Obstructive sleep apnea, cardiac function and exercise capacity

Sindromul de apnee obstructivă de somn, funcția cardiacă și capacitatea de efort

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Abstract

Background. *Obstructive sleep apnea syndrome (OSAS) is a risk factor for cardiovascular (CV) diseases due to high intrathoracic pressure variations, intermittent hypoxemia and sympathetic activation. Few studies evaluated the peak/maximal exercise capacity (peakVO_2) in patients with severe OSAS.*
Aim. *The evaluation of peakVO2 and its relation with cardiac morphology/function and indices of OSAS severity (the Apnea Hypopnea Index - AHI; the Oxygen Desaturation Index - ODI) in severe OSAS patients.*
Method. *PeakVO_2 and cardiac morphology and function (transthoracic echocardiography) were evaluated in severe OSAS patients without overt CV or respiratory comorbidities. The relationships between AHI, ODI, peakVO_2 and echocardiographic parameters were assessed.*
Results. *The study included 25 patients (among them 6 women), with the following characteristics: age 45.2±1.9 years; BMI 34.8±1kg/m^2; AHI 60±4.8 events/hour; ODI 47/hour (range 16.5-100); peakVO_2/kg 19.76±0.95 ml/min/kg. 21 patients had low peakVO_2/kg (≤ 25ml/min/kg). Nine out of seventeen patients had increased left atrial volume, and 13 had left ventricle (LV) diastolic dysfunction. Seven patients had low LV ejection fraction (LVEF<55%). PeakVO_2/kg had a negative correlation with AHI (r= -0.536), ODI (r= -0.441), the left atrial volume (r= -0.632) and the right ventricle outflow tract (r= -0.490).*
Conclusion. *We found a low peakVO_2 in 84% severe OSAS patients with no clinical findings of heart failure. The exercise capacity correlated with both OSA severity and cardiac anomalies. The use of cardiopulmonary exercise test (CPET) allows the identification of subclinical cardiac dysfunction in severe OSAS patients.*
Keywords: ***obstructive sleep apnea, cardiac function, exercise capacity***

Rezumat

Premise. *Sindromul de apnee obstructivă în somn (SASO) este factor de risc pentru boli cardiovasculare (CV) prin hipoxemie intermitentă, activare simpatică și variații mari ale presiunii intratoracice. Puține studii au evaluat capacitatea de efort de vârf (VO_2max) la pacienții cu SASO sever.*
Scop. *Evaluarea VO_2max și a relației acesteia cu morfologia/funcția cardiacă și indicii de severitate ai SASO (Indicele de Apnei Hipopnei - IAH; Indexul de Desaturare - ID) la pacienți cu SASO sever.*
Metodă. *VO_2max, morfologia și funcția cardiacă (ecocardiografie transtoracică) au fost evaluate la pacienți cu SASO sever fără comorbidități CV sau respiratorii evidente clinic. Au fost evaluate relațiile între VO_2max, IAH, ID și parametrii ecocardiografici.*
Rezultate. *Au fost incluși în studiu 25 de pacienți (dintre care 6 femei), cu următoarele caracteristici: vârstă 45,2±1,9 ani; IMC 34,8 ±1 kg/m2; IAH 60±4,8 evenimente/oră; ID 47/oră (interval 16,5-100); VO_2 de vârf/kg 19,76±0,95 ml/min/kg. 21 de pacienți au avut VO_2max/kg scăzut (≤ 25ml/min/kg). 9 din 17 pacienți au avut volum atrial stâng crescut, iar 13 au avut disfuncție diastolică de ventricul stâng (VS). 7 pacienți au avut fracție de ejecție VS redusă (FEVS<55%). VO_2max/kg a avut o corelație negativă cu IAH (r= -0.536), ID (r= -0.441), volumul atriului stâng (r= -0.632) și cu tractul de ejecție al ventriculului drept (r= -0.490).*
Concluzie. *Capacitatea de efort a fost scăzută la 84% dintre pacienții cu SASO sever fără insuficiență cardiacă manifestă clinic. Severitea SASO și anomaliile cardiace morfologice/funcționale s-au corelat cu capacitatea de efort scăzută. Testarea cardiopulmonară la efort permite identificarea disfuncției cardiace subclinice la pacienții obezi cu SASO sever.*
Cuvinte-cheie: ***apnee obstructivă de somn, funcție cardiacă, capacitate de efort***

Introduction

Obstructive sleep apnea syndrome (OSAS) is often associated with, and considered to be a risk factor for metabolic and cardiovascular disorders: obesity, type 2 diabetes, hypertension, ischemic heart disease, heart failure, stroke, cardiac arrhythmias (atrial fibrillation and flutter) and sudden death[1,2]. The pathophysiological mechanisms involved are sympathetic activation, cardiovascular variability, and release of vasoactive substances, systemic inflammation, oxidative stress, endothelial dysfunction, insulin resistance, and intrathoracic pressure changes[1,2].

Several clinical studies have evaluated the cardiorespiratory response to progressive exercise in moderate to severe OSAS patients and found anomalies like excessive increase in systemic blood pressure, blunted heart rate response, slow increase in cardiac output, or findings consistent with coronary artery disease, peripheral arterial disease, respiratory diseases or peripheral muscles dysfunction. Most patients from these studies had a low peak/maximal exercise capacity[3-16].

Due to the fact that OSAS and cardiovascular diseases have common risk factors (obesity, male sex, age, central body fat deposition, alcohol, smoking, lack of exercise), it is unclear if OSAS represents *per se* a cause of low peak exercise capacity.

We aimed to evaluate the relationship between OSAS severity, cardiac morphology/function and exercise capacity in newly diagnosed, moderate to severe OSAS patients, with no clinically significant cardiac or respiratory comorbidities. Obesity, systemic arterial hypertension and type 2 diabetes were not exclusion criteria.

Method

Study subjects. Consecutive newly diagnosed untreated moderate to severe OSAS patients (Apnea Hypopnea Index, AHI >15/hour) were enrolled. The patients were recruited from the 4th Pneumology Department from "Marius Nasta" Institute, Bucharest. OSAS diagnosis was made by cardio-respiratory polygraphy (Porti 7 or AliceNightOne devices). The subjects were eligible for participation if they were between 18 and 65 years old, they were capable of performing exercise testing, they were in good physical and mental health, without other comorbidities or therapies that could influence daytime sleepiness and had no history of chronic cardiovascular or respiratory conditions that are often associated with impaired exercise capacity. The research protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants.

Study protocol. Unattended (ambulatory or in-hospital) six-channel cardio-respiratory polygraphy was performed on patients referred to our department for high clinical suspicion of obstructive sleep apnea syndrome, including excessive daytime sleepiness (Epworth scale score of >10/24). All tests included measurements of nasal airflow *via* nasal pressure cannula, monitoring of respiratory effort with chest and abdominal band, continuous pulse-oximetry, body position and snoring. The cardio-respiratory polygraphy was performed and manually scored in accordance with American Academy of Sleep Medicine standards, by a trained doctor. All patients underwent a comprehensive interview concerning tobacco/professional exposure, medical history, clinical examination and blood tests, including complete blood count, liver and renal function, metabolic profile (fasting serum glucose, total cholesterol, LDL- and HDL-cholesterol, triglycerides, uric acid). In order to exclude respiratory comorbidities, standard chest X-ray and lung function tests were performed (body-plethysmography and lung diffusion tests using a Jaeger body-plethysmograph).

Transthoracic echocardiography was performed by the same doctor using a Mindray echocardiograph. Left ventricle posterior wall diastolic thickness (LVPW), interventricular septum diastolic thickness (IVS), left ventricle mass (LVM), LVM index (LVMI), systolic and diastolic left ventricle function (left ventricle ejection fraction - LVEF; E wave velocity, A wave velocity, E/A ratio), left atrium volume (LAV), indexed left atrium volume (ILAV), right ventricle outflow tract diameter above the aortic valve (RVOT) were some of the parameters evaluated.

The exercise capacity was assessed through a standard 6-minute walk test (6MWT), using a 50-meter hallway, and an incremental maximal cardiopulmonary exercise test (CPET), using a Cosmed cycle-ergometer. The predicted value for the six-minute walk distance (6MWD) was calculated using Enright and Sherrill equations[17] and peak oxygen uptake (peakVO_2) was calculated using Wasserman equation[18,19]. The results were expressed as percent predicted for the 6MWD and as absolute value (in milliliter oxygen uptake per kilogram body weight, ml/min/kg) for the peakVO_2.

Statistical analysis

The data were analyzed using a SPSS20 trial version. We performed the Kolmogorov-Smirnov normality distribution test for all the data and then reported the subjects' characteristics and findings as mean±SD, or median [IQR]. We checked for differences in subjects' characteristics after splitting them in two groups, smokers or ex-smokers versus non-smokers, using the Independent-Sample T test. We applied bi-variate correlation tests between data of interest and reported the Pearson correlation coefficient for normal distribution data and Spearman for non-normal data. A p value of less than 0.5 was considered significant.

Results and discussions

Twenty-five moderate to severe OSAS patients (among them six women) were included. Cardio-respiratory polygraphy data are presented in **Table 1**. Twenty-four patients had an estimated total sleep time (eTST) of more than 5 hours. Only one patient had a moderate obstructive sleep apnea syndrome (with an AHI of 28 events per hour of sleep), the rest of the subjects having an AHI of ≥ 30 events/hour.

Baseline characteristics. Baseline characteristics are presented in **Table 2 and Table 3**. One patient was overweight, with a BMI of 28 kg/m^2, one patient was morbidly obese, with a BMI of 42 kg/m^2, the rest of the subjects having grade I or grade II obesity. Ten patients had a significant smoking history (more than 5 pack-years), with 2 of them being active smokers.

Comorbidities were systemic hypertension - 10 cases (all receiving antihypertensive treatment and having resting arterial blood pressure values of less than 160/100 mmHg); dyslipidemia - 7 cases; asymptomatic hyperuricemia (e.g.>7.2mg/dl) - 3 cases; chronic rhinosinusitis - 10 cases; nasal septum deviation - 8 cases, noninsulin-necessitating type 2 diabetes mellitus - 1 case. All patients had a normal lung function.

Transthoracic echocardiography found 17 cases (68%) with left ventricle hypertrophy (defined as LVPW and IVS of >10mm), with 4 cases of left ventricle stage I diastolic dysfunction and 3 cases of left ventricle stage II diastolic dysfunction.

Left ventricle hypertrophy is a common finding in patients with arterial systemic hypertension. However, we found this anomaly in seven of our patients with normal resting blood pressure, which could represent a consequence of chronic nocturnal sympathetic activation due to sleep fragmentation.

Increased LAV (LAV of >52ml for women and >58ml for men) was seen in nine (approximately 50%) cases out of seventeen evaluated, which is explained by the diastolic dysfunction of the left ventricle, and may contribute to the exercise limitation despite a normal LVEF.

We also found an increased RVOT diameter (≥ 30mm) in four cases out of twenty-one evaluated.

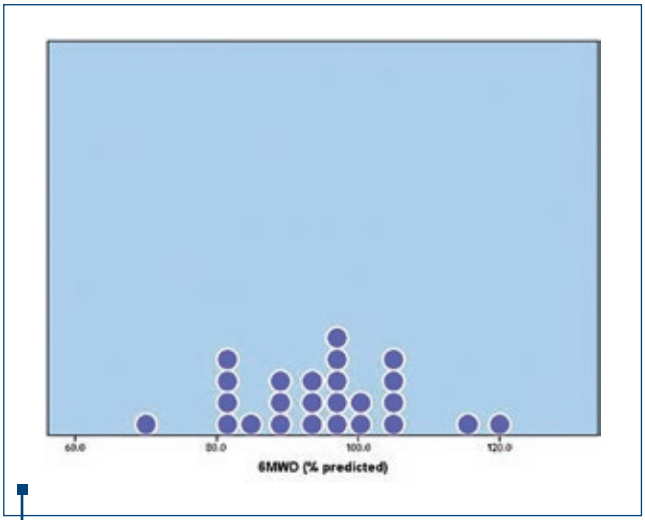

Figure 1. *The 6-minute walk distance (6MWD), % predicted*

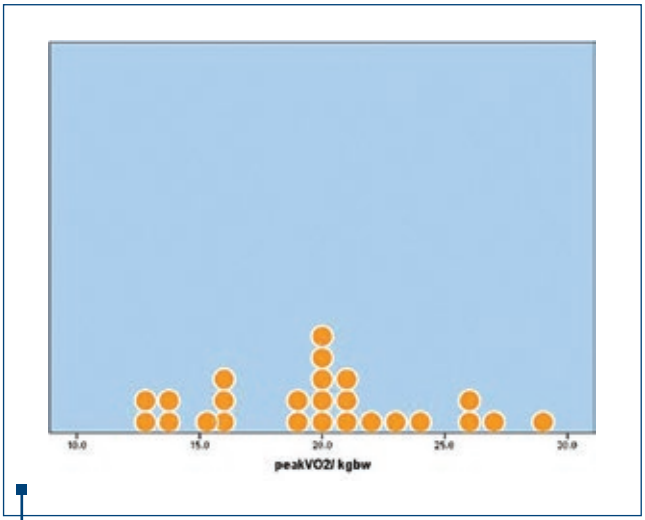

Figure 2. *The peak oxygen uptake achieved at the CPET (peak VO2/kg)*

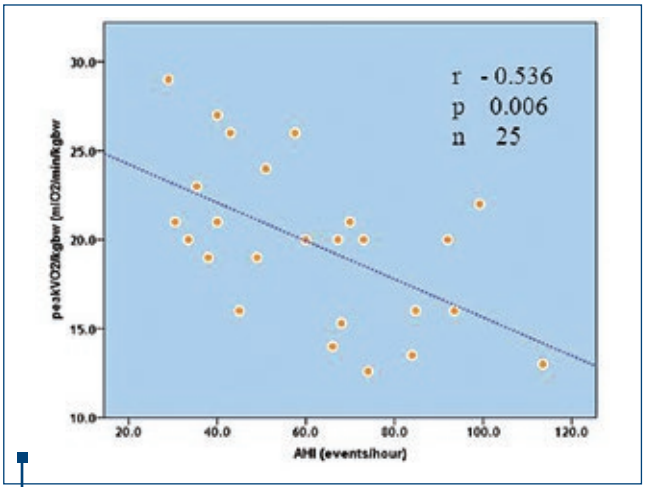

Figure 3. *Correlation between AHI and peak VO2/kg*

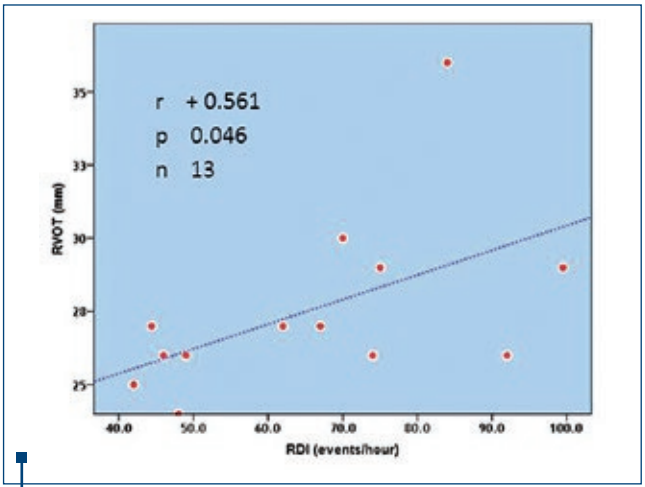

Figure 4. *Correlation between RDI and RVOT dimension*

Fifteen patients (out of twenty-two evaluated) had a normal LVEF (≥55%). The remaining 7 patients had an LVEF between 49% and 54%.

Exercise capacity, as evaluated through the 6MWT, was lower than expected (6MWD<85% predicted value) in 6 subjects (24%) (**Figure 1**), OSAS and obesity being the only identified risk factor. No oxygen desaturation or important increase in systemic blood pressure occurred during the tests.

At the incremental CPET, **21 subjects (84%)** had a low peakVO2 (less than 25ml/min/kg), with all having a peakVO_2 of less than 30 ml/min/kg (**Figure 2**). The exercise capacity data are presented in **Table 4**. No ECG signs or symptoms of ischemic heart disease and no arrhythmias were seen during the tests. Two test were stopped at physician's request due to an excessive increase in blood pressure (at 240/120 mmHg). The rest of the subjects ended the exercise test because of leg fatigue.

There were no significant differences between the two groups (smokers versus non-smokers) regarding age, BMI, respiratory function (FEV1), OSAS severity (AHI, average nocturnal SaO_2, Epworth score), cardiac morphology and function (A wave velocity, LAV, RVOT, LVEF) and exercise capacity (peak HR, 6MWD, VO_2 at the VT, peakVO_2/kg).

Correlations. When looking at the **entire group of patients**, we found a negative correlation between OSAS severity (AHI and ODI) and peak exercise capacity (peakVO_2/kg) in the CPET (r= -0.536, p =0.006, n=25), as well as with the oxygen uptake at the ventilatory threshold (VT) (r= -0.445, p=0.026, n=25), suggesting that the more severe OSAS was, the greater the decrease in exercise capacity (**Figure 3**).

A positive correlation between OSAS severity and cardiac morphology was also found. The Respiratory Disturbance Index (RDI) and the sleep time with SpO_2 below 90% (TB90%), expressed as percent from the eTST, correlated with RVOT diameter (r= +0.561, p=0.046, n=13; and r=0.447, p=0.042, n=21), suggesting a relation between OSAS severity and cardiac morphology and function (**Figure 4**). This is explained by the intermittent nocturnal hypoxemia that increases the afterload of the right ventricle, through the reflex vasoconstriction of the pulmonary vascular bed[20].

Table 1 Cardio-respiratory polygraphy data

Apnea Hypopnea Index (events/h)	60 ± 4.8
Oxygen Desaturation Index (events/h)	47 [16.5-100]
Total estimated sleep time (eTST), min	406.8 ± 20.4
Median Average SpO_2 (%)	92 [78-96]
Time with SpO_2 < 90% (% eTST)	11 [0-76]

Data are presented as mean ± SD, or median [IQR]

Table 2 Baseline characteristics – anthropometrical data and blood tests

Age (years)	45.2 ±1.9
Male sex, no (%)	19 (76%)
BMI (kg/m2)	34.8 ± 1
Blood test	
Hemoglobin (g/dl)	45.2 ±1.9
Glucose (mg/dl)	19 (76%)
ESR (mm/1h)	34.8 ± 1
Fibrinogen	45.2 ±1.9
Uric acid (mg/dl)	19 (76%)
Total Cholesterol (mg/dl)	34.8 ± 1
LDL Cholesterol (mg/dl)	45.2 ±1.9
HDL Cholesterol (mg/dl)	19 (76%)
Triglycerides (mg/dl)	34.8 ± 1

Data are presented as mean ± SD, or median [IQR]

Table 3 Baseline characteristics – lung function and echocardiography data

Lung function tests	
FEV1 (L, %)	3.63 [2-5], 95 ±4
FVC (L, %)	4.36 [2.97-7], 94.5 [78-125]
TLC pleth (L, %)	7.15 ±0.5, 107.5 ±4
DLCO (mmol/min/kPa, %)	9.4±0.6, 92.75 ±4.33
Echocardiography	
LVPW (mm)	11.35 ± 0.4
IVS (mm)	12.46 ± 0.53
LVEF (%)	60 [49-67]
A wave velocity (m/s)	58.85 ± 5.45
LAV (ml)	25.85 ± 2.1
ILAV (ml/kg)	27.47 ± 0.76
RVOT (mm)	27.76 ± 0.75

Data are presented as mean ± SD, or median [IQR]

FEV1 – forced expiratory volume at 1second; FVC – forced vital capacity; TLC – total lung capacity; DLCO – diffusion lung capacity for carbon monoxide; LVPW – left ventricle posterior wall thickness; IVS – interventricular septum; LVEF – left ventricle ejection fraction; (I) LAV – (indexed) left atrium volume; RVOT – right ventricle outflow tract

Table 4 Exercise capacity data

Six-minute walk distance (6MWD), m	584 ± 13.4
Six-minute walk distance (%)	94.35 ± 2.36
Cardiopulmonary exercise test	
peakVO_2 (ml/min)	2102 ± 105.5
peakVO_2 (ml/min/kg)	19.76 ± 0.95
VO_2 at the VT (ml/min/kg)	13 ± 0.58
VO_2 at the VT (% peakVO_2)	67.06 ± 2.88
Peak HR (bpm)	146.6 ± 4.25
Peak oxygen pulse (ml O_2/beat)	15 [10.8-20.73]
Peak oxygen pulse (% predicted)	93.8 ± 3.08

Data are presented as mean ± SD or median [IQR]

Several correlations between exercise capacity and cardiac morphology/function were also found. A positive correlation was found between the 6MWD and LVEF (r= +0.526, p=0.012, n=22). The 6MWD had a negative correlation with LAV (r= -0.516, p=0.034, n=17) and with RVOT (r= -0.435, p=0.049, n=21).

Despite the fact that there is a negative correlation between the 6MWD and the cardiac impairment, the 85% predicted cut-off for normality was not useful in identifying the patients with high cardiovascular risk in this population.

The maximal/peak exercise capacity (peakVO_2/kg and peak HR) negatively correlated with A wave velocity (r= -0.476, p=0.034, n=20, and r= -0.498, p=0.026, n=20). The peakVO_2/kg also had a negative correlation with LAV (r= -0.632, p=0.007, n=17) and RVOT (r= -0.490, p=0.024, n=21) (**Figure 5**). As expected, LAV and RVOT had a positive correlation (r=0.754, p=0.000, n=17).

The tobacco exposure (e.g., the number of pack-years) was not correlated with OSAS severity, cardiac morphology and function, or exercise capacity.

When looking at the **non-smoker group,** we found an even more powerful correlation between OSAS severity and exercise capacity. AHI had negative correlations with peakVO_2 (r= -0.615, p=0.015, n=15), peak VO_2/kg (**r= -0.779, p=0.001, n=15**) and VO_2 at the ventilatory threshold (VT/kg) (r= -0.604, p=0.017, n=15) (**Figure 6**). The ODI had a negative correlation with the peakVO_2/kg (r= -0.539, p=0.047, n=14) and TB90% with peakVO_2 (r= -0.576, p=0.031, n=14), peakVO_2/kg (r= -0.602, p=0.023, n=14) and with peak HR (r= -0.713, p=0.004, n=14).

Similar results were obtained for the correlations between OSAS severity and cardiac morphology. AHI correlated positively with LVPW (r=0.623, p=0.023, n=13) and RVOT (r=0.601, p=0.039, n=12), and TB90% with RVOT diameter (r= +0.620, p=0.031, n=12).

Despite the fact that TB90% was previously described as having a stronger correlation with the cardiovascular

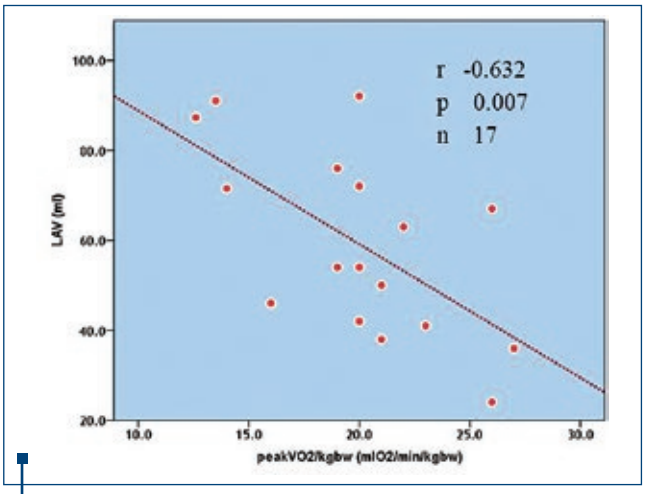

Figure 5. *Correlation between peak VO_2 and LAV*

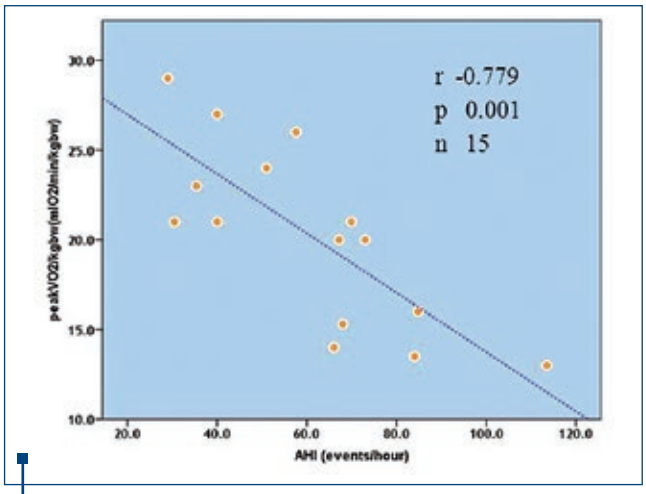

Figure 6. *Correlation between AHI and peak VO_2 in non-smokers*

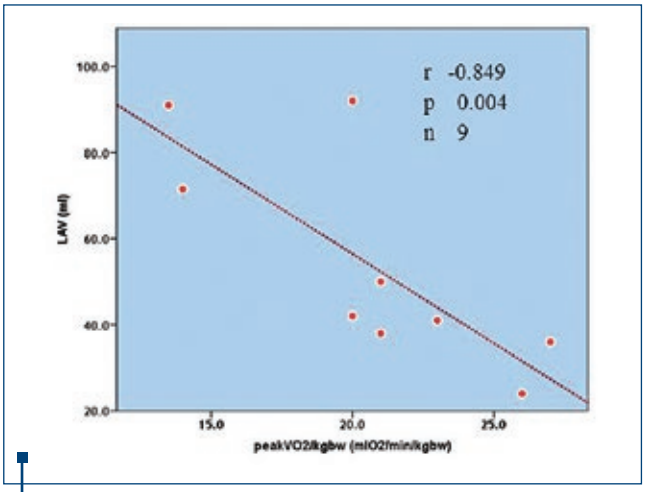

Figure 7. *Correlation between LAV and peak VO_2 in non-smokers*

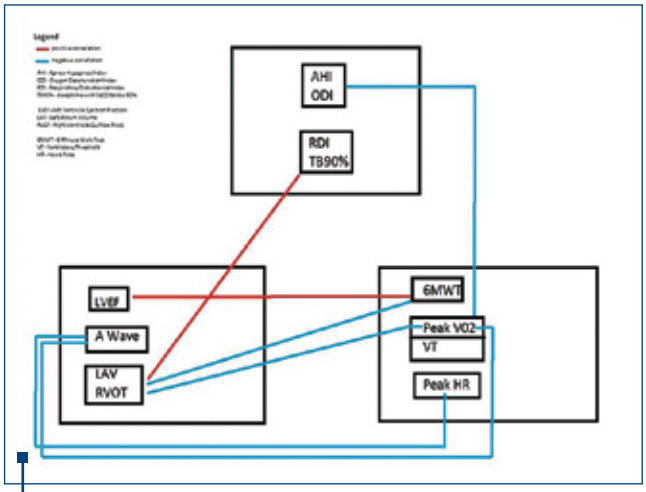

Figure 8. *Correlations of OSAS indices, cardiac parameters and exercise capacity*

risk than AHI, in our study we found a similar contribution of both aspects (AHI and TB90%), that express the OSAS severity.

Exercise capacity (peakVO_2/kg and 6MWD) had strong negative correlations with LAV (r= -0.849, p=0.004, n=9 and r= -0.940, p=0.000, n=9) and RVOT (r= -0.704, p=0.011, n=12 and r= -0.577, p=0.049, n=12) (**Figure 7**).

It is worth noticing that in the smokers group, the tobacco exposure had correlated with neither cardiac morphology and function, nor with the exercise capacity. Even more, OSAS severity had a negative correlation (r= -0.693, p=0.026, n=10) with tobacco exposure, which means that more the severe OSAS was, less tobacco exposure was identified in our patients.

A synthesis of our findings is presented in **Figure 8**.

Conclusion

The current research found a low exercise capacity (as evaluated by the peakVO_2) in 84% of newly diagnosed severe OSAS patients, with no subjective exercise limitation and good performance in the currently applied exercise field test (6MWT).

The peak exercise capacity had significant correlations with OSAS severity and with cardiac morphological and functional anomalies. Cardiac dysfunction, which is directly associated with the obstructive events in OSAS, or secondary to systemic hypertension induced by OSAS, seemed to be the main mechanism associated with reduced exercise capacity, independently of tobacco exposure.

Knowing that smoking represents a strongly recognized risk factor for atherosclerosis and cardiovascular diseases, the fact that the cardiac impairment was more closely related to OSAS severity in non-smokers could represent an argument in favor of the role of sleep apnea in cardiovascular morbidity.

As cardiac dysfunction and reduced exercise capacity are generally associated with poor outcome (reduced survival), using CPET in the initial evaluation of all severe OSAS patients, even if they are young, non-smokers and do not have obviously impaired exercise capacity, could be useful in identifying patients at high cardiovascular risk and in giving them a strong motivation to adhere to the necessary lifestyle changes and CPAP therapy. ■

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