EDITORIAL

Sleep Apnea and Cardiac Arrhythmia: A Timely Wake-Up Call!

Commentary on Shamsuzzaman et al. Obstructive sleep apnea in patients with congenital long QT syndrome: implications for increased risk of sudden cardiac death. SLEEP 2015;38:1113–1119.

Rajeev K. Pathak, MBBS; Rajiv Mahajan, MD, PhD; Dennis H. Lau, MBBS, PhD; Prashanthan Sanders, MBBS, PhD

Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia

Obstructive sleep apnea (OSA) and related comorbidities such as obesity and hypertension are associated with increased risk of cardiac arrhythmias.[1,2] These risk factors have been associated with cardiac structural, electrical, and autonomic remodeling that form the substrate leading to the development and progression of arrhythmias.[3,4]

There are several potential pathophysiologic contributors that may predispose a patient with OSA to develop cardiac arrhythmias. There are acute and chronic changes due to repetitive OSA. Acute OSA promotes arrhythmias via autonomic changes,[5] along with acute cardiac stretch and diastolic dysfunction.[6,7] Furthermore, chronic repetitive OSA produces cardiac remodeling, including left and right ventricular (LV) dilation, hypertrophy, and systolic and diastolic dysfunction. The intermittent hypoxia, oxidative stress, connexin-43 changes, and inflammation are all variably implicated as causes of fibrosis and cardiac remodeling.[8,9]

OSA is associated with severe nocturnal and diurnal autonomic imbalance.[10] Rise in sympathetic tone due to repeated nocturnal desaturation and diurnal stress along with enhanced parasympathetic drives due to repeated respiratory efforts are some of the putative mechanisms behind this altered autonomic balance.[11] The impaired autonomic regulation in patients with OSA leads to abnormal ventricular repolarization, impaired heart rate adaptation of QT interval (i.e., electrical depolarization and repolarization of the ventricles), and parasympathetic components of heart rate variability.[12,13] Delayed cardiac repolarisation leading to the prolongation of the QT interval is a well-characterized precursor of life-threatening arrhythmias.[14] Also, blunted rate dependence of the QT interval is associated with increased risk of ventricular arrhythmias and sudden cardiac death in diabetics with autonomic neuropathy.[15]

In the current issue of *SLEEP*, Shamsuzzaman and colleagues[16] evaluated the impact of sleep apnea on the QTc interval in patients with established diagnosis of long QT syndrome (LQTS). Their study correlates the sleep apnea related autonomic disturbance with prolongation of QTc. Bazett's formula was utilized to adjust for rate related variability.[17] Consistent with the epidemiological associations, LQTS with OSA subjects were significantly older and heavier compared with LQTS without OSA and control subjects. Incidence of OSA was 26% in LQTS patients. This highlights the importance of screening for OSA in patients with channelopathies.

In the study by Shamsuzzaman et al., RR intervals, QT intervals, and Bazett's-calculated QTc values, while awake and during both NREM and REM sleep stages, were increased significantly in patients with LQTS compared to controls.[16] Of note, patients with LQTS and OSA had significantly increased RR, QT, and QTc during wake and sleep compared to patients with LQTS but without OSA. There were no differences in these values between groups during each sleep stage. After multivariate adjustment for age, gender, body mass index, β-blocker use, and syncope—factors well described to cause autonomic imbalance—OSA was significantly associated with QTc intervals while awake. Additionally, their study has eloquently demonstrated the dose effect of severity of sleep apnea with degree of QTc interval prolongation.[16]

While the report of Shamsuzzaman et al. has clarified how sleep apnea related autonomic disturbance relates to prolongation of QTc, several other questions remain. Importantly, the prognostic implications of their findings remain to be determined. They did not report any clinical outcome such as arrhythmic event or sudden cardiac death (SCD). Large longitudinal prospective studies are necessary in this regard to establish the prognostic implications of QTc prolongation for ventricular arrhythmias and SCD. Moreover, nocturnal continuous positive airway pressure (CPAP) treatment is associated with reduction of the autonomic disorder and improvement in rate adaptation of QT interval associated with sleep apnea.[18] In the future it will be important to establish whether the improvement in repolarization inhomogeneity by CPAP treatment can result in reduction in arrhythmia burden and risk of SCD. Additionally, aggressive management of comorbid risk factors such as weight has been shown to reduce severity of OSA and atrial arrhythmia burden.[19,20] Whether this beneficial effect can be extended to ventricular arrhythmia remains to be determined.

The study of Shamsuzzaman et al.[16] had a higher proportion of female patients, and information about LQTS genotype was lacking. Moreover, the study is affected by fundamental limitations in the use of QT interval. It is well known that Bazett's formula is inaccurate at higher heart rates.[21] It overcorrects at faster heart rates and under corrects at lower heart rates. However, this was a limitation for all the groups in their study. These limitations notwithstanding, their study highlights the importance of screening for OSA in patients with

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Address correspondence to: Rajeev K. Pathak, Centre for Heart Rhythm Disorders, Department of Cardiology, Royal Adelaide Hospital, Adelaide, 5000, Australia; Tel: +61882222723; Fax: +61882222722; Email: rajeev.pathak@adelaide.edu.au

channelopathies. Timely diagnosis and adequate "upstream" treatment of OSA may result in either resolution or at least reduction of arrhythmia in this high-risk population.

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