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EDITORIAL

Sleep Apnea and Arrhythmias: Those Who Cannot Change Their Minds Cannot Change Anything

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This text aims to summarize ongoing advances in our understanding of the interactions between arrhythmias and sleep apnea. Recent, unexpected results from randomized trials of traditional sleep apnea treatments have highlighted the need for a more personalized and nuanced approach. We also consider potential future directions and ongoing efforts to improve arrhythmia outcomes in sleep apnea patients.

Why Consider Sleep Apnea in Patients with Arrhythmias?

Cardiac arrhythmias are among the costliest pathologies in developed countries, affecting 1 in 4 people over 40 years in the United States [1]. Given the rise in both overall longevity and the extension of the productive age, the prevalence of both atrial and ventricular arrhythmias is projected to increase further. The available treatments for arrhythmias require significant refinement. While advances have been achieved in both medication and procedural treatments of the most common types of arrhythmias, the goals of these treatments are commonly palliative rather than curative. Let us demonstrate the considerable need for improvement using the example of atrial fibrillation (AF). Recent data which considered five-year outcomes with state-of-the-art AF treatments (including both procedural as well as medication treatments) suggested that AF-free survival was achieved in only 50% of patients aged 60 and under, and only 20% of patients over the age of 80 [2]. Such outcomes are far from optimal, leading us to search for innovative, reversible risk factors – such as sleep apnea – that could potentially improve arrhythmia-free survival.

Potential Too Big for us to Disregard

Sleep apnea has attracted immense promise in the treatment of arrhythmias for the following three reasons:

1. The coexistence of sleep apnea and cardiovascular pathologies is remarkably frequent, making it highly relevant to patients with arrhythmias [3]. Current estimates suggest that more than half of patients with AF could also be diagnosed with at least mild sleep apnea, and these figures may even suffer from potential underdiagnosis (Figure 1) [9].

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2. Multiple observational, non-randomized studies suggest that cardiovascular patients who receive and tolerate sleep apnea treatment ultimately experience fewer adverse cardiovascular events during long-term follow-up, including reduced recurrence of arrhythmias [10].
3. Sleep apnea, in both its obstructive and central forms, can be modified with readily available treatments. These include traditional modalities such as sleep positioning, oral appliances, and positive airway pressure treatments, as well as novel therapeutics like implantable phrenic nerve stimulators and hypoglossal nerve stimulators.

Patho-Physiologic Mechanisms Linking Sleep Apnea and Arrhythmias

Delineating the exact mechanisms connecting sleep apnea to arrhythmias is complicated by common confounders, such as heart failure, obesity, diabetes, hypertension, and dyslipidemia [11]. Given the high prevalence of these comorbidities, the risk of arrhythmias in sleep apnea patients is expected to be high [3]. Nevertheless, mounting evidence suggests that sleep apnea also plays a direct role in promoting and sustaining arrhythmias. This occurs through mechanisms such as chronic sympathetic activation, adverse myocardial remodeling due to repetitive intrathoracic pressure swings, and a pro-arrhythmic milieu driven by frequent hypoxia and the diving reflex.

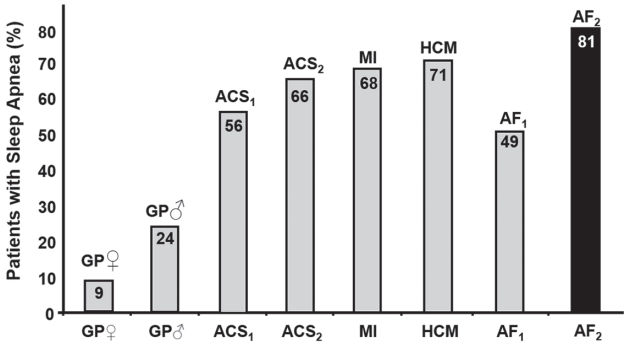

Figure 1 Prevalence of Sleep Apnea Among Women (♀) and Men (♂) in the General Population, as well as the Markedly Increased Prevalence of Sleep Apnea Among Patients with Various Forms of Cardiovascular Pathologies: Acute Coronary Syndromes (ACS), Myocardial Infarction (MI), Hypertrophic Cardiomyopathy (HCM), and Atrial Fibrillation (AF).
GP♀, ♂: Young et al., N Engl J Med 1993 [4]; ACS_1: BaHammam et al., Int J Clin Pract 2005 [5]; ACS_2: Mehra et al., Sleep Med 2006 [6]; MI: Konecny T et al., J Am Coll Cardiol 2010 [3]. HCM: Eleid M et al., J Am Coll Cardiol 2009 [7]; AF_1: Gami A et al., Circulation 2004 [8]; AF_2: Albuquerque FN et al., Chest 2012 [9].

The Sleep Apnea Treatment Paradox

The above findings provided considerable promise that treatment of sleep apnea would show an improvement in cardiovascular outcomes in prospective randomized trials. The promise was so strong that some clinical guidelines began adopting screening and treatment for sleep apnea in cardiovascular patients even before the results from randomized trials were available.

This notion was particularly noticeable in the recommendations for patients with arrhythmias, as the presence of AF became one of the leading indications for sleep apnea screening and treatment. Demonstrating this commitment, the 2019 guideline update published and endorsed by all the leading American organizations in the field of cardiology (American Heart Association, American College of Cardiology, and Heart Rhythm Society) indicated that "assessment and treatment of underlying sleep apnea" should be undertaken in all overweight and obese patients with AF (Class I-B recommendation) [12–14].

The results from prospective randomized trials were, therefore, surprising as these studies reported unexpected outcomes based on the intent-to-treat analyses. The concern was raised when the patients with central sleep apnea were studied in two large trials using continuous positive airway pressure (CPAP) and adaptive servo-ventilation (ASV) [15, 16]. The results consistently showed no benefit in treating central sleep apnea using these positive airway pressure modalities, and some endpoints even suggested a potentially detrimental effect.

Subsequent trials focusing on obstructive sleep apnea treatments further highlighted our gaps in understanding how to improve arrhythmia outcomes in the context of treating sleep apnea. In the seminal SAVE trial, the authors investigated how treatment with CPAP versus usual care alone affects the primary composite endpoint: death from cardiovascular

causes, myocardial infarction, stroke, and hospitalization for unstable angina, heart failure, or transient ischemic attack [17]. The results from the 2717 randomly assigned study subjects revealed that CPAP did not prevent cardiovascular events. Furthermore, one of the secondary endpoints identified patients who developed new-onset AF during the follow-up period; and while this study was underpowered for the given endpoint, it is notable that the percentage of sleep apnea patients who developed new-onset AF was higher in the group randomized to CPAP compared to the controls, although this difference was without statistical significance.

The stark difference – which we termed the sleep apnea treatment paradox [10] – between the observational results and the intent-to-treat randomized trials is under ongoing investigation. Potential explanations could lie in any of the following hypotheses, or in their combination:

Firstly, patients who are randomized to treatment with CPAP often do not tolerate such treatment for the entire duration of the night. As modern CPAP machines monitor the extent of time a patient is treated each night, we are able to determine that often less than five hours and sometimes even less than four hours, of effective CPAP treatment are delivered on an average night. This is notably different from observational studies, which usually divide patients based on the extent and effectiveness of the treatment they tolerate. An analogous comparison to hypertension would lead us to say that if we treat patients for high blood pressure with a certain medication regimen, but they only take the medications less than half of the time, it may also be difficult to effectively delineate advantages in terms of reduced outcomes in the patient arm assigned to the studied medication.

A second potential explanation could lie in the details of the study designs. As we recently published in our editorial in the Journal of the American Heart Association, it is important to note that a remarkable majority of studies that do not show benefit from sleep apnea treatment in terms of arrhythmia outcomes included a relatively modest follow-up of 12 months or less, while studies with longer follow-up monitoring were more likely to suggest a beneficial effect of CPAP on AF recurrence. To put this in perspective, it is common that CPAP treatment initiation takes some time, and there may exist a potential lag between its initiation and its effectiveness on the pro-arrhythmic substrate. Therefore, if we design a study that initiates CPAP at the time of AF diagnosis, and it takes three to six months to effectively titrate the treatment (by identifying an appropriate CPAP mask and settings that the patient can tolerate), it may be difficult to detect a difference in arrhythmia endpoints at the 12-month mark.

This is particularly relevant as even newly designed ongoing studies, which the scientific community hopes will provide us with more finalized answers, still include such relatively short follow-up periods [18]. To relate this conundrum using an analogy to hypertension, it would be similar to studying the treatment of hypertension by only attempting to detect a difference in stroke outcomes after one year, an approach which would likely not yield appropriately powered results.

Precision Medicine to the Aid

There is another potential explanation why the randomized studies employing sleep apnea treatments have not shown improved cardiovascular outcomes, and it lies in the relative lack of cardiovascular focus of the currently employed diagnostic and treatment algorithms used in Sleep Medicine. Traditionally, the diagnostic tests for sleep apnea have not focused on cardiovascular variables: While an electrocardiogram (ECG) is recorded as part of the standard polysomnogram (alongside oxygen saturation, airflow, neurological monitoring, and breathing effort), there is no analysis or utility to the ECG other than possibly for safety monitoring when sustained arrhythmias are detected, which is exceedingly rare. The polysomnogram was historically developed as more of a neurological test, and even the current diagnostic parameters used to identify sleep apneas and hypopneas do not take into account their effect on the cardiovascular system.

It is plausible that the current algorithms for diagnosing patients with sleep apnea, which employ the Apnea-Hypopnea Index (AHI), are not personalized enough for patients with high arrhythmic risk. For example, the widely used cutoffs for oxygen desaturation or length of breathing impairments are not based on robust assessments of their applicability to cardiac arrhythmogenesis. Therefore, it may be the case that we are applying CPAP or ASV to

incorrect patients or in an incorrect manner, as all of these decisions are traditionally guided by titration to reduce the AHI.

Also vice versa: Should we be tailoring our cardiovascular and anti-arrhythmic strategies based on the presence and severity of sleep apnea? Recent studies suggest that acute episodes of apnea and hypopnea profoundly affect atrial hemodynamics [19]. As sleep apnea episodes chronically recur during each hour of a patient's sleep, there appears to be a gradual buildup of pathological fibrosis and pro-arrhythmic substrate in specific atrial regions most susceptible to these hemodynamic changes [20]. These areas could potentially be studied for a more tailored ablation approach in patients with sleep apnea.

We propose that the above noted "sleep apnea treatment paradox" may suggest the existence of additional, yet unidentified variables that some sleep apnea patients inherently recognize, allowing them to instinctively decide whether to continue using sleep apnea treatments or not. Precision medicine and the analysis of large datasets may help us gain a more granular understanding of these variables. This, in turn, would allow us to adapt the available therapeutic regimens and apply them more effectively, thereby reducing arrhythmia burden in long-term follow-up.

Promise of Informed Technological Innovation

An important driver in improving our ability to treat sleep apnea and consequently ameliorate its effect on arrhythmogenesis lies in gaining a deeper understanding of the unique mechanistic pathophysiological interactions among sleep, breathing, cardiac, and autonomous variables, all of which ultimately combine to cause arrhythmogenesis. Only a more robust understanding of these intricate interactions can allow us to reliably propose the most effective treatment modalities, as well as how to apply the developing modalities in the most beneficial way. Let us demonstrate the ongoing innovation with a concrete example:

Central sleep apnea typically occurs in patients with existing chronic heart failure, but these same patients are uniquely susceptible to the adverse changes in cardiac preload and afterload. Historical studies suggested that application of positive airway pressure, which directly transmits to increases in intrathoracic pressure, may have detrimental effects on cardiac output. It is therefore not particularly surprising that the chronic application of CPAP would have an adverse effect on patients with pre-existing cardiomyopathy, as seen in the CANPAP trial [15]. The informed innovation came with the development of the phrenic nerve stimulator, which can be implanted similar to a standard pacemaker. This technology allows the patient to breath during sleep, but this time with a negative intrathoracic pressure caused by a more physiologic activation of the diaphragm, rather than the push of positive pressure ventilation into the chest. Understandably, the effects on cardiac hemodynamics are dramatically different, and the outcomes encountered by heart failure patients with central sleep apnea are superior in patients with the phrenic nerve stimulator.

Conclusion

"Those Who Cannot Change Their Minds Cannot Change Anything." – George Bernard Shaw

While it is never easy to encounter unexpected results in large randomized trials, these puzzling results may often lead us to discover valuable new information. In the case of sleep apnea, we must accept that the initial hope for across-the-board treatment for all patients does not seem to be effective. Instead, we could embrace the need for a deeper understanding of the complex interactions between sleep apnea and arrhythmias, and be prepared to adapt any traditional approaches to prioritize personalized care in patients with unique cardiologic needs.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Abbreviations

AF: Atrial fibrillation
AHI: Apnea-hypopnea index
ASV: Adaptive servo-ventilation
ECG: Electrocardiogram
CPAP: Continuous positive airway pressure therapy
OSA: Obstructive sleep apnea

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