Cardiovascular Profile in Patients with Obstructive Sleep Apnea

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Abstract

Background: Obstructive sleep apnea (OSA) is a risk factor for several cardiovascular conditions including increased cardiovascular mortality. It is therefore essential to know the major cardiovascular effects of sleep-disordered breathing during a clinical evaluation.

Objective: To analyze the cardiovascular characteristics of patients with OSA.

Methods: Patients underwent baseline polysomnography and were consecutively selected from the database of the Sleep Institute between March 2007 and March 2009. All patients were instructed to attend the clinic for blood collection, physical examination, 12-lead electrocardiogram, spirometry, cardiopulmonary exercise testing on a treadmill and transthoracic echocardiography. The study was approved by the Research Ethics Committee and recorded at http://clinicaltrials.gov/ under number: NCT00768625.

Results: We analyzed 261 patients and 108 controls. The main characteristics of patients with OSA were: obesity, hypertension, low plasma levels of high density lipoprotein (HDL) and increased left atrial diameter compared with controls (3.75 ± 0.42; 3.61 ± 0.41, p = 0.001), respectively. These associated characteristics correspond to a 16.6 increase in the likelihood of OSA regardless of reporting any symptoms of this disorder, such as sleepiness or snoring

Conclusion: In the sample studied, the mostly found cardiovascular profile of patients with OSA was: obesity, hypertension, low plasma levels of HDL and left atrial diameter increased. (Arq Bras Cardiol 2011;96(4):293-299)

Keywords: Sleep apnea, obstructive; obesity; hypertension; dyslipidemia.

Introduction

The Obstructive Sleep Apnea (OSA) is a common condition caused by intermittent airway collapse during sleep resulting in repetitive hypoxia, awakening, poor sleep quality and excessive daytime sleepiness. OSA is a risk factor for several cardiovascular conditions including arterial hypertension[1,2], congestive heart failure[3], cerebral vascular accident[4], coronary arterial disease[5], metabolic syndrome[6] and cardiac arrhythmias[7]. OSA has been recently associated with increased cardiovascular mortality[8-10] in patients with severe disease without treatment. In addition, adequate treatment with CPAP (Continuous Positive Airway Pressure) may improve survival[8]. It is therefore essential to know the major cardiovascular effects of sleep-disordered breathing during a clinical evaluation.

Furthermore, a low rate of diagnosis performed by cardiologists is reported[11]. This can be partly explained by the fact that inventories of research on sleep disorders were not included in the cardiac evaluations and cardiovascular characteristics of these patients are still under investigation. Therefore, the purpose of this study is to analyze the cardiovascular profile of patients with OSA.

Methods

Population

Patients underwent baseline polysomnography and were consecutively selected from the database of the Sleep Institute between March 2007 and March 2009. Inclusion criteria were: aged over 30 years, sedentary, no recent hospitalization or changing medications. Exclusion criteria were: BMI > 40, chronic lung disease defined as FEV1/FVC below 0.7[12] during spirometry, smoking, serious systemic diseases and pregnancy. An apnea/hypopnea index (AHI) > 5 was considered diagnostic for OSA. The control group consisted of patients with AHI < 5. Patients were divided according to the AHI in: mild (5-15 events/h); moderate (15 to 30 events/h) and severe (> 30 events/h).

All participants were instructed to avoid caffeine and smoking and attend the service with eight hours of fasting for blood collection, physical examination, filling the

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Epworth Sleepiness Scale (ESS), 12-lead electrocardiogram, spirometry, cardiopulmonary exercise testing on treadmill and transthoracic echocardiography. The study was approved by the Research Ethics Committee of the *Universidade Federal de São Paulo* and recorded at http://clinicaltrials.gov/ under number: NCT00768625.

Polysomnography

Polysomnography was performed using the EMBLA™ digital system 17 channels, Medicare Medical Devices). The following variables were monitored: electroencephalogram (4 channels: C3-A2, C4-A1, O1-A2, O2-A1), electro-oculogram (2 channels: LOC-A2, ROC-A1), electromyogram (2 channels: chin and anterior tibial muscle), electrocardiogram (1 channel), snoring and body position sensor.

Airflow was monitored using a thermistor and cannula and the respiratory effort was monitored by thoracic and abdominal strapping. Oxygen saturation and pulse were recorded by pulse oximetry (Nonin™, model 9500, Plymouth, USA). All polysomnography tests were performed and analyzed by technicians according to the guidelines for sleep studies[13] and were reviewed by a doctor specializing in sleep physiology. Awakenings were defined according to the guidelines of the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association[14] and respiratory events were classified using criteria from the American Academy of Sleep Medicine[15].

Laboratory tests

We collected 30 ml of venous blood to determine the following parameters: Brain Natriuretic Peptide (BNP), blood count, erythrocyte sedimentation rate (ESR), fasting glucose, cholesterol fractions, triglycerides, urea, creatinine, sodium and potassium.

Cardiac evaluation

Patients and controls underwent cardiac evaluation, within three months after completion of polysomnography, including: physical examination, blood pressure, 12-lead electrocardiogram (ECG) and ankle-brachial index (ABI). The 12-lead ECG was carried out with baseline heart rate assessments and QT interval corrected for heart rate (QTc) using Bazett's formula. The ABI was obtained after 10 min rest in the supine position and systolic blood pressure was performed by Doppler in the ankle, tibial artery and brachial artery. The highest systolic blood pressure in each leg was then divided by the average systolic pressure in both arms. In case of a difference ≥ 10 mmHg between arms, the procedure was repeated, considering the average of the two measures.

Anthropometric parameters such as weight, height, waist circumference and Body Mass Index (BMI) were also obtained.

Cardiopulmonary exercise test on a treadmill

A subgroup of 70 non-obese men defined with a Body Mass Index (BMI) < 28 was selected and subjected to the cardiopulmonary exercise testing (ErgoPC13, Micromed™, Brasília, Brazil) with electrocardiographic monitoring, blood pressure and pulse oximetry (Nonin™ model 9500, Plymouth, USA) and the following variables were analyzed: oxygen consumption (VO_2), carbon dioxide production (VCO_2), ventilation per minute (VE), respiratory rate (RR) and tidal volume (TV) through a mask (Vista CPX™, Vacumed, Ventura, CA, USA).

Transthoracic echocardiography

All patients underwent two-dimensional transthoracic echocardiography (iE33 - Philips Electronics™ Netherlands), according to the guidelines of the American Society of Echocardiography[16]. Linear measurements of the end systolic and diastolic diameters of the left ventricle were obtained, as well as their ejection fraction, using the Teichholz method. Left atrial anteroposterior diameter was measured from the posterior edge of the aortic root wall to the posterior edge of the left atrium at the end of the ventricular systole in a parasternal longitudinal section.

Spirometry

Lung function tests were performed using a computerized spirometer (Koko™, Pulmonary Data Service Instrumentation, Inc., Louisville, KY, USA), following the recommendations in force[12] to exclude pulmonary disease. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were evaluated for each individual and recorded as absolute values and predicted percentage.

Statistical analysis

The results were presented as mean and standard deviation. The groups were compared using ANOVA and Chi square tests. Bonferroni post hoc test was applied when necessary. P value ≤ 0.05 was considered significant.

We used logistic regression to estimate odds ratios. The final model was applied to patients with moderate and severe OSA (AHI > 15), including the variables that remained significant after adjustment for confounding factors, such as: BMI, gender and age.

Results

The study enrolled 380 individuals. Eleven were excluded; two of them because of history of asthma; eight because of smoking; and one because of clinical suspicion of unstable angina. A total of 261 patients (AHI > 5) and 108 controls were analyzed.

The baseline characteristics of the population are presented in Table 1. There were no differences in age, sex, frequency of hypertension or diabetes. Patients with OSA had higher BMI (29.6 ± 5.9 27.1 ± 4.3) and waist circumference (98.7 ± 14.2; 91.0 ± 11.1) compared with the control group (p < 0.001), respectively.

The polysomnographic parameters are presented in Table 2. As expected, the AHI was higher in OSA patients compared with controls (28.0 ± 22.2 and 2.9 ± 1.4, respectively, p < 0.001). The percentage of REM sleep and stage 1 of NREM sleep differ between groups (patients: 96.9 ± 15.4, controls:

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Table 1 - Baseline characteristics of OSA and control group

	OSA (n = 261)	Control (n = 108)	p
Age (years)	52.03 ± 9.27	53.27 ± 7.21	0.20
Male	142	52	0.12
BMI	29.60 ± 5.92	27.08 ± 4.28	< 0.001
Neck circumference	37.08 ± 3.76	33.61 ± 3.73	< 0.001
Abdominal circumference	98.70 ± 14.20	91.00 ± 11.16	< 0.001
Hypertension (%)	42	37	0.15
Diabetes (%)	11	9	0.23

Table 2 - Polysomnographic parameters of OSA and control group

	OSA (n = 261)	Controls (n = 108)	p
AHI	28.02 ± 22.18	2.93 ± 1.40	< 0.001
Total sleep time (min)	349.18 ± 82.22	340.85 ± 85.11	0.38
Stage 1 (%)	5.34 ± 4.88	4.21 ± 3.14	0.02
Stage 2 (%)	57.76 ± 12.32	57.79 ± 10.69	0.98
Stage 3 and 4 (%)	18.29 ± 10.07	19.96 ± 9.21	0.13
REM (%)	96.92 ± 15.46	99.97 ± 5.87	0.05
Effectiveness of sleep %	80.91 ± 12.20	80.20 ± 12.03	0.64
Minimum saturation (%)	82.93 ± 1.40	89.43 ± 3.78	< 0.001
Average saturation (%)	92.35 ± 10.29	93.96 ± 8.81	0.21
Sleep latency (minutes)	19.34 ± 21.24	22.74 ± 25.68	0.19
REM Latency (minutes)	121.12 ± 73.27	104.80 ± 57.80	0.04

99.9 ± 5.9, p = 0.05 and patients: 5.3 ± 4.8; controls: 4.2 ± 3.1, p = 0.02, respectively).

Minimum saturation was lower in patients than controls (82.9 ± 1.4, 89.4 ± 3.8, respectively, p < 0.001). The REM latency was longer in patients with OSA than controls (121.1 ± 73.3, 104.8 ± 57.8, p = 0.04). OSA patients were characterized by high levels of systolic and diastolic blood pressure compared with the control group. The baseline heart rate, corrected QT interval and ABI did not differ (table 3).

Left atrial diameter was higher in OSA patients compared with controls (3.75 ± 0.42 and 3.61 ± 0.41, respectively, p = 0.001). Other echocardiographic parameters showed no significant differences.

Blood tests among groups are shown in Table 4. Glucose was higher in patients compared to controls (110.51 ± 30.79 and 103.24 ± 22.40, respectively, p = 0.002). Figure 1A shows the level of fasting glucose according to OSA severity. High-density lipoprotein (HDL) was lower in patients with OSA compared to controls (53.25 ± 11.43 and 56.80 ± 14.23, respectively, p = 0.001). Post hoc analyses showed again a significant difference between patients with severe OSA and controls (p = 0.001) and moderate OSA and controls (p = 0.002).

Figure 1B shows the levels of fasting glucose according to OSA severity. Cardiopulmonary exercise test was performed

Table 3 - Clinical characteristics of patients with OSA and controls

	AOS (n = 261)	Controles (n = 108)	p
Systolic blood pressure (mmHg)	136.32 ± 19.88	129.62 ± 15.17	0.001
Diastolic blood pressure (mmHg)	87.13 ± 12.90	81.12 ± 9.30	<0.001
Heart rate (bpm)	69.86 ± 10.98	72.70 ± 10.54	0.26
QT interval (ms)*	379.08 ± 42.33	377.50 ± 30.25	0.82
ABI	1.03 ± 0.32	1.05 ±0.15	0.35
Epworth Sleep Scale	10.37 ±6.08	8.94 ± 5.27	0.09

**Epworth Sleep Scale*

Table 4 - Analysis of blood between the groups

	AOS (n = 261)	Controles (n = 108)	p
Hemoglobin	14.93 ± 1.47	15.04 ± 2.31	0.55
Hematocrit	44.43 ± 15.04	44.62 ± 7.05	0.78
ESR	14.32 ± 13.79	13.61 ± 14.48	0.64
Glucose	110.51 ± 30.79	103.24 ± 22.40	0.002
Total cholesterol	210.54 ± 43.23	213.90 ± 40.32	0.48
LDL	129.86 ± 35.95	129.64 ± 32.84	0.95
HDL	53.25 ± 11.43	56.80 ± 14.23	<0.001
VLDL	27.47 ± 16.43	26.69 ± 12.53	0.66
Triglycerides	149.55 ± 91.03	145.02 ± 86.98	0.62
Creatinine	0.90 ± 0.20	0.93 ± 0.79	0.58
Urea	34.33 ± 9.58	33.01 ± 10.00	0.23
Sodium	140.49 ±2.32	140.63 ± 2.49	0.60
Potassium	4.24 ± 0.40	4.20 ±0.67	0.51
BNP	17.76 ± 16.22	14.31 ± 8.77	0.30

in 44 non-obese patients with OSA and 26 controls. There were no differences in age (51.13 ± 8.59, 48.16 ± 9.16, p = 0.18), BMI (25.49 ± 2.35, 25.27 ± 1.85, p = 0.69), systolic blood pressure (123.48 ± 14.74, 120.60 ± 11.30, p = 0.40), diastolic blood pressure (81.27 ± 8.93, 82.00 ± 8, 29, respectively, p = 0.74) or heart rate (78.41 ± 14.42, 79.64 ± 10.39, p = 0.71) between groups. The data related to peak exercise are presented in Table 5. There was no difference in the variables analyzed. Cases of myocardial ischemia or cardiac arrhythmias were not observed. Univariate associations between OSA and cardiovascular characteristics are presented in Table 6. Table 7 shows the odds ratio after adjusting for confounding factors.

Discussion

OSA is related to several pathophysiological mechanisms triggered by hypoxia[17-19] and sleep fragmentation[9,20,21]; including sympathetic activation[17,22], inflammation[23,24], endothelial dysfunction[25-27], change in coagulability[28], among

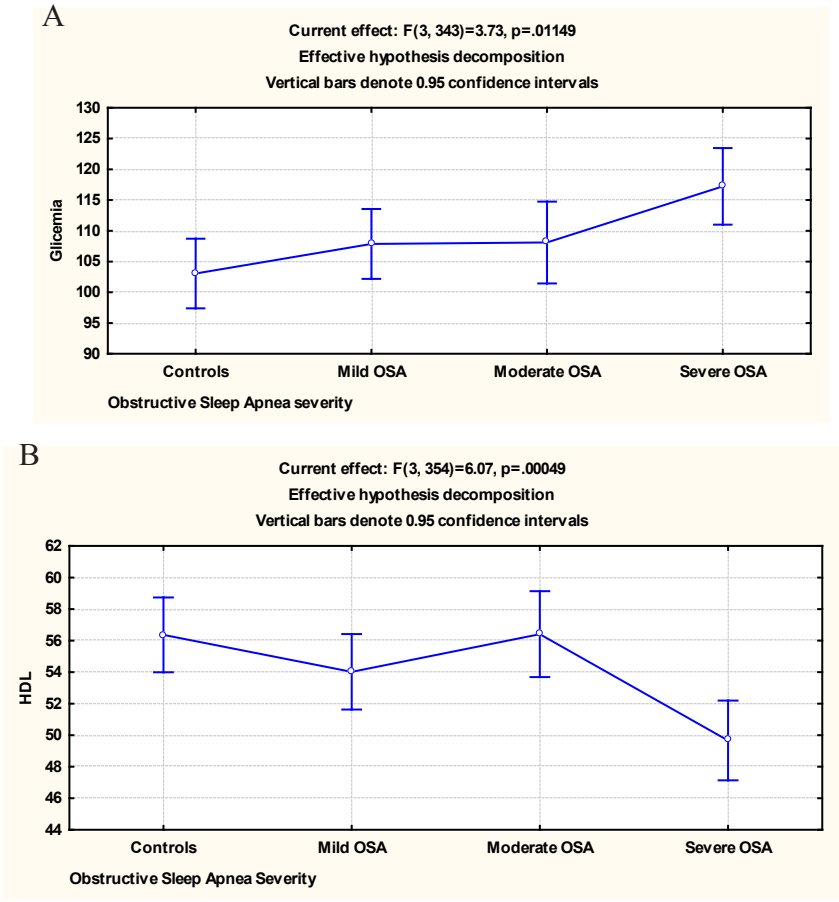

Figure 1 -Blood parameters according to OSA severity. (A) Fasting blood glucose in control, mild, moderate and severe OSA. (B) HDL level in all groups.

Table 5 - Exercise peak analysis in patients with AOS and controls

	OSA (n = 44)	Controls (n = 26)	p
Peak VO_2 (L/min)	36.02 ± 8.77	34.88 ± 8.26	0.60
Peak VCO_2	36.27 ± 11.16	35.81 ± 8.77	0.87
Peak SaO_2 (%)	94.38 ± 3.13	94.05 ± 3.09	0.75
Peak heart rate (bpm)	163.04 ± 14.49	168.36 ± 11.16	0.12
Peak systolic BP	183.37 ± 25.37	187.40 ± 24.62	0.52
Peak diastolic BP	82.79 ± 12.96	84.40 ± 8.81	0.58
O_2 Pulse (ml.min-1.beat -1)	16.04 ± 3.65	15.85 ± 4.62	0.87

others. These mechanisms may lead to cardiovascular outcome, such as hypertension[29], cardiac arrhythmias[30], metabolic syndrome[31] and heart failure[32]. Therefore, it is difficult to determine a single cardiovascular characteristic in patients with OSA.

This is the first study to assess both the cardiovascular characteristics in patients with OSA, including the individual contribution of each parameter analyzed, such as: clinical, anthropometric, echocardiographic and cardiopulmonary data. As a result, the cardiovascular profile of patients with OSA includes: obesity, hypertension, low plasma levels of HDL and increased left atrial diameter. Together, these characteristics correspond to 16.6 times more chances of OSA events, regardless of the investigation of any symptoms of this disorder (e.g., sleepiness or snoring).

As expected, the polysomnography variables differed between OSA and non-OSA individuals. OSA individuals had lower oxygen saturation and higher AHI, stage 1 of non-REM sleep and REM sleep latency. The latter is probably associated with decreased REM sleep in this group. Interestingly, the OSA group was not significantly sleepier than non-OSA individuals. We believe that a possible explanation for this finding is that the Epworth Sleepiness Scale (ESS) is not properly adapted to our population. However, the OSA group's average score was slightly above that of the non-OSA and was above the threshold value for sleepiness.

Hypertension is the most common consequence of OSA in clinical practice. Peppard et al[29] found a relationship between sleep-disordered breathing and hypertension,

Table 6 - Analysis of cardiovascular risk factors in patients with OSA (AHI > 15)

Cardiovascular risk	Measurement Unit	*Odds Ratio* (95% IC)	p
BMI (kg/m²)	Eutrophic(≤25)	1.0	
	Overweight (25.1 - 28)	1.9 (1.2 - 3.0)	<0.01
	Obese (≥ 28)	3.7 (2.3 - 6.1)	<0.01
Abdominal circumference (cm)	<102 for men <88 for women	1.0	
	>102 for men >88 for women	3.4 (2.4 - 5.0)	<0.01
HDL (mg/dl)	>40 for men >46 for womem	1.0	
	<40 for men <46 for women	3.0 (1.5 - 6.1)	<0.01
Blood glucose (mg/dL)	≤99	1.0	
	100 - 126	2.1 (1.4 - 3.1)	<0.01
	>126	2.6 (1.44 - 4.7)	<0.01
Hypertension	No	1.0	
	Yes	2.5 (1.7 - 3.5)	<0.01
Left atrial diameter (cm)	<4.0	1.0	
	≥4.0	2.4 (1.5 - 4.0)	<0.01

Table 7 - Multivariable model of cardiovascular risk for OSA (AHI>15)

Cardiovascular risk	Measurement Unit	Odds Ratio (95% CI)	p
BMI (kg/m²)	Eutrophic (≤ 25)	1.0	
	Overweight (25.1-28)	1.3 (0.7-2.5)	0.34
	Obese (≥ 28)	1.9 (0.9-3.7)	0.06
HDL (mg/dl)	> 40 for men > 46 for women	1.0	
	< 40 for men < 46 for women	2.7 (1.1-6.9)	0.03
Hypertension	No	1.0	
	Yes	1.8 (1.1-3.0)	0.01
Left atrial diameter (cm)	<4.0	1.0	
		1.8 (1.0-3.1)	0.03

after adjustment for habits, age, sex, smoking and alcohol use. Patients with light sleep and severe sleep-disordered breathing had about two to three times greater chances of having hypertension compared with individuals without apnea or hypopnea. In a case-control study[33], researchers studied the association between resistant hypertension and sleep disorders assessed by the Berlin Questionnaire and ESS, and showed that high risk for the diagnosis of OSA was highly associated with resistant hypertension.

However, when hypertension was considered in isolation, our results showed that the risk of a diagnosis of OSA increased only 1.8 times. Although hypertension is the most common consequence of OSA, obesity is a very common finding in these patients. Therefore, the possibility of OSA is reduced when the sample is adjusted. Low HDL cholesterol levels alone represent 2.7 times more chances for the OSA diagnosis. When the calculation takes into account high blood pressure and lower levels of HDL together, however, there is an increased likelihood of OSA by 4.8 times in our study, for both sexes.

The relationship between HDL-cholesterol and OSA has been studied. Tan et al[34] showed changes in HDL in patients with OSA, and AHI was the main determinant of this change. In experimental protocols, Savransky et al[35] investigated whether chronic intermittent hypoxia could induce atherosclerosis in mice. Nine out of ten rats exposed to intermittent hypoxia and a diet rich in cholesterol developed atherosclerotic lesions with significant increases in total cholesterol and LDL-cholesterol levels and a decrease in HDL-cholesterol levels. In turn, our findings were not replicated by other authors. Kono et al[36] found no differences in HDL-cholesterol levels in patients with OSA compared with controls.

Another interesting finding is the significant increase in left atrial diameter in individuals with OSA, compared with non-OSA individuals. The mechanisms involved in left atrial enlargement remain under investigation. Oliveira et al[37] reported an impairment in diastolic left ventricular function in patients with OSA who did not have hypertension. The increase in left ventricular filling pressure could hinder the left atrial emptying, which would eventually trigger a process of structural and functional remodeling in the left atrium. Orban et al[38] studied the acute changes in left cardiac diameters during a simulation of OSA using the Mueller maneuver. Sudden imposition of severe negative pressure led to a sharp decrease in left atrial volume and a reduction in left ventricular systolic performance. Repeated changes in chamber afterload and volumes may have increased the left atrial diameter in our group of patients, since the left atrial size can be regarded as a morphological expression of increased ventricular filling pressures, ventricle, which in turn is directly related to increased afterload[39]. Moreover, Khan et al.[40] retrospectively identified 47 OSA patients receiving CPAP who had echocardiogram performed before and after polysomnography. The left atrial volume did not decrease significantly ($p = 0.65$) with CPAP, whereas there was an increased cavity ($p < 0.006$) in patients who abandoned the treatment. Moreover, in the untreated group, increased left atrial volume was not associated with significant changes in blood pressure.

Anthropometric measurements showed a significant difference in BMI and waist circumference between groups. There is a growing debate about the role of obesity in OSA, with specific focus on whether obesity is part of the OSA syndrome. The odds ratio of obesity for OSA was 1.9, similar to hypertension. Thus, if the team of cardiologists examine the BMI alone, they could underestimate the suspicion of OSA. Importantly, the control group included individuals without OSA (AIH <5), which is considered a limitation of this study, once it could include some mild forms of sleep-disordered breathing.

In conclusion, a powerful single marker is unlikely to be found in a multifactorial disease like OSA. Thus, associations of characteristics such as obesity, hypertension, low plasma levels of HDL and increased LA diameter represent the cardiovascular profile of patients with OSA.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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