Sleep Apnea and Atrial Fibrillation: Role of the Cardiac Autonomic Nervous System

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ABSTRACT: Sleep apnea is highly associated with atrial fibrillation (AF), and both diseases are highly prevalent in the United States. The mechanistic underpinnings that contribute to their association remain uncertain, but numerous possible mechanisms have been proposed, including dysfunction of the cardiac autonomic nervous system (ANS). Studies have reported that apnea induces hyperactivity of the ANS, leading to increases in AF susceptibility. This review compiles the latest evidence on the role of the ANS in sleep-apnea-induced AF.

INTRODUCTION

Atrial fibrillation (AF), the most common sustained arrhythmia in adults,[1-4] is highly associated with both obstructive and central sleep apnea.[5-8] Individuals with sleep apnea have 2- to 4-fold higher odds of having AF than those without sleep apnea, even after adjustment for potential confounders.[5] Sleep apnea is characterized by intermittent cessation or attenuation of breathing of at least 10 seconds during sleep, leading to oxygen desaturation. In obstructive sleep apnea (OSA), this results from a partial or complete collapse of the upper airways, whereas in central sleep apnea, this results from a decline or absence of adequate respiratory effort.[1,8] Sleep apnea increases the risk of hypertension, coronary artery disease, congestive heart failure, stroke, diabetes, and heart arrhythmias.[9] AF increases the risk of stroke, heart failure, and dementia by 5-fold, 3-fold, and 2-fold, respectively,[10-15] as well as increased overall mortality and healthcare costs.[16,17] Sleep apnea has been identified as a risk factor for initiation, maintenance, and recurrence of AF, and its presence reduces the efficacy of current AF therapies, including catheter ablation.[2,8,18,19] A study investigating whether continuous positive airway pressure (CPAP) improved success rates of AF catheter ablation found that OSA was an independent predictor of ablation failure and that patients not treated with CPAP were 8 times more likely to fail the procedure.[20]

Although the mechanistic underpinnings that contribute to the association between sleep apnea and AF remain uncertain, numerous possible mechanisms have been proposed, including dysfunction of the cardiac autonomic nervous system (ANS). Apnea induces hyperactivity of the ANS, which is thought to contribute to the genesis of sleep apnea-induced AF.[21-25] This literature review summarizes the latest evidence on the role of the ANS in sleep apnea-induced AF.

PREVALENCE OF AF AND SLEEP APNEA

The prevalence of AF in the United States ranges from 2.7 million to 6.1 million and is predicted to increase to 12.1 million cases by 2030.[26] Approximately 15 to 20 million American adults suffer from OSA. It is estimated that roughly 20% of adults have at least mild OSA, and 7% of adults may have moderate-to-severe OSA. The prevalence of OSA is higher in men, older adults, and obese individuals.[27,28] Central sleep apnea is much less common than OSA; in fact, the overall prevalence in a population-based study on polysomnography was 0.9% in adults aged 40 and older.[29] In a more recent cohort of patients undergoing diagnostic polysomnography, OSA prevalence was 53.3% while central sleep apnea was 8.4%. The prevalence of central sleep apnea is higher in men, older adults, people with heart failure, those who chronically use opioids, and those who had a stroke.[8]

CARDIAC ANS ACTIVITY DURING APNEA AND INCREASED AF SUSCEPTIBILITY

Growing evidence points to the cardiac ANS as a significant contributor to the association between OSA and AF.[21,22,30] The cardiac ANS (Figure 1, first panel) comprises the extrinsic cardiac autonomic system, centrally derived parasympathetic and sympathetic nerves, and the intrinsic cardiac autonomic system, which consists of epicardial ganglionated plexi (GP) embedded in fat pads that contain efferent parasympathetic and sympathetic neurons, interneurons, afferent sensory neurons, and others.[24,31,32] Apnea induces acidosis, hypoxia, hypercarbia, and increased pulmonary pressure, all powerful stimuli for increasing cardiac ANS activity. This causes hemodynamic and electrophysiological changes that culminate in increased AF susceptibility.[21,24,33]

In an acute canine model of OSA published in 2019,[24] we performed simultaneous nerve recordings from bilateral vagal nerves, left stellate ganglion (SG), and anterior right GP (ARGP) before and

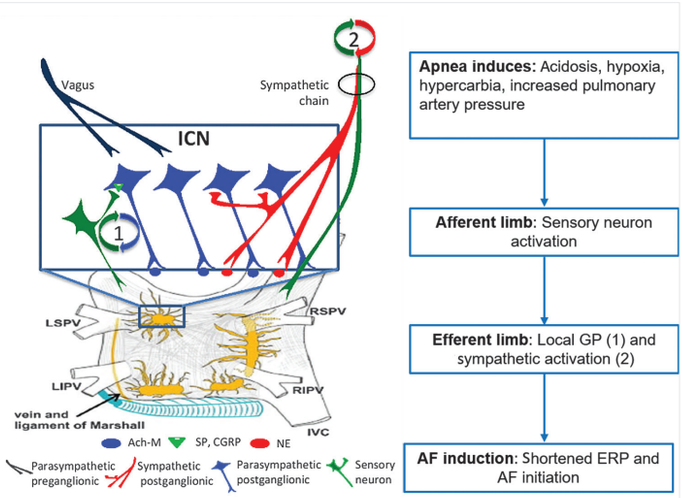

Figure 1.
Autonomic response to apnea that contributes to initiation of atrial fibrillation (AF). Proposed integrated autonomic response to apnea: upon apnea, sensory neurons respond to hypoxia and hypercapnia, thus activating a local reflex loop. The loop (1) activates postganglionic parasympathetic neurons that, via muscarinic receptors, lead to decreased ERP. Sympathetic afferents increase sympathetic outflow in a central loop, which leads to (2) increased blood pressure and contributes to AF inducibility. Ach-M: acetylcholine-muscarinic; CGRP: calcitonin gene-related peptide; ERP: effective refractory period; ICN: intrinsic cardiac nervous system; IVC: inferior vena cava; GP: ganglionated plexi; LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; NE: norepinephrine; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein; SP: substance P

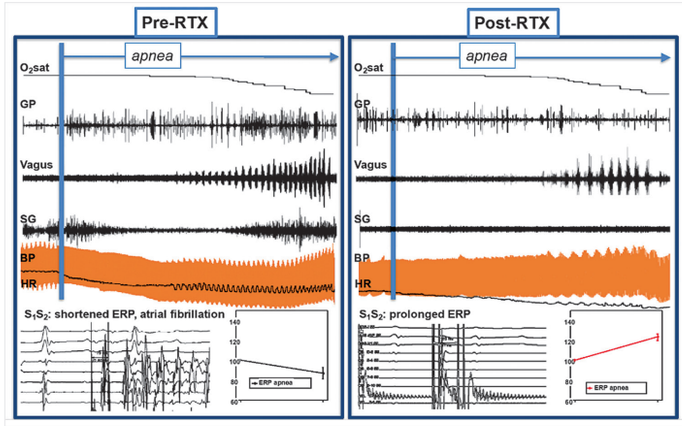

Figure 2.
Extrinsic and intrinsic autonomic response to apnea before and after GP sensory denervation. Top: examples of GP, vagal, and SG responses to apnea along with their hemodynamic and electrophysiological correlates. O_2sat: oxygen saturation; RTX: resiniferatoxin; GP: ganglionated plexi; SG: stellate ganglion; BP: blood pressure; HR: heart rate; S_1 and S_2: stimulus 1 and 2; ERP: effective refractory period

during apnea and before and after resiniferatoxin (RTX) injection in the ARGP. RTX is an ultrapotent analogue of capsaicin—the active compound of chili peppers that causes the transient receptor potential vanilloid 1 (TRPV1), present in sensory neurons, to become permanently permeable to cations[34-36]—and causes neuronal death, desensitization, and analgesia.[37-39] The atrial effective refractory period (ERP) and AF inducibility upon single extra stimulation were also assessed before and during apnea and before and after RTX, and we showed that GP sensory neurons play a significant role in apnea-induced AF (Figure 1, second panel, and Figure 2). A consistent sequence of events occurred with oxygen desaturation, including (1) increases in GP activity; (2) progressively increasing phasic bursts of vagal activity, which closely correlate with heart rate (HR) and blood pressure (BP) oscillations; and (3) tonic increase in sympathetic activity, which correlates with steady increases in HR and SBP. When GP sensory neurons were denervated with RTX, decreases in sympathetic and GP nerve activity were seen. In addition, apnea's electrophysiological response (ERP shortening) was also abolished, and AF inducibility during apnea no longer occurred (Figure 2).[24] This study expanded on previous experimental studies that demonstrated a close mechanistic association between the cardiac ANS and apnea-induced AF[21, 22,30] by recording from both intrinsic and extrinsic cardiac ANS and showing the orchestrated intrinsic (GP) vs extrinsic ANS (vagal and SG) response to apnea and their changes after sensory denervation with RTX. These results support the fundamental role of the cardiac ANS in mediating the atrial myocardium's electrophysiological responses to apnea and suggest cardiac afferents as a possible therapeutic target for autonomic modulation.[24]

Further studies are needed to provide a more detailed description of the mechanistic underpinnings that contribute to the impact of the ANS on OSA and AF and to clarify which component of the ANS could more effectively be targeted therapeutically—whether it be the parasympathetic,[23] the GP as a whole (with radiofrequency ablation),[21] the sympathetic,[40] the sensory afferent,[24] or a combination thereof. Until such therapies are developed, treatment of sleep apnea remains the main strategy to reduce the incidence of AF in the general population and in patients receiving therapies to lower the recurrence of AF.

CONCLUSION

Sleep apnea is highly associated with AF. The cardiac ANS plays an important role in this association, and studies have shown that different components of this system could potentially be therapeutically targeted to decrease AF inducibility in patients with OSA. Cardiac afferents are a crucial component of the cardiac ANS and have therapeutic potential in reducing AF in those with sleep apnea.

KEY POINTS

- Sleep apnea is highly associated with atrial fibrillation (AF) and reduces the efficacy of current AF therapies, including catheter ablation.
- The precise mechanisms behind this association are unclear, but studies support a prominent role of the cardiac autonomic nervous system (ANS).
- Apnea induces hemodynamic and electrophysiological changes that culminate in increased AF susceptibility.
- Cardiac afferents are a crucial component of the cardiac ANS and have therapeutic potential in reducing AF in those with sleep apnea.

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atrial fibrillation, sleep apnea, obstructive sleep apnea, central sleep apnea, autonomic nervous system, sensory neurons

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