Obesity, exercise capacity and systemic inflammation in severe obstructive sleep apnea

Obezitatea, capacitatea de efort și inflamația sistemică în cazul apneei severe obstructive de somn

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Abstract

Background. *Obesity and obstructive sleep apnea syndrome (OSAS) are associated with systemic inflammation, secondary cardiovascular comorbidities and low exercise capacity.*
Aim. *To assess the relations between obesity, exercise capacity and systemic inflammation in patients with severe OSAS. Method. Newly diagnosed severe OSAS patients (Apnea-Hypopnea Index [AHI] >30/hour, cardiorespiratory polygraphy), with no clinically significant cardio-respiratory comorbidities, were evaluated by anthropometric measurements (Body Mass Index [BMI]; neck, waist and hip circumference and ratio [WHR]); complete blood count and markers of systemic inflammation: erythrocyte sedimentation rate (ESR), fibrinogen (Fb), neutrophils and platelets to lymphocytes ratios (NLR, PLR). All subjects underwent a six-minute walk test, with measure of the 6-minute walk distance, and an incremental cardio-pulmonary exercise test with measurement of the peak oxygen uptake (peakVO2), in order to asses maximal exercise capacity. The relations between these parameters were analyzed.*
Results. *In a group of 30 severe OSAS patients (23 men), with mean/median values for age 45±9 years, BMI 34.9±4.7 kg/m2, WHR 1 (0.9-1.2), AHI 58.8/hour (26-113.5), Oxygen Desaturation Index (ODI) 46/hour (16.5-100.3), hemoglobin (Hb) 15 g/dl (11.6-17), ESR 8 mm/1 hour (1-39), FB 336 mg/dl (232-652), NLR 2 (1-3.73), PLR 97.5 (55-166), we found a peakVO2 of 82.11±2.58% predicted value. A statistically significant negative correlation between BMI and peakVO2 (r=-0.493, p=0.006) was found. OSAS severity (AHI, ODI) also negatively correlated with VO2 peak (r=-0.477, p=0.008; r=-0.379, p=0.043). Surprisingly, BMI negatively correlated with PLR (r=-0.401, p=0.042). No correlation between peak exercise capacity and OSAS severity with PLR was identified.*
Conclusion. *Both obesity and severe OSAS are associated with decreased exercise capacity. In our study group, we did not find a relation between markers of systemic inflamation and OSAS severity or peak exercise capacity. Systemic inflammation may not be the main mechanism of reduced exercise capacity in severe OSAS, other mechanisms being probably involved (cardiac dysfunction).*
Keywords: ***cardiopulmonary exercise testing, OSAS, systemic inflammation, exercise capacity***

Rezumat

Introducere. *Obezitatea și apneea obstructivă în somn (OSAS) sunt asociate cu inflamație sistemică, comorbidități cardiovasculare și capacitate de efort fizic scăzută.*
Scop. Evaluarea relației între capacitatea de efort fizic și inflamația sistemică la pacienți obezi cu OSAS severă.
Metodă. *Pacienți cu OSAS severă (Index de Apnei-Hipopnei [IAH] >30/oră, poligrafie cardiorespiratorie) nou diagnosticați, fără comorbidități cardiorespiratorii semnificative clinic, au fost evaluți, notându-se următoarele date: indicii antropometrici (indicele de masă corporală [IMC]; circumferința gât, talie și sold, raportul talie/șold [TSR]); hemoleucograma, cu formula leucocitară și indici celulari; markeri de inflamație sistemică: viteza de sedimentare a hematiilor (VSH), fibrinogenul (Fb), raportul dintre neutrofile și limfocite (NLR), respectiv trombocite și limfocite (PLR). Toți pacienții au efectuat un test de mers de 6 minute, cu măsurarea distanței parcurse, și un test cardiopulmonar la efort, în scopul evaluării capacității de efort maximal, cu măsurarea consumului de oxigen de vârf (peakVO2). Au fost analizate relațiile între acești parametri.*
Rezultate. *În lotul studiat, 30 de pacienți (23 de bărbați) cu OSAS severă, cu valori medii/mediane pentru vârstă 45±9 ani, IMC 34,9±4,7 kg/m2, TSR 1 (0,9-1,2), IAH 58,8/oră (26-113,5), Index de Desaturare (ID) 64/oră (16,5-100,3), hemoglobină (Hb) 15 g/dl (11,6-17), VSH 8 mm/1 oră (1-39), Fb 336 mg/dl (232-652), NLR 2 (1-3,73), PLR 97,5 (55-166), am găsit un peakVO2 de 82,11±2,58% din prezis. Am identificat o corelație negativă și semnificativă statistic între IMC și peakVO2 (r=-0.493, p=0,006). Severitatea OSAS (IAH, ID) s-a corelat, de asemenea, negativ cu peakVO2 (r=-0.477, p=0,008; r=-0.379, p=0.043). În mod surprinzător, IMC s-a corelat negativ cu PLR (r=-0.401, p=0.042). Nu a fost identificată o relație între PLR și capacitatea de efort fizic maximal, respectiv severitatea OSAS.*
Concluzii. *Atât obezitatea, cât și OSAS severă sunt asociate cu o capacitate de efort fizic scăzută. În grupul studiat, nu a fost identificată o relație între markerii de inflamație sistemică și severitatea OSAS sau capacitatea de efort fizic maximal. Este posibil ca inflamația sistemică să nu fie mecanismul principal al scăderii toleranței la efort în OSAS severă, alte mecanisme fiind probabil implicate (disfuncția cardiacă).*
Cuvinte-cheie: ***test cardiopulmonar la efort, apnee obstructivă în somn, capacitate de efort fizic, inflamație sistemică***

Introduction

Aerobic exercise maximal capacity depends on the integrity of the systems involved in the oxygen uptake, transport and utilization. Respiratory, cardio-vascular, hematological and peripheral muscle diseases may be, alone or combined, responsible for a low exercise capacity[1].

Chronic low grade systemic inflammation is currently believed to be involved in the pathogenesis of cardiovascular disease, diabetes, muscle weakness, osteoporosis, weight loss and depression[2-7]. Obesity is the main risk factor for obstructive sleep apnea syndrome (OSAS) and both conditions are associated with systemic inflammation[8-10].

The anomalies that were identified in previous studies during incremental exercise in unselected OSAS subjects were diverse: 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[11-20].

We aimed to evaluate the relation between obesity, exercise capacity and systemic inflammation in untreated severe OSAS subjects, without other clinically significant diseases that could contribute to low exercise capacity. The patients with controlled systemic arterial hypertension and type 2 diabetes were not excluded from the research.

Method

Study subjects. Subjects referred to a Pulmonology department for high clinical suspicion of obstructive sleep apnea underwent a cardio-respiratory polygraphy. Patients diagnosed with severe OSAS (Apnea Hypopnea Index [AHI] >30/hour) with no history of chronic cardiovascular or respiratory conditions were enrolled. Subjects were eligible if they were between 25 and 65 years old, capable of performing exercise testing on a cycle-ergometer, in good physical and mental health. The research protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants.

Study protocol. Severe OSAS diagnosis was made through an unattended (ambulatory or in-hospital) six-channel cardio-respiratory polygraphy (AliceNightOne and Porti 7 poligraphs), which 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 tests were manually scored in accordance with American Academy of Sleep Medicine standards by a trained medical doctor.

All patients underwent clinical examination – blood tests, including complete blood count and inflammatory markers: erythrocyte sedimentation rate (ESR) and fibrinogen (Fb); standard chest X-ray and pulmonary function tests (lung volumes and flows, lung diffusion test).

Exercise capacity was assessed through a standard 6-minute walk test (6MWT, ERS/ATS Technical Standard, 2014[21]), and an incremental cardiopulmonary exercise test (CPET, ATS/ACCP Statement 2003[22]), using a cycle-ergometer. The predicted value for the six-minute walk distance (6MWD) was calculated using Enright and Sherrill equations[23] and peak oxygen uptake (peakVO_2) was calculated using Wasserman equation[24,25]. The results were expressed as percent predicted for both the 6MWD (6MWDpp) and peakVO_2 (peakVO2pp).

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 searched for relations between obesity, exercise capacity and systemic inflammation using bi-variate correlation tests. A p value of less than 0.05 was considered significant.

We split the patients into different groups, as follows: a) the overweight and mildly obese (BMI<35 kg/m^2) and those with moderate to severe obesity; b) men and women; c) subjects with low exercise capacity and those with normal exercise capacity; d) subjects aged less or more than 40. We searched for significant differences for the parameters of interest in these groups using Man Whitney U test.

Results and discussions

Thirty severe OSAS patients (23 men) were included. The cardio-respiratory polygraphy data are presented in **Table 1**. Twenty-nine patients had an estimated total sleep time (eTST) of more than 4 hours.

Baseline characteristics. Baseline characteristics are presented in **Table 2** and **Table 3**. Four patients were overweight, four patients were morbidly obese (BMI≥40 kg/m^2), the rest of the subjects having grade I or grade II obesity. **Eleven** patients had a significant smoking history (more than 5 pack-years), with two being active smokers, all with normal pulmonary function tests. Two patients with controlled type 2 diabetes mellitus were enrolled.

Table 1 Cardio-respiratory polygraphy data

Apnea Hypopnea Index (events/h)	58.8 [26-113.5]
Oxygen Desaturation Index (events/h)	46 [16.5-100]
Total estimated sleep time (eTST), min	410 ± 97.56
Median Average SpO_2 (%)	92 [78-96]
Time with SpO_2 < 90% (% eTST)	12.5 [0-76]

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

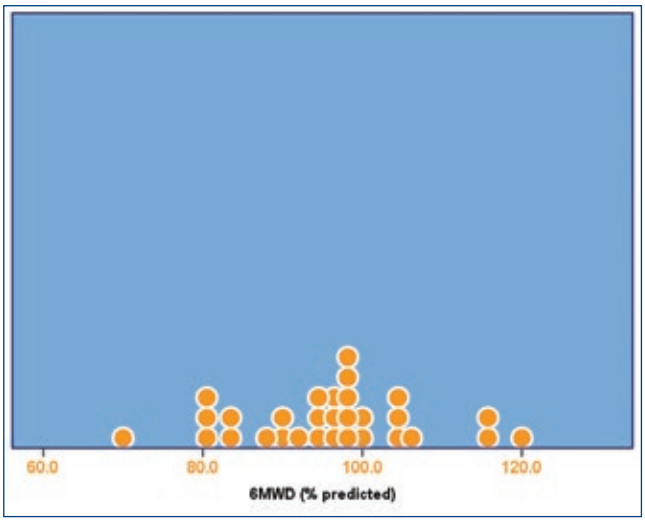

Figure 1. *Results of the 6MWT*

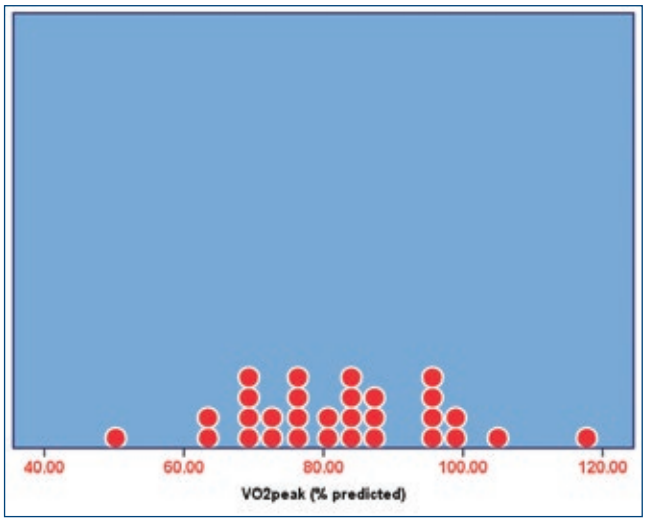

Figure 2. *Results of the Cardio-pulmonary Exercise Test*

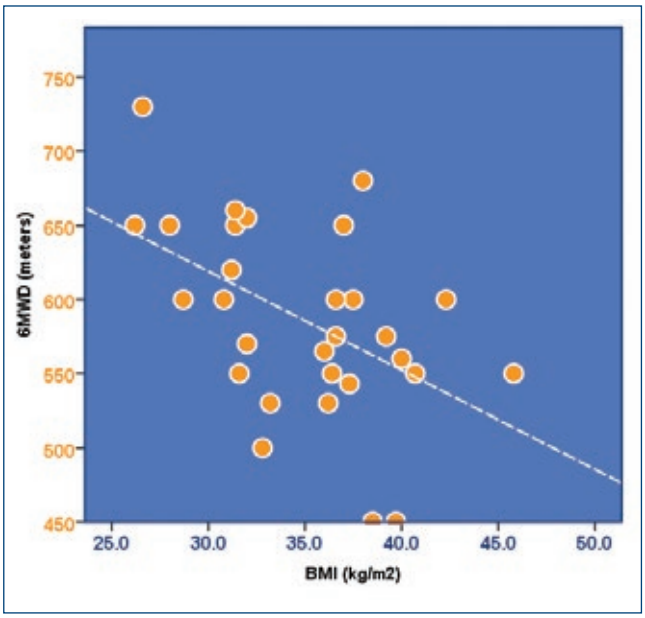

Figure 3. *Correlation between BMI and the 6MWD*

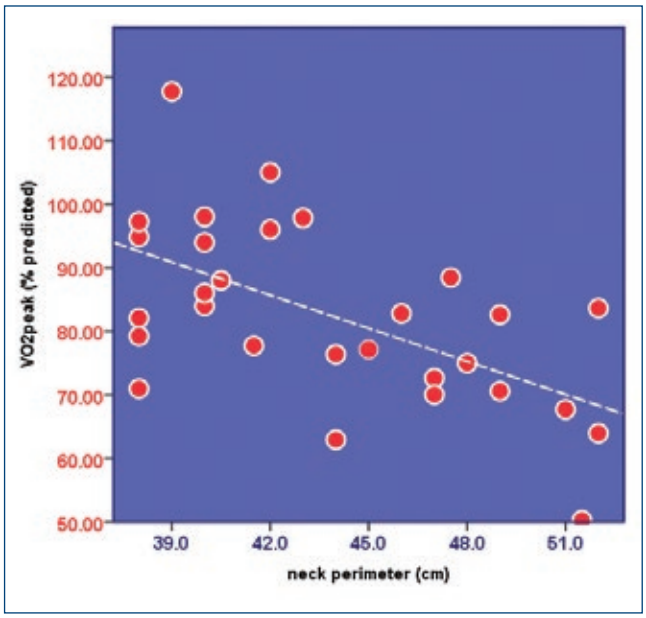

Figure 4. *Correlation between neck perimeter and peakVO2pp*

ESR and fibrinogen values were higher than the upper limit of normal in two cases (ESR >20 mm/1 hour, Fb>450 mg/dl), in the diabetic patients. In the rest of the patients, these parameters commonly used to assess systemic inflammation were in the normal range, despite the fact that subjects were obese and had severe OSAS. This suggests that in subjects without manifest cardiovascular or respiratory impairment, these classic parameters have a low accuracy in detecting systemic inflammation.

The Platelets to Lymphocytes Ratio (PLR) and Neutrophil to Lymphocytes Ratio (NLR) were in the normal range of reference values[26-28]. Six patients had NLR value of >3 and three of them also had a PLR >137.3, both cut-offs associated with higher risk of heart failure[29,30]. This findings weren't associated with a low exercise capacity at the 6MWT (all with normal 6MWDpp), but the maximal exercise capacity was impaired in four of them (low peakVO_2pp).

Exercise capacity was evaluated using the six-minute walk test and an incremental cardiopulmonary exercise test (CPET). All patients completed the tests without incidents.

The patient's physical performance at the 6MWT (6MWDpp) was lower than expected (<85% predicted value) in 6 subjects (20%) (**Figure 1**).

The maximal (peak) exercise capacity observed at the incremental CPET was lower than expected (VO_2 peak of less than 80% predicted value) in 14 subjects (46.66%) (**Figure 2**).

The exercise capacity data are showed in **Table 4**. The majority (28) of the patients ended the exercise test because of leg fatigue with only two cases of excessive increase in blood pressure (at 240/120 mmHg).

As we expected, according to data from literature, the 6MWT was less accurate in identifying patients with impaired exercise capacity than the CPET.

Table 2 Baseline characteristics – anthropometrical data and blood tests

Age (years)	45.27 ± 9.15
Male sex, no (%)	23 (76.6)
BMI (kg/m²)	34.92 ± 4.72
Neck circumference (cm)	43 [38-52]
Waist circumference (cm)	114 [95-157]
Hip circumference (cm)	118 ± 10.68
Waist to Hip Ratio (WHR)	1 [0.9-1.2]
Blood test	
Hemoglobin (g/dL)	15 [11.6-17.0]
Glucose (mg/dL)	90 [77-149]
ESR (mm/1h)	8 [1-39]
Fibrinogen (mg/dL)	336 [232-652]
Uric acid (mg/dL)	6.52 [3.9-9]
NeLy	2 [1-3.73]
PltLy	97.5 [55-166]
Total Cholesterol (mg/dL)	199 [143-277]
LDL Cholesterol (mg/dL)	126 [84-206]
HDL Cholesterol (mg/dL)	49 [33-60]
Triglycerides (mg/dL)	138 [64-410]

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

Correlations

When looking at the **entire group of patients**, we found significant negative correlations between **obesity and exercise capacity, as we expected**.

The absolute value of the 6MWD correlated with the BMI (r=-0.465, p=0.011) **(Figure 3)**. At the CPET, the peakVO_2pp negatively correlated with neck perimeter (r=-0.528, p=0.003) **(Figure 4)**, but not with waist or hip ratio. Self-reported diurnal somnolence (Epworth Sleepiness Scale Score) also had no correlation with OSAS severity and exercise capacity.

BMI had a significant negative correlation with the mean average nocturnal SaO_2 (r=-0.496, p=0.006), which represents the result of both intermittent hypoxemia induced by OSAS and continuous hypoxemia secondary to obesity-associated chronic hypoventilation.

The PLR was negatively correlated with obesity, especially with the neck perimeter (r=-0.559, p=0.003, **Figure 5**) and weight (r=-0.536, p=0.005). In severe OSAS, obesity seems to be less contributive to systemic inflammation than OSAS itself and/or other contributive factors (smoking, insulin-resistance).

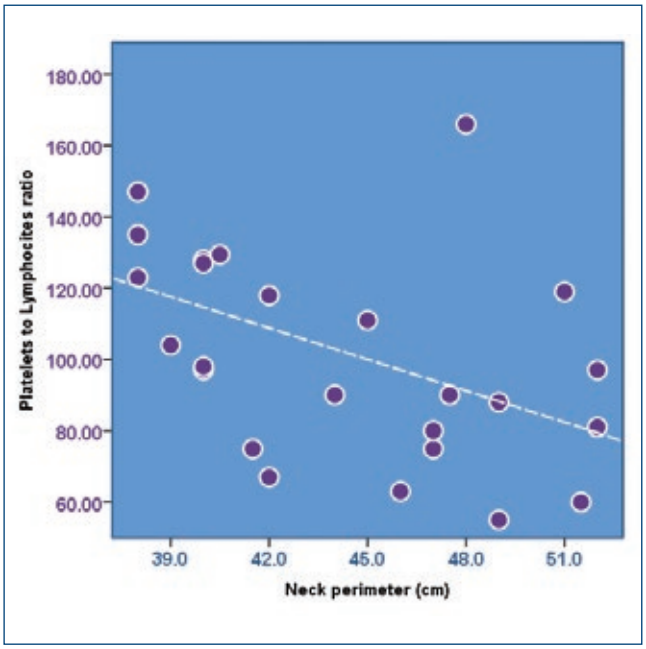

Figure 5. *Correlation between PLR and neck perimeter*

Peak exercise capacity (peakVO_2pp) was negatively correlated with OSAS severity (AHI, r=-0.474, p=0.008 and ODI, r=-0.472, p=0.010), which was not the case for the 6MWT (6MWDpp), probably due to the fact that more intense exercise is needed to reveal a subclinical cardiovascular impairment.

As expected, the maximal exercise capacity (peakVO_2pp) had a negative correlation with ESR and a positive one with the hemoglobin level.

Age had a positive correlation with markers of systemic inflammation, but only with ESR and Fb; the tobacco exposure and the fasting glucose level weren't correlated with those parameters. No correlation between PLR and OSA severity or maximal exercise capacity (peakVO_2pp) was found.

We also analyzed the impact of some characteristics of the studied subjects (age, sex) on the exercise capacity and systemic inflammation.

When comparing subjects according to age (less or more 40 years), we found that older patients had a better performance at the 6MWT (the difference between median values of 6MWDpp was 10%, p=0.025), despite the fact that the groups were similar in terms of BMI and OSAS severity. This could be explained by different response modalities to systemic inflammation.

When looking for gender-related differences, we found that women had a better exercise performance at the 6MWT (p=0.022), even though they had higher values of inflammatory markers (ESR, p=0.046, and PLR, p=0.019), possibly associated with older age and loss of hormonal protection (p=0.037). There was no significant difference in BMI between men and women.

When comparing the subjects according to the **exercise capacity** (e.g., the ability to achieve at peak exercise a VO_2 of more than 80% predicted value), the only parameter related to exercise tolerance was the oxygen desaturation index (ODI), a higher ODI being associated with lower exercise capacity. Median values of ODI in the two groups were: 36/hour in subjects with VO_2peak of >80% predicted, and 69/hour in subjects with VO_2peak of <80% predicted (Man-Whitney U = 52.5, n0=16, n1=14, p=0.024).

Conclusion

The study evaluated a selected OSAS population – e.g., subjects without clinically significant cardiovascular comorbidities. It was revealed that an important proportion of these subjects had a low exercise capacity. As we expected, the peak exercise performance (peakVO_2pp) correlated negatively with both obesity and OSAS severity. The submaximal exercise performance (6MWDpp) had a negative correlation with obesity and no correlation with OSAS severity, probably due to the fact that more intense exercise is needed to reveal a subclinical cardiovascular impairment. The CPET is more sensitive than the 6MWT in identifying incipient impairment of exercise capacity.

PLR (as marker of systemic inflammation) was higher in subjects with a lower BMI. So, in obese subjects with severe OSAS, obesity seems to be less contributory to systemic inflammation than OSAS itself and/or other factors (smoking, insulin-resistance). Systemic inflammation may not be the main mechanism of reduced exercise capacity in severe OSAS without clinically significant cardiovascular comorbidities, other mechanisms being probably involved (cardiac dysfunction). ■

Table 3 Baseline characteristics – lung function

Lung function tests	
FEV1 (L, %)	3.48 [2-5], **95** [76-126]
FVC (L, %)	4.1 [2-7], **94** [74-125]
TLC pleth (L, %)	7 [5-10.53], **103** [87-135]
DLCO (mmol/min/kPa, %)	9.23 [6-12.8], **88.6** [70-119]

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.

Table 4 Exercise capacity data

Six-minute walk test	
Six-minute walk distance (6MWD), m	575 [450-730]
Six-minute walk distance (%)	96 [70-119]
Cardiopulmonary exercise test	
peakVO2 (ml/min)	2099 [1206-3260]
peakVO2 (ml/min/kg)	20 [12.6-38]
peakVO2 % predicted	93.5 [68-132]
VO2 at the VT (% peakVO2)	66 [34 – 96]
Peak HR (bpm)	150 [112-185]
Peak HR % predicted	85.56 [64.74-100]
Peak oxygen pulse (ml O2/beat)	15 [10.8-20.73]
Peak oxygen pulse (% predicted)	93.8 ± 3.08
Peak RER	1.175 [0.87 – 1.76]

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

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