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Risk for stroke and chronic kidney disease in patients with sleep apnea syndrome and heart failure with different ejection fractions

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Abstract

English:

Background: *Patients with sleep apnea syndrome (SAS) and heart failure (HF) have concomitant different comorbidities and increased risk of morbidity.*
Aim: *The aim of this study was to analyze differences between patients with SAS and heart failure with preserved ejection fraction (HFpEF; ejection fraction [EF]≥50%) – group 1 and those with SAS and heart failure with reduced ejection fraction (HFrEF; EF<50%) – group 2.*
Methods: *We evaluated 51 patients with SAS and HF in the sleep laboratory of Timisoara Victor Babes Hospital. We collected general data, sleep questionnaires, anthropometric measurements (neck circumference [NC], abdominal circumference [AC]), somnography for apnea–hypopnea index (AHI), oxygen desaturation index (ODI), echocardiographic data, comorbidities, and laboratory test.*
Results: *The study included 51 patients who were divided into two groups depending on EF, with the following characteristics: Group 1 (HFpEF): 26 patients, 19 males, seven females, age 61.54±9.1 years, body mass index (BMI) 37±6.4 kg/m², NC 45.4±3.6 cm, AC 126.6±12.9 cm, AHI 48.3±22.6 events/hour, central apnea 5.6±11.4 events/hour, obstructive apnea 25.7±18.7 events/hour, ODI 41.2±21.2/hour and lowest SpO_2 –72.1±14%.*
Group 2 (HFrEF): 25 patients, 18 males, seven females, age 63.6±8.8 years, BMI 37.9±7.5 kg/m², NC 46±4.4 cm, AC 127.2±13.9 cm, AHI 46.4±21.7 events/hour, central apnea 4.6±8.3 events/hour, obstructive apnea 25.9±18.5 events/hour, ODI 44.8±27.1/hour and lowest SpO_2 –70.6±12.1%. Differences between groups regarding anthropometric and somnographic measurements and lipidic profile were not statistically significant.
Significant differences were observed regarding stroke (23% vs. 4%, p=0.04) in the group with HFpEF and regarding creatinine measurements (1.1±0.2 vs. 1.4±0.7, p=0.049), aortic insufficiency (11.5% vs. 36%, p=0.04) and tricuspid insufficiency (6.1% vs. 80%, p=0.01) in the group with HFrEF.
Conclusions: *Patients with SAS and HFpEF have a higher risk of stroke. Patients with SAS and HFrEF have a significantly increased risk of developing a life-long chronic kidney disease and aortic and tricuspid insufficiency. These results may suggest pathogenic links between SAS and the mentioned comorbidities, and this may explain the higher mortality when this association is present.*

Keywords

sleep apnea • stroke • chronic kidney disease • heart failure

Riscul de atac ischemic și boală cronică de rinichi la pacienții cu sindrom de apnee în somn și insuficiență cardiacă cu diferite fracții de ejecție

Rezumat

Romanian:

Introducere. *Pacienții cu sindrom de apnee în somn (SAS) și insuficiență cardiacă (HF) au concomitent diferite comorbidități și risc crescut de morbiditate.*

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Obiectiv. *analiza corelațiilor dintre SAS–HF la pacienții cu fracție de ejecție păstrată (HFpEF) – grup 1, versus fracție de ejecție scăzută (HFrEF) – grup 2.*
Metodă. *Am evaluat 51 de pacienți cu SAS și HF în laboratorul de somnologie al Spitalului Victor Babeș Timișoara. Am colectat date generale, chestionare de somn, măsurători antropometrice (circumferința gâtului – NC, circumferința abdominală – AC), somnografie pentru indexul apnee-hipopnee (AHI), indicele de desaturare a oxigenului (ODI), date echocardiografice, comorbidități, analize de laborator.*
Rezultate. *Studiul a inclus 51 de pacienți împărțiți în două grupuri în funcție de fracția de ejecție, cu următoarele caracteristici: Grupul 1 (HFpEF): 26 de pacienți 19 bărbați, 7 femei, vârsta 61.54±9.1 ani, BMI 37±6.4 kg/m^2, NC 45.4±3.6 cm, AC 126.6±12.9 cm, AHI 48.3±22.6 evenimente/oră, apnee centrală 5.6±11.4 evenimente/oră, apnee obstructivă 25.7±18.7 evenimente/oră, ODI 41.2±21.2/oră, SpO_2 minim – 72.1±14%.*
Grupul 2 (HFrEF): 25 pacienți, 18 bărbați, 7 femei, vârsta 63.6±8.8 ani, BMI 37.9±7.5 kg/m^2, NC 46±4.4 cm, AC 127.2±13.9 cm, AHI 46.4±21.7 evenimente/oră, apnee centrală 4.6±8.3 evenimente/oră, apnee obstructivă 25.9±18.5 evenimente/oră, ODI 44.8±27.1/oră, SpO_2 minim-70.6±12.1%. Diferențele dintre grupuri privind măsurătorile antropometrice și somnografice și profilul lipidic nu au fost statistic semnificative.
S-au observat diferențe semnificative statistic în privința atacurilor ischemice (23% vs. 4%, p=0.04) în grupul cu HFpEF și valorilor creatininei (1.1±0.2 vs. 1.4±0.7, p=0.049), insuficienței aortice (11.5% vs. 36%, p=0.04) și insuficienței tricuspidiene (6.1% vs. 80%, p=0.01) în grupul cu HFrEF.
Concluzii.
Pacienții cu SAS–HF cu fracție de ejecție păstrată au un risc mai mare de atac ischemic. Pacienții cu SAS–HF cu fracție de ejecție redusă au un risc semnificative crescut de a dezvolta boală cronică de rinichi, insuficiență aortică și insuficiență tricuspidă.
Aceste rezultate pot sugera legături patogenice între comorbiditățile SAS-ului și pot explica creșterea mortalității când aceste asocieri sunt prezente.

Cuvinte-cheie

apnee în somn • atac ischemic • boală cronică de rinichi • insuficiență cardiacă

Introduction

Breathing disorders occurring during the night are more commonly associated with cardiovascular diseases (1).
Obstructive sleep apnea syndrome (SAS) has many phenotypes, and efforts are made for better understanding of this particular aspect (2).
It is well known that both obstructive and central SAS are more common in patients with heart failure (HF) than general population and can contribute to progression of HF due to intermittent hypoxia, endothelial dysfunction, increasing preload and afterload and activation of the sympathetic nervous system (SNS) (3).
HF is a common disease with a severe prognosis. In Europe, more than 14 million of patients are estimated and 3 million new cases are diagnosed annually (4). The mortality at 5 years for these patients is 40%–60% (5).
The purpose of this study was to observe the differences between patients with SAS and heart failure with reduced ejection fraction (HFrEF) and those with SAS and heart failure with preserved ejection fraction (HFpEF).

Methods

We enrolled consecutive patients evaluated for SAS at the "Victor Babes" Timisoara Hospital between 2011 and 2016 and for HF at the Timisoara Institute for Cardiovascular Diseases. In this study were included patients >40 years old who were diagnosed with HF and SAS based on polygraphy, echocardiography and blood test evaluation. Patients with incomplete evaluation and those with no SAS were excluded. Research protocols were approved by the ethical committee of institution, and a signed informed consent was obtained from all the patients. For sleep study, we followed the European standards for diagnostic of Sleep apnea syndrome (6).
Fifty-eight patients were screened, and 51 met the inclusion criteria. Patients were initially evaluated through a standard datasheet with the following parameters: age; gender; height; weight; body mass index (BMI; weight in kilogram/squared height in meter); neck, abdominal and hips circumference; presence and duration of hypertension; maximum and current value of blood pressure; medication; reported apneas; snoring; sleepiness; Epworth Scale; morning headache; restless sleep; nicturia; nocturnal awakenings; Chronic Obstructive Pulmonary Disease; diabetes; dyslipidemia; coronary artery disease; HF; arrhythmias; stroke; nasal septum deviation; polyposis; hypertrophic uvula; smoking status and SAS score. The somnographic recording was done with Stardust Respironics and Porti. Several parameters were measured: the number of central, obstructive, mixed apnea and hypopnea; both the total number of events and the number of events per hour; the apnea–hypopnea index (AHI); the desaturation index; the mean saturation; the lowest saturation; and the longest desaturation period. The somnographic recording

was performed and scored manually according to American Academy of Sleep Medicine standards and European Sleep Research Society recommendation (6,7).

The laboratory test was performed in Romanian Accreditation Association-RENAR certified medical laboratories: erythrocyte sedimentation rate (ESR; mm/h), uric acid (mg/dl), creatinine (mg/dl), erythrocyte count (*10^6/µ1), total cholesterol (mg/dl), LDL- Low-Density Lipoprotein, HDL- High-Density Lipoprotein cholesterol (mg/dl), HDL-cholesterol (mg/dl) and triglycerides (mg/dl).

The cardiological evaluation was performed for all patients at the Institute of Cardiovascular Diseases in Timisoara using the same diagnostic algorithm.

HF was categorised according to the left ventricle ejection fraction (LVEF), with HF with LVEF ³50% referred to as HFpEF and HF with LVEF <50% referred to as HFrEF (1). Recently, according to ESC- European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF published in 2016, HFrEF has been subdivided into mid-range (LVEF 40%–49%) and reduced ejection fraction (LVEF<40%). Because we enrolled patients between 2011 and 2016, we did not include this subdivision.

The echocardiographic method for measurement of ejection fraction (EF) was the apical biplane method of discs (the modified Simpson's rule) and was performed by a highly specialized cardiologist with the same equipment.

The morphological aspect, the area (cm), degree of regurgitation and stenosis and transvalvular presionale gradients were determined for the mitral, aortic, tricuspid and pulmonary valves (8).

Statistical analysis

The statistical analysis was performed using Microsoft Excel 2013. The results are expressed as mean ± standard deviation. The differences in the characteristics of the subjects were evaluated after they were divided into two groups, depending on the EF. For comparing the groups, the "*t*-test" for the continuous variables was used.

The standard significance level was set at 0.05; so if the calculated probability was below this threshold, the differences were considered to be significant.

Results

The initial patient lot was divided into two study groups according to the EF. Thus, 25 patients (49%) had HFrEF and 26 patients (51%) had HFpEF.

Anthropometrics

Regarding anthropometric parameters, the analysis revealed that the statistical differences between the two groups of patients were not significant, with similar age, gender, BMI and neck and abdominal circumferences (Table 1).

Sleep measurements

Comparative analysis of cardiorespiratory polygraphic parameters in the two groups of patients (AHI; central, obstructive and mixed apnea; mean, lowest, longest <88% and desaturation index; Epworth scale and SAS score) shows no statistically significant differences (Table 2).

Table 1. Anthropometric values in the groups with HFrEF versus HFpEF.

	HFrEF (25 patients)	HFpEF (26 patients)	
	Mean value ± standard deviation	Mean value ± standard deviation	*p* value
Age (years)	63.6±8.8	61.54±9.1	0.39
Gender	7 females (28%) 18 males (72%)	7 females (27%) 19 males (73)	
BMI (kg/m^2)	37.9±7.5	37±6.4	0.65
Neck circumference (cm)	46±4.4	45.4±3.6	0.57
Abdominal circumference (cm)	127.2±13.9	126.6±12.9	0.87

Table 2. The values of the polygraphic parameters in the groups with HFrEF and HFpEF.

	HFrEF	HFpEF	
Polygraphic parameters	Mean value ± standard deviation	Mean value ± standard deviation	*p* value
AHI (n/h)	**46.4±21.7**	**48.3±22.6**	**0.75**
Central apnea (n/h)	4.6±8.3	5.6±11.4	0.7
Obstructive apnea (n/h)	25.9±18.5	25.7±18.7	0.97
Mixed apnea (n/h)	4.6±7.6	6.2±10.7	0.44
Desaturation index (n/h)	44.8±27.1	41.2±21.2	0.59
Mean saturation (%)	90.2±6.3	89.8±5.3	0.84
Lowest SpO_2 (%)	70.6±12.1	72.1±14	0.69
Longest SpO_2 <88% (min)	3±5.8	10.5±33.5	0.29
Epworth scale	14±6	13.3±5.6	0.69
SAS score	4.6±0.8	4.5±0.7	0.71

Comorbidities

Regarding comorbidities, there was a statistically significant difference between the two groups only in the incidence of stroke and there was no significant differences for COPD, diabetes mellitus, dyslipidemia, coronary artery disease, arrhythmias and smoking status (Table 3).

Laboratory parameters

Patients with HFrEF had a significantly higher serum creatinine level than patients with HFpEF (1.4±0.7 vs. 1.1±0.2, respectively; *p*=0.049).

For the other laboratory parameters such as ESR, uric acid, erythrocyte count, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, it can be seen that patients with HFrEF have higher values than patients with HFpEF, but no statistically significant differences were observed in the analysis (Table 4).

Echocardiography

Echocardiographic evaluation shows that the number of patients with aortic impairment (*p*=0.004) and tricuspid insufficiency (*p*=0.01) is significantly higher in the HFrEF group (Table 5).

Discussion

Analysis of anthropometric and somnographic parameters did not reveal statistically significant differences between the two groups, including respiratory events, oxygen desaturation measurements, Epworth somnolence scale and SAS prediction score. Somnolence evaluated with the Epworth scale has a better prediction value when it is included in a validated prediction score (9).

In comparison with the existing algorithm, SAS score is a more appropriate screening tool for monitoring large populations, due to its improved specificity, but probably because of a small number of patients, it fails to show a significant difference between the two groups of our population (10).

Obesity is an important comorbidity associated with SAS and HF, but in our cohort, both groups show a similar level 2 BMI of obesity (11). Central events are more frequent in HF, but in our population, differences were not significant (12).

Cardiovascular disease patients show a high sleep-disordered breathing prevalence and poor outcome but only a systematic screening based on measures of respiration-related parameters (i.e., respiratory flow, blood oxygen saturation, etc.) allows a reliable assessment (13).

Table 3. The number of patients with different comorbidities in the groups with HFrEF and HFpEF and p value.

Comorbidities	HFrEF (n, %)		HFpEF (n, %)		*p* value
COPD	8 patients	32%	3 patients	11.5%	0.07
Diabetes	7 patients	28%	14 patients	53.8%	0.06
Dyslipidemia	15 patients	60%	18 patients	69.2%	0.5
Coronary artery disease	20 patients	80%	18 patients	69.2%	0.38
Arrhythmias	18 patients	72%	13 patients	50%	0.11
Stroke	1 patient	4%	6 patients	23%	0.04
Smoking status	11 patients	44%	11 patients	42.3%	0.9

Table 4. Laboratory parameter values in groups with HFrEF and HFpEF and p value.

Laboratory parameters	HFrEF Mean value±standard deviation	HFpEF Mean value±standard deviation	*p* value
ESR (mg/dl)	21.5±24.3	14.4±9	0.21
Uric acid (mg/dl)	7.4±2.8	6.6±1.8	0.36
Creatinine (mg/dl)	**1.4±0.7**	**1.1±0.2**	0.049
Erythrocyte count (*10^6/ml)	4.9±0.9	4.8±0.5	0.8
Cholesterol (mg/dl)	164.7±38.4	164.7±54.2	0.9
LDL-cholesterol (mg/dl)	94.1±29	79.1±25.3	0.15
HDL-cholesterol (mg/dl)	42.4±10.7	41.9±10.4	0.88
Triglycerides (mg/dl)	133.5±81.6	191.4±105.6	0.06

Table 5. The number of patients with valvular pathology in the groups with HFrEF and HFpEF and p value.

Valve alteration	HFrEF (n, %)		HFpEF (n, %)		*p* value
Mitral insufficiency	24 patients	96%	21 patients	80.7%	**0.09**
Aortic insufficiency	**9 patients**	**36%**	**3 patients**	**11.5%**	**0.04**
Tricuspid insufficiency	**20 patients**	**80%**	**12 patients**	**46.1%**	**0.01**
Pulmonary insufficiency	1 patient	4%	3 patients	11.5%	**0.32**

We observed that there are no significant differences between certain comorbidities in the group of patients with reduced EF and preserved EF (COPD, diabetes, dyslipidemia, coronary artery disease, arrhythmias, smoking status). However, a statistically significant higher number of patients presented with stroke in the group with preserved EF.

HF has been recognized as a risk factor for stroke (14). Left ventricular dysfunction, even mild (EF 41%–50%), was associated with an increased risk of ischemic stroke (15,16). Moreover, the risk of stroke was at least as great for patients with mild dysfunction (EF 41%–50%) as for patients with moderate dysfunction to severe dysfunction (EF ≤40%) (17,18). Our data regarding the prevalence of stroke in HFpEF are different from those of other trials. However, limited information is available about comorbidities and risk factors for incident HFpEF, and the fact that there is a lack of therapies that improve the prognosis of this condition reflects an incomplete understanding of its pathogenesis. More studies are needed to focus on HFpEF. SAS is associated with multiple comorbidities and may play a role in increasing the cardiovascular risk (19).

Significantly higher values of creatinine were found in the group with reduced EF. Patients with early chronic kidney disease (CKD) are more likely to die of cardiovascular disease than to progress to terminal stages of the disease, due to well-known risk factors (hypertension, diabetes and coronary artery disease) and novel factors (subclinical ischemia, arteriosclerosis, arterial stiffening, hemodynamic insults) (20,21,22).

CKD prevalence in a population of 7700 subjects from a large European Sleep Apnea Database was 8.7% or 6.1%, according to the Modification of Diet in Renal Disease or the Chronic Kidney Disease Epidemiology Collaboration equations. In SAS, CKD is largely predicted by comorbidities and anthropometric characteristics. In addition, severe nocturnal hypoxemia, even for only a small part of the night, may play an important role as a risk factor for kidney dysfunction (23).

In patients with SAS, the identification, diagnosis and treatment of sleep disorders is complicated by the overlapping presentation with CKD and other commonly comorbid conditions. In patients with CKD, sleep disorders are more prevalent, with an additional morbidity and mortality burden. The complex and dynamic relationship between sleep disorders and CKD remains relatively little investigated (24).

The cause of renal dysfunction is multifactorial, but reduced renal perfusion and venous congestion are prominent factors, which are probably mediated and modified by a multitude of cardiorenal connectors like activation of rennin–angiotensin–aldosterone system (RAAS) and SNS, endothelial dysfunction, inflammation and anemia. Through the progression of heart failure, which can be caused by (re)hospitalizations, patients enter a vicious circle of mutual organ dysfunction, resulting in end-stage renal disease, end-stage heart failure, or a combination of both (25).

In the studied population, the differences were significantly higher for HFrEF regarding aortic insufficiency and tricuspid insufficiency. In the first phases of chronic aortic insufficiency, LVEF is normal or even increased; patients may remain asymptomatic during this period. Through the progression of aortic insufficiency, EF starts to decrease. The increase in left ventricular systolic volume is a sensitive indicator of progressive myocardial dysfunction (26).

Patients with moderate or severe tricuspid insufficiency have a lower survival rate than those with mild tricuspid insufficiency, irrespective of pulmonary artery pressure or EF. Thus, tricuspid insufficiency should be considered as an additional risk factor for mortality (27).

In the studied population, even if EF was decreased, valvular dysfunction was mild and moderate. It remained unclear if valvular disease was the underlying cause of HF or it was a consequence of HF; thus, some studies demonstrated that EF decreased through the progression of valvular insufficiency.

If SAS is a truly established independent cardiometabolic risk factor and if SAS should be included in integrated cardiometabolic risk reduction management are questions still waiting for definitive answers (28).

Conclusions

Patients with SAS and HFpEF have been shown to be at a higher risk for stroke. CKD and aortic and tricuspid insufficiency are higher in the group with reduced EF compared to those with SAS associated with preserved EF.

These results may suggest pathogenic links between SAS comorbidities considering that many of the pathophysiological consequences of SAS (activation of RAAS and SNS, endothelial dysfunction, inflammation) are precursors for these comorbidities and the mortality is higher when this association is present.

Ethics approval and consent to participate are not applicable as this is a retrospective observational study.

The authors declare that they have no competing interests.

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