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Sleep-Related Breathing Disorders and Cardiac Arrhythmia

Ahmad Salah Hersi
King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia

1. Introduction

Sleep-disordered breathing (SDB) includes a range of conditions characterized by abnormalities in the frequency and/or depth of breathing during sleep. Cessations in breathing rhythm (apneas) are momentary and often cyclical, while reductions in breath amplitude (hypopneas) may be momentary or sustained (Dempsey et al., 2010). Obstructive sleep apnea (OSA)/hypopnea syndrome (HS), obesity hypoventilation syndrome, central sleep apnea (CSA), upper airway resistance syndrome, and Cheyne-Stokes respiration (CSR) are the primary sleep-related respiratory disorders.

Although CSA is accompanied by alterations in neural input, the obstruction characteristic of OSA, the most common form of SDB, is also neurally mediated (Veasey, 2009). Intermittent episodes of partial or complete obstruction of the upper airway during sleep characteristic of OSA result from collapse of the upper airway. The concomitant disruption of normal ventilation and sleep architecture is typically associated with snoring, repeated arousals from sleep, and daytime sleepiness (Bradley & Floras, 2003; Lattimore et al, 2003; Quan & Gersh, 2004; Shamsuzzaman et al; 2003;).

Prevalence studies indicate that SDB, and particularly OSA, are common problems worldwide, affecting millions of individuals. However, OSA is also considered to be largely undiagnosed (Young et al, 1993; Young et al, 2002; Lavie, 2007). In the United States, for example, the estimated proportions of adults with OSA who are not diagnosed range from 60% to 80%, with an even greater under diagnosis suspected for children (Carter III, 2008). The increasing prevalence can be intuitively associated with the global obesity epidemic; however, a reverse association has also been postulated based on emerging evidence that OSA promotes weight gain (Carter III, 2008).

The clinical relevance of OSA was thought for years to be limited to what was considered a benign but often annoying manifestation as snoring, ranging to the possibly serious consequences of daytime sleepiness affecting cognitive function and work performance, mental state, and driving ability. OSA is now known to be a risk factor for other serious conditions, and has been associated with increased cardiovascular morbidity and mortality (Bradley & Floras, 2009; Devulapally et al., 2009; Lattimore et al, 2003; Lopez-Jiminez et al., 2008). Cardiac arrhythmias are common in OSA, and the potential link between tachyarrhythmias and bradyarrhythmias and adverse outcomes in OSA patients continues to be an important area of research (Chan & Wilcox, 2010; Verrier & Josephson, 2009). However, the complex cascade of events triggered by OSA, the difficulty in determining

cause and effect from the preponderance of observational studies addressing these issues, lack of standardization of variable definitions, and heterogeneous patient samples allowing the influence of a multitude of confounders have been a constraint to producing consistent and definitive explanatory. Study variations complicate comparisons among reports, and require that sufficient individual design details are considered when evaluating the results of each study. Despite these limitations, our rapidly expanding knowledge promises to provide guidance for the assessment and management of patients both with SDB and arrhythmias.

2. Epidemiology and diagnosis of SDB

The worldwide recognized prevalence of OSA accompanied by daytime sleepiness is estimated to be 3% to 7% for adult men and 2% to 5% for adult women in the general population, with higher risks reported for some subgroups (Punjabi, 2008). OSA with or without daytime sleepiness may reach 24% in men and 9% in women by middle age (Young et al., 1993).

The main risk factors for SDB include obesity, upper airway obstruction including abnormalities of craniofacial morphology, and male gender (Parati et al., 2007; Partinen, 1995; Young et al., 1993; Young et al., 2002). Age also plays a role; however, the effect of age on SDB prevalence is not linear. The Sleep Heart Health Study reported a plateau effect in age-related prevalence beginning at approximately 60 years of age (Young et al., 2002a). In addition, SDB in the elderly may be different from the typical SDB of middle age. In one study, increased age, obesity, and snoring were significantly associated with progression of apnea in subjects aged 30 to 60 years at baseline; however, other studies suggest little or no association among these and other common OSA correlates of middle age with OSA in the elderly (Young et al., 2002b).

2.1 REM and nonREM sleep

Sleep stages include rapid eye movement (REM) and nonREM sleep. NonREM sleep typically comprises 75% to 85% of the sleep time in adults, and is characterized by decreased metabolic demands, relative autonomic stability with dominant vagus nerve activity, high baroreceptor gain, and stable sympathetic nerve activity (Arias & Sanchez, 2007; Somers et al, 1993; Verrier & Josephson, 2009). During stage 4 of nonREM sleep, that is, during deep sleep, cardiovascular system input is reduced by more than half compared with that of wakefulness. Parasympathetic tone increases and sympathetic tone decreases durn nonREM sleep. The resultant increase in vagal nerve activity elicits bradycardia, and during the transition from nonREM to REM sleep bursts of vagal nerve activity can produce asystole or pauses in heart rhythm. REM sleep, occurring at approximately 90 minute intervals of increasing length during sleep, is characterized by surges in cardiac sympathetic nerve activity that can reach levels higher than those achieved during wakefulness, and is accompanied by suppression of efferent vagus nerve tone and reduced baroreceptor gain. During this time of increased brain excitability, breathing patterns are also irregular. The apneic events of SDB have been shown to occur in both REM and non-REM sleep; however, a recent study showed that when SDB occurred only during REM sleep, SDB was not associated with sleepiness, impaired quality of life, or difficulty maintaining sleep (Chami et al., 2010).

2.2 Diagnosing SDB

The polysomnogram is considered the "gold standard" for OSA diagnosis. Measuring multiple physiological signals during sleep, including electroencephalography, electro-oculography, electrocardiography, electromyography, nasal airflow, respiratory effort (thoracic and abdominal impedence), pulse oximetry, snoring (tracheal microphone), and leg and sleep position allows identification and classification of apneas and hypopneas.

Obstructive, central, and mixed apneas can be distinguished based on the presence of a ventilatory effort during the event. Decreased upper airway muscle activation can result in a collapsible pharyngeal airway and produce an obstructive event, which is not uncommon in the unstable ventilatory control experienced by patients with CSR and CSA, resulting in both central and obstructive events in these patients (Somers et al., 2008).

According to the American Academy of Sleep Medicine (AASM), an apnea is a complete cessation of airflow for ≥10 seconds (Iber et al., 2007). A hypoponea is a ≥30% decrease in airflow from baseline of ≥10 seconds associated with a 4% oxygen desaturation, or a ≥50% reduction in airflow from baseline for ≥10 seconds associated with either a 3% oxygen desaturation or electroencephalographic data supporting a cortical microarousal from sleep. The apnea-hypopnea index (AHI) quantifies the average number of apneas and hypopneas per hour of sleep. The AASM defines OSA categories based on AHI as well as the extent of daytime sleepiness, with mild OSA having an AHI of 5 to 15 (Table 1)(AASM, 2008). Some restrict using the term OSA to indicate an AHI ≥5, and reserve the term OSA syndrome (OSAS) for when symptoms are also present, especially excessive daytime sleepiness (EDS) (Lee et al., 2008; Young et al., 2002b).

Type	AHI	Attention Requirements of Activities Affected by Involuntary Sleepiness
Mild	5-15	Little (e.g., watching TV, reading)
Moderate	15-30	Some (e.g., meetings, presentations)
Severe	>30	More Active (e.g., talking, driving)

KEY: AHI - apnea/hypopnea index

Table 1. AASM Obstructive Sleep Apnea Classification

EDS is typically measured by a subjective rating using questionnaires that have 3 to 5 items (Lee et al., 2008). The Epworth Sleepiness Scale, comprising 8 questions, is also commonly used. Among the physiological disturbances produced by apneic events, oxygen desaturation indexes more reliably predict sleepiness relative to other polysomnographic parameters including sleep time, AHI, or arousal index (Engleman & Douglas, 2004; Kingshott et al., 2000; Tihonen et al., 1998).

Categorization of apnea is often arbitrary, and studies frequently use different definitions of OSA and its severity, which seriously complicates comparisons among reports. Although the AHI alone is often considered adequate to define the severity of OSA, polysomnography results are sometimes presented as the respiratory disturbance index (RDI), which includes respiratory event related arousals (RERAs) that do not technically meet the definition of apnea or hypopnea, in addition to hypopnic and apneic events.

3. Evidence linking SDB to arrhythymia

The multiple physiologic and anatomic events associated with sleep apneas are conducive to the development of cardiac arrhythmias. Several observational studies have shown an association between OSA and the spectrum of arrhythmias (Table 2). Some tachyarrhythmias, such as persistent supraventricular tachycardia, atrial fibrillation (AF) or flutter, and ventricular arrhythmias, in particular sustained or nonsustained ventricular tachycardia, have been shown in some studies to be more likely to occur in the setting of preexisting structural heart disease (Grimm et al., 1996).

3.1 Cardiac arrhythmias in community-based studies and in subjects referred for sleep testing

In the seminal study by Guilleminault et al. (1983), 48% of 400 patients with OSA were shown by 24-h Holter monitoring to have arrhythmias, which included 18% with bradycardia. There is some indication that longer monitoring may be warranted, as shown by the results in a small sample of 23 patients with moderate or severe OSA who underwent 2 months of monitoring with an insertable loop recorder (Simantirikas et al., 2004). Almost half (47%) were shown to have severe cardiac rhythm disturbances, of whom all but 2 had severe bradycardia.

In a study of 247 patients with OSAS who had been referred for polysomnography who were shown to have an AHI >=5 and daytime symptoms, 46 (18.6%) had rhythm disturbances during sleep (Olmetti et al., 2008). Tachyarrhythmias occurred in 35 (14.2%) and bradyarrhythmias in 11 (4.4%) patients. All bradyarrhythmias occurred during an episode of apnea or hypopnea, while 13 (37%) tachyarrhythmic events occurred either during the episode or during the subsequent phase of recovering ventilation. Premature ventricular complex events occurred throughout the recording interval without association with sleep or wakefulness. The OSA in bradyarrhythmia patients was significantly more severe than that in tachyarrhythmia patients. Although patients with bradyarrhythmia compared with those without arrhythmia had a significantly greater AHI (58.8 vs. 27.3; P=.02), mean desaturation amplitude (8.9 vs. 5.9; P=.03), and a lower oxygen saturation nadir (69% vs. 77%; P=.003), they were similar in BMI (34.5 vs. 36.1) and age (51.8 vs. 53.6). The prevalence of bradyarrhythmia was, however, significantly higher in patients with AHI >=30 (7.8%) compared with patients with AHI <30 (1.5%; OR 5.33; 95% CI: 1.13, 25.3; P=.03). Conversely, OSA patients with tachyarrhythmia were not different from those without arrhythmias with respect to AHI, mean desaturation amplitude, and oxygen saturation nadir, nor was the prevalence of tachyarrhythmia in patients with AHI >=30 (15.5%) different from that in patients with AHI <30 (13.0%). COPD was the only comorbidity associated with either arrhythmia, with tachyarrhythmia more common in patients who had both COPD and OSA than it was in patients who had OSA alone (OR 2.53; P=.03).

Study (N)	%	Arrhythmia
Tilkian et al., 1977 (15)	93	Marked sinus arrhythmia
	40	Extreme sinus bradycardia
	33	Asystole
	13	Second-degree AV block
	67	VA-complex premature ventricular beats
	13	VT
Guilleminault et al., 1983 (400)	18	Bradyarrhythmia
	2	Sustained VT
	11	Sinus arrest
	8	Second-degree AV block
	19	Frequent premature ventricular contractions
Flemons et al., 1993 (263)	1.3	Complex ventricular ectopy (including VT)
	2.6	Frequent premature ventricular beats
	1.3	Second-degree AV block
	5.2	Sinus arrest
Becker et al., 1995	7	Sinus arrest and AV block
Mooe et al., 1996 (121) Incident AF in CABG patients pre-discharge	32	AF with AHI >=5
	18	AF with AHI <5
Javaheri et al., 1998 (81)	22	AF (all patients with HF)
Simantirakis et al., 2004 (23)	48	Rhythm disturbances
Mehra et al., 2006 (566)	4.8	AF
	5.3	Nonsustained VT
	25	Complex ventricular ectopy
Mehra et al., 2009 (3135 men ≥65 years of age)	4.7	AF
	36	Complex ventricular ectopy

KEY: AF - atrial fibrillation, AHI - apnea/hypopnea index, AV - atrioventricular, CABG - coronary artery bypass graft, VA - ventricular arrhythmias, VT - ventricular tachycardia

Table 2. Prevalence of Cardiac Arrhythmias in Obstructive Sleep Apnea

The community-based Sleep Heart Health Study, which compared arrhythmia prevalence in 228 persons with (RDI ≥30) and 338 persons without (RDI <5) SDB, provided important data on the risk of complex arrhythmias in persons of both genders who were at least 46 years of age (Mehra et al., 2006). After adjusting for age, sex, BMI, and prevalent coronary artery disease (CAD), risk for arterial fibrillation (OR 4.02; 95% CI: 1.03, 15.74), nonsustained ventricular tachycardia (OR 3.40; 95% CI: 1.03, 11.20), and complex ventricular ectopy (OR 1.74; 95% CI: 1.11, 2.74) remained almost 2- to 4-fold greater in persons diagnosed with OSA.

Trigeminy, supraventricular tachycardia, and all conduction delay arrhythmias were not significantly different between subjects with and without SDB on univariate analysis.

Other community-based studies also failed to show an increase in conduction delays in persons with SDB compared with those without SDB. There was also no difference in conduction delay arrhythmias according to SDB severity in data from the elderly men in U.S. MrOS Sleep Study (Mehra et al., 2009), and conduction delay prevalences in subjects with and without OSA in the Norwegian Akershus Sleep Apnea Project (ASAP) were similar (Namtvedt et al., 2011).

The ASAP study, which included randomly recruited subjests from the general Norwegian population, showed similarities with other reports; for example, ventricular premature complexes occurred significantly more frequently both at night and during daytime in the presence of OSA, defined as AHI ≥5 (Namtvedt et al., 2011). Increases in AHI were significantly associated with an increased prevalence of ventricular premature complexes, which remained after adjusting for clinically relevant confounders. In addition to conduction delays, supraventricular arrhythmias, including atrial fibrillation, were not different between subjects with and without OSA in this study.

Diagnosis of 1456 Japanese patients suspected of having sleep apnea revealed 97.0% had at least mild (AHI ≥5) sleep apnea (Abe et al., 2010). CSA, defined as having more than 50% central apneas, was diagnosed in 62 patients. OSA in the remaining 1412 patients was classified according to mild, moderate, and severe OSA, using AASM levels. The occurrence of paroxysmal AF (P=.051), premature atrial complex (P=.005), premature ventricular complex (P=.004), sinus bradycardia (P=.036), and sinus pause (P<.001) were increased with increasing OSA severity. Nonsustained ventricular tachycardia and second- and third-degree atrioventricular block were not related to OSA severity; however, prevalence was very low, with no cases in subjects without OSA, and prevalence ranging from 1.0% to 1.3%, 0.3% to 1.3%, and 0% to 0.1% among OSA the 3 OSA severities for these 3 arrhythmias, respectively.

This was contrasted by data from the Sleep Heart Health Study where 5.3% of subjects with SDB had nonsustained ventricular tachycardia compared with 1.2% of subjects without SDB (P=.004)(Mehra et al., 2006). Complex ventricular ectopy (25.0% vs. 14.5%; P=.002) and atrial fibrillation (4.8% vs. 0.9%; P=.003) were also significantly more prevalent in subjects with SDB.

Other studies have failed to show a difference in atrial fibrillation prevalence between subjects with and without SDB, or in the prevalence of SDB in patients with and without atrial fibrillation (Roche et al., 2003). Requiring an AHI of at least 15 as diagnostic for OSA, a case control study failed to show a difference in OSA prevalence between 59 patients with lone atrial fibrillation (i.e., without chronic or acute risk factors) and controls who were age, gender, and co-morbidity matched controls (32% vs. 29%; P=0.67)(Porthan et al., 2004).

Another study (Leung et al., 2005) that excluded patients with a history of congestive heart failure (CHF), CAD, or stroke, enrolled 60 patients each without SBD, with CSA, and with OSA. The prevalence of atrial fibrillation was significantly higher in patients with CSA (27%) compared with OSA (1.7%) or no SBD (3.3%; P<.001). Patients with OSA had more hypertension and more extreme oxygen desaturation.

Nocturnal bradycardia was present in 17 of 239 (7%) patients with OSA who were diagnosed using a validated ambulatory recording device that measured heart rate, oxygen saturation, snoring, and body position (Becker et al., 1995; Koehler et al., 2000). Patients with bradycardia were then given polysomnograms. Two-thirds of 1575 bradyarrhythmic events

recorded during 24-hour Holter ECG monitoring occurred during REM sleep, and all occurred concomitant with an apneic or hypopneic event. Oxygen saturation was similar in patients with and without bradyarrhythmia at the beginning of the apnea or hypopnea; however, end values were significantly lower in patients with bradyarrhythmia. RDI was significantly higher in patients with bradyarrhythmias, who had an RDI of at least 60. However, 80 patients with an RDI >=60 did not have bradyarrhythmia. BMI was also significantly higher in patients with bradyarrhythmias, and the authors concluded that the obesity and high RDI associated with the bradyarrhythmias may be interrelated in their development.

3.2 OSA in patients with cardiovascular disease

Javaheri et al. (1998) recruited 81 ambulatory men with stable heart failure for polysomnography and nocturnal Holter monitoring. In previous studies, these authors had used an AHI threshold of 20 to classify sleep apnea; however, for this study the threshold was set at AHI ≥15 to accommodate patients with a lower AHI but with significant arterial oxyhemoglobin desaturation. Forty-one (51%) patients had sleep apnea, with a mean AHI of 44 ± 19. Compared with patients without sleep apnea, patients with sleep apnea were more likely to have atrial fibrillation (22% vs. 5%; P=.026), with a non-significant higher prevalence of nocturnal ventricular tachycardia (51% vs. 37%; P=.23). The mean numbers of premature ventricular depolarizations (P=.0002) and couplets (P=.0001) were significantly higher in sleep apnea patients, with a non-significantly higher ventricular tachycardia rate (P=.07). When Sin et al. (1999) compared the prevalence and characteristics of CSA and OSA in 450 patients with CHF, the prevalence of CSA (33%) was similar to that of OSA (38%) using a threshold for SDB of AHI 10; however, atrial fibrillation was significantly greater in CSA patients (23.0%) compared with OSA patients (11.9%) and with patients without SBD (7.5%; P<.05).

Sleep apneas have been suggested to play a role in the recurrence of arrhythmias following successful therapy. In a study of 44 patients with sustained ventricular tachycardia without heart failure or other structural heart disease who underwent catheter ablation therapy, 17 (39%) were diagnosed with sleep apnea by polysomnography using a threshold of AHI ≥10 (Koshino et al., 2010). Arrhythmia recurrence in successfully ablated patients with apnea (5/11, 45%) was significantly greater than that in patients without sleep apnea (1/17, 6%; P=.02).

When sleep studies were performed in 45 patients with implantable cardioverter defibrillators (ICD), over half (57.87%) were diagnosed with SDB, using a threshold of AHI ≥10 (Zeidan-Shwiri et al., 2011). The mean number of ventricular arrhythmias was significantly higher in patients with SDB (P=.03). A significant increase in the number of ventricular arrhythmias occurred with increasing AHI quartiles (0–7, 8–11, 12–33, and 34–66 events/h; P=.003), as seen in other studies (e.g., ventricular premature complexes in the general population study of Namtvedt et al., 2011). Increases in ventricular arrhythmias in the ICD patients were predominantly related to increased ventricular arrhythmic events occurring from midnight to 6 a.m. SDB was a significant, independent predictor of nocturnal appropriate ICD therapy after adjusting for baseline variables including age, BMI, and serum creatinine (OR 3.8; 95% CI: 1.2, 12.1; P=.02). Similar results were reported by Serizawa et al. (2008), who enrolled 71 patients with heart failure and an ICD, of whom 47 (66%) were diagnosed with SDB, also using an AHI threshold of 10. Appropriate ICD therapies occurred more frequently in SDB patients (43%) compared with those without

SDB (17%; P=.029). In addition, ICD therapy from midnight to 6 a.m. was more frequent in patients with (34%) than in those without (13%) SDB (P=.046), and SDB was an independent predictor for appropriate ICD therapy in multivariate analysis (HR 4.05; 95% CI: 1.20 , 13.65; P=.015).

The recurrence rate of atrial fibrillation during 1-year of follow-up in 39 patients who underwent DC cardioversion for atrial fibrillation/atrial flutter was compared with that in 79 postcardioversion patients (controls) who did not have a previous sleep study (Kangala et al., 2003). Recurrence in 27 OSA patients who received no treatment for their OSA was 82%, compared with 42% for those with treated OSA (P=.013), and 53% in the control group (P=.009). Comparing nocturnal decrease in oxygen saturation in untreated OSA patients with recurrence of atrial fibrillation with that of untreated patients without a recurrence revealed a significantly greater decrease occurred in untreated OSA patients (18% vs. 8%; P=.034), who had a greater portion of sleep time with oxygen saturation <90% (23% vs. 4%; P=.063). The increased risk of recurrence of atrial fibrillation in untreated patients with OSA in this study prompted the authors to propose that patients with atrial fibrillation should be screened for OSA; and, similarly, OSA patients should be screened for atrial fibrillation.

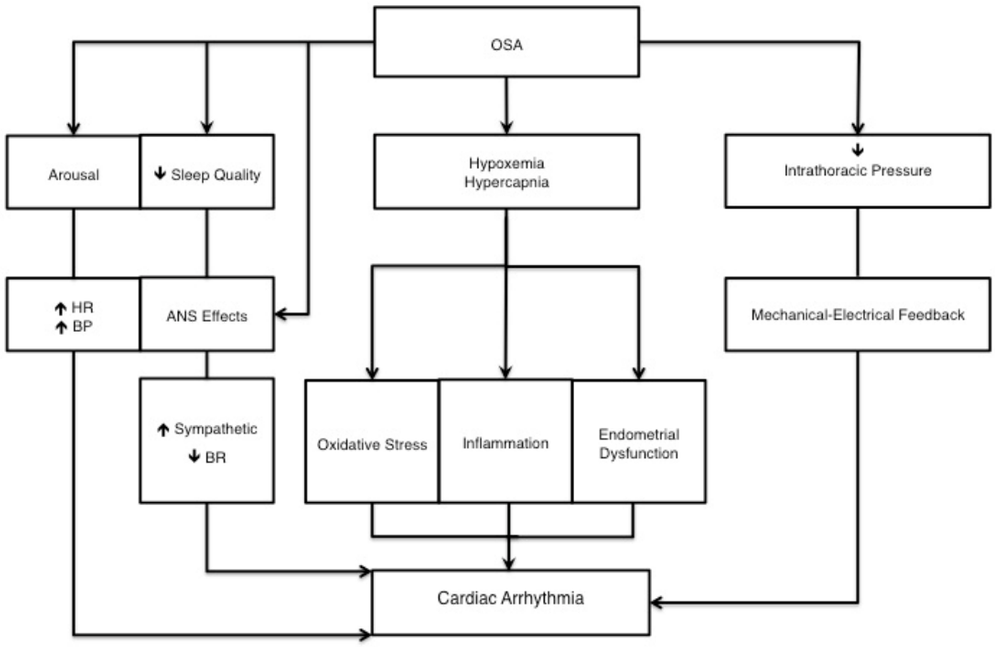
Gami et al. (2004) compared the prevalence of OSA, diagnosed using the Berlin questionnaire, in 151 patients undergoing cardioversion for atrial fibrillation with the prevalence in 312 general cardiology practice patients.r Significantly more patients with atrial fibrillation had OSA compared with the general cardiology group (49% vs. 32%; P=.0004); with a multivariate adjusted OR for the association between atrial fibrillation and OSA of 2.19 (95% CI: 1.40, 3.42; P=.0006). To accommodate any misclassifications that might have occurred without using polysomnography for diagnosis, a separate analysis adjusted patient numbers per group using validation data acquired from 44 patients on whom polysomnography was performed. After decreasing OSA in the atrial fibrillation group by the false-positive rate and increasing it in the general cardiology group by the false negative rate, the difference in prevalence between the 2 groups remained statistically significant (48% vs. 37%, P=.022). These authors also concluded that the presence of OSA should be considered in all patients with atrial fibrillation, particularly those with obesity or hypertension. This should be considered particularly sage advice considering the current epidemic increase in atrial fibrillation and its associated morbidity and mortality (Steinberg, 2004).

The incidence of post surgical atrial fibrillation in 121 consecutive coronary artery bypass surgery patients was assessed by Mooe et al. (1996). All patients underwent preoperative diagnosis of disordered breathing, defined as AHI ≥5 or an oxygen desaturation index (ODI) ≥5. Atrial fibrillation was diagnosed in 25 of 78 (32%) patients with AHI ≥5 compared with 7 of 39 (18%) of patients with AHI <5 (P=.11), and in 19 of 49 (39%) patients with ODI ≥5 compared with 13 of 72 (18%) patients with an ODI <5 (P=.02). Using ODI ≥5, disordered breathing was an independent predictor of atrial fibrillation in a multiple-logistic regression model (RR 2.8, 95% CI: 1.2, 6.8).

In summary, these studies revealed some differences and similarities in the manifestation of arrhythmias associated with SDB. For example, bradyarrhythmias, premature ventricular complexes, and atrial fibrillation have been shown in some studies to be increased with increasing severity of SDB, while no effect of SDB severity was shown for tachyarrhythmias. Bradyarrhythmias occur with the apneic or hypopneic event, while tachycardias also occur during recovery. Finally, premature ventricular complexes have been shown to occur during waking hours as well as during sleep in patients with SDB. These results indicate the importance of identifying the mechanisms associating SDB with cardiac arrhythmias.

4. Pathophysiological mechanisms of arrhythmia in SDB

The exact mechanisms linking SDB and arrhythmia are not completely understood, as there are several complex and interrelated pathways by which arrhythmias may be produced or become more severe in the presence of SDB. Autonomic, hemodynamic, chemical, inflammatory, and metabolic mechanisms may be involved to varying degrees in relation to patient demographic and health characteristics (Figure 1). Research is ongoing, with the understanding that exploring the physiological effects of SDB should not be limited to sleep, as patients with sleep apnea exhibit elevated sympathetic nerve activity and blood pressure during wakefulness (Verrier & Josephson, 2009).



KEY: ANS – autonomic nervous system, BP – blood pressure, BR – barorecptor gain, OSA – obstructive sleep apnea

Fig. 1. Obstructive Sleep Apnea and Cardiac Arrhythmia – Possible Mechanisms

The increased risk of arrhythmias and sudden cardiac death in obesity is well known, and the common occurrence of SDB in obese subjects suggests overlapping mechanisms may contribute to arrhythmia development in these patients. Prolonged corrected QT (QTc) interval, increased vasomotor tone and ventricular instability, development of dilated cardiomyopathy, and impairment in autonomic nervous system cardiac modulation may be involved (Arias & Sanchez, 2007). Intermittent hypoxemia, sympathetic hyperactivity, and increased left-ventricular after load that occur secondary to each apneic event in OSA impose an additional burden.

The severity of OSA was shown to be independently associated with elevated inflammatory markers, including C-reactive protein (Shamsuzzaman et al., 2002), which is also elevated in atrial fibrillation (Chung et al., 2001). Decreases in some of these markers have been reported when OSA was treated with continuous positive air pressure (CPAP) therapy (Arias & Sanchez, 2007; Svatikova et al., 2003).

Some generalized mechanisms that may be involved with SDB and its effect on arrhymogenesis have been described, which are often linked to the specific type of arrhythmia evoked. For example, apneas are known to induce several arrythmogenic dysregulations including alterations in cardiac sympathetic and parasympathetic activity, myocardial hypoxemia (Schafer et al., 1997), and deformation of the cardiac chambers resulting from intrathoracic pressure fluctuations (Condos et al., 1987).
Mechanisms related to specific sleep stages may also impact the development of arrhythmias in SDB. REM-induced cardiac events may include both direct effects, such as alterations in electrophysiological stability, or indirect effects on heart rate and arterial blood pressure. Subsequent platelet aggregation or plaque disruption can be associated with the release of arrhythmogenic molecules. Metabolic imbalances can stimulate neural activity that results in myocardial ischemia or arrhythmias. Some studies have shown that arrhythmias were more common in SDB patients who had severe nocturnal hypoxemia during REM sleep (Findley et al., 1985; Shepard et al., 1985).

4.1 Ventricular arrhythmias

Surges in sympathetic nerve activity during REM sleep have been suggested to cause nocturnal ventricular arrhythmias and myocardial ischemia in patients with cardiovascular disease (Nowlin et al., 1965). The purported decrease in vagus nerve activity and unopposed cardiac sympathetic nerve activity in these patients may foster development of ventricular tachycardia and fibrillation (Verrier & Josephson, 2009).
The surge in arterial blood pressure and sympathetic nerve activity that occur with apneas may explain the temporal association between the apnea and the onset of nonsustained ventricular tachycardia (Monahan et al., 2009; Somers et al., 1995; Somers et al., 2008). In one sub-study from the Sleep Heart Health Study, polysomnograms from 57 patients with 62 episodes of paroxysmal atrial fibrillation or nonsustained vetricular tachycardia (NSVT) were reviewed (Monahan et al., 2009). Respiratory disturbances (apneas or hypopneas) occurring during hazard periods defined as the 90s intervals preceding an AF event were compared with those occurring during referent control periods in the same subject. Approximately three-fourths (n=47; 76%) of the events were NSVT, and two-thirds (68%) occurred in nonREM sleep (atrial fibrillation: 80%; NSVT: 64%). The overall risk of occurrence after a respiratory disturbance was 17.5-fold greater (95% CI: 5.3, 58.4) than the risk of an event during normal nocturnal breathing, and was similar for each arrhythmia type (atrial fibrillation OR: 17.9; NSVT OR: 17.4). When each variable was considered independently, there was no association between EEG-defined arousal or hypoxia and arrhythmia risk. Based on this data, the authors postulated that additional mechanisms may be involved in the link between sleep-related respiratory disturbances and arrhythmias, including large changes in intrathoracic pressure and stimulation of baroreflexes (Gami et al, 2008). However, they also suggested that the small number of respiratory disturbances in their study may have inhibited detection of an effect. In fact, others have suggested that the oxygen desaturation that occurs with apnea may be involved as an independent risk factor for ventricular arrhythmia (Bradley & Flores, 2003a; Bradley & Flores, 2003b).

4.1.1 The MrOS sleep study - A model for design and analysis of community-based studies

The MrOS Sleep Study, an ancillary cohort of the multicenter Osteoporotic Fractures in Men Study, enrolled 3135 men ≥65 years of age to explore the association of SDB with complex

ventricular ectopy (CVE) and nocturnal atrial fibrillation in elderly men (Mehra et al., 2009). This elaborate study warrants detailed discussion. The design included clearly defined variables across SDB severities and types, supported by rigorous, standardized data collection from a large, community-based sample. The study investigated the occurrence of nocturnal CVE and atrial fibrillation as primary endpoints, and also evaluated the occurrence of any atrial arrhythmias, other ventricular arrhythmias, and conduction delay arrhythmias. Polysomnography data were used to produce RDI data, which provided an overall severity of SDB by including both obstructive and central apneas per hour, summarized into quartiles. The upper limit of the lowest quartile was only slightly above the commonly used threshold for SDB (<5.9 vs 5, respectively); therefore, the lowest quartile was approximately equivalent to no SDB. An obstructive AHI index (OAHI), limited to obstructive events, was also categorized by quartile. A Central Apnea Index (CAI) was created from categories made from the distribution of data for central apneas/hour of sleep. Categories were prepared from percent of total sleep time (TST) with arterial oxygen saturation <90% (defining hypoxia) that accommodated the right-skewed data distribution.
In the MrOS Sleep Study, 1048 (36%) subjects had CVE. There was a significant association between the fourth quartile of OAHI severity (RDI ≥23.9) and CVE (adjusted OR 1.37; 95% CI: 1.08, 1.75); however, the relationship between CSA and CVE was not significant after adjusting for confounders including cardiovascular disease. CVE was also associated with hypoxia, with both unadjusted and unadjusted ORs significant when at least 10% of TST was spent at <90% oxygen saturation (adjusted OR 1.62; 95% CI: 1.23, 2.14). The authors concluded that CVE is more likely to result in patients who experience intermittent hypoxia and collapse of the upper airway, which are triggers for intrathoracic pressure changes, blood pressure surges, and sympathetic nervous system activation. They compared their results to the study of Javaheri (2000), in which treatment of SDB resulted in reduced RDI and hypoxia.

4.2 Atrial fibrillation

Several studies in addition to those discussed in section 4.1 have explored potential mechanisms for atrial fibrillation to occur in the setting of SDB. Hypertension is an established risk factor for atrial fibrillation (Kannel et al. 1998; Chugh et al., 2001), and the relationship between OSA and both hypertension and left-ventricular hypertrophy has been documented (Arias & Sanchez, 2007; Nieto et al., 2000; Peppard et al., 2000). Data from OSA patients describe cardiac structural and functional changes, including right and left ventricular performance and left atrial enlargement (Otto et al., 2007; Romero-Corral et al., 2007). Shifts in transmural pressures and concomitant changes in cardiac chamber dimensions can occur in response to the futile ventilatory efforts during apnea (Condos et al., 1987; Hall et al., 1998), and may trigger stretch-activated ion channels in the atria (Franz & Bode, 2003) that can lead to atrial fibrillation. The mechanical effects of negative intrathoracic pressure can allow cardiac stretching, whereby a mechanical-electrical feedback mechanism could predispose to atrial fibrillation (Franz, 2000). These data support a mechanistic association of OSA with the development of atrial fibrillation; however, causation has not yet been proven.
Heart rate variability studies have shown that nocturnal atrial fibrillation is induced during periods of intense vagus nerve activity (Bettoni & Zimmerman, 2002). These vagally-mediated episodes of atrial fibrillation are usually preceded by bradycardia (Verrier & Yosephson, 2009). In addition, the apnea-induced hypoxemia, sympathetic nerve activity,

and surges in blood pressure that can affect diastolic function by distending and remodeling atrial chambers may also contribute to atrial fibrillation development.

In a study of atrial fibrillation radiofrequency ablation in 424 patients, OSA was a significant risk factor for conduction recurrence after multivariable adjustment (RR 2.16; 95% CI: 1.32, 3.94; P=.01)(Sauer et al., 2006). This was postulated to be mechanistically related to left atrial electrical modeling, fibrosis, and chamber enlargement resulting from OSA (Gami et al., 2008).

In many studies of atrial fibrillation in association with OSA, oxygen saturation variables were independently predictive of atrial fibrillation, suggesting that hypoxemia is an important pathophysiological mechanism linking OSA and atrial fibrillation (Gami et al, 2008). In addition to decreased oxygen saturation, obesity, male gender, and coronary artery disease in persons 65 years of age, and heart failure in older subjects, have been shown to be associated with the development of atrial fibrillation in patients with apnea (Wang et al., 2004).

In the MrOS Sleep Study, atrial fibrillation had a stronger association with CSA than OSA (Mehra et al., 2009). Adjusted analysis revealed increasing severity of SDB was only significantly related to atrial fibrillation in patients with the most severe CSA (OR 2.69; 95% CI: 1.61, 4.47), which remained significant after excluding subjects without heart failure from the analysis. The effect of hypoxia on atrial fibrillation, however, was not significant. Although these results were based on self-reported heart failure, the authors suggested that their results agree with those of Leung et al. (2005), that atrial fibrillation is more strongly associated with CSA than OSA, even in the absence of heart failure. They concluded that it may be beneficial to screen patients with AF for CSA.

4.3 Bradyarrhythmias

While repeated hypoxemia and arousals enhance sympathetic nervous activity and may be involved with the tachyarrhymias seen in OSA, the simultaneous hypoxemia and apnea also induce the diving reflex, with cardiac parasympathetic vagal nerve activation and peripheral sympathetic activation that produces vasoconstriction in muscle, renal, and splanchnic, but not cerebral, vasculature (Daly et al., 1979; Madden et al., 1997; Somers et al., 1992). This may result in severe nocturnal bradyarrhythmia. In the study of 239 OSA patients by Becker et al. (1995), bradyarrhythmia occurred only during apnea and hypopnea. In some studies, these bradyarrhythmias occurred more frequently during REM sleep accompanied by at least a 4% decrease in oxygen saturation (Becker et al, 1995; Koehler et al., 1998; Koehler et al., 2000). Conversely, in the study by Guilleminault et al. (1983), in 3 patients extreme sinus bradycardia occurred during nonREM sleep, and sinus arrest was associated with apneas during REM sleep. These patients had both sinus arrest and extreme sinus bradycardia that were of similar duration.

The lack of a difference in conduction delay arrhythmias between subjects with and without SDB in both the MrOS Sleep Study (Mehra et al., 2009) and Sleep Heart Health Study (Mehra et al., 2006) was remarked by the authors to be at variance with the opinion that SDB is associated with increased vagal tone. They offered that there may be differences in the underlying comorbidities in these 2 studies compared with data from studies of clinic referral subjects that suggested an association of SDB with bradyarrhythmia and heart failure.

The clinical significance of these OSA-related arrhythmias is not completely understood, and their association with adverse outcomes warrants further investigation in studies

designed to accommodate the numerous confounders influencing results. The possible relationship between nocturnal oxygen desaturation and arrhythmias and sudden death in heart failure patients was suggested 20 years ago (Davies et al., 1991). More recently, Gami et al. (2005) reported that sudden cardiac death in almost half of 78 heart failure patients with OSA occurred during sleeping hours from midnight to 6:00 a.m., significantly deviating from the typical time of death during early morning waking hours (6:00 a.m. to noon).

In summary, despite differences among studies and gaps in understanding the mechanisms by which SDB impacts arrhythmias, data suggest that patients with moderate to severe OSA are at increased risk for arrhythmias during sleep. the majority of data support the importance of identifying patients with SDB and treating them appropriately.

5. Treating OSA

Tracheostomy was the standard treatment for SDB until CPAP was introduced in 1981. Although CPAP is not as invasive as tracheostomy, it can present challenges. The equipment and devices can be cumbersome and annoying, with treatment compliance commonly less than 50% due to rhinitis, nose bleeds, facial abrasions, and improper fit (Gami et al., 2008; Veasey, 2009). Pressure must be titrated to a level high enough to prevent not only apneas and hyponeas, but also to prevent snoring that can cause arousal. However, pressure must also be kept at a level below what would cause sleep interference.

There have been no long-term, large, randomized controlled trials comparing OSA treatment with placebo on cardiovascular outcomes. Several studies, however, associated failing to treat OSA with increased mortality or morbidity (He et al., 1988). Data from 3 large observational studies that included a total of 2396 patients showed increased fatal and nonfatal cardiovascular outcomes in patients with severe OSA, compared with patients who were treated with CPAP (Buchner et al., 2007; Campos-Rodriguez et al., 2005; Marin et al., 2005).r One of the studies (Buchner et al., 2007) enrolled 449 patients, of whom 364 received OSA treatment, which provided a 64% cardiovascular risk reduction after adjusting for age, gender, cardiovascular risk factors, and baseline comorbidities.

In the Japanese study of the relationship between OSA and arrhythmias, 316 of 1047 patients with AHI ≥20 accepted treatment with CPAP therapy, and were re-evaluated an average of 3.9 weeks after polysomnography to determine the effectiveness of CPAP therapy and arrhythmia status (Abe et al., 2010). AHI and arousal index were among the OSA variables that were significantly improved with CPAP therapy ($P<.001$ for both). Premature atrial complex and nonsustained ventricular tachycardia were unchanged, as were the numbers of second- and third-degree AV block; however the latter were present in only 5 patients before treatment and 1 patient after treatment. The proportions of patients with premature ventricular complex, sinus bradycardia, pause, and paroxysmal atrial fibrillation were significantly decreased after treatment.

There is no clinical basis for treating nighttime atrial fibrillation differently from that occurring during the day. However, patients who have nocturnal onset of atrial fibrillation should be monitored for SDB and provided treatment with CPAP if warranted.

A recent study followed 47 OSA patients on CPAP for 12 months to assess changes in cardiac biomarkers from baseline (Colish et al., 2011). Systolic and diastolic abnormalities were reversed as early as 3 months after starting treatment, with additional improvements evident over 1-year as evidenced by transthoracic echocardiography and CMR. Levels of

biomarkers, including CRP, did not change significantly during 12 months of follow-up, however.

Ventricular arrhythmias are assumed to be one of the major causes of sudden in heart failure. Screening for OSA in heart failure and treating patients may reduce the incidence of these fatal arrhythmias and improve survival.

Treating OSA has also been shown to resolve arrhythmias in many studies. Fifty OSA patients with arrhythmias in the study by Guilleminault et al. (1983) underwent tracheostomy, and after 3 to 6 months arrhythmias were no longer occurring in 46 patients. Arrhythmias in 4 patients with premature ventricular contractions decreased during sleep, and remained frequent during wakefulness.

Several other case series have shown that nocturnal cardiac rhythm disturbances were reduced following OSA treatment (Becker et al; 1995; Grimm et al., 2000; Harbison et al., 2000; Koehler et al, 1998; Tilkian et al., 1977). It was surprising, therefore, in a recent retrospective cohort study of 2626 patients with OSA, that CPAP use did not affect the incidence of atrial fibrillation (Gami et al., 2007). The authors commented that determining CPAP use in the retrospective study relied on subjective reporting with subsequent documentation in medical records. This precluded accurately determining frequency of use, compliance, and treatment outcome. In addition, in that study CPAP treatment was used by patients who had more severe OSA. These factors may have confounded the association between CPAP use and incident atrial fibrillation.

In the study of Beckers et al. (1995), only 1 of 17 patients with bradyarrhythmia did not achieve resolution of their arrhythmia after CPAP therapy. Similarly, OSA patients with severe cardiac rhythm disturbances reported by Simantirakis et al. (2004) experienced a significant reduction in bradycardias from a median of 5.5 per week in the 8-week pre-treatment period to 0.5 per week in the first 8 weeks of CPAP therapy (P=.028). No bradycardias or pauses were reported beginning 5 months after starting treatment through 14 months of follow-up.

In response to reports noting an association between OSA and bradyarrhythmias, several studies were performed in the last 10 years exploring the potential for pacemakers to resolve OSA. As reviewed by Simantirakis & Vardas (2006), positive results were reported from a small study of patients with CSA but not in several studies of OSA. These authors postulated that in patients with predominantly OSA, the functional changes elicited by atrial overdrive pacing have no effect on the anatomical obstructions that cause the apnea. In CSA, functional and autonomic nervous system changes were able to affect the pathophysiological causes of respiration disturbances during sleep. The recent ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (Eptsein et al., 2008) conclude that results of randomized controlled trials (RCTs) failed to suggest a role for atrial overdrive pacing in OSA, and that CPAP has been shown to be highly effective. However,r the possible role of cardiac pacing in patients with OSA who continue to have persistent bradycardia episodes despite CPAP has not been confirmed. Data from a subsequent meta-analysis by Baranchuk et al. (2009) of 10 crossover RCTs in patients with AHI >=15 that enrolled 175 patients revealed that atrial overdrive pacing caused a significant 4.65 episode/h reduction in AHI (P=.01). However, this was substantially less than that achieved with CPAP treatment reported in the literature and the mean 42.5 episode/h reduction achieved in the 3 studies in the meta-analysis that included CPAP arms. The authors concluded that, although it was statistically significant, the reduction on atrial overdrive pacing was not clinically significant, and that patients with

sleep apnea should not be treated with cardiac pacing unless there is a conventional indication. Conversely, studies suggest that increased parasympathetic input to the heart may be the main mechanism for nocturnal bradycardias (reviewed by Bradley & Flores, 2009). Therefore, treatment of OSA-induced nocturnal bradycardia may obviate the need for cardiac pacing; however, more studies are needed.

6. Future directions

Since the first suggestion was made of an association between OSA and cardiovascular morbidity and mortality, a rapidly expanding volume of observational data link OSA with the development of arrhythmias. Much research must be done, however, to answer the numerous questions that remain. In addition to larger epidemiological studies, randomized controlled trials must be performed that use robust designs similar to those used in cardiovascular intervention trials, with standardized definitions and adequate control of confounders.

A major issue with properly investigating OSA and arrhythmias in both research and clinical settings is the expense and limited availability of sleep laboratories for the diagnosis of OSA. Once OSA is suspected, although other forms of diagnosis have been used, polysomnography remains the gold standard for diagnosis. Ambulatory in home devices may become a reasonable alternative, particularly in developing countries that have availability, access, and cost constraints (Ng et al., 2009). Many other methods are being investigated, and reports suggest some of these may be appropriate for initial screening in suspected cases, followed by full polysomnography when warranted.

The Berlin questionnaire has been used as the diagnostic test in some studies, and has been validated as part of one study (Gami et al., 2004). It has also been shown to be comparable to other checklists and questionnaires that have been suggested as being valid screening tools (Chung et al., 2008a,b).

The high prevalence of SDB in patients on cardiac pacing prompted several investigations of the potential for diagnosing OSA in patients who have rate-responsive pacemakers with minute ventilation sensors (Simantirakis & Vardas, 2006). These devices could provide preliminary screening for SDB, subsequent monitoring of correlations between arrhythmias and apnea/hypopnea events, and evaluate therapeutic efficacy. Limitations include the inability to distinguish between central and obstructive apneas and to recognize specific sleep stages. However, its benefits can be acquired by interrogating extant devices without additional cost in patients with pacemakers; therefore, this may be useful in patients who are already on permanent pacemakers, but does not justify pacemaker placement without a clinical indication.

Data have shown that OSA in the setting of cardiac arrhythmias may confer a higher risk of stroke and cardiovascular events (Marin et al., 2005) on affected patients,r and early treatment of OSA in these patients may reduce cardiovascular morbidity (Kanagala et al., 2003; Barcena & Fang, 2007). Putting these understandings into practice is necessary. The importance of this is exemplified by considering the association between sleep apnea and heart failure, which has not resulted in increased vigilance or therapy. For example, despite the high prevalence (40% to 60%) of sleep apnea in heart failure, a recent study was reported summarizing data in U.S. Medicare files for over 30,000 incident heart failure patients, of whom only 4% were suspected to have sleep apnea (Javaheri et al., 2011). Less than half of these received testing and treatment, and were shown to have significantly greater 2-year

survivals compared with patients who were not tested (P<.0001) or were tested but not treated (P=.009). Policies for addressing issues relating to SDB and arrhythmia should be developed and implemented.

In summary, continuing research should focus on acquiring high quality, standardized data. As new data are acquired, policies should be developed and implement to assure screening for and treating SDB is available to high risk populations.

7. Conclusions

Many studies suggest that there is a significant association between SDB and increased prevalence and incidence of cardiac arrhythmias. The pathophysiological pathways between arrhythmias and SDB have not been clearly defined, but apnea-induced hypoxia, intrathoracic pressure changes, inflammation, and autonomic instability that can lead to adverse cardiovascular consequences are presumed to be involved. Larger epidemiological studies and RCTs are required to define the association and its mechanisms, which should control for confounding and apply standardized definitions. While studies are limited, initial results suggest that intervention with CPAP may be effective in reducing the arrhythmia burden in the OA population, however, additional RCTs are necessary.

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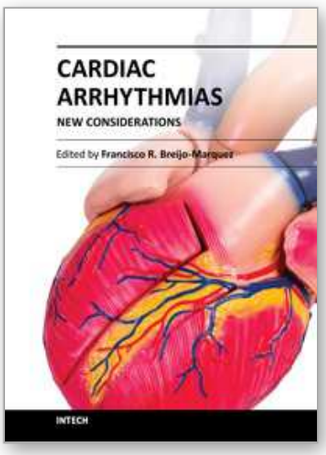

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The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographyc features, ion channel alterations, heart diseases still unknown , and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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