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Review

Sleep-Disordered Breathing and Cardiac Arrhythmias

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ABSTRACT

Over the past few years sleep-disordered breathing has been identified as an important factor in arrhythmogenesis and a potential target of therapy to prevent cardiac arrhythmias in selected patients. In this review we highlight the role of obstructive sleep apnea and Cheyne-Stokes respiration in the pathophysiology of arrhythmias, address their clinical effect in supraventricular and ventricular tachyarrhythmias, and in conduction disturbances, and address the role of current treatment options for sleep-disordered breathing in the primary and secondary prevention of arrhythmic events.

RÉSUMÉ

Au cours des dernières années, il a été reconnu que les troubles respiratoires du sommeil sont un facteur important de l'arythmogenèse et une cible potentielle de traitement pour prévenir les arythmies cardiaques chez certains patients. Dans cette revue, nous soulignons le rôle de l'apnée obstructive du sommeil et de la respiration de Cheyne-Stokes dans la physiopathologie des arythmies, abordons leurs conséquences cliniques dans les tachyarythmies supraventriculaires et ventriculaires, et dans les troubles de conduction, puis abordons le rôle des options actuelles de traitements contre les troubles respiratoires du sommeil dans la prévention primaire et secondaire des événements arythmiques.

Patients with underlying cardiac disease face an enhanced risk of cardiac arrhythmias. Clinical presentations range from asymptomatic incidental electrocardiographic findings to palpitations, syncope, and sudden cardiac death (SCD). Although in previous decades enormous efforts have been spent on reducing the burden of ventricular arrhythmic events, current research on ventricular arrhythmias aims to avoid potentially lethal ventricular arrhythmias, including sustained ventricular tachycardias and ventricular fibrillation, and not to reduce ventricular ectopic burden.[1-3]

Likewise, attributes for antibradycardic treatment have changed. Although previous guidelines concentrated on electrocardiographic presentations of conduction disorders, current European Society of Cardiology guidelines propagate a more sophisticated approach that distinguishes between clinical presentation of persistent and intermittent bradycardias and between suspected and documented events and extrinsic and intrinsic causes.[4]

With respect to atrial arrhythmias, atrial fibrillation (AF) and atrial flutter are diseases of major clinical importance with increasing trends in prevalence and hospitalization rates.[5] Although atrial arrhythmias are not directly linked with SCD, AF is accompanied by symptoms leading to subjective and objective exercise capacity impairment and a 5-fold increase in stroke risk and an increased mortality risk.[5,6]

Pathophysiological Effects of Sleep-Disordered Breathing

Adults spend 75%-85% of their total sleep time in non-rapid eye movement sleep, which is generally considered a time of parasympathetic tone predominance and cardiovascular quiescence with reduced sympathetic nerve system activity and altered cardiac repolarization that prevents patients from cardiac dysrhythmias.[7-10] Underlying mechanisms to understand the pathophysiological effects of sleep-disordered breathing (SDB) on arrhythmia evolution are currently under intensive investigation.

Recently, several studies elucidating the interplay between obstructive sleep apnea (OSA) and AF have been published. As one of the most marked consequences, patients with SDB present with intermittent hypoxemic episodes. Acute hypoxemia and hypercapnia are associated with increased sympathetic nerve system activity.[11,12] Moreover, apnea episodes disturb normal sleep patterns with induction of autonomic neural inputs to ganglionated plexi.[13] Enhanced ganglionated plexus activity is associated with shortening of atrial refractory periods that promote premature stimuli to activate the atrium. In an animal study, Ghias and coworkers demonstrated that after neural

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ablation of the ganglionated plexi, AF inducibility was significantly inhibited.[14] Recently, renal denervation was shown to reduce shortening of atrial effective refractory periods in an animal model of OSA.[13] However, taking into account the complex interplays of the sympathetic and parasympathetic nerve system in the pathophysiology of cardiac arrhythmias, exact mechanisms leading to AF seem difficult to elucidate.

Apneic or hypopneic phases of OSA are associated with excessive negative intrathoracic pressure changes that alter transmural pressure and volume relations.[15] Acute distension of the atrium might be an important trigger for the onset of AF in these patients.[16] Furthermore, negative intrathoracic pressure changes were shown to trigger AF episodes by shortening of atrial effective refractory periods, mainly due to enhanced vagal activation.[17]

OSA is also associated with surges in blood pressure and heart rate, which enhance the myocardial oxygen demand and cardiac workload.[18,19] Apart from promoting local vasodilating effects, apneic events are associated with systemic vasoconstriction that further increases cardiac afterload, workload, and myocardial oxygen demand.[20] Intrathoracic pressure changes and hypoxemia-induced vasoconstriction increase shear stress. Chronic shear stress leads to remodelling of the myocardium.[21,22] In an animal model, Iwasaki and coworkers were able to demonstrate that OSA causes left ventricular hypertrophy, dilation, and diastolic dysfunction, and a connexin dysregulation and an increased atrial fibrous tissue content. These changes were clearly associated with enhanced AF inducibility.[23] Linz et al. found increased plasma renin activity and aldosterone concentrations, and an increased expression of connective tissue growth factor, a redox-sensitive mediator of fibrosis, in a pig model mimicking OSA using exposure to repetitive obstructive respiratory events for 4 hours.[13]

There is only weak evidence to support an association of SDB with increased serum levels of angiotensin II and aldosterone in human patients.[24,25] Dimitri et al. demonstrated in 40 patients who underwent ablation of paroxysmal AF that OSA is associated with severe atrial remodelling and reduction in voltage, and site-specific and widespread conduction disturbances.[26] Correspondingly, several studies found the left atrium to be more dilated in patients with OSA, and left atrial function impaired compared with control subjects.[21,27] Another trigger for remodelling is inflammation. Previous data confirmed OSA and central sleep apnea (CSA) with Cheyne-Stokes respiration to be associated with an enhanced inflammatory status.[28,29]

Shifting attention to ventricular arrhythmias, several of the aforementioned mechanisms also play a major role in the pathophysiological interplay between sleep apnea and tachyarrhythmic events in the ventricle.[22] For example, intermittent hypoxemia and increased sympathetic nerve system activity related to apneic episodes in OSA are associated with the occurrence of premature ventricular beats.[11,30,31] A decline in systolic and diastolic left ventricular function was also found during respiratory events in OSA.[15,32] In addition, SDB affects cardiac electrophysiology by modifying conduction velocity and refractoriness. Rossi and coworkers, for instance, demonstrated that OSA is associated with prolongation of the corrected QT interval and corrected Tpeak to Tend interval intervals and TpTe/QT ratio.[33] OSA similarly impacts QT dispersion and T-wave alternans, which might predispose these patients to malignant arrhythmias and SCD.[34-37]

Bradyarrhythmias in OSA are linked with vagal activation that can be found at the end of apneic events. Vagal activation is mediated by hypoxemic triggering of the glomus caroticum.[38]

Clinical Effect of SDB

The clinical association between SDB and cardiac arrhythmias has been studied for 3 decades. Several population-based studies have shown an association between OSA and rhythm disorders.[39,40] Recently, a Brazilian study involving 767 volunteers demonstrated rhythm disturbances in 53.3% of the sample without SDB, and 92.3% of patients with severe OSA showed cardiac arrhythmias.[41]

Most of those arrhythmic events do not have prognostic relevance and thus need no specific treatment.[1] In this review we focus on common arrhythmias with clinical importance, namely ventricular and atrial tachyarrhythmias and bradyarrhythmic events.

AF/flutter

The prevalence of SDB among patients with paroxysmal AF, persistent AF, or atrial flutter is high.[42-44] Contrastingly, a monocausal relationship is difficult to prove because both diseases share common risk factors such as hypertension or obesity.[45-47] Gami and coworkers demonstrated an increased incidence of AF in a large cohort of patients with OSA.[48] Furthermore, even in specific patient cohorts, such as hypertrophic cardiomyopathy, OSA is independently associated with a greater risk of new-onset AF.[49]

Identification of AF patients with comorbid SDB is a difficult target. In OSA patients without cardiac disease, excessive daytime sleepiness has been identified as a major symptom.[50] Applying standardized questionnaires such as the Epworth Sleepiness Scale thus is a helpful tool to identify people at risk.[51] Unfortunately none of those questionnaires has ever been validated in AF patients. Albuquerque and coworkers, for instance, found no association between the Epworth Sleepiness Scale score and the severity of SDB.[52] One explanation might be that AF per se is associated with poor sleep quality.[53]

Focusing on the prognostic importance of OSA in patients with AF, one major issue that has been addressed is reoccurrence of AF on rhythm control therapy. Monahan et al. demonstrated that nonresponders to successful antiarrhythmic drug treatment are more likely to have severe OSA (52% vs 23%).[54] Even more strikingly, Kanagala et al. demonstrated that the recurrence of AF after electric cardioversion at 12 months was 82% in patients with untreated OSA compared with 53% in patients who were not evaluated for SDB.[55] Currently, great efforts are being spent to investigate the effects of SDB on expensive and invasive catheter-based procedures. We previously conducted a study showing that SDB had negative effect on sinus rhythm persistence after cryoballoon ablation (Fig. 1).[56] Similar data have been published for other ablation techniques such as radiofrequency ablation of AF or cavotricuspid isthmus radiofrequency ablation of atrial flutter.[44,57,58] One should keep in mind that the diagnosis of sleep apnea must be obtained by means of technical investigations. A