

# Pathophysiological correlations between obstructive sleep apnea syndrome and atrial fibrillation

*Corelații fiziopatologice între sindromul de apnee obstructivă în somn și fibrilația atrială*

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## Abstract

Both obstructive sleep apnea syndrome (OSA) and atrial fibrillation (AF) are common disorders among the population, with a particular impact on quality of life and with significant consequences in terms of morbidity and mortality. It has been observed that the two diseases often associate, they can potentiate each other negatively, and the knowledge of the pathophysiological mechanisms that interfere with these diseases is essential in their prevention and treatment. The purpose of this article is to review these pathophysiological correlations.

**Keywords:** obstructive sleep apnea, atrial fibrillation, pathophysiological mechanisms

## Rezumat

Atât sindromul de apnee în somn de tip obstructiv (SASO), cât și fibrilația atrială (FA) reprezintă afecțiuni frecvent întâlnite în rândul populației, cu un impact deosebit asupra calității vieții și cu importante consecințe la nivel de morbiditate și mortalitate. S-a observat că aceste două boli se asociază frecvent, se pot potența negativ, iar cunoașterea mecanismelor fiziopatologice care interferează în aceste boli este esențială în prevenirea și tratamentul lor. Scopul acestui articol este o trecere în revistă a acestor corelații fiziopatologice.

**Cuvinte-cheie:** apnee în somn de tip obstructiv, fibrilație atrială, mecanisme fiziopatologice

## Introduction

Obstructive sleep apnea syndrome (OSA) is a condition characterized by a complete and/or incomplete intermittent obstruction in the upper airway that occurs during sleep. These obstructive episodes have as a consequence the immediate absence of ventilation (apnea), respectively, diminishing the ventilation (hypopnea). The severity of obstructive sleep apnea is defined by the total number of respiratory events (apnea and/or hypopnea) occurring during one hour of sleep, meaning the Apnea-Hypopnea Index (AHI).

The main symptoms of the disease are intense snoring, excessive drowsiness, and breathing stopping during sleep. In addition to these symptoms, patients with OSA may experience morning headaches, nocturnal awakenings accompanied by suffocation, frequent night micturition, disrupted and poor quality sleep, decreased concentration and memory capacity, irritability, depressive symptoms, palpitations, high blood pressure, and frequent obesity.

A close correlation between OSA and cardiovascular diseases have been observed. Numerous studies have shown that OSA is associated with increased cardiovascular morbidity and mortality, being involved in the initiation and progression of cardiovascular disease, and is considered to be an independent risk factor in the development of these diseases<sup>(1)</sup>.

Sleep apnea syndrome can be associated with arterial hypertension, or it can precipitate it. Also, it's the primary cause of resistant arterial hypertension, and it can initiate or aggravate arrhythmias, pulmonary hypertension, heart failure, coronary artery diseases (myocardial infarction, sudden coronary death) and stroke<sup>(2)</sup>.

The observation of an increased prevalence of AF in patients diagnosed with OSA has raised interest in pointing out some correlations and interconditions of the pathophysiological mechanisms encountered in these two diseases.

## Prevalence and risk factors in OSA

OSA is a disease with increasing prevalence, often underdiagnosed, with repercussions on day-to-day activity, and with cardiometabolic and cerebrovascular consequences.

The prevalence of the disease varies in different studies. Earlier studies have estimated that this disease affects approximately 6% of the population between the ages of 30-60 years old, being more common in 4% of men compared to 2% in women, to an Apnea-Hypopnea Index of more than 10 per hour. In more recent studies that define OSA from an AHI of over 5 per hour, the OSA prevalence was 24% in males and 9% in women between the ages of 30-60 years old, and in those with sleepiness symptoms, the prevalence was 3-7% in adult males and

2-5% in adult women<sup>(3,4)</sup>. Male gender, age and obesity are important risk factors for the disease. Also, alcohol consumption, smoking and sedentariness are associated with increased disease frequency.

### Prevalence and risk factors in atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia that affects morbidity and mortality in the general population, and its prevalence doubles with each decade of aging from 0.5% at 50-59 years old to 9% at 80-89 years old, as it has been evaluated in some studies<sup>(5)</sup>. In Western countries, the incidence and prevalence of atrial fibrillation increased and is expected to increase in the future. This is due to the increasing age in the general population, increased prevalence of obesity, better survival after the first cardiovascular event, and to improved means of diagnosis in FA and other arrhythmias<sup>(6)</sup>. However, epidemiological studies are missing in Eastern European countries. In the USA, the risk of developing AF depends on race/ethnicity, being higher in the Caucasian population. It is important to determine whether variations in the global incidence of AF are due to phenotypic or genotypic differences.

The main risk factors for atrial fibrillation are the age over 60, hypertension, diabetes, obesity or pre-existing heart disease. Another risk factor for AF is represented by OSA<sup>(5,7)</sup>. Obstructive sleep apnea syndrome was identified as an independent risk factor in the onset and recurrence of AF<sup>(8)</sup>. There are different AF phenotypes with different risk factors, so that prevention and therapeutic strategy differs from one type to another. AF is associated with an increased risk of death, congestive heart failure, other cardiovascular diseases, stroke, cognitive impairment, dementia, and non-cardiovascular disease, such as the risk of cancer<sup>(6)</sup>.

### OSA pathophysiology

OSA pathophysiology is complex, multifactorial and varies from one individual to another. Age, gender, obesity, genetic, anatomical, hormonal factors interact in various ways by modulating the phenotypic expression of the disease<sup>(9)</sup>. In obstructive sleep apnea syndrome, there is a repetitive pharyngeal collapse that occur during sleep, which leads to complete stopping of the respiratory flow (apnea) or decreased of the respiratory flow, despite the effort made by the respiratory muscles during breathing<sup>(9,10)</sup>. With age, muscle tone decreases, leading to the narrowing of the upper airway, explaining the increase in OSA prevalence with age<sup>(9)</sup>.

The frequency of the disease is higher in males than in females, women displaying a higher tonus of genioglossus muscle than men, which maintains airway permeability. Estrogen and progesterone hormones improve the tone of the pharyngeal muscles and the nervous control of breathing, and androgens increase the fat deposits at the level of the throat and lower the tone of the pharyngeal muscles. Because of the hormonal changes, the prevalence of OSA in women increases after

menopause. Genetic factors that involve the nervous control of the superior airway and the central nervous regulation of respiration play a role in the occurrence of the disease<sup>(9)</sup>.

Other involved causes are craniofacial abnormalities (e.g., micrognathia and retrognathia), fat deposits around the neck, short neck, hypertrophied tonsils, soft palate modifications, nasal polyposis obstruction, nasal turbinate hypertrophy and nasal septum deviation.

Abdominal obesity, neck circumference, and dorsal recumbent position are also predisposing factors.

Endocrine diseases, such as acromegaly and hypothyroidism, represent risk factors for OSA, and the treatment of these diseases leads to the improvement and cure of OSA<sup>(11)</sup>. Obstructive sleep apnea syndrome is also associated with polycystic ovary syndrome and hypogonadism, and the OSA treatment helps in relieving the two diseases<sup>(11)</sup>.

### OSA and cardiovascular diseases

An increased prevalence of OSA in patients with cardiovascular diseases has been observed. Understanding the pathophysiological mechanisms by which OSA contributes to the initiation and progression of cardiovascular (CV) disease is of high importance, as is the impact of OSA treatment on the improvement of CV diseases and the reduction of mortality.

Stopped breathing during sleep is accompanied by blood gas changes (hypoxemia, hypercapnia) and increased sympathetic activity<sup>(10,13)</sup>. Breathing halts and intermittent hypoxemia lead to repeated awakenings and sleep disruptions, with oscillations between waking and sleeping states, having important consequences on the whole organism.

These breathing disruptions during sleep lead to modifications of the physiological interactions between sleep and the cardiovascular system. Thus, the sleep fragmentation or other abnormalities in patients with OSA, such as increased sympathetic activity, decreased parasympathetic activity, large variations of the intrathoracic pressure (Muller), endothelial vascular dysfunction, increased oxidative stress, systemic inflammation, increased platelet aggregation and metabolic modifications (insulin resistance, leptin resistance), may be involved in the initiation and worsening of cardiovascular diseases<sup>(12,13)</sup>.

The hemodynamic consequences of OSA are sympathetically mediated vasoconstriction, increased systemic and pulmonary pressure, increased left ventricular postload and changes in the heart rate related breathing. Thus, sleep apnea syndrome can be associated with hypertension ("non dipper" profile) or it may worsen (HT resistance), it can initiate or aggravate heart rhythm disorders, pulmonary hypertension (when associating other causes of hypoxemia and/or hypercapnia, such as obesity hypoventilation syndrome or COPD), heart failure, ischemic coronary diseases, stroke, and sudden death in sleep may occur<sup>(12,13)</sup>. In randomized trials, the continuous positive airway pressure treatment (CPAP)

of moderate-to-severe OSA has lowered the blood pressure, alleviated the signs of early atherosclerosis and improved cardiac function in patients with heart failure<sup>(12)</sup>. A key condition for achieving these benefits is adherence to CPAP.

## OSA and atrial fibrillation

A close association between obstructive sleep apnea syndrome (OSA) and atrial fibrillation (AF) has been observed. There is an increased prevalence of atrial fibrillation among patients diagnosed with OSA. The prevalence of OSA in patients diagnosed with atrial fibrillation varies between 32% and 49% in studies<sup>(14)</sup>. There are studies that have demonstrated a higher frequency of OSA in patients diagnosed with AF than in those with other unselected cardiovascular disease (49% versus 32%)<sup>(15)</sup>.

Sleep apnea syndrome and atrial fibrillation have common risk factors, such as old age, male gender, obesity, high blood pressure and coronary artery disease<sup>(16,17)</sup>. There are pathophysiological mechanisms underlying atrial fibrillation in sleep apnea syndrome. OSA is characterized by breathing and repetitive collapses of the upper airway, resulting in hypoxemia, hypercapnia, awakenings, changes in intrathoracic pressure and increased sympathetic activity<sup>(16,17)</sup>. Some studies have shown that OSA can produce cardiac remodelling and systemic inflammation<sup>(18,19,20)</sup>. Hypoxia and increased sympathetic activity lead to tachycardia and increased blood pressure, especially at the end of the apneic episode<sup>(20,21)</sup>. Tachycardia and hypertension increase the necessary myocardial oxygen, while oxygen intake is low because of the hypoxia. Myocardial ischemia, atrial and ventricular fibrosis, atrial and ventricular arrhythmias, and sometimes sudden death can occur during sleep<sup>(19,20)</sup>.

Intermittent hypoxemia and arrhythmia repetitive episodes of hypooxygenation-reoxygenation increase the oxidative stress, that plays a major role in inflammation<sup>(20,22)</sup>. Repeated oxidative stress leads to cardiac remodeling, systemic and endothelial inflammation, and thus to the production of the substrate for AF. Certain studies reported increases of C-reactive protein levels in patients with OSA compared to the control group, as well as an independent increase of C-reactive protein related to the severity of OSA<sup>(23)</sup>. Inflammation and oxidative stress lead to vascular endothelial dysfunction and atherosclerosis<sup>(22)</sup>.

Complete or incomplete pharyngeal collapse episodes lead to large negative variations in intrathoracic pressure during the attempt of breathing during obstructed airways. Intracardiac negative pressure produces increased transmural pressure of the left ventricle (afterload)<sup>(24,25)</sup>. The increase in postload leads to left ventricular hypertrophy. Excessive intrathoracic negative pressure is transmitted to the atrial wall and leads to atrial dilatation. Both atrial dilatation and atrial fibrosis are known to be predisposing factors for AF<sup>(24-26)</sup>. It has been suggested that intrathoracic negative pressure during apnea is an impor-

tant trigger in the occurrence of AF by shortening the effective atrial refractory period and increasing vagal activity<sup>(24,25)</sup>. OSA, structural atrial remodeling and electrical remodeling contribute to the pathogenesis of AF. A few studies have shown that OSA may result in increased left atrial size, leading to conduction abnormalities<sup>(27-30)</sup>. In a study of 720 consecutive patients diagnosed with AF who performed cardiac MRI before ablation, Neilan et al. reported that patients with OSA had high blood pressure, increased right ventricle volume, left atrial size and left ventricular mass<sup>(31)</sup>. High blood pressure is the most important risk factor for atrial fibrillation, in addition to heart failure, valvulopathy, ischemic coronary artery disease and obesity<sup>(21)</sup>, but the non-rheumatic AF echocardiographic predictors are left atrial dilatation, left ventricular ejection fraction and left ventricular hypertrophy.

Several studies have shown that OSA is associated with the increased risk of atrial fibrillation recurrence after chemical or electrical cardioconversion or after pulmonary vein isolation by catheter ablation. Despite the limitations of epidemiological and cohort studies, data consistency identifies OSA as a cause of recurrent atrial fibrillation<sup>(32)</sup>. CPAP treatment is associated with lower blood pressure, decreased atrial size, ventricular mass and decreased risk of atrial fibrillation recurrence after the isolation of pulmonary veins by catheter ablation. A recent meta-analysis, which included four randomized controlled trials, with a total of 3780 patients, indicated that CPAP therapy is not effective in lowering the overall risk of major cardiovascular events unless it is used for more than four hours per day<sup>(33)</sup>.

Considering that OSA prevalence is higher in patients with atrial fibrillation, is particularly important to study the effect of CPAP therapy on the risk of atrial fibrillation recurrence after cardioconversion or after catheter ablation.

## Conclusions

The patients with OSA require a complex, multidisciplinary assessment, given their frequent association with cardiovascular, metabolic, ENT, neurocognitive and psychiatric disorders.

Sleep apnea syndrome is an important risk factor for atrial fibrillation and for its recurrence after conversion to sinus rhythm (medication or ablation procedures).

The patients with atrial fibrillation should be evaluated for the identification of OSA and treated when it is present in a moderately severe and symptomatic form. Similarly, patients with OSA should be assessed for the possible existence of cardiovascular comorbidities, especially AF and HT resistance, given the proven interrelation between the two pathologies that share common risk factors and pathophysiological mechanisms.

The knowledge of the pathophysiological mechanisms is important in the management, as well as in the treatment of OSA through currently validated methods (CPAP, mandibular advancement devices, surgical procedures, ENT or bariatric), and in the control of AF when the two diseases are associated. ■

## References

1. McNicholas WT, Bonsignore MR. Sleep apnea as an independent risk factor for cardiovascular disease; current evidence, basic mechanisms and research priorities. *European Respiratory Journal*. 2007; 29(1), 157-178.
2. Lavie P, Lavie L. Cardiovascular Morbidity and Mortality in Obstructive Sleep Apnea. *Curr Pharm Des*. 2008; 14(32); 3466-3473.
3. Youg T, Mari Palta, Dempsey J, Skatrud J et al. The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults. *N England J Med*. 1993; 328; 1230-1235.
4. Lindberg E, McNicholas WT, Bonsignore M. Epidemiology of OSA. *European Respiratory Society Monograph*. 2010; 50 (Sleep Apnea), 51-68.
5. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis and predisposing conditions for atrial fibrillation: population-based estimates. *The American Journal of Cardiology*. 82(7) 2N-9N, 1998.
6. Conen D. Epidemiology of atrial fibrillation, *Eur Heart J*. 2018; 39(16):1323-1324.
7. Youg T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA*. 2004; 291(16);2013.
8. Youssef I, Kamran H, Yacoub M, Patel N, Goulbourne C, Kumar S, Kane J, Hoffner H, Salifu M, McFarlane S. Obstructive Sleep Apnea as a Risk Factor for Atrial Fibrillation: A Meta- Analysis. *J Sleep Disord Ther*. 2018; 7(1).pii.282.
9. Martins AB, Tufik S, Moura SM. Physiopathology of obstructive sleep apnea-hypopnea syndrome. *Journal Brasileiro de Pneumologia*. 33(1), 93-100, 2007.
10. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thoracic Society*. 2008; 5:144-153.
11. Sharma MV. Obstructive sleep apnea and endocrine disorders. *Med J DY Pattil Univ*. 2017; 10;467-9.
12. Bradley TD, Floras J. Obstructive sleep apnea and its cardiovascular consequences; *Lancet*. 2009 Jan; 373(9657):82-93. Epub 2008 Dec 26.
13. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russel R, Woo M, Young T. Sleep Apnea and Cardiovascular Disease. *JACC*. 2008; 52:686-717.
14. Gami AS, Friedman PA, Chung MK. Therapy insight: inter-actions between atrial fibrillation and obstructive sleep apnea. *Nat Clin Pract Cardiovasc Med*. 2005; 2: 145-9.
15. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davidson DE, Malauf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004; 110:364-367.
16. Kasai T, Bradley TD. Obstructive sleep apnea and heart failure: pathophysiologic and therapeutic implications. *J Am Coll Cardiol*. 2011; 57: 119-27.
17. Patil SP, Schneider H, Schwartz AR, et al. Adult obstructive sleep apnea: pathophysiology and diagnosis. *Chest*. 2007; 132:325-37.
18. Arias MA, Sanchez AM, Alonso-Fernandez A, et al. Atrial fibrillation, obesity, and obstructive sleep apnea. *Arch Intern Med*. 2007; 167:1552-3.
19. Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. *Heart Rhythm*. 2012; 9:321-7.
20. Pepin JL, Levy P. Pathophysiology of cardiovascular risk in sleep apnea syndrome (SAS). *Rev Neurol (Paris)*. 2002; 158:785-97.
21. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol*. 1983; 52:490-4.
22. Pashayan AG, Passannante AN, Rock P. Pathophysiology of obstructive sleep apnea. *Anesthesiol Clin North America*. 2005; 23:431-43.
23. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation*. 2002; 105:2462-4.
24. Linz D, Schotten U, Neuberger HR, et al. Combined blockade of early and late activated atrial potassium currents suppresses atrial fibrillation in a pig model of obstructive apnea. *Heart Rhythm*. 2011; 8:1933-9.
25. Linz D, Schotten U, Neuberger HR, et al. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. *Heart Rhythm*. 2011; 1436-43.
26. Valenza MC, Baranchuk A, Valenza-Demet G, et al. Prevalence of risk factors for atrial fibrillation and stroke among 1210 patients with sleep disordered breathing. *Int J Cardiol*. 2014; 174:73-6.
27. Stevenson IH, Roberts-Thomson KC, Kistler PM, et al. Atrial electrophysiology is altered by acute hypercapnia but not hypoxemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. *Heart Rhythm*. 2010; 7:1263-70.
28. Iwasaki YK, Shi Y, Benito B, et al. Determinants of atrial fibrillation in an animal model of obesity and acute obstructive sleep apnea. *Heart Rhythm*. 2012; 9:1409-16.
29. Ghias M, Scherlag BJ, Lu Z, et al. The role of ganglionated plexi in apnea-related atrial fibrillation. *J Am Coll Cardiol*. 2009; 54:2075-83.
30. Iwasaki Y, Kato T, Xiong F, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. *J Am Coll Cardiol*. 2014; 64:2013-23.
31. Neilan TG, Farhad H, Dodson JA, et al. Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. *J Am Heart Assoc*. 2013; 2:e000421.
32. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar k, Kramer DB, Zimetbaum PJ, Buxton AE, Josephson ME, Anter E. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol*. 2013 Jul 23; 62(4):300-5.
33. Abuzaid AS, Al Ashry HS, Elbadawi A, Ld H, Saad M, Elgendy IY, Elgendy A, Mahmoud AN, Mentias A, Barakat A, Lal C. Meta-Analysis of Cardiovascular Outcomes with Continuous Positive Airway Pressure Therapy in Patients with Obstructive Sleep Apnea. *Am J Cardiol*. 2017 Aug 15; 120(4):693-699.