Sleep Apnea and Atrial Fibrillation

The Autonomic Link*

Samuel J. Asirvatham, MD,†‡ Suraj Kapa, MD§
Rochester, Minnesota; and Philadelphia, Pennsylvania

The intuitive and postulated links (1,2) between the established association of obstructive sleep apnea with atrial fibrillation (AF) are hypertension, diastolic dysfunction, and the resultant long-term atrial remodeling (3–6). However, studies suggest that the relationship between sleep apnea and AF is independent of hypertension, cardiac function, or body mass index. Further, untreated sleep apnea doubles the risk of AF recurrence within 12 months of cardioversion independent of other risk factors (7). Thus, is the relationship between sleep apnea and AF an epiphenomenon, or is it truly causative and the linking mechanism is simply not yet explained?

A surge of new discovery in AF modulation has occurred over the last decade. Thoracic vein triggers and, even more recently, the role of autonomic dysregulation has formed the basis for interventional electrophysiological procedures (8,9). Pulmonary vein isolation and even autonomic ablation to functionally “denervate” the atria have been suggested and used as mechanisms to treat AF (9).

In this issue of the Journal, Ghias et al. (10) report an elegant series of experiments proposing an autonomic link between sleep apnea and AF inducibility. This group’s presently reported work is an addition to their seminal observations and documentation of the integral role of the periatrial ganglionated plexi and arrhythmogenesis (9,11,12). In this article, their results suggest, through a carefully constructed series of experiments in an animal model similar to sleep apnea, that reproducible incidence of AF may be attenuated by ablation of the pulmonary artery-associated ganglionated plexi or pharmacological inhibition of autonomic inputs.

To fully appreciate the context of these findings and assess whether the link between sleep apnea and AF is cardiac autonomies, we need to understand the pathogenic effects of apnea on autonomic tone, the established relationships between variation in autonomic tone and AF pathogenesis, and the limitations of animal models for sleep apnea.

Sleep Apnea and Autonomic Tone

Autonomic dysregulation may connect sleep apnea and AF. During normal sleep, there are profound fluctuations in autonomic tone (13,14). Sleep apnea markedly alters both vagal and sympathetic drive. An analogous situation occurs with the diving reflex seen in mammals. During sustained submersion under water, during which the subject is effectively apneic, the body responds to apnea by increasing sympathetic tone to the peripheral vasculature and parasympathetic tone to the heart, resulting in a decrease in myocardial oxygen demand and thereby improving the chances for cardiac survival. A similar effect is seen in sleep apnea, where simultaneous increases in cardiac parasympathetic and vasoconstricting sympathetic tone may be seen (2).

Autonomic Modulation and AF

The exact mechanisms by which autonomic modulation mediates triggering, propagation, and termination of AF remain unclear. Several ideas have been advanced to explain or suggest how we explore the relationships between atrial refractoriness, the ganglionated plexi, pulmonary veins, and different elements of the intrinsic cardiac nervous system. The extraordinary anatomical and physiological complexity of the sympathetic and parasympathetic innervation of the heart, including the extensive cross-talk between the ganglia, create the lack of clarity on what the best mechanism is to define the functional significance of recorded complex signals seen during electrophysiologic testing. Largely through the efforts of Ghias et al. (10), both inducibility and termination of AF, as well as the specific mechanisms of arrhythmia during AF being affected by autonomic modulation, are established (15,16).

Connecting the Dots

The primary strengths of the present study by Ghias et al. (10) are the elegant design and rigorous evaluation of the effects of apnea on several aspects of AF electrophysiology
including inducibility, neuronal firing, electrogram amplitude, and the suppressive effects of pharmacotherapy and ablation. Despite the limitations of the experimental model discussed in the following text, the study provides unique insights to support the hypothesis that apnea-related AF is mediated by autonomic neuronal inputs to ganglionated plexi that, in turn, may stimulate AF. This role for the ganglionated plexi compliments their prior work showing similar importance in both onset and propagation of nonapnea-associated AF (9,17). AF occurred spontaneously in 1 dog, and in most dogs (14,17), AF was inducible during apnea and was associated with progressive increase in neural activity in the ganglionated plexi. Importantly, the authors report that in most cases, there was concurrent slowing of the heart rate and rise in systolic blood pressure soon after apnea, similar to the diving reflex postulated to underlie some of the pathology seen during obstructive sleep apnea. Even more significant is the ample evidence to support the combined role of elevated sympathetic and parasympathetic tone in AF initiation. This evidence is highlighted by the findings of atrial refractory period shortening and overall increase in systolic blood pressure as well as the development of mechanical alternans during programmed stimulation. Prior studies have suggested that AF initiation depends on local parasympathetic and sympathetic nerves separately shortening atrial refactororiness and triggering early after-depolarizations, respectively (18). Most telling were the reported findings of the inability to induce AF after ablation of the right pulmonary artery ganglionated plexus, which is considered to be the gateway point for extrinsic innervation to the heart (19).

The study by Ghias et al. (10) further demonstrated the effects of autonomic blockade on AF inducibility. In 4 dogs, AF was noninducible when the animals were given beta-blockers and atropine intravenously. Further, when removing the right pulmonary artery ganglionated plexus, AF was no longer inducible in 6 other dogs. These provocative findings lend support to the premise of significant autonomic contribution to apnea-mediated AF.

Minding the Gaps

A significant limitation to the study, however, is in extending their acute apnea model to chronic obstructive sleep apnea, for which the risk of AF has been best characterized. In obstructive sleep apnea, there is not a single, long period of apnea but rather periodic, frequent nocturnal desaturations. Thus, in some ways, the model used in this study is more representative of prolonged anoxia, such as with drowning or central sleep apnea. The ST-segment depression and hypotension requiring resuscitation seen in several animals in this study may suggest that many became actively ischemic during the prolonged anoxic stress. How this ischemia may have affected the perceived electrical and hemodynamic changes is unclear. It has been previously demonstrated that atrial ischemia promotes AF in dogs (20). The finding that effectively removing the neural component attenuated AF induction suggests, however, that AF was not due to atrial ischemia alone. However, without a nonanoxic control group, it is difficult to conclusively attribute this inability to induce AF to denervation alone. Further, we do not know if AF would have still been inducible after pharmacologic or ablative denervation when more aggressive pacing protocols are used.

Other remaining gaps in using the autonomic link between AF and obstructive sleep apnea include the observation that patients with obstructive sleep apnea are not more prone to paroxysms of AF solely during nocturnal apneic episodes but are also prone to them in the daytime when they are awake. One can speculate as to whether recurrent apneic episodes result in tonic activation of autonomic neural inputs leading to nonapnea-related triggering of AF; however, this needs to be demonstrated. Finally, the differential effects of apnea by the autonomic system on pulmonary vein smooth muscle, syncytial myocardium in the atria as well as the pulmonary veins, and sites of ostial pulmonary vein exit delay will need to be elucidated as well (21–23).

Conclusions

Despite the limitations, this study by Ghias et al. (10) provides important, novel support to prior hypothesized relationships between sleep apnea and AF. By virtue of their carefully executed, elegant experiments, we can conclude that the primary causative link between apnea and AF is the autonomic.

Reprint requests and correspondence: Dr. Samuel J. Asirvatham, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, Minnesota 55905. E-mail: asirvatham.samuel@mayo.edu.

REFERENCES


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