Přehledový článek | Review article

Cardiovascular autonomic control under obstructive sleep apnea combined with atrial fibrillation: Its role in pathogenesis and therapy

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SOUHRN

Tento přehledový článek se podrobně zabývá mechanismy autonomní regulace kardiovaskulárního systému během spánku, během jednotlivých i opakovaných apnoických pauz, jejich úlohy v patogenezi fibrilace síní (FS) a upozorňuje na metody autonomní modulace. Dysfunkce autonomní regulace kardiovaskulárního systému představuje v podmínkách jednorázové nebo chronické expozice obstrukční spánkové apnoe jeden z hlavních faktorů umožňujících vznik FS a její recidivy. Vrátit do fyziologického stavu autonomní regulaci a příznivě ovlivnit substrát vedoucí k rozvoji a progresi arytmie může kombinace různých způsobů ovlivňování rizikových faktorů vzniku FS (jejich úprava, léčba kontinuálním přetlakem v dýchacích cestách, farmakoterapie a intervenční metody).

Keywords:
Atrial fibrillation
Cardiovascular autonomic control
Obstructive sleep apnea

ABSTRACT

This review examines in detail the mechanisms of cardiovascular autonomic control in the course of sleep, during single and multiple repetitive episodes of apnea, their role in pathogenesis of atrial fibrillation (AF), and also highlights the methods of autonomic modulation. In conditions of a single or chronic exposure to obstructive sleep apnea, cardiovascular autonomic dysfunction is one of the leading factors providing the possibility of AF development and recurrence. A combined effect on AF risk factors (their modification, use of continuous positive airway pressure therapy, drug therapy, and interventional techniques) can normalize the autonomic control and positively affect the substrate leading to the development and progression of arrhythmia.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. AF is associated with increased cardiovascular morbidity and mortality.[1] At the same time, obstructive sleep apnea (OSA) is no less widespread than AF: it is ubiquitous both in the general population[2,3] and in specialized cohorts with diseases of the cardiovascular system.[4]

Recent studies demonstrated that the incidence of OSA is significantly higher among patients with AF, compared with the general population.[3,5,6] This fact is explained by the presence of such joint risk factors for OSA and AF as older age, obesity and systemic arterial hypertension (hereafter referred to as hypertension), which, acting together, could increase cardiovascular risk. Some recent studies revealed that autonomic dysfunction may contribute to the development of AF in conditions of OSA.[7,8]

Therefore, methods aimed at influencing the imbalance of the autonomic nervous system (ANS) can be a promising therapeutic target in AF combined with OSA.[7] This is especially true for patients undergoing ablation for AF in order to maximize the clinical benefit of the procedure.[9]

This literature review examines in detail the physiological mechanisms of cardiovascular autonomic control in the course of sleep, during single and multiple

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repetitive episodes of apnea, their role in AF pathogenesis, and also highlights the methods of autonomic modulation.

The role of the autonomic nervous system in maintaining sleep

Sleep is a complicated and complex physiological process that includes various mechanisms of biological control, including the activity of the cardiovascular system. Normal sleep consists of two different physiological phases: slow-wave sleep (non-rapid eye movement sleep, NREM) and paradoxical sleep (rapid eye movement sleep, REM). It is recognized that the ANS state changes during sleep. In slow-wave sleep, parasympathetic activity predominates (heart rate, blood pressure, and respiratory rate are minimal). During paradoxical sleep, mixed and combined activity of sympathetic and parasympathetic ANS divisions is recorded, causing a significant impact on the cardiovascular system.[7,10] Therefore, ANS plays a critical role in the functional control of the cardiovascular system, reflecting the patterns of autonomic control during different phases of sleep.

Methods for assessing autonomic control in the course of sleep

The main clinical methods for assessing cardiovascular autonomic control in the course of sleep are heart rate variability (HRV), the level of catecholamines in blood and urine, and microneurography.[11]

HRV analysis is widely used as a conventional method for assessing ANS functions. The method is implemented when recording an electrocardiogram for different time periods. The obtained data are analyzed via simultaneous temporal and spectral analysis. The resulting spectral characteristics and their derivatives are a reflection of the activity of both sympathetic and parasympathetic divisions of the ANS.[12,13]

Laboratory methods for investigating the sympathetic activity include determining the levels of catecholamines in urine and blood.[14]

The most reliable method for recording the activity of the ANS sympathetic division is microneurography. Sympathetic activity is invasively measured using a microelectrode placed in the postganglionic sympathetic efferent fibers of the peroneal nerve.[15]

Mechanisms of a single sleep apnea episode in AF pathogenesis

Transient autonomic activation is observed with each individual respiratory event during sleep. Although OSA may occur during any sleep phase, REM sleep apnea tends to last longer due to the muscle atony inherent in this sleep phase. An apnea episode is accompanied by hypoxemia and, with a pronounced duration, by hypercapnia. The end of an apnea episode is characterized by hyperinflation of the lungs. Both mechanisms (impaired gas exchange and pulmonary hyperinflation) are powerful stimuli for increasing the sympathetic tone of the ANS.[16]

On the other hand, during the apnea episode per se, the vagus nerve is activated, which is reflected in the emergence of severe bradycardia and various conduction disorders.[17] It is believed that the basis of the vagus nerve activation is represented by a breath-holding reflex (similar to what is occurring during diving) causing hypoxemia. This leads to a substantial heart rate reduction aiming at centralization of blood flow. The sharp increase in blood pressure during sleep apnea causes stimulation of the vagus nerve as well, apparently, via baroreceptors. Simultaneous activation of sympathetic and parasympathetic ANS divisions leads to the development of the accentuated antagonism. The latter sharply disrupts the autonomic control via mutual reinforcement of action of ANS divisions.

Difficulty breathing during sleep apnea leads to fluctuations in intrathoracic pressure. The operation of this mechanism has been demonstrated in a biological model (a pig model of obstructive sleep apnea). Linz et al. demonstrated that fluctuations in intrathoracic pressure can lead to a reduction in the atrial effective refractory period and an augmented risk of AF initiation. The arrhythmia induced in this way was entirely controlled by the administration of atropine or direct vagotomy, which indirectly confirmed the role of vagus nerve activation in the development of paroxysmal AF in OSA.[18]

In another experiment, conducted on dogs by Yu et al., animals developed acute intermittent hypoxia at the time of breath-holding implying that both sympathetic and parasympathetic activity increased over the next 30–60 minutes from the onset of acute intermittent hypoxia.[19] Invasive recording of neural activity of peripheral ANS elements in dogs (stellate ganglion and renal sympathetic nerve) for 1 hour demonstrated that simultaneous activation of sympathetic and parasympathetic ANS divisions contributed to the onset of AF.[20]

Apnea often ends with short periods of awakening from sleep (microarousals or electroencephalographic activation responses), resulting in sleep fragmentation and an increase in the production of proinflammatory plasma cytokines. This contributes to the redistribution of ANS balance due to excessive activation of its sympathetic division. Studies involving HRV analysis in patients with OSA confirmed the fact.[21–23] After respiration is restored, there is an increase in venous return and cardiac output, which, in conjunction with an increased total peripheral vascular resistance, leads to a short-term sharp increase in blood pressure. Clinical data supported the role of hypertension in increasing the relative risk of developing AF after acute obstructive respiratory events.[24]

Role of chronic exposure to OSA in AF pathogenesis

It is worth noting that the prolonged presence of OSA in anamnesis affects the central link of the ANS as well. Studies using magnetic resonance imaging revealed that OSA was often accompanied by a significant damage to brain regions in charge of the central region of autono-

mic control.[25] Lee et al. found that chronic intermittent hypoxia in rats could increase the intensity of oxidative stress and inflammation, as well as neuronal activation in the paraventricular nucleus of the hypothalamus – i.e., the area of the brain responsible for controlling the sympathetic ANS link and blood pressure.[26]

A study by Dyavanapalli et al. established that chronic intermittent hypoxia resulted in a significant decrease in efferent parasympathetic impulses due to the predominance of afferent sympathetic impulses, which led to tachyarrhythmias and hypertension.[27]

In addition to autonomic remodeling, long-term exposure to OSA is also associated with progressive arrhythmogenic structural and electrophysiological changes. The findings suggest that repetitive fluctuations in intrathoracic pressure during chronic OSA lead to atrial dilatation (predominantly, in the left atrium), which is a well-established risk factor for AF.[28] The prolonged course of OSA was also associated with an increase in circulating biomarkers of inflammation and oxidative stress, and with activation of the renin-angiotensin-aldosterone system, contributing to the development of atrial fibrosis.[29–31] In turn, fibrosis led to a reduction in the atrial effective refractory period and increased dispersion of refractoriness. In patients with OSA, atrial conduction disorders were observed in the form of extensive areas of delayed impulse conduction.[32]

In animals, an increase in the sensitivity of chemoreceptors and a reduction in the sensitivity of baroreceptors contributed to the weakening of the reflex control of blood pressure,[33] which contributed to the development of hypertension in chronic intermittent hypoxia.[33,34]

In a few studies conducted in patients with OSA, persistent excessive sympathetic activity was observed, which was associated with an increased risk of cardiovascular disease.[35] Long-term predominance of sympathetic excitation leads to the formation of a non-dipper daily profile of blood pressure, which is also associated with an increased risk of developing cardiovascular diseases.[36]

From the foregoing, it can be concluded that OSA-induced chronic activation of the sympathetic nervous system, along with well-known risk factors, plays an important role in autonomic, structural, and electrical atrial remodeling, providing a substrate for the onset and recurrence of AF.[7]

Parallel development and correlations of OSA and AF

The relationship between the presence of OSA and AF was shown for the first time on a large statistical material by Gami et al. in the publication based on a retrospective analysis of data from a sleep study of 3,542 patients without arrhythmia in anamnesis over a 15-year period. A decrease in the saturation level at night was a strong predictor of developing the first paroxysm of AF during the observation period (odds ratio, OR: 3.29; 95% confidence interval [CI]: 1.35–8.04). An important fact discovered in that study was the impact of obesity and OSA on the incidence of AF. It was recorded more often in patients under 65 years old. The authors suggested that other risk factors (heart failure and ischemic heart disease) may play a major role in the development of AF in the elderly population.[37]

The role of OSA as an important risk factor for the development of AF was also confirmed by the results of the Sleep Heart Health Study that involved over 6,000 participants. The researchers established that in the presence of severe OSA, the risk of developing AF was fourfold (OR: 4.02; 95% CI: 1.03–15.74).[38] The incidence of OSA was significantly higher in patients with AF (49% vs. 32%, respectively, $p = 0.004$).[39] ANS disorders, often recorded in patients with OSA, may influence the AF development. Hence, it is ANS that can become a promising therapeutic target in the treatment of OSA combined with AF.[7]

Methods of autonomic modulation in treating the AF combined with OSA

Main currently known methods of autonomic modulation include the prevention of AF risk factors, continuous positive airway pressure (CPAP) therapy, drug therapy, and interventional techniques for influencing the ANS.

Modification of risk factors

Management of modifiable risk factors for the development of AF (hypertension, coronary heart disease, symptomatic heart failure of functional classes II–IV sensu New York Heart Association, impaired thyroid function and carbohydrate metabolism, overweight status and obesity, OSA), along with the expansion of the motor activity level, substantially improve the results of surgical treatment of AF and contribute to long-term rhythm control.[40] Several studies showed that the combination of weight loss, antihypertensive treatment and CPAP therapy led to a significant reduction in sympathetic activity. Hence, it is the complex management of risk factors that is a powerful strategy for influencing the ANS, leading to a slower progression, or even reverse structural remodeling, of the heart.[41]

CPAP therapy

The gold standard for treating moderate and severe forms of OSA is CPAP therapy.[42] The positive pressure generated in the upper airways prevents those from collapsing, thereby maintaining their patency throughout the entire sleep period. By eliminating the obstruction of the upper respiratory tract, the main link in the pathogenesis of OSA, CPAP therapy has a direct impact on the autonomic and structural heart remodeling. Shah et al. studied 720 patients with AF and discovered that OSA was independently associated with left ventricular remodeling, whereas CPAP therapy prevented its progression.[41] In another study, after 12 weeks of CPAP therapy, patients with severe OSA exhibited a significant improvement in echocardiographic volume and left ventricular myocardial deformation, as evaluated by speckle tracking echocardiography.[43] In a study by Hall et al., patients with heart failure and OSA exhibited enlarged accumulation of hydroxyephedrine in the myocardium via positron emission tomography after 6–8 weeks of CPAP therapy, which was

indicative of a decrease in activation of the sympathetic ANS division.[44]

Considering the positive effect on the autonomic and structural remodeling of the heart, patients on CPAP therapy exhibited better long-term results with both conservative and surgical methods of treating AF. Monahan et al. reviewed data on patients with AF who underwent a sleep study against the background of medical therapy. Patients with poor response to antiarrhythmic medicines were more likely to have severe OSA (52% vs. 23%, p <0.05).[45] There is also evidence that in patients with a combination of OSA and AF, and not receiving CPAP therapy, the frequency of arrhythmia recurrence was significantly higher after cardioversion or catheter therapies.[45–47] In particular, the study by Kanagala et al. demonstrated that the recurrence rate of AF a year after cardioversion was 82% in patients with untreated OSA, compared with 42% in the CPAP group.[48] Fein et al. showed that AF recurrence rate after arrhythmia surgery was significantly higher in patients not subjected to CPAP (OR 2.4, p <0.02), whereas CPAP therapy contributed to a significantly greater absence of arrhythmia recurrences (71.9% vs. 7%, p = 0.01) in the immediate postoperative period.[47] Based on the data of the above studies, the latest recommendations for the management and treatment of patients with AF, for the first time, proposed screening AF patients for the presence of OSA and, if indicated, initiating OSA therapy prior to surgical interventions.[1]

Drug therapy

The use of beta-blockers in patients with OSA is still a subject of dispute. It is known that bradyarrhythmia, often recorded in patients with severe forms of OSA, can be aggravated by taking beta-blockers. However, in recent years, evidence has emerged of their positive effect on the sympathetic ANS link in conditions of OSA. According to the data obtained by Wolf et al., cardioselective beta-blockers reduce the heart rate after the end of an apnea episode, but do not significantly reduce it at the peak of apnea.[49] Besides, there is evidence that moxonidine reduces the number of postablation AF recurrences in patients with hypertension[50].

Medicines inhibiting acid-sensitive potassium channels (TASK) are currently undergoing clinical trials. These channels are also found in the neurons of the respiratory center of the brainstem, carotid bodies, motoneurons of the hypoglossal nerve, cardiomyocytes, vascular smooth muscle cells, and are involved in the regulation of heart rate and respiratory movements.

In experimental animal models, nasal administration of TASK inhibitors caused depolarization of mechanoreceptors in the upper airways, resulting in increased muscle tone and prevention of upper airway collapse.[51,52]

The only recognized direct TASK blockers are arachidonamides, anandamide (an endogenous cannabinoid receptor ligand) and its methanandamide homologue,[53] and doxapram.[54]

Interventional procedures

Several intervention strategies have been proposed to prevent paroxysms in patients with AF and OSA. These include renal denervation, ablation of nerve plexuses at the pulmonary vein ostia, stellate ganglion ablation, vagus nerve stimulation, and baroreceptor stimulation. As was shown, all proposed approaches are based on a reduction in the activity of the sympathetic nervous system, which can probably have an antiarrhythmogenic effect due to a decrease in autonomic, structural, and electrical remodeling associated with OSA.

Renal denervation

In their earlier publications, Linz et al. clarified that pigs, subjected to OSA, experienced an increase in blood pressure and a prolongation of spontaneous AF episodes. Renal denervation prevented an increase in blood pressure, led to a decrease in plasma renin and aldosterone levels, and a reduction in the frequency and duration of AF episodes[55]. Even though renal denervation did not met expectations for blood pressure control in conditions of resistant hypertension, recent experimental evidence confirmed that renal denervation was effective in suppressing AF associated with apnea and reduction of the atrial effective refractory period. Also, renal denervation was able to suppress elevation of blood pressure after apnea.[56,57] Currently, renal denervation has the highest evidence base as an interventional technique in patients with AF and OSA.

Ablation of nerve plexuses at the openings of pulmonary artery

In a randomized controlled trial, the addition of nerve plexus ablation during pulmonary vein ostia ablation yielded better outcomes than either procedure alone in patients with paroxysmal AF.[58,59]

Sympathetic denervation: stellate ganglion ablation

In a recent study by Tavares et al., OSA increased vagal activation and caused tonic excitation of stellate ganglia, which correlated with a shortened effective refractory period and higher AF inducibility.[60] In patients with paroxysmal AF, unilateral ablation of the stellate ganglion reduced an incidence and duration of AF.[61]

Vagal stimulation

Other studies showed that transcutaneous low-level electrical stimulation of the vagus nerve auricular branch in the tragus area, without reducing heart rate and atrioventricular conduction velocity, also suppressed the reduction of atrial refractoriness, autonomic and structural remodeling, and expression of proinflammatory cytokines, which prevented the development of AF caused by OSA.[20]

Stimulation of baroreceptors

In their pig models, Linz et al. demonstrated that low-level stimulation of carotid sinus baroreceptors under conditions of simulated OSA led to the reduction of the atrial effective refractory period and decreased AF inducibility, whereas high-level stimulation resulted in reverse effects.[62]

Conclusion

In conditions of a single or chronic exposure to OSA, cardiovascular autonomic dysfunction is one of the leading

factors providing the possibility of AF development and recurrence. A combined effect on AF risk factors (their modification, use of CPAP therapy, additional pharmacological and/or interventional procedures) can normalize the autonomic control and positively affect the substrate leading to the development and progression of arrhythmia.

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