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EXERCISE CAPACITY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

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Obstructive sleep apnea syndrome (OSAS) is a common disease characterized by repetitive partial or complete closure of the upper airway during sleep. Cardiovascular disturbances are the most important complications responsible for increased morbidity and mortality. It is suggested that daytime somnolence, chronic fatigue, and nocturnal hypoxemia may further impair muscle function and decrease exercise fitness. The aim of this study was to evaluate cardiopulmonary response to exercise in OSAS patients. One hundred and eleven middle aged (50.2 ±10 yr), obese (BMI 31.0 ±4.6 kg/m^2) patients (109 M, 2F) with severe OSAS (AHI 47.2 ±23.1 h^{-1}) were enrolled into the study. OSAS was diagnosed with overnight polysomnography and a symptom-limited cardiopulmonary exercise test was performed on a treadmill using Bruce protocol. The results showed that the most frequent reason for exercise termination were: muscle fatigue and/or dyspnea (66%), increase in systolic blood pressure >220 mmHg (20%), ECG abnormalities, and chest pain (6%). Although the mean $\dot{V}_{O_2}$ peak was within the reference value (29.6 ±6 mlO_2/kg/min), in 52 patients (46%) $\dot{V}_{O_2}$ peak was <84% of predicted. Hypertensive response to exercise was diagnosed in 39 of patients (35%). Patients with severe sleep apnea (AHI≥40 h^{-1}) were characterized by higher mean blood pressure at rest, at 25%, 50% of maximal work load, at peak exercise and at post-exercise recovery. Several significant correlations between hemodynamic responses to exercise and sleep apnea severity were also noted. We conclude that exercise tolerance can be limited due to hypertensive response in about 20% of patients. Patients with severe OSAS have exaggerated hemodynamic response to exercise and delayed post-exercise blood pressure recovery. Cardiopulmonary response to exercise seems to be related to sleep apnea severity.

Key words: *arterial hypertension, cardiopulmonary exercise test, exercise tolerance, obstructive sleep apnea, oxygen uptake*

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common disease. Epidemiologic surveys estimate that this syndrome affects 4% of middle-aged males and 2% of females (1). OSAS is characterized by episodes of partial or complete closure of upper airways during sleep, despite increased respiratory effort. It is now well recognized that airflow obstruction is caused by a collapse of the upper airway soft tissue. Although the exact mechanisms responsible for the decrease in upper airway patency are not fully understood, it is known that disorders of respiration during sleep can be abolished with positive airway pressure (2) or bypassed with tracheostomy (3). Apneas and hypopneas during sleep result in decreased arterial oxygen pressure, increased carbon dioxide pressure, excessive sympathetic nervous system activation, increase in heart rate and blood pressure during disturbed breathing and arousals reestablishing ventilation. There are two main symptoms overshadowing clinical picture of OSAS: snoring and daytime somnolence. Snoring is usually very loud, disturbing sleep of the room-mate, who frequently observes repetitive respiratory arrests. The severity of snoring and the frequency of respiratory pauses increase in supine position and after alcohol consumption (4). The degree of daytime somnolence may vary from a tendency to fall asleep during monotonous activities to a significant medical condition compromising marital, social and professional life (5). Several recent studies indicate that sleepiness, chronic fatigue and cognitive impairment significantly increase the risk of motor vehicle accidents in sleep apnea patients (6). Many reports have also indicated that cardiovascular disturbances are the most important complications responsible for increased morbidity and mortality. It is suggested that OSAS patients are at increased risk of developing arterial hypertension, stroke and ischemic heart disease (7, 8). The underlying mechanisms linking disturbances of respiration during sleep and cardiovascular complications are not clearly defined. There is growing evidence that some homeostatic control mechanisms including baroreflex function (9), levels of circulating hormones regulating fluid volume (10), blood pressure response to hypoxia (11) vascular endothelium function (12), peripheral chemoreceptor and sympathetic nervous activity are altered in sleep apnea patients (13). Cardiopulmonary exercise testing (CPET) is frequently used to assess integrated response of cardiovascular, respiratory and muscular systems to graded physical exercise. Cardiovascular reactivity to exercise, especially heart rate and blood pressure response, was recognized as an important endpoint measure in many epidemiological studies. There are data suggesting that hypertensive response to exercise is independently associated with increased risk of future arterial hypertension and can be used in determining hypertension risk (14). Since one of the hallmarks of OSAS is obesity, patients can exhibit lung function abnormalities related to their weight. These functional alterations can lead to an increase in breathing work. Increased body weight is also associated with greater energy requirements during physical exercise, and this can further increase ventilatory

stress. Sleep apnea patients are also characterized by somnolence, fatigue and decreased daily activity which, together with nocturnal hypoxemia, can be responsible for muscle energy metabolism impairment and decreased exercise tolerance (15). The purpose of this study was to examine cardiopulmonary response to clinical exercise testing in a group of recently diagnosed OSAS patients.

MATERIAL AND METHODS

Subjects

The study material consisted of data obtained from 125 consecutive patients (123 males, 2 females) admitted to our Sleep Laboratory due to the signs and clinical symptoms suggestive of sleep apnea. Fourteen patients were excluded from the analysis because of incomplete polysomnographic or exercise data. Patients were excluded if they had a history of ischemic heart disease, metabolic, endocrine disorders, orthopedic or musculoskeletal limitations precluding vigorous exercise on a treadmill. We also did not enroll patients with body weight >120 kg due to technical limitations of the treadmill. Each patient gave written informed consent and the study protocol was approved by the institutional Ethics Committee at the Medical University of Warsaw.

Study protocol

Anthropometric data, including age, body mass index (BMI) were collected for each patient at the study entry. All patients underwent standard medical interview and physical examination with a special emphasis on sleep apnea risk factors and signs of comorbidities. In addition, all patients completed standardized sleep disorders questionnaire (16). Fasting blood samples for the determination of cholesterol and triglyceride tests, serum glucose and blood cell count were obtained. All patients also underwent spirometry (Lung Test 1000, MES, Cracow, Poland).

Sleep studies

Diagnosis of OSAS was confirmed by overnight polysomnography (SomnoStar 4250, SensorMedics, Yorba Linda, CA, USA or ALICE 4, Respironics Inc, Pittsburgh, PA, USA). Sleep studies were performed with standard instrumentation and procedures according to the guidelines of the American Academy of Sleep Medicine (17). Airflow through the nose and mouth was monitored with a thermistor. Airflow cessation for at least 10 s was termed an apnea. Hypopnea was diagnosed when there was a decrease in airflow greater than 50% lasting at least 10 s accompanied by a decrease in arterial oxygen saturation (SaO_2) ≥4% and an arousal. Sleep apnea severity indices used in our laboratory included the AHI (apnea + hypopnea index; number of apneas and hypopneas per hour of sleep), mean, minimum SaO_2 during sleep, percentage of total sleep time (TST) spent in apnea/hypopnea, total minutes and percentage of TST with SaO_2 >90%, 80-90%, and below 80%. We also calculated T_{90} (number of minutes of sleep with SaO_2 <90%), T_{90}%TST and number of desaturation events per hour of sleep (ODI).

Cardiopulmonary exercise testing

All subjects underwent maximal exercise on a treadmill using standard Bruce protocol in the morning hours. Ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$) was measured using a computer controlled breath-by-breath analyzer (Start 2000, MES, Poland).

Predicted value for oxygen consumption was calculated according to Wasserman et al (18). Predicted maximal heart rate was determined using following equation: 220-age. Anaerobic threshold (AT) was calculated by the V-slope method (18). The electrocardiogram and heart rate was monitored on a standard 12-lead tracing and SaO_2 was monitored continuously with a pulse-oximeter (Trident 400 HS, Trident Med, Warsaw, Poland). Blood pressure measurements using a cuff manometer (Arden, NC, USA) with stethoscope were taken every minute during the exercise and throughout 8 min of recovery. Mean arterial blood pressure (MAP) was calculated as one-third pulse pressure + diastolic pressure.

Two samples of arterial blood were also taken: at baseline and at exercise peak. The exercise test was terminated on patient's demand (symptom limited CPET) or when an increase in systolic blood pressure >220 mmHg, ischemic changes in any other indications for test discontinuation were noted (19). A hypertensive response to exercise was diagnosed when systolic and diastolic blood pressure were ≥210 and ≥105 mmHg, respectively (20).

Data analysis

Statistical analysis was performed using Statistica 7.1 data analysis software system (StatSoft Inc.). Results are given as means ±SD, unless stated otherwise. Inter-group differences were compared using independent *t*-tests or nonparametric U Mann-Whitney test, where appropriate. Correlations were analyzed with Spearman correlation coefficient. $P<0.05$ was considered to be statistically significant.

RESULTS

Table 1 presents descriptive characteristics of the study population *Table 2* shows the results of sleep studies, and *Table 3* shows the cardiopulmonary response to exercise.

The most frequent reason for exercise termination was muscle fatigue (n=55; 49%) and an increase in systolic blood pressure >220 mmHg (n=22; 19.8%). Other reasons, including severe dyspnea (n=19; 17.1%), ischemic changes in ECG, and chest pain (n=7; 6.3%) were less frequently encountered. Although the mean value for $\dot{V}_{O_2}$peak was within the normal range (85.3±17.8% of predicted), in 52 patients (46%) $\dot{V}_{O_2}$ peak was <84% of predicted with a mean

Table 1. Baseline characteristics of the patients.

VARIABLE	
Male/female (n)	109/2
Age (years)	50.2±10.0
BMI (kg/m^2)	31.0±4.6
FVC (% predicted)	106.9±18.1
FEV_1 (% predicted)	104.9±17.1
FEV_1%FVC	78.8±7.2
Smokers [n (%)]	43 (39)
Arterial hypertension [n (%)]	32 (29)

Table 2. Sleep study results.

VARIABLE	
AHI (h^{-1})	47.2±23.1
% of TST with disturbed breathing	32.3±17.8
Mean duration of apnea/hypopnea (sec)	24.7±6.2
Mean SaO_2 during sleep (%)	90.8±9.4
Minimum SaO_2 during sleep (%)	68.5±19.2
Desaturation index (h^{-1})	38.8±23.4
T_{90} (min)	95.4±87.3
T_{90} (%TST)	23.4±20.7

Table 3. Cardiopulmonary response to exercise.

VARIABLE	
$\dot{V}O_2$peak (ml/kg/min)	29.6±6
$\dot{V}O_2$peak (% predicted)	85.3±17.8
$\dot{V}CO_2$peak (l/min)	2.8±0.9
Anaerobic threshold (% $\dot{V}O_2$peak)	50.2±10.2
Minute ventilation at peak exercise (l/min)	91.2±24.7
Breathing reserve (%)	38.8±16
Respiratory quotient at peak exercise	1.03±0.14
PaO_2 at rest (mmHg)	77.4±10.3
$PaCO_2$ at rest (mmHg)	39.4±2.9
pH at rest	7.42±0.02
PaO_2 at peak exercise (mmHg)	93.7±10.9
$PaCO_2$ at peak exercise (mmHg)	37.9±5.3
pH at peak exercise	7.3±0.05
Heart rate at peak exercise (min^{-1})	157.6±20.7
Heart rate at peak exercise (% predicted)	92.5±10.3
Systolic BP at peak exercise (mmHg)	192.6±25.0
Diastolic BP at peak exercise (mmHg)	86.5±11.6
MAP at peak exercise (mmHg)	111.9±12.5

value of 70.3 ±10.3% of predicted (25.5 ±3.8 ml O_2/kg/min). Patients with decreased peak oxygen uptake did not differ from the others in terms of polysomnographic indices.

Hypertensive response to exercise was diagnosed in 39 of patients (35%). There were no differences in age, BMI, or sleep apnea severity indices between patients with the normotensive and hypertensive responses to exercise. Nor did we find any statistical difference in the distribution of arterial hypertension between the groups with normotensive and hypertensive responses to CPET. Chronotropic incompetence defined as a failure to increase heart rate at peak exercise to 80% of maximal predicted heart rate was found in 14 patients (12.6%). We did not observe any significant differences in sleep apnea severity between these patients and the remaining sample.

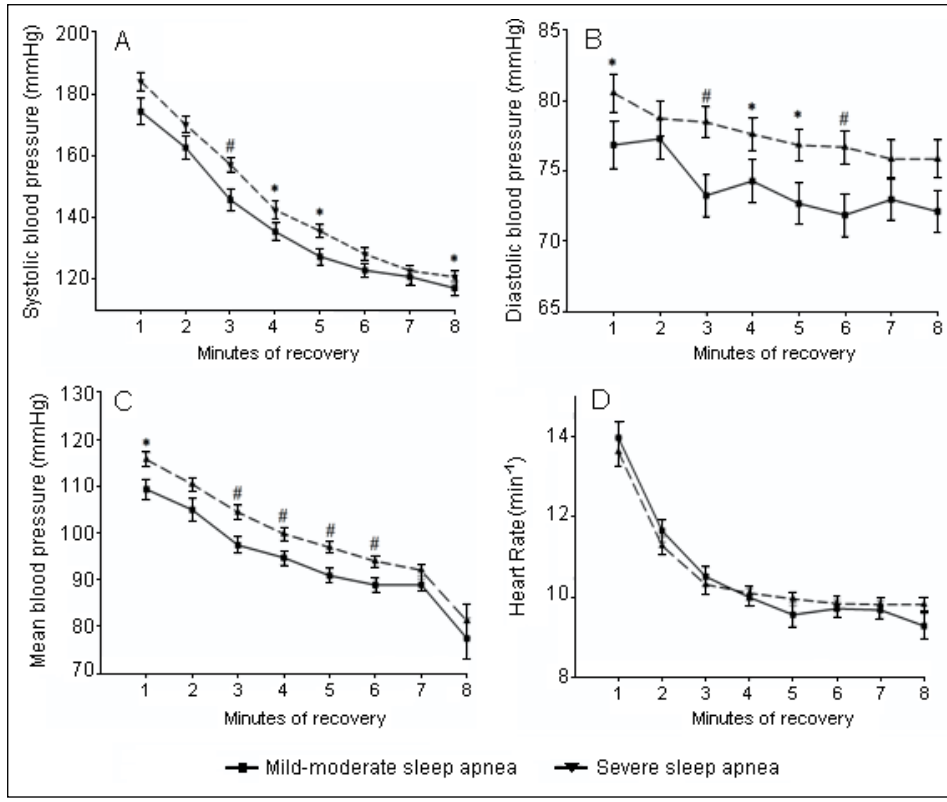

Fig. 1. Blood pressure and heart rate during post-exercise recovery: A - Systolic blood pressure; B - Diastolic blood pressure; C - Mean blood pressure; and D - Heart rate. Data are means ±SE; *P<0.05 and #P<0.01 for severe *vs*. mild-moderate sleep apnea.

Forty five patients (40.5%) were diagnosed with mild-moderate OSAS (AHI<40) and 66 patients (59.5%) with severe sleep apnea (AHI ≥40). Patients with severe sleep apnea patients were at similar age but their BMI was significantly higher compared with mild-moderate OSAS (29.1 ±3.8 *vs*. 32.2 ±4.7 kg/m^2, P<0.05).

Ventilatory response to exercise

Peak oxygen uptake in severe OSAS was insignificantly lower when compared with mild-moderate patients (29.1 ±6.5 *vs*. 30.3 ±6.8 ml O_2/kg/min; 82.3 ±18.1 *vs*. 89.7 ±16.5%). Severe OSAS patients had significantly increased breathing frequency (35.4 ±9.4 *vs*. 31.2 ±7.5 min^{-1}; P<0.05) and lower tidal volume at peak exercise (2.6 ±0.5 *vs*. 2.9 ±0.7 l; P<0.05). However, there were no differences in minute ventilation and breathing reserve between the patients with mild-moderate and severe sleep apnea at peak exercise.

Table 4. Comparison of cardiorespiratory responses to exercise between the patients with severe and mild-moderate sleep apnea.

VARIABLE	Severe OSAS	Mild-moderate OSAS	P
BASELINE			
Heart rate (min^{-1})	85.9±11.7	81.2±13.5	<0.05
Systolic BP (mmHg)	130.3±15.3	123.3±15.2	<0.05
Diastolic BP (mmHg)	84.5±10.0	80.1±9.1	<0.05
Mean BP (mmHg)	99.8±10.5	94.5±9.4	<0.05
25% OF WORK LOAD			
Heart rate (min^{-1})	110.4±12.4	108.8±13.2	ns
Systolic BP (mmHg)	152.9±14.9	146.2±12.7	ns
Diastolic BP (mmHg)	84.8±9.7	80.4±9.5	ns
Mean BP (mmHg)	107.5±10.1	102.3±8.4	<0.05
50% OF WORK LOAD			
Heart rate (min^{-1})	127.5±14.8	125.4±15.9	ns
Systolic BP (mmHg)	173.5±19.2	164.0±15.4	<0.05
Diastolic BP (mmHg)	87.8±11.7	81.3±9.7	<0.05
Mean BP (mmHg)	116.4±12.5	108.8±9.2	<0.05
75% OF WORK LOAD			
Heart rate (min^{-1})	143.7±20.1	145.8±17.8	ns
Systolic BP (mmHg)	182.5±18.2	176.5±16.4	ns
Diastolic BP (mmHg)	88.1±9.2	83.6±9.7	ns
Mean BP (mmHg)	119.5±9.7	114.6±9.4	ns
PEAK EXERCISE			
Heart rate (min^{-1})	155.9±19.0	159.2±18.8	ns
Heart rate (% predicted)	91.2±9.7	94.3±10.9	<0.05
Systolic BP (mmHg)	198.3±18.2	191.9±24.0	ns
Diastolic BP (mmHg)	88.9±12.0	83.0±9.5	<0.05
Mean BP (mmHg)	125.4±12.2	116.6±21.6	<0.05

Cardiorespiratory response to exercise

Cardiorespiratory responses to exercise are presented in *Fig. 1* and *Table 4*. Resting heart rate was significantly correlated with AHI (r=0.29; P=0.002), ODI (r=0.23, P<0.05) and T_{90} (r=0.34; P=0.0004). Heart rate at peak exercise expressed in beats/minute and as a percentage of age adjusted maximum heart rate was positively correlated with mean SaO_2 during sleep (r=0.28, P=0.004 and r=0.21, P<0.05 respectively). Significant correlations between resting systolic, diastolic and mean arterial blood pressure and AHI, ODI, T_{90} were also observed (data not shown). Diastolic blood pressure at peak exercise was correlated with AHI (r=0.23; P<0.05), ODI (r=0.25; P<0.05) and T_{90} (r=0.20; P<0.05). Mean arterial blood pressure at peak exercise was correlated with AHI (r=0.23; P<0.05) and ODI (r=0.25; P<0.05). Systolic, diastolic, and mean blood pressure at 50% of work load also correlated with AHI (*Fig. 2*). Additionally, significant correlations between diastolic blood pressure and MAP at 50% of work load and both, ODI, and T_{90} were also noted.

Table 5. Correlations between sleep apnea severity and cardiorespiratory changes during recovery phase.

VARIABLES		r	P
AHI	MAP at 1st min	0.26	<0.05
	MAP at 3rd min	0.27	=0.004
	MAP at 4th min	0.27	=0.004
	MAP at 5th min	0.23	<0.05
	MAP at 6th min	0.27	=0.005
	Heart rate at 5th min	0.23	<0.05
T_{90}	MAP at 2nd min	0.22	<0.05
	MAP at 4th min	0.35	<0.001
	MAP at 6th min	0.35	<0.001
	MAP at 7th min	0.35	<0.001
	MAP at 8th min	0.30	=0.002
	Heart rate at 4th min	0.24	<0.05
	Heart rate at 5th min	0.32	=0.001
	Heart rate at 6th min	0.25	<0.05
ODI	MAP at 4th min	0.25	<0.05
	MAP at 5th min	0.26	<0.05
	Heart rate at 4th min	0.28	0.006
	Heart rate at 5th min	0.28	0.005

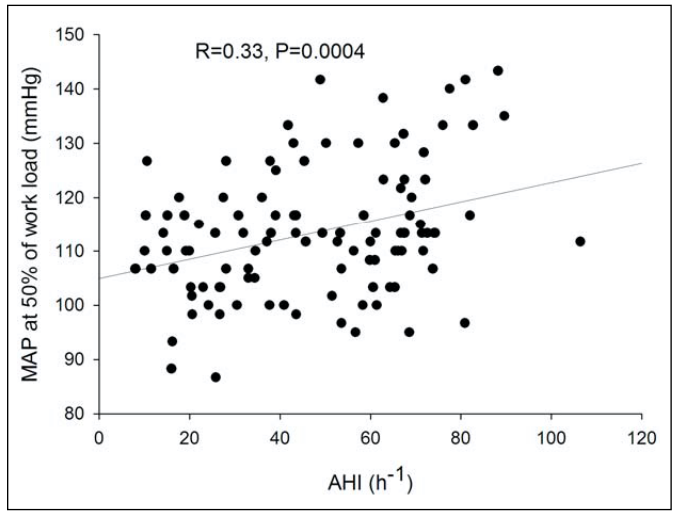

Fig. 2. Correlation between mean arterial blood pressure (MAP) and apnea-hypopnea index (AHI).

Blood pressure and heart rate recovery

Blood pressure decline during 8 min of the recovery phase after exercise was significantly slower in severe sleep apnea compared with mild-moderate sleep apnea (*Fig. 1*). *Table 5* presents significant correlations between the markers of sleep apnea severity and cardiorespiratory changes during the recovery phase.

DISCUSSION

The present study provides evidence suggesting that obstructive sleep apnea can result in decreased exercise tolerance and augmented cardiovascular response to exercise. Our main findings are:

- in about 40% of patients a decrease of $\dot{V}_{O_2}$ peak to <84% can be expected
- an excessive increase in blood pressure can be a factor limiting exercise capacity in 20% of sleep apnea patients
- severe sleep apnea is associated with augmented blood pressure response to exercise and delayed decline in arterial blood pressure during post-exercise recovery.

In general, factors that may contribute to exercise limitation in OSAS patients include leg weakness, dyspnea, cardiac dysfunction, abnormalities of respiratory mechanics, respiratory muscle dysfunction, arterial hypoxemia, lack of fitness, and other factors like motivation and peripheral vascular disease. In nearly 50% of our subjects CPET was terminated due to muscle fatigue and this can be associated with lack of fitness resulting from sleepiness, chronic tiredness and decreased daily activity (21). The ability to perform physical exercise can be further decreased in sleep apnea patients as a result of muscle energy metabolism impairment. Vanuxem et al (15) have suggested that the very important factor limiting exercise tolerance in OSAS is an abnormal glycolityc metabolism and a defect in oxidative metabolism of exercising muscles. Recently Bonnani et al (22) also have suggested a primary impairment in muscle oxidative metabolism in sleep apnea patients, possibly caused by muscle adaptation to nocturnal hypoxemia.

It seems that ventilatory limitation of exercise tolerance can be ruled out in our patients. There are at least three factors making a limitation of pulmonary origin unlikely: resting spirometry was in our patients within normal range, there were no signs of arterial hypoxemia at peak exercise, and the mean value of breathing reserve (38.8%) was greater than the theoretical inferior limit of 30% proposed by other authors (18, 23). Increased frequency of breathing and decreased tidal volume at peak exercise in severe sleep apnea can be caused by decrease in lung compliance due to obesity (24). The mean value of oxygen consumption obtained in our patients (29.6 ±6 ml/kg/min) was higher than the value reported by Kaleth et al (25) (21.9 ±0.8 ml/kg/min), Lin et al (26) (21.6 ±3.3), and only slightly higher than reported by Vanuxem et al (15) (26.4 ±1.2 ml/kg/min). These differences can be attributed to the methodology: our patients performed CPET on a treadmill and due to activation of different muscle groups peak oxygen uptake on a treadmill is approximately 5-10% higher than during cycling (27). Much larger population enrolled to our study could (111 *vs*. 11) could have also played a role.

Previous reports also have suggested altered hemodynamic response to exercise in obstructive sleep apnea (25, 26, 28-30). In general, the present study supports those observations. The prevalence of chronotropic incompetence was much lower than reported by Grote et al (28) (12.6% *vs*. 26.4). On the other

hand, significantly lower age adjusted maximum heart rate in severe sleep apnea (91.2 ±9.7%), compared with mild-moderate sleep apnea (94.3 ±10.9%), provide further evidence for blunted chronotropic response to graded exercise, what is consistent with other reports (25, 28, 31). The reasons for decreased chronotropic response to exercise in OSAS patients are not clear. It is suggested that the main causative factor is impaired cardiovascular autonomic function resulting from structural downregulation of cardiac ß-receptors and/or altered baroreflex set-point (25). Statistically significant correlations between heart rate at peak exercise and mean SaO_2 during sleep suggest relationship between nocturnal hypoxemia and chronotropic incompetence in OSAS. This is a very important observation because there are reports on the association between blunted heart rate response at 40-100% of maximal workload and increased risk of death due to cardiovascular diseases (32).

An important finding in the current study was that severe sleep apnea patients are characterized by increased arterial blood pressure during resting condition, early phase of exercise on a treadmill, at peak exercise and post-exercise recovery. It is noteworthy that, in contrast to Tryfon et al (29), we did not observe significant increases in diastolic blood pressure at peak exercise. In our group, out of the 111 patients only in 26 (23%) diastolic blood pressure exceeded 100 mmHg and in only 4 the peak diastolic blood pressure was >110 mmHg. Tryfon et al (29) found that diastolic blood pressure at peak exercise was >100 mmHg in 17 out of 17 patients and it was ≥110 mmHg in 14 out of 17 sleep apnea patients.

There are few literature data on recovery of hemodynamic variables after the exercise test. A tendency for normalization of arterial blood pressure was also noted by Kaleth et al (25), although the authors have reported changes only for 2 min after exercise termination. In the present study we showed that MAP in severe sleep apnea is higher at 6 min of recovery, compared with mild-moderate sleep apnea. Since some of the observed differences were still significant in a subgroup of normotensive OSAS patients, it seems that these differences are associated with sleep apnea *per se* and not with arterial hypertension. In a study by Matthews et al (14), the presence of an exaggerated blood pressure response to exercise accounted for nearly one third of the overall risk of developing arterial hypertension. The hypertensive response to physical exercise on a treadmill can provide additional information about additional risk factors in sleep apnea patients. Several authors suggest that delayed blood pressure recovery after exercise can be associated with greater likelihood of ischemic heart disease (33). Therefore, better understanding of the influence of sleep apnea on hemodynamic response to exercise can help prevent cardiovascular events in this group of patients.

Significant correlations between the blood pressure response during graded exercise and sleep apnea severity suggest the existence of a relationship between exaggerated blood pressure response during exercise, delayed normalization of arterial blood pressure during post-exercise recovery and respiratory disturbances with hypoxemia during sleep.

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