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DOCTORAL THESIS

SLEEP APNEA SYNDROME- PREDICTION FACTOR OF PROGNOSIS IN PATIENTS WITH HEART FAILURE NYHA CLASS II AND III

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INTRODUCTION

In recent years, obstructive sleep apnea syndrome (OSAS) has increased in prevalence, occurring in up to 10% of healthy subjects, due to the greater frequency of obesity and the aging of the population. Consequently, this has had an increasingly important impact on the health system. The prevalence of OSAS in subjects with cardiovascular disease, reported in earlier studies, was between 50% and 80%, and in half of subjects with heart failure (HF), it is associated with increased mortality and worse prognosis.

OSAS is globally known as a major factor for the occurrence of cardiometabolic comorbidities due to intermittent hypoxia which leads to oxidative stress, endothelial dysfunction, increase of sympathetic activity and systemic inflammation. Furthermore, activation of the sympathetic nervous system leads to activation of the renin-angiotensin-aldosterone system, which increases hydro-saline retention and thus the level of blood pressure. However, hydro-saline retention due to heart failure can also play an important role in the pathogenesis of OSAS. These data suggest that the relationship between HF and OSAS is not fully understood.

Large studies have demonstrated that OSAS prevalence is higher in patients with coronary artery disease (CAD), HF, resistant arterial hypertension associated with risk of stroke, and uncontrolled arrhythmias.

Patients with OSAS present a variety of symptoms that correlate with anthropometric measurements, smoking habits, sedentarism and association of comorbidities. In recent years, new perspectives regarding clinical presentations of OSAS with description of different phenotypes and clusters have emerged.

Different structural or functional cardiac abnormalities can lead to occurrence of typical symptoms and signs of HF as defined by the European Society of Cardiology (ESC) guidelines, increased morbidity and mortality and higher costs for the health system. HF is more common in elderly patients, especially those over 60 years.

The measurement of the left ventricle ejection fraction (LVEF) is used to define HF. Accordingly, HF is classified as HF with preserved LVEF, ≥50% (HFpEF) and HF with reduced LVEF, <40% (HFrEF). Recently, the latest guidelines on the diagnosis and management of heart failure published by the European Society of Cardiology proposed a new class of HF patients with LVEF = 40%–49% called HF with mid-range EF (HFmrEF), in order to better differentiate HF patients from the point of view of etiology, developing mechanisms and response to treatment strategy.

MATERIALS AND METHODS

This study was conducted after obtaining the written consent of all participants and the approval of the Ethics and Human Research Commission of the University of Medicine and Pharmacy "Dr. Victor Babes", Timisoara (no. 22/2014). 143 patients were enrolled between 12 March 2014 – 19 November 2018, after they were evaluated for OSAS and HF in the Somnology Laboratory of "Victor Babeș" Hospital in Timisoara and respectively the Cardiology Department of the Institute of Cardiovascular Diseases in Timisoara and of the Municipal Emergency Clinical Hospital of Timisoara.

The main objectives of this study were:

- to proactively investigate patients according to the inclusion / exclusion criteria, in order to detect and analyze the association between sleep apnea syndrome and heart failure.
- to demonstrate that obstructive sleep apnea syndrome is a powerful predictor of prognosis in patients with heart failure NYHA class II and III.
- Decreased number of hospitalizations in patients with heart failure, increased quality of life and implicitly reduced economic costs.

The eligibility for enrollment in the study was based on the following inclusion criteria: patients over 40 years of age, patients' ability to complete sleep questionnaires, patients with a diagnosis of heart failure and SASO who performed cardiac-respiratory polygraphy, echocardiography and evaluation of blood tests. Exclusion criteria were: lack of demographic or anthropometric data, impossibility of

collecting clinical data through sleep questionnaires, impossibility to perform cardio-respiratory polygraphy, patients without SASO or with predominantly central type sleep apnea (CSA), pulmonary cancers, pregnancy.

After vverification of the inclusion and exclusion criteria, 143 patients were enrolled in the study between March 12, 2014 - November 19, 2018. For each participant who consented to participate in this study, the following data were given:

- socio-demographic and anthropometric data (age, sex, body mass index (BMI), neck circumference (NC), abdominal circumference (AC) and smoking status);
- history of the disease in order to highlight the diurnal symptoms suggestive for the presence of OSAS (excessive daytime sleepiness, unexplained asthenia and fatigue, nocturnal symptoms such as intense snoring with respiratory pauses, nocturia, restless sleep with arousals, morning headache);
- data on the medical history, with greater attention for the cardiovascular history;
- results of routine blood tests;
- assessment of daytime sleepiness using the Epworth sleepiness scale with 8 questions, 4 answer variants, score between 0-24, suggestive for SAS over 10;
- Cardio-respiratory polygraphy for the evaluation of sleep apnea, was performed with the help of STARTDUST RESPIRONICS and PORTI devices;
- Echocardiography for heart failure assessment, was performed according to the same standards and similar diagnostic equipment;
- Data related to the treatment of heart failure.

All data were analyzed with Stata 15.1 (Statacorp, TX, USA). Differences between the characteristics of the subjects were evaluated after initially being divided into three groups, according to EF, HF with reduced EF, <40% (HFrEF), HF with mid-range EF, between 40% -49% (HFmrEF) and HFpreserved EF, ≥ 50% (hfpEF). Subsequently, for a more detailed statistical analysis the patients were stratified into two groups according to ejection fraction, HF with rpreserved ejection fraction, ≥50% (HFpEF), IC with reduced ejection fraction, <50 % (HFrEF) and then each group was stratified by AHI into two subgroups, AHI <30% (mild-moderate OSAS), AHI ≥30% (severe OSAS). Data were presented as proportions, medians and interquartile range (IQR) for variables with an skewed distribution. We used the

chi-square test (two degrees of freedom) to compare categorical data between patient groups. Continuous data were tested for normality using the Kolmogorov - Smirnov test. Non-normal distribution data were compared using the Kruskal-Wallis test. The p-value was set at the statistical significance threshold <0.005.

RESULTS AND DISCUTIONS

In our population, 23.07 % of the patients had HFmrEF, higher than reports from recent studies where the percentage of the HFmrEF category is between 13% and 17%. Men are more likely to have OSAS in patients with HF. Moreover, men have a higher incidence of HF in patients with OSAS. In our study, among the patients of the initial groups, those with HFmrEF were older, with no significant differences regarding gender or neck and abdominal circumferences.

In our group, patients with severe OSAS, regardless of FE, were more obese, with greater neck and abdominal circumference. Increased BMI, abdominal circumference and neck circumference are strong indicators of overweight and obesity and the direct association between OSAS and overweight has already been confirmed in numerous studies and indeed, our conclusions are in agreement with these data from the literature.

It is well known that obesity is an important risk factor for heart failure, and this association leads to multiple complications. In addition, obesity seems to be more prevalent in HF patients with preserved ejection fraction; this may occur due to poor echocardiographic images and error in LVEF measurement. In our study, we included only patients with OSAS, and patients with HFmrEF were in stage 2 of obesity, with higher BMIs, but differences were not statistically significant. Central sleep apnea (CSA) is particularly noted in patients with HFrEF, and decompensated HF has been recognized as a risk factor for CSA.

There were no differences between initial groups of patients regarding blood pressure (BP) measurement and sleep study, systolic and diastolic BP at visit, AHI, type of apneas, desaturation index, medium and lowest desaturation, longest desaturation <88% and sleep questionnaire. Significant differences were observed in patients with HFmrEF regarding the highest systolic BP reported by the patients (p = 0.016).

Severe OSAS was associated with significantly higher Epworth sleepiness scores only in patients with HFpEF. Some studies have shown that patients with heart failure and OSAS are less symptomatic, regardless of AHI, and the Epworth Sleepiness Scale does not correlate with AHI. The questionnaires do not accurately predict OSAS in patients with cardio-vascular disease. Studies have shown that the Epworth sleepiness scale and the SAS score can be beneficial in predicting OSAS.

In our group, all patients have severe OSAS, regardless of EF. Some studies show that patients with severe and untreated OSAS have a higher risk of fatal cardiovascular events.

Our patients with HFmrEF had higher serum glucose and creatinine levels and a lower glomerular filtration rate. Among patients with mild-moderate OSAS, those with low EF showed a higher frequency of diabetes. Nielson demonstrated in a study that patients with high blood glucose, but with no confirmed diabetes have an increased risk of developing HF. Therefore, these patients should be carefully monitored to prevent the occurrence of HF.

Further statistical analysis revealed that these changes in renal function are more common in patients with HFrEF and severe SAS. Indeed, it is known that renal dysfunction - defined by low glomerular filtration rate and / or high urinary albumin-creatinine ratio - is one of the most common comorbidities in patients with HF and this association becomes stronger with age and severity of HF. Many studies have shown that even slightly altered renal function, with a high transient level of serum creatinine, is an important predictor for worsening heart failure. The pathophysiology remains unclear, but venous congestion and intra-abdominal pressure serve as challenges for the development of new therapeutic approaches. The severity of SASO was correlated with increased serum creatinine, whereas stage 3 of chronic kidney disease is considered a significant predictor of CSA, as demonstrated by Fleischmann et al.

In this study, the lipid profile is homogeneous, which is different from the results of a cohort comprising all degrees of disease severity, where OSAS severity was independently correlated with cholesterol and triglyceride levels, probably because all our patients have severe OSAS.

Often, patients with HFpEF have only an increase in LV wall thickness or LA size, which makes diagnosis even more difficult. In our study, LA diameter was higher in patients with HFrEF ($p = 0.0002$), regardless of the severity of OSAS, similar to other publications. Moreover, the role of the left atrium in modulating LV function is well known and there are considerable amounts of data that demonstrate that the LA size is directly proportional to the increased risk of cardiovascular events; this parameter is not sufficiently used in clinical practice to determine the progression of HF.

Patients with HFmrEF had a higher frequency of tricuspid and aortic insufficiency. Among patients with mild to moderate OSAS, those with low EF showed a higher frequency of tricuspid regurgitation. Wang et al. demonstrated in a recent meta-analysis that patients with moderate to severe tricuspid regurgitation (TR) have a higher risk of hospitalization for worsening HF and increased cardiac mortality. Patients with TR, regardless of severity, have a higher risk of all-cause mortality compared to patients without tricuspid valve disease.

In patients with HFpEF, those with mild-moderate OSAS had a higher frequency of aortic regurgitation. Asymptomatic patients with HFpEF, but with severe aortic regurgitation (AR), have a higher risk of fatal heart events [170].

Comorbidities are very important in HF patients. Thus, comorbidity management plays a major role in the treatment and progression of heart failure.

COPD is significantly more frequent in HFrEF in our population. COPD and OSAS have common pathophysiological mechanisms, such as sympathetic nervous system activation and inflammation, which can increase cardiovascular risk. Moreover, patients with the association of these diseases, so-called "overlap syndrome", are at even greater risk. Some patients with advanced stages of COPD have right HF with peripheral edema and have a high probability of OSAS due to displacement of the rostral fluid from the legs during the night.

In patients with mild to moderate OSAS, the frequency of COPD was significantly increased for HFrEF cases. These results are in contrast to the available clinical data showing a slightly higher prevalence for COPD in patients with

HFpEF. This finding requires further studies to clarify whether concomitant cardiac and pulmonary dysfunction may be of particular importance for patients with HFrEF.

Chronic kidney disease is significantly more common in patients with HFrEF. Reports from the ESADA cohort study (Sleep apnea network / European sleep apnea database) identify that in patients with OSAS, decreased of GFR was predicted by baseline characteristics such as age, female, obese patients, and severe nocturnal hypoxemia and comorbidities such as heart failure and high blood pressure.

In our group, patients with HFrEF had a higher frequency of myocardial infarction and coronary heart disease, regardless of the severity of OSAS. Several studies have reported that patients with HFmrEF have an increased risk of coronary heart disease compared with patients with HFrEF, but all-cause mortality was similar to HFpEF. The prognosis of HF, regardless of EF, was correlated with common risk factors, such as age, basic disease and comorbidities.

Among the whole group of patients, we found a significant correlation (OR) between AHI and atrial fibrillation ($p = 0.029$) and between AHI and aortic insufficiency ($p = 0.052$) and in the group of patients with HFmrEF, a significant correlation between AHI and COPD ($p = 0.009$).

Chioncel et al. found that the long-term mortality rate in HFmrEF was between those patients with HFpEF and HFrEF, while Pascual-Figa et al. have shown that patients with HFmrEF fit a clinical profile similar to HFrEF, with an increased risk of cardiovascular mortality, rather than HFpEF.

However, there are contradictory data from other recent studies that have shown that patients with HFmrEF have a similar prognosis with patients with HFpEF.

Chan and colleagues found, in a small study, the presence of significant TRS in 11 of 20 patients studied and they used prolonged deceleration time to show that those with TRS had more severe diastolic dysfunction. Bitter and co-workers studied 244 patients with IC-FEP and observed the presence of respiratory disturbance during sleep in 69% of patients (40% with OSAS and 29% with CSA). The frequency of TRS, especially CSA, increased directly proportional with diastolic

dysfunction which suggests that SASC acts as a marker of IC-FEP severity, as in IC-FER. Elderly patients, more severe NYHA functional class, obesity, and higher N-terminal pro-BNP values were associated with both types of TRS. Diabetes and higher BMI were predictors of SASO. In another study that included a population similar to Bitter's, the prevalence of SASO was 64%. Higher BMI was significantly associated with SASO.

However, in these studies, TRS was evaluated by using unsupervised nocturnal cardiorespiratory polygraphy; only patients studied by Chan and their colleagues performed nocturnal assisted polysomnography.

Among patients with HFrEF, the frequency of ACE inhibitors use was higher in patients with mild-moderate OSAS (p=0.028) and the frequency of use of angiotensin receptor inhibitors was higher in patients with severe OSAS (p = 0.034).

Also, we observed that among patients with mild to moderate OSAS, the frequency of use of diuretics (p = 0.031) and digoxin (p = 0.028) was higher in patients with HFrEF.

In patients with severe OSAS, the frequency of use of angiotensin receptor inhibitors (p=0.034) and digoxin (p=0.020) was higher in HFrEF patients and the frequency of ACE inhibitors use was higher in HFpEF patients (p=0.031). These data are in line with the observation that ACE inhibitors, angiotensin receptor inhibitors and specific beta blockers have been shown to be beneficial in patients with reduced EF, but not in those with preserved EF.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

The personal contribution consists mainly in the fact that this prospective study brings new information regarding the predictive factors of prognosis in patients

with heart failure and especially in the new class of patients with mid range ejection fraction.

Patients with OSAS and HF with mid-range EF may represent a new group of patients with increased risk of developing life-long chronic kidney disease, diabetes mellitus, and tricuspid and aortic insufficiency. COPD, myocardial infarction, impaired heart parietal kinetics and CAD are the most prevalent comorbidities in HFrEF patients, but the prevalence of these is closer to that of HFmrEF than HFpEF. More studies are needed, on larger groups of patients, to determine how OSAS is involved in the progression of HF, from borderline ejection fraction to more severe heart failure.

Sleep apnea syndrome is a significant cardiovascular risk factor, due to the increasing prevalence in the general population but also to complex pathogenic mechanisms that lead to its association with a number of conditions such as HTA, cardiomyopathy, atrial fibrillation, coronary heart disease, heart failure, pulmonary hypertension, chronic pulmonary heart.

Summarizing, we can conclude that heart failure is a major public health problem despite advances in the therapeutic field, being associated with increased morbidity and mortality, multiple hospitalizations and implicitly high economic costs. That is why it is becoming increasingly important to find and treat the factors or comorbidities that contribute to the progression of heart failure. Thus, by demonstrating that sleep apnea syndrome, along with other factors already known, is a predictive factor of prognosis in HF and that patients with heart failure and respiratory disturbance during sleep are generally less symptomatic, it is necessary amending the protocol for evaluating these patients to include cardio-respiratory polygraphy as a routine test. The consequence is that any beneficial effect of diagnosis and treating of SAS on cardiovascular effects could have an even greater medical and public health impact.