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CLINICAL REVIEW

Atrial arrhythmogenesis in obstructive sleep apnea: Therapeutic implications

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SUMMARY

The prevalence of sleep disordered breathing like obstructive sleep apnea (OSA) among patients with atrial fibrillation (AF) is 40–50%. OSA reduces success rate of catheter based and pharmacological antiarrhythmic treatment. Additionally, efficient treatment of OSA by continuous positive airway pressure ventilation (CPAP), the first line therapy of OSA, has been shown to improve catheter ablation success rates in AF-patients. A systematic literature search using several databases was performed to review the pathophysiology of obstructive apneas in OSA potentially leading to the development of a substrate for AF and to explain potential mechanisms involved in the clinically observed atrial antiarrhythmic effect of effective CPAP therapy.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with relevant morbidity and mortality. 1% of the European population suffers from AF and the number of AF patients is expected to double or triple within the next two to three decades [1–5]. The clinical presentation of AF is highly variable, ranging from the complete absence of symptoms to palpitations, heart failure, and hemodynamic collapse. Importantly, AF increases the risk of stroke about five times [6,7]. AF doubles mortality and causes marked morbidity [8]. Symptoms and complications of AF result from the irregular and often rapid ventricular response, loss of atrial contraction as well as from AF-associated hypercoagulability.

A condition, which is associated with a high prevalence of AF is obstructive sleep apnea (OSA) [9–11] and OSA in patients with AF is an independent predictor of stroke [12]. OSA is characterized by obstructive respiratory events due to periodic or complete occlusion of the upper airways resulting in intermittent hypoxia, hypercapnia and intrathoracic pressure swings during the ineffective breathing attempts. Continuous positive airway pressure ventilation (CPAP) is a non-invasive respiratory support and is the first-line treatment for OSA.

In this review, we describe the pathophysiology of obstructive apneas in OSA potentially leading to the development of a substrate for AF and discuss the potential mechanisms underlying the atrial antiarrhythmic effects of CPAP therapy.

Obstructive sleep apnea

Pathophysiology and definitions of sleep apnea

There are three basic mechanisms for the disruption of respiration during sleep: upper airway obstruction, dysregulation of respiratory control, and hypoventilation. Two main breathing abnormalities are obstructive sleep apnea (OSA) and central sleep apnea (CSA). Disease severity is determined by the number of respiratory events per hour of sleep time (the apnea-hypopnea index [AHI]), and the number and severity of oxygen desaturations.

Abbreviations: AERP, atrial effective refractory period; AF, atrial fibrillation; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; CSA, central sleep apnea; NTP, negative thoracic pressure; OSA, obstructive sleep apnea; PVI, pulmonary vein isolation; RAAS, renin angiotensin aldosterone system; RDN, renal denervation.

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Sleep disordered breathing is usually defined as mild when the AHI is 5–15/h, moderate when AHI is 15–30/h and severe when the AHI is > 30/h. OSA is the most common type of sleep disordered breathing in the general population and is characterized by recurrent partial (hypopnea) or complete (apnea) collapses of the upper airway during sleep, which cause decreased or interrupted airflow in spite of continued respiratory effort.

Prevalence and incidence of atrial fibrillation in sleep apnea

In young patients with paroxysmal AF with a high AF burden or persistent AF with preserved left ventricular function a high prevalence of sleep disordered breathing can be found (62% vs. 38% in patients without AF) [13]. However, the prevalence of daytime symptoms like excessive daytime sleepiness in OSA patients with cardiac disease like AF or congestive heart failure is rare [14]. Therefore, the prevalence of OSA in AF patients may be even underestimated. Gami et al. [11] showed that the severity of OSA is a strong predictor of incident AF in individuals younger than 65 y. AF patients with severe OSA show a lower response rate to antiarrhythmic drug therapy than those with milder forms of OSA [15]. Additionally, a prospective analysis by Kanagala et al. [10] demonstrated that patients with OSA have a higher recurrence rate of AF after initial successful cardioversion than patients without OSA. Patients with OSA have a higher risk of AF recurrence after catheter based electrical isolation of the pulmonary veins (pulmonary vein isolation, PVI), than those without OSA [16]. PVI is an important and effective treatment modality of symptomatic AF. During the procedure, radiofrequency energy is applied at the tip of a catheter to form circular ablation lines around the ostium if the pulmonary veins thereby electrically disconnecting them from the left atrium. This reduces triggers for AF generated in the pulmonary veins of patients with paroxysmal and persistent AF [1].

Arrhythmogenic mechanisms in obstructive sleep apnea

The above mentioned studies suggest that OSA predisposes patients to develop AF, but it is not clear whether the relationship is completely independent of hypertension, diabetes mellitus, or other confounding factors. Here, we discuss potential underlying pathophysiologic mechanisms that support the plausibility of this interplay.

Obstructive apneas caused by the collapse of the upper airway during sleep result in intrathoracic pressure swings resulting in myocardial stretch of the heart chambers and changes in transmural pressure gradients, particularly affecting the thin-walled atria (Fig. 1) [17]. Additionally, obstructive respiratory events induce intermittent apnea-associated hypoxemia and hypercapnia as well as sympathetic activation and subsequent intraapneic and postapneic hemodynamic fluctuations [18]. Interestingly, in OSA, paroxysms of AF were found to be nocturnal and, at least partly, temporally related to respiratory obstructive events [19,20]. This temporal link between sleep disordered breathing and the occurrence of AF suggests that the trigger for AF may be mainly caused by acute changes during apneas and not by chronic remodeling processes in the atria alone [21]. However, acute factors directly associated with obstructive respiratory events like intrathoracic pressure changes, changes in blood gases and sympatho-vagal imbalance may contribute to the creation of the atrial arrhythmogenic substrate in OSA-patients (Fig. 2).

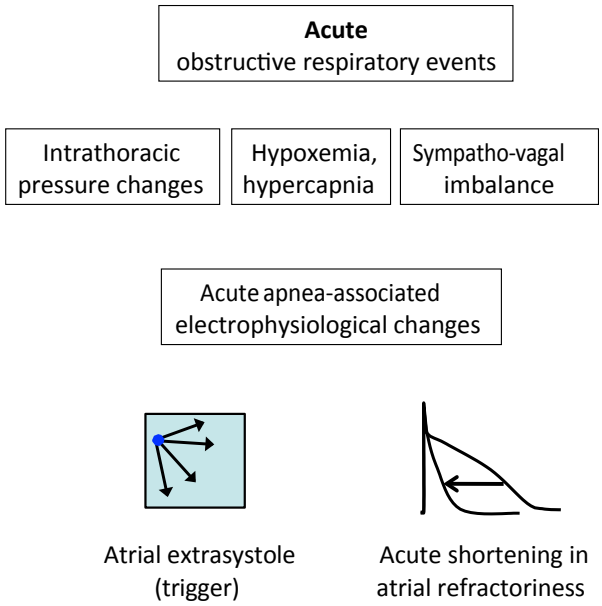

Fig. 2. Atrial arrhythmogenic mechanisms during acute obstructive respiratory events.

Acute effects of obstructive respiratory events on atrial arrhythmogenesis

Intrathoracic pressure changes

Obstructed inspirations generate wide fluctuations in intrathoracic pressure, resulting in changes in cardiac transmural pressure, which in turn lead to atrial stretch. Negative tracheal pressures as low as −80 to −100 mbar were observed in OSA patients [17,19].

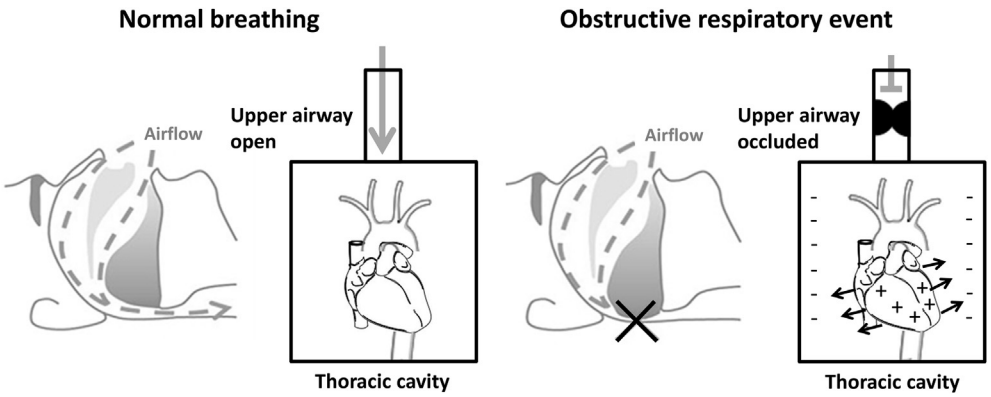

Fig. 1. Pathophysiology of obstructive sleep apnea (OSA) and resulting intrathoracic pressure changes.