

## Editorial

# Atrial Fibrillation and Obstructive Sleep Apnea: Something More Than a Coincidence

## Fibrilación auricular y apnea obstructiva del sueño: algo más que una coincidencia

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### INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice and accounts for one-third of all hospital admissions for cardiac arrhythmias.<sup>1</sup> Hospitalizations for this condition continue to increase due to the aging of the population, a higher prevalence of chronic cardiovascular conditions, and more frequent detection of arrhythmia with the use of many types of ambulatory monitoring devices. Obstructive sleep apnea hypopnea syndrome (OSAHS), an underdiagnosed condition that affects approximately 5% of the general population,<sup>2</sup> is characterized by repeated upper airway obstruction during sleep and symptoms associated with unrefreshing sleep. The apnea hypopnea index (AHI) is the number of complete or partial obstructions of the airway per hour of sleep, and is the main parameter used to diagnose and estimate the severity of OSAHS in sleep studies. An AHI score >4 is considered pathologic: OSAHS is considered mild when the AHI is between 5 and 14, moderate between 15 and 30, and severe at a score >30. In addition to its elevated prevalence in patients with various types of cardiovascular disease, OSAHS is associated with considerable morbidity and mortality, mainly of cardiovascular causes.<sup>2</sup> It is estimated that two-thirds of patients with AF may also have OSAHS. The notion that OSAHS may originate AF is attractive, but the fact that the two conditions share many of the same risk factors, such as age, obesity, male sex, hypertension, coronary disease, and heart failure,<sup>2</sup> makes it difficult to establish a clear independent causal relationship between them.

Several recent studies have highlighted the important relationship between AF and OSAHS, two highly prevalent diseases, from both the epidemiologic and pathophysiologic viewpoints. This relationship has considerable implications for the results obtained in clinical practice with standard therapies used to treat AF in these patients.

### ASSOCIATION BETWEEN ATRIAL FIBRILLATION AND OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME

Numerous studies have indicated that cardiac arrhythmias are more common in patients with OSAHS than in healthy persons, and that the arrhythmia rate increases in tandem with the severity of the OSAHS.<sup>3</sup> In a prospective sleep study investigating cardiac arrhythmias in 458 patients with suspected sleep apnea, Hoffstein et al.<sup>4</sup> documented a 58% prevalence of arrhythmias in those who had OSAHS and 42% in controls without OSAHS ( $P < .001$ ). In addition, the authors found that the associated rate of cardiac arrhythmias rose along with the increase in AHI (ie, the severity of OSAHS): in patients with severe OSAHS (AHI >40), the prevalence of arrhythmias was 70%, whereas in patients with mild OSAHS (AHI ≤10), the prevalence was 42%. However, in that study, the presence of AF was not submitted to an analysis separate from that of other supraventricular arrhythmias.

One of the first studies that separately analyzed the prevalence of AF in OSAHS patients was performed by Guilleminault et al.<sup>5</sup> A 24-h Holter monitoring in 400 patients with moderate or severe OSAHS (AHI >25) found a 3% prevalence of AF, which is three-fold higher than that observed in similar cohorts of the general population. Comparable results were found more recently in the Sleep Heart Health Study, in which patients with severe OSAHS were found to have a four-fold higher risk of AF.<sup>6</sup> Another study compared the prevalence of OSAHS in a group of 151 AF patients who underwent electric cardioversion with that of 463 patients with no history of AF evaluated in a cardiology practice.<sup>7</sup> Although the two groups were comparable for patient age, body mass index, sex, and prevalence of hypertension and heart failure, the patient group with AF had a significantly higher prevalence of OSAHS (49% vs 33%). Furthermore, multivariate analysis revealed a significant independent association between OSAHS and AF. Not only is OSAHS common in patients with AF, it is also associated with a higher incidence of AF. In a retrospective study of 3542 adults with no history of AF who underwent a sleep study, Gami et al.<sup>8</sup> observed that in subjects younger than 65 years, OSAHS and nocturnal hypoxemia were significant independent predictors of a higher incidence of AF.

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## PHYSIOPATHOLOGIC MECHANISMS OF THE ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME AND ATRIAL FIBRILLATION

Various mechanisms could link OSAHS and AF, thereby establishing a complex pathophysiologic meshwork that would result in both conditions being found concomitantly in many patients. Briefly, the hemodynamic and autonomic changes triggered by repeated apneas have an essential role in promoting autonomic dysregulation, inflammation, endothelial dysfunction, and atrial distension, which can ultimately lead to the development and persistence of AF. In patients with established cardiovascular comorbidity, which is favored by OSAHS in many cases, the effects of cardiovascular involvement in promoting AF are added to those of apneas in starting and maintaining the arrhythmia. Hypertension has a well-recognized causal relationship with OSAHS and is particularly relevant in this regard.

The ineffective respiratory effort against the occluded upper airway during apnea results in a sudden drop in intrathoracic pressure, a rise in left ventricular transmural pressure, and an increase in postload. This is bolstered by the sympathetic hyperactivity and vasoconstriction caused by the incomplete waking (arousal) that accompanies each apnea. The intermittent hypoxia resulting from repeated apneas is associated with hemodynamic changes in left and right ventricular function and a progressive alteration in ventricular filling,<sup>9</sup> which, in turn, is associated with structural and functional atrial changes due to the increase in left ventricular end-diastolic pressure. The diastolic dysfunction is facilitated by the intrathoracic pressure changes, severity of hypoxemia related to the apneas, and increased adrenergic state.<sup>9</sup> This series of processes promotes fibrosis, distension, and structural and electrical atrial remodeling. The development of atrial remodeling<sup>10,11</sup> and the autonomic influence include the pulmonary vein ostia, an anatomic region with extensive adrenergic and vagal innervation that contributes to the initial development of AF. There is evidence that these changes may be partially reversible when the deleterious effect of apneas is eliminated by treatment with continuous positive airway pressure (CPAP),<sup>9,11</sup> an essential pillar of OSAHS treatment. The pressure changes and hypoxemia resulting from interruption of air exchange during apnea also would favor autonomic dysregulation,<sup>12</sup> which could shorten the atrial tissue refractory periods and increase the susceptibility to AF, mediated by increased cardiac vagal tone and subsequent bradycardia.

Studies in animal models have shown that blocking both arms of the autonomic nervous system at the ganglionated plexi near the pulmonary veins inhibits AF inducibility due to apneas.<sup>13</sup> The concomitant changes in sympathetic activity and atrial pressure (with later dilation) resulting from repeated airway obstruction can make a patient more prone to developing AF when there is cardiac vagal activation secondary to apnea. Thus, atrial conduction velocity is decreased and the degree of spatial heterogeneity in conduction is increased, which could facilitate the reentry circuits and AF. These factors, together with vagal activation, provide an ideal set of circumstances for the onset and perpetuation of arrhythmia. The role of the alternating cycles of hypercapnia and eucapnia during apneas has been investigated in animal models.<sup>14</sup> During hypercapnia phases, there is prolongation of the atrial refractory periods and an increase in conduction velocity. With subsequent normocapnia, the refractory periods normalize but decreased conduction velocity persists in the atrial tissue; this disassociation increases vulnerability to develop AF.

Both OSAHS and obesity are associated with atherogenic vascular changes. These effects would mainly be related to generation of a proinflammatory state through various mediators, such as C-reactive protein, interleukin 1, and tumor necrosis factor

and its receptors,<sup>15</sup> and through an increase in oxidative stress, the genesis of varying degrees of endothelial dysfunction, and establishment of a prothrombotic state. Nonetheless, all these pathogenetic pathways are altered in patients with OSAHS independently of obesity. Inflammation can favor the development of AF in subjects with a susceptible substrate, but it can also occur directly by promoting atrial fibrosis. The increase in oxidative stress<sup>16</sup> and the appearance of endothelial dysfunction observed in OSAHS patients could also favor the development of AF. The prothrombotic state present in patients with OSAHS is due to increased platelet aggregation and activation, a rise in fibrinogen, and a reduction in fibrinolytic activity during sleep. Thus, the risk of thromboembolic complications could be increased in patients with AF and concomitant OSAHS, although this hypothesis requires confirmation.

## INFLUENCE OF OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME AND ITS TREATMENT ON ATRIAL FIBRILLATION THERAPY OUTCOMES

Use of nocturnal CPAP is the key point in treating OSAHS, and may significantly reduce cardiovascular risk in these patients. One limiting factor is the somewhat low tolerance many patients have to this treatment, which leads to a high percentage of voluntary therapy interruption. A large ongoing study is attempting to minimize this factor. From the pathophysiologic viewpoint, adequate treatment with CPAP reduces or eliminates most of the above-mentioned pathogenetic pathways that sustain the association between OSAHS and AF. By abolishing the sleep apneas, fluctuations in intrathoracic pressure are averted and arousal-associated sympathetic hyperactivity is reduced. Furthermore, there are improvements in the overall autonomic imbalance,<sup>14</sup> the middle- and long-term hypoxemia/reoxygenation and hypercapnia/eucapnia cycles, structural changes in diastolic ventricular function<sup>9</sup> and the atrial myocardium,<sup>11</sup> the proinflammatory state,<sup>15</sup> and the increased oxidative stress.<sup>16</sup> In addition, nocturnal and diurnal blood pressure values are reduced, which helps to control hypertension in affected patients and favors inverse atrial remodeling, both structural and functional. All these effects should theoretically result in a lower arrhythmic load and better AF control with standard treatments. A study by Abe et al.<sup>17</sup> that included a cohort of more than 1300 OSAHS patients found that CPAP treatment significantly reduces episodes of paroxysmal AF in patients with moderate or severe forms of OSAHS.

Kanagala et al.<sup>7</sup> investigated the effect of CPAP therapy on the rates of recurrent AF following effective electric cardioversion, and analyzed recurrent AF at one year after cardioversion. The authors observed that the risk of recurrence in OSAHS patients was 82% in those who were not treated with CPAP and 42% in those receiving this therapy. The analysis demonstrated that AF recurrence was not related to the underlying disease or the age and hypertension status of the patients; it was, however, highly related to the time period in which the patient had an oxygen saturation value of <90%, another parameter related to OSAHS severity. In similar terms, the severity of OSAHS seems to have an influence on the effectiveness of antiarrhythmic drugs for maintaining sinus rhythm in patients with paroxysmal AF.<sup>18</sup>

The number of catheter ablation procedures to treat AF has multiplied in recent years because of substantial improvements in the techniques used and the results obtained.<sup>19</sup> The results of these ablation procedures are also influenced by the presence of OSAHS and its treatment, and as occurs in other AF patient profiles, the prevalence of OSAHS is very high in those who are candidates for ablation.<sup>20</sup> Thus, patients with OSAHS experience more AF recurrences following the ablation procedure,<sup>20–22</sup> a fact that

has clinical and economic implications because recurrence may require a new ablation in many such cases. Although the data are based exclusively on observational studies, patients with OSAHS would have a 40% greater risk of recurrence following an AF ablation procedure.<sup>22</sup> In these patients, CPAP treatment achieves a reduction in the excess risk of recurrent AF after ablation,<sup>20,21</sup> a finding that underlines the importance of identifying and treating OSAHS before the intervention.

It is well recognized that AF often coexists with common atrial flutter in the same patient. The prevalence of OSAHS is also elevated in patients undergoing catheter ablation of the cavo-tricuspid isthmus for definitive treatment of atrial flutter,<sup>23,24</sup> and adequate treatment of OSAHS with CPAP has been associated with a lower rate of AF episodes during follow-up.<sup>23</sup> It could also be a clinically relevant strategy to identify and adequately treat the sleep disorder in patients with atrial flutter, because of the high prevalence of OSAHS and the long-term consequences of persistent OSAHS in relation to both arrhythmogenic and overall cardiovascular conditions.

## CONCLUSIONS

Although the pathophysiologic bases of the association between OSAHS and AF are coherent and well established, and the extensive epidemiologic data are consistent with the notion that AF can be a consequence of OSAHS, the growing body of information regarding the influence of OSAHS treatment on the outcome of patients with FA remains scant. Current evidence indicates that untreated OSAHS reduces the efficacy of AF therapy in clinical practice, and what is more, it can originate or contribute to the progression of various types of cardiovascular disease, which in turn are associated with AF. In this sense, it is well recognized that adequate CPAP treatment for OSAHS patients leads to a decrease in blood pressure and concomitant hypertension. Because of these circumstances and the high prevalence of OSAHS in patients with AF, it seems advisable to maintain a high degree of clinical awareness to identify and adequately treat the sleep disorder in this population.

## CONFLICTS OF INTEREST

None declared.

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