Twelfth Symposium on Cardiac Arrhythmias

Sleep Apnea, Cardiac Arrhythmias, and Sudden Death

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Normal physiologic sleep consists of rapid-eye-movement (REM) sleep and non-rapid-eye-movement (NREM) sleep, which alternate within sleep cycles of approximately 90 minutes in length. Non-REM sleep constitutes about three quarters of each 90-minute cycle and is characterized by increased parasympathetic tone and decreased sympathetic activity, which together decrease the heart rate, blood pressure, and cardiac output. On the other hand, REM sleep can be described as erratic, and it is characterized by irregular breathing patterns and varying heart rate.[1,2] It constitutes the remaining quarter of each sleep cycle.

Arrhythmias during Normal Sleep

Normal sleep sets the stage for several benign physiologic arrhythmias. Sinus arrhythmia can result from the coupling of heart rate and breathing into sinusoidal patterns.[3] During inspiration, R-R interval decreases, which leads to brief increases in cardiac output. This phenomenon is physiologic and is often expressed as heart-rate variability. Attenuation of such heart-rate variability is associated with cardiovascular morbidity.[4] Physiologic bradyarrhythmias can result from the changes in autonomic output, particularly from the increase in vagal activity during NREM (benign pauses and low-degree atrioventricular block have been described).[3,5] The refractory period increases during NREM, and premature ventricular contractions occur less frequently.[6]

The end of sleep is associated with increased sympathetic drive and consequent increases in blood pressure, heart rate, and cardiac output. These arousal-related hemodynamic mechanisms presumably evolved as a protection for human beings and animals alike, because in the wilderness one might have to respond to a potential threat with a brisk resumption of upright posture. However, these same mechanisms might play a maladaptive role in modern human beings, and could explain the increased incidence of adverse cardiovascular events in the early hours of the morning after awaking from sleep.[7,8]

Types of Sleep Apnea

Sleep apnea (often termed sleep-disordered breathing, or SDB) is characterized by a cessation of air flow during sleep, and, depending on the causative mechanism, it can be divided into 2 types: obstructive sleep apnea (OSA) and central sleep apnea. Obstructive sleep apnea ensues when the soft tissues around the upper airway collapse, obstructing air flow partly or completely, despite increased ventilatory effort.[9] Central sleep apnea is characterized by a ventilatory pause during sleep that lasts 10 seconds or more and is secondary to a loss in respiratory effort.

Sleep apnea constitutes an important connection between sleep disorders and cardiovascular disease. The prevalence of sleep apnea in the general population is strikingly high, for it affects an estimated 15 million adult Americans (at least mild OSA is found in approximately 1 of 5 adults in the United States).[9] The prevalence of OSA in patients with cardiovascular disease is estimated to be 2 to 3 times higher than in the general population.[10] Unfortunately, the degree of under-diagnosis of OSA—hence of under-treatment—remains high, even in cardiac patients (Fig. 1).[11-14]

Autonomic Nervous System

The key to understanding the hemodynamic responses to OSA lies in grasping the concept of the "diving reflex." This oxygen-saving reflex is particularly pronounced

in sea mammals and elite human divers, and probably evolved in response to repetitive episodes of hypoxemia. During the diving reflex, apnea induces hypoxemia, which stimulates cardiac parasympathetic activity and leads to bradycardia; increased peripheral sympathetic activity constricts the peripheral vessels and increases arterial resistance. The evolutionary explanation for these changes might be that myocardial oxygen consumption decreases at the outset of the diving reflex, when the organism's supply of oxygen is reduced. In consideration of the fact that episodes of OSA often produce profound hypoxemic states, it is not surprising to see similar autonomic nervous system changes in patients who have sleep apnea (Fig. 2A).[15-17] A typical episode of OSA results in bradycardia (or even brief sinus arrest, as seen in Fig. 2B) and in gradually increased peripheral sympathetic neural activity (SNA). When the obstruction is released, SNA reaches its maximum, and this dramatically increases blood pressure and heart rate, because these increases coincide with the hyperpneic compensatory breathing (Fig. 2A).[16,18] Since the surges in SNA occur repetitively with each obstructive apnea episode, OSA as a disease entity accounts for chronically increased SNA activity during sleep, and this autonomic imbalance persists even during the daytime. Treatment of OSA by continuous positive airway pressure (CPAP) reduces SNA, and it seems to also reduce nighttime urinary catecholamine levels and daytime blood pressure.[18,19]

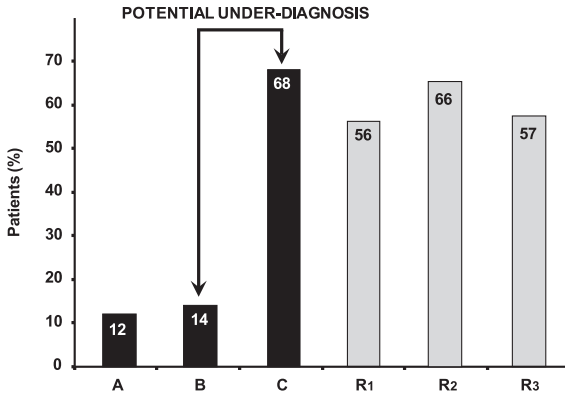

Fig. 1 *Differences between the probable prevalence of obstructive sleep apnea (OSA) in patients with acute myocardial ischemia and the documented prevalence of obstructive sleep apnea during their hospital stay.*

A *= Documented or suspected OSA in patients with myocardial infarction (MI).* ***B*** *= Documented or suspected OSA in MI patients recruited for polysomnography.* ***C*** *= Prevalence of OSA in MI patients recruited for polysomnography.* $\boldsymbol{R_1}$*–*$\boldsymbol{R_3}$ *= Previously reported prevalence of OSA in studies of patients with acute coronary syndromes, shown for comparison.[11-14] (Reprinted from Konecny T, Kuniyoshi FH, Orban M, Pressman GS, Kara T, Gami A, et al. Under-diagnosis of sleep apnea in patients after acute myocardial infarction. J Am Coll Cardiol 2010;56(9):742-3.[11] With permission from Elsevier.)*

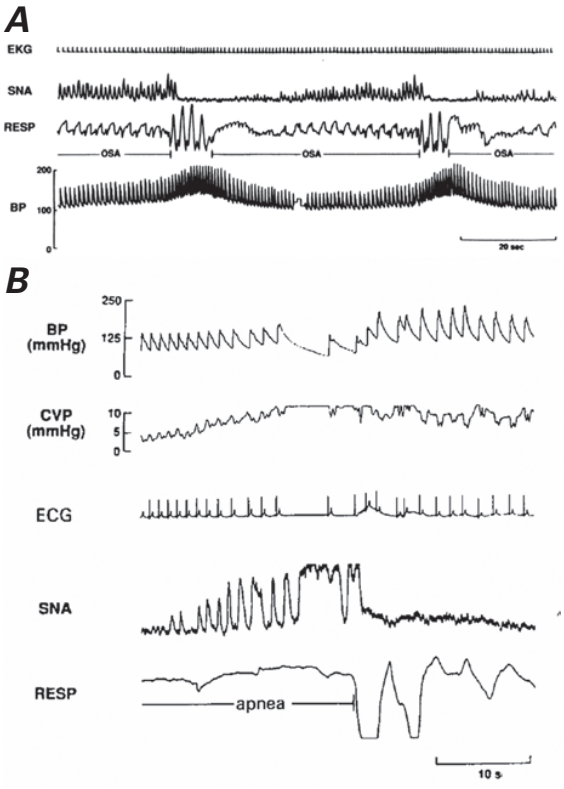

Fig. 2 ***A****) Recordings during sleep of patients with obstructive sleep apnea (OSA). Sympathetic neural activity (SNA) increases during the apneic episode and peaks at the time of the release. Blood pressure (BP) and heart rate decrease during the apnea but dramatically increase after the release of the obstruction. (Adapted with permission from Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96(4):1897-904.[16])* ***B****) Recordings showing sinus arrest (absence of P waves on ECG) during OSA. (Adapted from Somers VK, Dyken ME, Mark AL, Abboud FM. Parasympathetic hyperresponsiveness and bradyarrhythmias during apnoea in hypertension. Clin Auton Res 1992;2(3):171-6. With kind permission of Springer Science+Business Media.[17])*

CVP = central venous pressure; ECG = electrocardiogram; RESP = respirations

Atrial Fibrillation

Atrial fibrillation (AF) is a multifactorial disorder, and recent evidence supports the contention that OSA is one of the modifiable factors that contribute to AF. In a study of more than 3,500 adults who underwent polysomnographic evaluation and had no history of AF, the severity of nocturnal hypoxemia was found to be an independent predictor of AF occurrence, but only in those ≤65 years old.[20] In postoperative coronary-artery-bypass patients, AF seems also to be associated with OSA.[21] An observational study of patients who underwent successful cardioversion for AF reported that untreated OSA was associated with an 82% risk of recurrence within 1 year, approximately twice the risk of recurrence in OSA patients who were on CPAP treatment.[22]

Even though the exact pathophysiologic links between AF and sleep apnea continue to be investigated, it is likely that OSA contributes to AF via several pathways, including obesity, atrial enlargement, hypertension, and autonomic imbalance. Simulation of OSA in healthy subjects (via the Müller maneuver) produces acute changes in left atrial size; chronic increases in atrial size among patients with OSA have also been reported.[23-25] Obstructive sleep apnea leads to changes in the activity of ganglionated plexuses, as well as to changes in activity elsewhere in the intrinsic cardiac nervous system, all of which appear to affect the atrial refractory period.[26] Strong support for OSA as a direct contributor to AF has been provided by a recent study in dogs, which shows that AF can be produced by prolonged episodes of OSA (Fig. 3),[27] and also that such OSA-initiated AF can be prevented by autonomic blockade (via ablation of the right pulmonary artery ganglionated plexus).[18] Randomized studies that investigate the effect of CPAP on AF are under way.

Hypertrophic Cardiomyopathy

In patients with hypertrophic cardiomyopathy, sleep apnea and its severity correlate positively both with left atrial size and with the presence of AF.[28] Because AF constitutes the most important determinant of death in patients with hypertrophic cardiomyopathy, screening for SDB and treatment of SDB in this population might improve survival; however, further studies are necessary to confirm this hypothesis. Recent data show that hypertrophic cardiomyopathy patients who have SDB suffer from significantly decreased exercise tolerance, as measured by cardiopulmonary exercise testing.[29]

Sudden Cardiac Death

Both complex ventricular ectopy and nonsustained ventricular tachycardias during sleep occur more commonly in patients who have OSA.[30] Long-term study of OSA patients shows that after an average of 7 years, sudden cardiac death is less common in compliant CPAP patients than in noncompliant ones.[31] Patients with untreated OSA appear to have higher morbidity and mortality rates than do patients with treated OSA, and this finding is in accord with the increased mortality rates associated with other diseases of the respiratory-pulmonary system.[32,33] A study of the diurnal timing of sudden cardiac death suggests that patients with OSA are more likely to experience their sudden events at night (12 AM to 6 AM) than are those without OSA, who are more likely to die in the well-recognized window between 6 AM and 12 PM.[34] This study also reports a direct relationship between the severity of OSA (as measured by the apnea-hypopnea index) and the risk of sudden cardiac death at night. Recent data suggest that this predilection for nighttime events in patients with OSA can be explained, in part, by the greater number of nocturnal ischemic events that occur in these patients.[35]

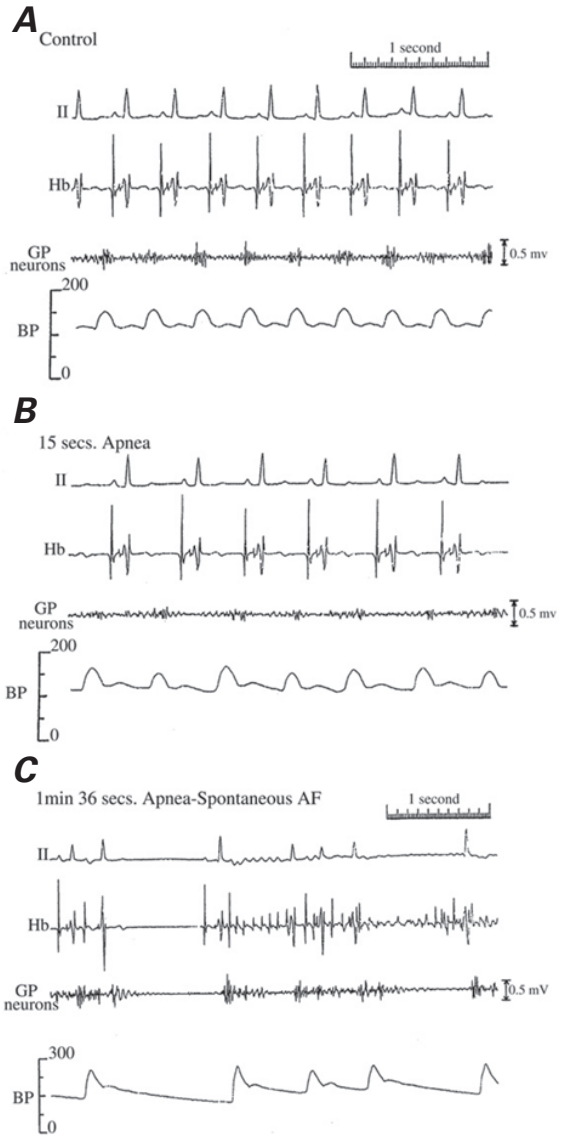

Fig. 3 *Spontaneous onset of atrial fibrillation during induced obstructive apnea in dogs.* ***A****) Control recording. Compare with* ***B****) decreased neural firing from the anterior right ganglionated plexus during induced apnea.* ***C****) The onset of apnea-induced atrial fibrillation. (Reprinted from Ghias M, Scherlag BJ, Lu Z, Niu G, Moers A, Jackman WM, et al. The role of ganglionated plexi in apnea-related atrial fibrillation. J Am Coll Cardiol 2009;54(22):2075-83. With permission from Elsevier.[27])*

AF = atrial fibrillation; BP = blood pressure; GP = ganglionated plexus

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