Obstructive Sleep Apnea and Cardiovascular Events
Clinical correlations

DELIA LIDIA SALARU[1,2], CARMEN ELENA PLESOIANU[1,2]*, ADINA OLARU[1], CATALINA ARSENESCU GEORGESCU[1,2]
[1]University of Medicine and Pharmacy Grigore T. Popa, 16 Universitatii, Str., 700115, Iasi, Romania
[2]Institute of Cardiovascular Diseases George I.M.Georgescu, 50 Bd. Carol I,Blvd., 700503, Iasi, Romania

Obstructive sleep apnea (OSA) has been described as an independent predictor of mortality and cardiovascular morbidity, and several studies link OAS and atrial fibrillation, although further investigations are needed to fully understand the common physiological mechanisms. The aim of the study was to identify the cardiovascular risk and events of a population diagnosed with OAS and to discover the predisposing factors of the appearance of AF in these patients. Demographic, clinical, laboratory and echocardiographic data were taken from 101 patients previously diagnosed with OSA and admitted to our cardiovascular unit. In a population with cardiovascular risk factors and cerebrovascular events, the prevalence of atrial fibrillation was 63.7%, whereas ventricular arrythmias occurred in 31.4%. The only prediction factor for AF in OSA population was the history of myocardial infarction; other predisposing factors take account for a small number of cases. The presence of a significant association between OSA and markers of cardiovascular disease would warrant the development of a strategy to consider more aggressive therapeutic approaches.

Keywords: Sleep apnea, myocardial infarction, atrial fibrillation

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder affecting at least 2% to 4% of the adult population[1], characterised by episodes of apnea and hypopnea resulting from repetitive narrowing and collapsing of the upper airway that lead to cycles of hypoxemia, hypercapnia, and arousals, and thus to sleep fragmentation. OSA is defined as an apnea/hypopnea index (AHI) of more than 5 events/h. Untreated OSA is associated with multiple adverse health outcomes including systemic hypertension, coronary artery disease, stroke, atrial fibrillation (AF), increased motor vehicle accidents, congestive heart failure, daytime sleepiness, decreased quality of life, and increased mortality[2].

Moderate to severe sleep apnea has been described as an independent predictor of mortality[3] and there is an increasing amount of evidence that these patients have an increased risk of cardiovascular disease and cardiovascular death[4].

There are several studies that link OAS and atrial fibrillation, although further investigations are needed to fully understand the common physiological mechanisms [5]. Patients with AF and OAS share a number of risk factors and comorbidities, including age, male sex, hypertension, congestive heart failure and coronary artery disease (CAD) [6].

The purpose was to study the cardiovascular risk and events of a population diagnosed with OAS and to identify the predisposing factors of the appearance of AF in these patients. Early recognition of a clinical pattern may significantly impact risk stratification and subsequent risk factor reduction in these patients.

Experimental part

Materials and methods

A retrospective study of 101 patients previously diagnosed with OSA was carried out from January 2014 to December 2016 in our tertiary cardiovascular medical center. Demographics and clinical data, including age, gender, smoking and alcohol intake, obesity, other cardiovascular risk factors, and medical history were obtained from hospital medical records. Chronic kidney disease was diagnosed when the glomerular filtration rate was < 90 mL/min/m^2 (CKD-EPI). Hypertension was defined as blood pressure values >140/90 mmHg and/or use of antihypertensive drugs. Dyslipidemia was defined as total cholesterol >5.2 mmol/L and/or HDL-cholesterol <0.9 mmol/L and/or LDL-cholesterol >2.6 mmol/L and/or triglycerides >2.3 mmol/L and/or use of lipid-lowering drugs. Obesity was determined using Body Mass Index (> 30kg/m^2). Diabetes mellitus was defined as fasting plasma glucose levels > 5.5 mmol/L and/or use of antidiabetic medication/insulin. Diagnosis of stroke and myocardial infarction were taken from patients medical history, and episodes of atrial fibrillation and ventricular arrythmias were registered from ECGs or Holter monitorisations.

The echocardiography assessed the systolic pulmonary pressure (PAPs), values > 35mmHg being noted as pulmonary hypertension (PAH). Left ventricle hypertrophy (LVH) was determined either by electrocardiography or echocardiography. The left ventricle ejection fraction (LVEF) was determined by Simpson method.

Statistical analysis

Data are presented as proportions for categorical variables and means ± SD or medians for continuous variables. For categorical variables, we used the chi-square test. Correlation analysis used Pearson test and logistic regression. For the determination of other models of prediction of atrial fibrillation we used Principal Component Analysis, a method that reduces the number of variables in a dataset by identifying the most important factors. A P-value < 0.05 was considered significant. Statistical analysis was performed using IBM SPSS Statistics.

Results and discussions

Patients characteristics are summarised in table I.

Most of the patients in our study group are in the 6th and 7th decade of life, mostly male (4:1 ratio), obese, hypertensive, and dyslipidemic. Smoking and daily alcohol intake are common habits.

The prevalence of atrial fibrillation in our OSA population was 63.7%, whereas ventricular arrythmias occurred in

*email: carmenplesoianu@gmail.com, Phone:+40742126934

Table 1
CLINICAL CHARACTERISTICS OF THE OSA POPULATION

Age, y	29-91 (60.8±10.5)
Male, %	82 (80.4%)
Smoking, %	57 (55.9%)
Alcohol intake, %	53 (52%)
Obesity, %	80 (78,4%)
Hypertension, %	87 (85.3%)
Diabetes, %	38 (37.3%)
Dyslipidemia, %	67 (65.7%)
Chronic kidney disease, %	24 (23.5%)
Pulmonary hypertension, %	15 (14.7%)
Left ventricle hypertrophy, %	48 (47.1%)
Stroke, %	14 (13.7%)
Coronary artery disease, %	50 (49%)
Atrial fibrillation, %	65 (63.7%)
Ventricular arrythmias, %	32 (31.4%)
Left ventricle ejection fraction, mean	49.6±15.6

only 31.4%. The Pearson correlation and the logistic regression showed that the only prediction factor for AF in OSA population is the coronary artery disease (P=0.01). Other models of prediction for the occurrence of AF were determined by Principal Component Analysis, namely 52.49% of cases of AF could be explained by the 4 factors identified by the model. The Bartlett's test rejects the null hypothesis of having a 1 diagonal and 0 all other values. All variables are loaded in the components with at least .5 value for correlations. Consequently, 15.6% of cases of AF have smoking, alcohol abuse and history of stroke as cumulated risk factors. 14.09% of OSA patients with a history coronary artery disease and chronic kidney disease would develop AF, and 12.2% of patients having LVH, PAH and daily alcohol intake are also at risk. 10.6% of AF cases appeared in patients with hypertension and dyslipidemia.

Patients with OSA have an underlying substrate for AF, that is, LV hypertrophy, LV diastolic dysfunction, and left atrial dilatation. In addition, OSA patients were shown to have structural and electrical atrial remodeling[7]. In our population, the structural component as an arrythmic background was moreover determined by the coronary artery disease, even though the ventricular arrythmias are known to be more specific for ischemia.

The following key mechanisms are thought to be relevant for the pathophysiology of the cardiovascular consequences of OSA: intermittent hypoxia, hypercapnia, sleep fragmentation, and intrathoracic pressure swings[8,9]. The unique pattern of intermittent hypoxia, that is, short periods of desaturation followed by reoxygenation, seems to be a key pathophysiological driver of adverse cardiovascular effects of OSA. Three mechanisms resulting from intermittent hypoxia/arousals relevant to the pathophysiology of the cardiovascular consequences of OSA have been proposed: sympathetic activation, oxidative stress, and systemic inflammation [10]. All these processes are exacerbated in the ischemic myocardium, as well as in relation with different cardiovascular risk factors: hypertension, dyslipidemia, smoking, and diabetes, all of them present in a high proportion in our study group. These predisposing factors take account for a small number of cases of AF, suggesting that there is still a missing link in the physiopathology of arrythmias in sleep apnea.

An association between OSA and atherosclerotic diseases, in particular, coronary artery disease, and in a smaller proportion in our study with cerebrovascular events, is plausible from the suspected underlying pathophysiology and highly suggestive from a number of observational and epidemiological studies[10]. There is a clear relationship between AHI score, arterial calcifications and the presence of atheromas[11].The prevalence of OSA among patients with acute coronary syndromes is very high, 66.4% being identified with AHI≥10 and 26% with AHI≥30 in a small study[12]. We considered a limitation of our study the high prevalence of (acute) coronary syndromes in our patients' population, but in fact the results harmonise and overlap with data from the literature.

The myocardial stress during apnea, coupled with cathecolamines release, and post-apnea tachycardia are common pathological ways that could lead to the appearance of both atrial fibrillation and myocardial infarction. Frequent cathecolaminic discharges following episodes of apnea stimulate the receptors in pulmonary veins, that are very sensitive due to a high number of adrenergic and vagal terminations [13].

Limitation

Along with the small number of our OSA population (due to the cardiovascular profile of the hospital), these individuals represent a high-risk population, the majority being selected from the patients presenting with the whole spectrum of coronary syndromes. Therefore it is difficult to generalise the cardiovascular continuum in this population.

The fenotype of OSA patients includes multiple factors that could trigger themselves the arrythmias. Because most of the patients are male obese, with diabetes, hypertension or cardiovascular events, it is difficult to assess how much of the sleep apnea itself potentiates the atrial fibrillation [14,15].

Conclusions

Our study showed that in a population with obstructive sleep apnea the prevalence of atrial fibrillation is very high and in a direct relationship with the coronary artery disease. The presence of a significant association between OSA and markers of cardiovascular disease would warrant the development of a strategy to consider more aggressive therapeutic approaches. Also, the significant prevalence of AF should trigger methods of early diagnosis and prevention of stroke in these patients. Such an association would also provide evidence for pertinent stakeholders to consider whether OSA warrants being included as one of the risk factors in the algorithms for determination of future risk of CVD events.

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