

COMMENTARY

Sleep Apnea and Nocturnal Cardiac Arrhythmia: Understanding Differences Across Ethnicity

Commentary on Neo et al. Prevalence of cardiac arrhythmias in Asian patients with obstructive sleep apnea: a Singapore sleep center experience. *J Clin Sleep Med*. 2017;13(11):1265–1271.

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The association of sleep-disordered breathing and cardiac arrhythmia has been the focus of several United States-based multicenter epidemiologic and clinic-based studies.^{1–5} These existing studies have involved predominantly white participants with limited ethnic diversity.^{1–5} Sleep architectural alterations of slow wave sleep and arousal index as an atrial fibrillation (AF) risk have been identified—as has the association of sleep apnea and electrocardiography-based markers of atrial abnormality—in the Multi-Ethnic Study of Atherosclerosis (MESA). This United States-based cohort comprised white, black, Hispanic, and Chinese (12%) participants although ethnic-specific subgroup analyses have not been reported.^{6–8} In an effort to examine whether these existing sleep apnea-cardiac arrhythmia findings are generalizable to the Asian population, in the current issue of the *Journal of Clinical Sleep Medicine*, Neo et al. sought to examine the association of obstructive sleep apnea (OSA) and nocturnal polysomnographically identified cardiac arrhythmia in a clinic-based Singapore study.⁹

The investigators performed a retrospective, single-center study of 2,019 patients who were overall overweight, most of them male (72.4%) with a median age of 46 years and approximately 80% were of Chinese descent. The authors identified an overall higher prevalence of nocturnal cardiac arrhythmia in those with OSA (defined as apnea-hypopnea index ≥ 5) of 8% versus 4.8% in those without OSA. They found that older age and increasing body mass index (BMI) were associated with cardiac arrhythmia. Although there was an increase in nocturnal cardiac arrhythmia across increasing OSA category and a significant association of OSA and cardiac arrhythmia in adjusted analyses, after adjustment for age, obesity, and cardiovascular risk factors, the latter findings were no longer statistically significant. However, percentage of sleep time with less than 90% oxygen saturation was significantly associated with cardiac arrhythmia after adjustment for BMI and cardiovascular risk, albeit adjustment for comorbid pulmonary disease was not performed. There were no specific patterns reported in terms of arrhythmia subtype (ie, supraventricular, ventricular, sinus, conduction delay, or mixed) and association with OSA.⁹

The authors' work is laudable given the paucity of data characterizing the OSA-nocturnal cardiac arrhythmia relationship in the non-white population. The strengths are the large sample size and the visual inspection of the polysomnogram-based electrocardiography data blinded to respiratory events. Limitations include the lack of characterization of obstructive versus central apnea subtypes (those with central sleep apnea were excluded), inability to examine ectopy per unit time as a continuous variable, and lack of data on antiarrhythmic medications, smoking, and alcohol intake. The consideration of all arrhythmia types as the composite main outcome is also somewhat limiting as there are different risk profiles and underpinning electrophysiological mechanisms of the generation of atrial, ventricular, and conduction delay arrhythmias.

The race-specific differences in phenotypic and genotypic profiles of both sleep apnea risk and cardiac arrhythmogenesis combined with the recently reported high prevalence of moderate to severe OSA in Singapore of approximately 30%,¹⁰ makes a compelling case for the current work which sheds light on this important area. Unlike findings from studies with predominantly white individuals that have demonstrated significant obesity and cardiovascular risk/outcome-adjusted associations of sleep apnea and both atrial and ventricular arrhythmia, discrepant findings were observed in the current study. This was characterized by lack of a significant association of sleep apnea and a composite of nocturnal cardiac arrhythmias after accounting for obesity and cardiovascular risk factors. A potential explanation is that the OSA phenotype appears to differ across ethnicity. For example, not only are craniofacial differences thought to provide a rationale for varied OSA prevalence in Asians versus other races, but also Asians have lower anthropometric thresholds for a given level of obesity likely attributable to a higher percentage of body fat.¹¹ Recent data also demonstrate significant ethnic variation in OSA prevalence in those with acute coronary syndrome such that the largest magnitude of BMI effect was in the Chinese population compared with other ethnicities.¹² Therefore, it is possible that the high

background risk of adiposity in the Asian population may have precluded identification of a significant association of OSA and cardiac arrhythmogenesis. Notably, the OSA-arrhythmia odds ratio point estimate decreased substantially from 1.93 to 1.54 after adjustment for both age and BMI; however, hypoxia defined as percentage of sleep time less than 90% remained significant in the final adjusted model. These findings suggest hypoxia-mediated pathways of OSA in Asians may be less influenced by age and obesity in terms of arrhythmogenic risk.

Although the overall sample size was over 2,000 patients, the authors comment on the lower arrhythmia event burden in this Asian clinic-based sample compared with other clinic-based studies that therefore may have led to an underpowered study due to a lower outcome event. The findings of a significant graded stepwise increase in arrhythmia percentage with increasing category of OSA severity somewhat supports this assertion. The observed arrhythmia prevalence, however, does appear to be comparable to epidemiologic studies such as the Sleep Heart Health Study, perhaps somewhat reducing likelihood for this rationale.³ Furthermore, the investigators considered a hypopnea definition of 30% reduction in flow with a $\geq 4\%$ oxygen desaturation, which is a higher bar than considered in prior epidemiologic and clinic-based studies that could provide an explanation for the disparate ethnic findings.^{1,3,4} Perhaps more importantly, unlike prior studies that have involved older individuals likely to have higher arrhythmia burden,^{1,3-5} the study by Neo et al. involved middle-aged patients who were less predisposed overall. The racial paradox provides an alternate explanation, ie, despite higher conventional risk factors for arrhythmia, the prevalence of cardiac arrhythmia such as AF is lower in black and South Asian compared with white populations. This may be attributable to a variety of factors such as variations in genetic predisposition, Asian-specific smaller atrial size (which may thereby be protected from intrathoracic pressure-induced atrial alterations), and/or varied electrophysiological substrate.¹³

Given the differences in race-specific genetic^{14,15} and phenotypic contributions of OSA to cardiac arrhythmogenesis and also differences in cardiometabolic profiles in the Asian versus non-Asian populations, there is a strong interest and rationale to pursue investigation of race-specific differences pertaining to sleep apnea and cardiac arrhythmia outcomes. Although the current findings of a lack of a significant adjusted association of OSA and cardiac arrhythmia in this Singapore clinic-based study provide a much-needed step in the right direction, it is unclear whether these findings are truly indicative as such, possibly because of the well-described racial paradox or inherent differences in age, definition of hypopnea, or lower prevalence of arrhythmia outcome compared with findings in predominantly white patient samples. However, findings suggest Asian-specific vulnerability to nocturnal hypoxia as a potential viable risk for nocturnal cardiac arrhythmia. Therefore, further verification and validation of these findings in Asians and also investigations in other non-white populations are warranted,

including longitudinal studies to examine sleep apnea indices as predictors of incident development of cardiac arrhythmia and sleep apnea interventional studies focused on arrhythmia outcomes to better elucidate ethnic-specific differences and treatment responses.

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