

COMMENTARY

Clarifying the Role of Hypoxia in Obstructive Sleep Apnea as a Potential Promulgator of Atrial Fibrillation in Ischemic Stroke

Commentary on Chen et al. Nocturnal desaturation is associated with atrial fibrillation in patients with ischemic stroke and obstructive sleep apnea. *J Clin Sleep Med*. 2017;13(5):729–735.

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The burden of ischemic stroke in terms of incidence, mortality and disability-adjusted life-years has increased over the last several decades.¹ Approximately 800,000 new or recurrent strokes are diagnosed every year in the United States alone.² Atrial fibrillation (AF), an established risk factor for ischemic stroke, is recognized as the most prevalent of cardiac arrhythmias, affecting approximately 34 million persons globally³ and associated with increased cardiovascular-specific and all-cause mortality.⁴ Obstructive sleep apnea (OSA) shares an intricate relationship with AF and ischemic stroke.⁵ Epidemiologic and clinic-based data suggest OSA serves as a risk factor for the development of both AF⁶ and stroke.⁷ Although OSA has direct effects on stroke risk, OSA also likely operates via indirect pathways to contribute to development of stroke (eg, via increased atrial arrhythmogenesis).³ The interrelationships of OSA, AF, and stroke are likely mediated by OSA-related pathophysiological perturbations including intermittent hypoxemia, oxidative stress, autonomic nervous system dysregulation, augmented systemic inflammation, intrathoracic pressure swings, and increased levels of prothrombotic markers.⁸ OSA has been recognized as a risk factor for secondary prevention in ischemic stroke according to American Heart Association/American Stroke Association guidelines.⁹ Nearly one-fourth of strokes occurring in the United States are recurrent events. Therefore, determining the cause of stroke is a key element in developing specific management strategies to reduce a patient's risk of subsequent events. Identifying specific aspects of OSA pathophysiology contributing to AF in ischemic stroke patients provides an opportunity to implement more efficient risk stratification strategies to stroke management.

In the current issue of *Journal of Clinical Sleep Medicine*, Chen and colleagues aimed to elucidate the association of OSA and AF in patients with ischemic stroke.¹⁰ They conducted a cross-sectional examination of 158 patients (111 men) with ischemic stroke (occurring more than 1 week prior and within 1 year) admitted for neurorehabilitation. Patients were grouped into categories of paroxysmal AF identified prior to stroke (n = 26) and non-AF, and underwent in-laboratory polysomnography. The median scores of mean desaturation tended to be higher in the AF group compared to the non-AF group (6.7% versus 5.6%). Although in unadjusted analyses no significant association was

observed between mean desaturation and AF, multivariable logistic regression analysis adjusted for age, neck circumference, body mass index (BMI), and high density lipoprotein revealed that each percentage increase in mean oxygen desaturation was associated with 19% higher odds of AF. Associations of apnea-hypopnea index (AHI) and desaturation index in relation to AF were not statistically significant. The authors concluded that the extent of nocturnal desaturation represents a plausible pathophysiological factor driven by OSA contributing to AF in ischemic stroke patients, and based on these findings suggest consideration of overnight pulse oximetry to assess nocturnal hypoxia to predict paroxysmal AF in those with stroke.

A strength of the study by Chen et al. is the use of standard polysomnography in characterizing OSA indices, careful selection of the sample, and excluding comorbid conditions that can be causal factors of hypoxemia.¹⁰ Although those with known obstructive lung disease were excluded, the possibility of residual confounding due to undiagnosed pulmonary disease cannot be ruled out. A potential explanation for lack of a statistically significant association in the unadjusted analysis and significance in the adjusted model includes negative confounding characterized by one of the covariates in the model, resulting in attenuation of apparent effect of the predictor in the unadjusted model. Another perhaps more likely explanation for the incongruence of the results is that extreme levels of mean desaturation that contributed to the non-normality of the measure (evidenced by the presentation of median and interquartile range on univariable analysis), could have affected the estimate in the multivariable fit. In addition, the number of factors in the multivariable model suggests potential overfitting of the data,¹¹ though the number of predictors is on the lower bound of acceptable event to variable ratios for the purposes of confounding control.¹² Furthermore, the associations between mean desaturation and other measures of OSA relative to obesity ascertained by BMI is of interest, particularly as BMI may represent an effect modifier of the relationship between hypoxia as ascertained by mean desaturation and AF, as was seen in the relationship between sleep apnea and intermittent hypoxia in relation to postcardiac surgery AF.¹³ Another strength of the study is that the findings appear to be generalized to paroxysmal

AF, which is associated with stroke and was based on diagnosis before the stroke, although rigor of the ascertainment of paroxysmal AF is unclear given that this was based on objective electrocardiographic data collected only if first-line investigation did not reveal etiology—therefore, misclassification is possible.

Intermittent hypoxia via OSA-related autonomic nervous system alterations has been observed to enhance arrhythmogenesis in AF in experimental animal models.¹⁴ Recently published data from a mouse model demonstrate that intermittent hypoxia contributes to alterations in cardiac connexins and gap functions, thereby resulting in a predisposing cardiac substrate for AF generation.¹⁵ Clinic-based and epidemiologic data corroborate the importance of hypoxia in the development of AF and stroke. For example, those with untreated OSA and greater degree of hypoxic burden had higher AF recurrence after cardioversion.¹⁶ Also, severe nocturnal hypoxemia defined by the percentage of sleep time less than 90% oxygen saturation is associated with increased incident stroke in older men; this finding is not observed with other indices of sleep-disordered breathing.¹⁷ These data support a growing body of evidence suggesting that hypoxia is a critical factor in atrial arrhythmogenesis and stroke and raises the possibility that untreated sleep apnea/hypoxia may represent a perpetuating factor not only for AF, but also recurrent episodes of ischemic stroke.

The current findings of Chen and colleagues of a significant association of mean oxygen desaturation and paroxysmal AF in those with ischemic stroke therefore are particularly compelling given existing experimental, clinic-based, and epidemiologic data consistently demonstrating the importance of hypoxia in AF and stroke. There are, however, challenges to interpretation of the data. These include the possibility of negative confounding versus instability of the point estimate for mean oxygen desaturation and lack of significance of association of other hypoxia measures and AF. Although this may indicate that mean oxygen desaturation may represent a more physiologically representative hypoxia measure in OSA predicting AF compared to other hypoxia indices, further studies are warranted to verify and validate these findings. Basic studies are needed to examine complex cardiovascular physiologic changes in OSA and ascertain contribution to AF and stroke risk. Large-scale, longitudinal studies are also needed to enhance understanding of mechanisms by which OSA contributes to AF and stroke risk and how these change with the treatment of OSA and the effect of stroke outcomes. Data generated will be key for enhancing clinical management strategies to ameliorate the risk of recurrent stroke in patients with OSA.

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