in the genesis of tachyarrhythmias observed in patients with OSA.\(^{25}\)

Finally, we comment that the prevalence of OSA is not greater in patients with chronic obstructive pulmonary disease than in the general population, but this association, so-called Overlap Syndrome, is not rare since chronic obstructive pulmonary disease and OSA are both frequent diseases. The occurrence of tachyarrhythmias in this subgroup of OSA patients could also be likely related to the need for beta2-agonists treatment.

Arrhythmias in OSA

The whole spectrum of cardiac arrhythmias has been observed in patients with OSA. The cardiac rhythm disturbances in patients with OSA mainly have a nocturnal nature, in contrast with those disturbances occurring in patients with structural heart disease. The risk of cardiac arrhythmias with OSA appears to be related to severity of the disease, such that the great majority of OSA patients presenting significant arrhythmias have moderate or severe forms of the disease.\(^{8,11,13,14,16,26}\) However, the clinical significance and prognostic implications of such an association remain unclear for the majority of patients and remains to be determined.

The most common cardiac rhythm abnormality seen in patients with OSA is marked sinus arrhythmia (also termed cyclic variation of heart rate) characterized by bradycardia during the apneic phase with subsequent tachycardia on resumption of respiration. This arrhythmia is practically omnipresent in patients with severe OSA and has been proposed as a predictor of a positive diagnosis of OSA;\(^{27}\) while sensitive, it lacks enough specificity for OSA. The degree of hypoxemia and changes in autonomic nervous system activity elicited by apneas (the diving reflex) are involved in the mechanism responsible for this phenomenon. Bradycardia is due to parasympathetic hyperactivity, and tachycardia occurs as a consequence of arousal from sleep and vagal withdrawal in the postapneic phase.

Because of their episodic behavior (nocturnal predominance) and paucity of large studies undertaking long-term monitoring, the exact incidence of cardiac arrhythmias associated with OSA is not well known. The most relevant available data on the association of OSA and cardiac rhythm disturbances are summarized below.

Bradyarrhythmias and Conduction Disturbances

Studies investigating the occurrence of cardiac bradyarrhythmias in patients with OSA have provided inconsistent results.\(^{8-16}\) This fact is probably due to differences in the extent of monitoring, number of patients studied and study designs. Moreover, older studies included OSA patients who were not well characterized with respect to underlying heart disease. One of the first studies in this field reported the occurrence of bradyarrhythmias in 18% of patients with severe OSA after evaluation by polysomnography and 24-hour Holter monitoring.\(^{11}\) In a series of 239 OSA subjects, episodes of second and third degree AV block and sinus arrest of more than 2 seconds occurred in 17 patients. Patients with nocturnal bradyarrhythmias were more obese and had severe forms of OSA.\(^{8}\) In 29 OSA patients with documented severe nocturnal bradyarrhythmias, the same group performed an electrophysiological study, and abnormalities in the sinus node function or AV conduction were not found in any of the 29 patients.\(^{28}\)

Importantly, CPAP therapy has been shown to abolish the majority of bradyarrhythmias in OSA patients.\(^{9,14,29-31}\) This information strongly suggests that the appropriate treatment of OSA could avoid the need for pacemaker therapy in some patients in whom bradyarrhythmias are solely related to obstructive respiratory events. Therefore, clinicians must be aware and diagnose and treat patients primarily referred for pacemaker therapy for previously undiagnosed OSA, thus potentially avoiding the need for pacemaker implantation in some patients.\(^{31}\) This idea is further supported by a recent study showing that undiagnosed OSA was present in approximately half of patients with pacemakers implanted for the management of symptomatic bradycardia, AV block, or heart failure.\(^{32}\) Those patients with bradyarrhythmias occurring predominantly during sleep should also be screened for OSA.

Recently, in a subanalysis from the Sleep Heart Health Study,\(^{16}\) an epidemiological longitudinal study from a large community-based sample to determine the cardiovascular consequences of sleep-related disordered breathing, 228 subjects identified with severe OSA were compared with 338 subjects without OSA who were matched for age, sex, race, and body mass index. OSA patients showed an independent increased prevalence of atrial fibrillation, nonsustained ventricular tachycardia, and complex ventricular ectopy during sleep of statistical significance; but contrary to other studies, there was no reported increase in conduction-delay arrhythmia rates. Electrocardiographic data in this study were derived only from the sleep period during an overnight polysomnography. In order to avoid the limitation of such a short period of monitoring and in an attempt to provide information about the night-to-night variability in apnea-related
nocturnal arrhythmias, Simantirakis et al. studied a group of 23 patients with severe (83%) or moderate (17%) OSA, in whom an insertable loop recorder device was implanted for this purpose. All patients were free of any cardiac disease. The occurrence of significant nocturnal bradyarrhythmias was reported in 47% of untreated patients showing a tremendous intrapatient variability during a 2-month period of recording before treatment with CPAP (Fig. 2). The authors also used 48-hour Holter monitoring in this study, and bradyarrhythmias were noted only in 13% of patients. The difference in the observed rate of arrhythmias might be the main clue for the low rate of arrhythmias reported in some previous studies.

The frequency and severity of apnea-related nocturnal bradyarrhythmias correlated with body mass index, the AHI and the degree of oxygen desaturation during the sleep study. No episodes of nocturnal bradyarrhythmias were recorded after 8 months of CPAP application, thus confirming the result of previous works.

Supraventricular Tachyarrhythmias

The presence of nocturnal (usually nonsustained) supraventricular tachycardias, although much less common than significant bradyarrhythmias, has been reported in several studies and CPAP treatment markedly reduced the occurrence of these events in OSA patients.

The occurrence of atrial tachyarrhythmias in patients with OSA was described more than twenty years ago, but only until recently has more detailed information about such a relationship been reported. Patients with a history of atrial fibrillation present a high prevalence of OSA. In a cross-sectional study, Gami et al. found OSA in 49% of 151...
patients with atrial fibrillation, compared with 32% of 373 control patients without atrial fibrillation. Importantly, the association between atrial fibrillation and OSA was independent of gender, age, hypertension, heart failure, and body mass index. The same research group reported that treatment of OSA with CPAP was associated with a significant reduction in arrhythmia recurrence in atrial fibrillation patients following electrical cardioversion, which was likewise independent of age, hypertension, and body mass index. The effect of CPAP application on the recurrence of atrial arrhythmias in OSA patients who have undergone electrical cardioversion is being studied in an ongoing prospective clinical trial. In a recent retrospective cohort study of 3542 subjects without a history of atrial fibrillation, in addition to established risk factors for atrial fibrillation, obesity and severe OSA strongly predicted incident atrial fibrillation in subjects < 65 years old, over an average of 5 years of follow-up (Fig. 3). Importantly, the risks conferred by both conditions, obesity and OSA were independent of one another.

These findings suggest that in a heart susceptible to atrial fibrillation, the presence of OSA would predispose to the subsequent development of atrial fibrillation. Furthermore, the frequent presence of atrial fibrillation in OSA may contribute to the increased risk for stroke and heart failure in this patient population. There are no prospective data addressing a definitive pathogenetic role for OSA in atrial fibrillation. However, in the main epidemiological study addressing the association between OSA and cardiac arrhythmias, the Sleep Heart Health Study, a four-fold increase in the prevalence of atrial fibrillation in subjects with an AHI > 30 has been reported, further supporting such a pathogenetic role. It is plausible to speculate that factors directly related to OSA, such as repetitive hypoxemia, autonomic nervous system imbalance, systemic inflammation, fluctuations in intrathoracic hemodynamic, and diastolic dysfunction may serve as a trigger for atrial fibrillation and may favor the perpetuation of the atrial arrhythmia by altering the atrial substrate.

Ventricular Arrhythmias

In contrast with healthy patients without OSA, an increased rate of ventricular premature beats during sleep, compared with wakefulness, has been long reported in patients with OSA, and a direct relationship with both the degree of nocturnal desaturation and disease severity measured by AHI has also been noted. The proposed increased risk of ventricular tachycardia or fibrillation in OSA patients has not, however, always been observed. In the main study from a community-based sample to evaluate the association between OSA and cardiac arrhythmias, both nonsustained ventricular tachycardia and complex ventricular ectopy (bigeminy, trigeminy, or quadrigeminy) were more common in subjects with OSA than in those without OSA (5.3 vs 1.2%, P = 0.004, for nonsustained ventricular tachycardia; and 25.0 vs 14.5%, P = 0.002, for complex ventricular ectopy). Adjustment for diabetes mellitus, hypertension, lipid profile, and heart failure did not influence the findings.

An increased rate of ventricular arrhythmias in association with sleep-related disordered breathing in patients at high risk for arrhythmias and reduced left-ventricular ejection has been reported, and the potential presence of coexistent undiagnosed OSA in many patients implanted with a defibrillator might contribute to the higher rate of appropriate defibrillator therapies in some subgroups of such patients.

Both untreated OSA patients and heart failure patients are at increased risk of cardiac death, and at least one-third of heart failure patients have coexistent OSA. Ryan et al. studied the effects of CPAP usage on ventricular premature
beats in a randomized controlled trial of 18 heart failure patients who had >10 ventricular premature beats per hour of sleep. The group of patients treated with CPAP experienced a 58% reduction in ventricular premature beats, as well as a reduction in daytime systolic pressure and increased left-ventricular ejection fraction and overnight urinary norepinephrine.

All the aforementioned data provide a possible explanation for the observed increase in sudden nocturnal cardiac death in OSA patients,22,41,42 but future studies are necessary to elucidate the exact mechanisms of death in this patient population.

**Sudden Cardiac Death**

The highest risk for sudden cardiac death in the general population is around the time of waking from sleep (6:00 a.m.–10:00 a.m.). In 60–80% of cases, sudden cardiac death occurs in the setting of coronary artery disease, and for those patients sudden cardiac death is mainly caused by ventricular tachycardia degenerating into ventricular fibrillation. In contrast, sudden cardiac death seems to occur more commonly during sleeping hours in patients with OSA,22,41,42 Gami et al.22 have reported a higher sudden cardiac death rate during sleep time (12 midnight to 6:00 a.m.) in patients with OSA (relative risk of 2.57). The authors retrospectively reviewed the cases of 112 patients who died suddenly and had previously undergone polysomnography. Almost half of the patients with sleep apnea died during sleep hours, compared with 21% of those without OSA, and that temporal pattern was also directly associated to disease severity with increased risk observed with mild-to-moderate OSA and a higher risk with severe OSA (Fig. 4). In view of this intriguing information, it is conceivable to think that OSA could play an important role in triggering sudden death during sleep by effects on myocardial ischemia and cardiac arrhythmias.

Whether OSA is an independent cause of increased risk for sudden cardiac death is unknown. Likewise, the real mechanisms responsible for sudden cardiac death during sleep in OSA patients remain unknown, although malignant ventricular arrhythmias or severe bradyarrhythmias are likely implicated.

A recent area of research has been the role of cardiac pacing as a novel form of treatment for patients with OSA. A provocative study by Gaggue et al.43 demonstrated a significant reduction in the number of respiratory events (reduced AHI) when OSA patients who were already being paced for symptomatic bradycardia were subjected to atrial overdrive pacing, as compared with baseline conditions. Unfortunately, subsequent studies have not confirmed this finding.44 Although further investigation is needed, it is possible that atrial overdrive pacing could play a beneficial role in sleep apnea in patients with heart failure who also have significant bradyarrhythmia.45

**Conclusions**

OSA is a very common disorder, although a high percentage of patients in the general population remain undiagnosed. Cardiac arrhythmias are frequently observed in patients with OSA, especially in those with moderate or severe degrees of this sleep-related disordered breathing. The pathophysiological mechanisms on the cardiovascular system elicited by repetitive obstructive respiratory events as well as comorbid conditions frequently present in patients with OSA are probably responsible for the occurrence of cardiac rhythm disturbances. The true clinical importance of these arrhythmias as well as the preventive and therapeutic role of OSA treatment for the occurrence of cardiac arrhythmias still need to be determined in future prospective studies.

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