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SCIENTIFIC INVESTIGATIONS

Vascular Response During Mental Stress in Sedentary and Physically Active Patients With Obstructive Sleep Apnea

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Study Objectives: To compare vascular function of sedentary (SED) versus physically active (ACTIVE) patients with obstructive sleep apnea (OSA) during rest and mental stress.

Methods: Patients with untreated OSA without other comorbidities were classified into SED and ACTIVE groups according to the International Physical Activity Questionnaire. Blood pressure (BP), heart rate (HR), forearm blood flow (FBF) (plethysmography), and forearm vascular conductance (FVC = FBF / mean BP × 100) were continuously measured at rest (4 minutes) followed by 3 minutes of mental stress (Stroop Color Word Test).

Results: We studied 40 patients with OSA (men = 24, age = 50 ± 1 years, body mass index = 29.3 ± 0.5 kg/m^2, apnea-hypopnea index = 39.3 ± 4 events/h). Leisure time physical activity domain in SED (n = 19) and ACTIVE (n = 21) was 20 ± 8 and 239 ± 32 min/wk, ($P < .05$). Baseline profile and perception of stress were similar in both groups. Baseline FBF (3.5 ± 0.2 mL/min/100 mL versus 2.4 ± 0.14 mL/min/100 mL) and FVC (3.5 ± 0.2 U versus 2.3 ± 0.1 U) were significantly lower in the SED group than in the ACTIVE group, respectively ($P < .05$). HR and BP increased similarly during mental stress test in both groups. Changes during mental stress in FBF (0.65 ± 0.12 versus 1.04 ± 0.12) and FVC (0.58 ± 0.11 versus 0.99 ± 0.11) were significantly lower in the SED group than in the ACTIVE group, respectively ($P < .05$). There was a significant correlation between leisure time physical activity and FBF ($r = .57$, $P < .05$) and FVC ($r = .48$, $P < .05$) during mental stress.

Conclusions: The vascular response among patients with OSA is influenced by the level of physical activity. A high level of physical activity may partially protect against the cardiovascular dysfunction associated with OSA.

Keywords: forearm blood flow, forearm vascular conductance, mental stress, obstructive sleep apnea, physical activity

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Leisure time physical activity is associated with vascular benefits in several diseases. However, the effect of physical activity on vascular function at rest and during stress in patients with obstructive sleep apnea is unknown.

Study Impact: Among patients with moderate to severe obstructive sleep apnea and no comorbidities, moderate physical activity during leisure time (approximately 4 h/wk) is associated with better vascular function at rest and during stress than in sedentary patients. Physical activity may protect vascular function in patients with obstructive sleep apnea.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep,[1] futile efforts to breath during the obstructive events, oxygen desaturation, and arousals from sleep.[2] Previous studies showed that as compared with healthy individuals, patients with OSA have compromised vascular function as observed by flow-mediated dilatation in the brachial artery.[3,4] The endothelial dysfunction in OSA could be explained by intermittent hypoxemia and reoxygenation during sleep associated with enhanced generation of superoxide free radicals, sympathetic nervous system stimulation, augmented systemic inflammation, or enhanced expression of adhesion molecules.[5] Impaired endothelial function is associated with development of atherosclerosis[6] and increased risk of future cardiovascular events.[7] Epidemiological research indicates that OSA is associated with increases in the incidence and progression of coronary heart disease, heart failure, stroke, and atrial fibrillation.[7,8]

In addition to OSA, mental stress also represents an important risk factor for cardiovascular morbidity and mortality.[9] Mental stress causes an acute increase in sympathetic nerve activity,[10] heart rate, and blood pressure.[11] A study including healthy subjects demonstrated that the harmful effects after 5 minutes of stress are noticeable for the next 90 minutes.[12] Previous studies have shown that mild mental stress in obese subjects[13] and metabolic syndrome[5] are associated with impaired endothelial function, as reflected by the decrease in forearm blood flow and flow-mediated dilation.

There is growing evidence that physical exercise may decrease OSA severity and improve cardiovascular function. Increases in blood flow velocity and shear rates are the main physiological stimuli for the beneficial adaptations in endothelial structure and function induced by physical exercise that provides an important stimulus for vasodilation of conduit arteries during exercise.[14] Regular physical activity has also been shown to be beneficial to the vascular wall in individuals with hypertension[15] and increases forearm blood flow in patients with congestive heart failure and sleep-disordered breathing when compared with baseline values.[16] A previous study also demonstrated that one session of aerobic exercise prevented a reduction in the flow-mediated dilation induced by mental stress among subjects with metabolic syndrome.[17] Regular physical activity was effective in increasing forearm vascular conductance during a mental stress test in obese women compared with controls.[18] However, there is little information about the influence of physical activity on vascular function in patients with OSA and no comorbidities during stress conditions. The aim of this study was to compare vascular function at rest and during mental stress in sedentary and physically active patients with moderate to severe OSA and no other comorbidities. We hypothesized that the vascular response is impaired during mental stress in sedentary compared with physically active patients.

METHODS

Patients

Male and female individuals, 40 to 65 years of age in whom OSA was recently diagnosed as defined as apnea-hypopnea index (AHI) ≥ 15 events/h by complete nocturnal polysomnography, were considered for the study. Patients with body mass index (BMI) > 40 kg/m^2, smoking or alcohol abuse (2 or more drinks/d), cardiopulmonary disease, chronic renal disease, diabetes mellitus, a history of psychiatric disorders, any OSA treatment, shift workers, resting blood pressure (BP) higher than 140/90 mmHg, use of medicines that affect sleep and the vascular system, less than 2 years of formal education, and any sleep apnea treatment were excluded from this study. Because hormonal variability during the regular menstrual cycle may affect BP and the perception of stress, all nonmenopausal women were studied between the first and the fifth day after the onset of menstruation. This study was approved by the ethics committee and research on human subjects at the University of São Paulo (CAAE: 43676515.1.0000.5390). All subjects gave written informed consent.

Sleep Analysis

Sleep stages, apneas, hypopneas, and arousals were defined and scored according to American Academy of Sleep Medicine guidelines.[19] Apnea was defined as a ≥ 90% drop of respiratory amplitude, lasting at least 10 seconds. Hypopnea was defined as a 50% drop of respiratory amplitude, lasting at least 10 seconds, associated with oxygen saturation drops ≥ 3% (absolute criteria) or at least 30% drop of respiratory amplitude, lasting at least 10 seconds, associated with oxygen saturation drops ≥ 4% or arousals (alternative criteria). The AHI was calculated based on the total number of respiratory events (apneas and hypopneas) per hour of sleep. Obstructive apnea was defined as a cessation of respiratory airflow for 10 seconds with thoracoabdominal effort, which was detected by using a piezo respiratory effort sensor. The average time from the diagnosis of OSA to enrollment in the research study was 1 month for all participants.

Brachial Blood Pressure

Clinical BP readings were obtained from the left arm of subjects while seated, after 5 minutes of quiet rest, with a mercury sphygmomanometer. All subjects had at least three office BP measurements obtained on separate occasions taken by one investigator. Systolic and diastolic BP was recorded at the first appearance and disappearance (phases I and V, respectively) of Korotkoff sounds. The subjects were classified as normotensive if the average systolic and diastolic BP levels were ≤ 140 or 90 mmHg.

Anthropometric Measures

Body weight (in kilograms) was measured by digital scale with 50-g precision and a 200-kg capacity. Height was measured using a Sanny stadiometer with 0.1-cm precision. Body composition was measured by bioelectrical impedance (Quantum II, RJL Systems, Clinton Township, Michigan, United States). Briefly, two signaling electrodes were placed on the dorsal surface of the right foot between the second and third toe, as well as the dorsal surface of the right hand between the second and third digits. Two sensor electrodes were placed on the right hand and right ankle. Participants were asked to remain motionless in the supine position with legs and arms slightly abducted so there was no contact between the extremities and torso. Data output included reactance, resistance, and impedance. Data were entered into the software program provided by the manufacturer (Cypress, RLJ Systems). Data output included body fat mass (%) and fat-free mass (%).

Level of Physical Activity

The physical activity level was evaluated using the International Physical Activity Questionnaire (IPAQ) that allows estimation of the weekly time spent in moderate, intense physical activity and walking in various areas of everyday life: domestic, work, transportation, leisure, and also the time that a person remains seated.[20] IPAQ was previously validated in a Brazilian sample[20] and showed a significant and high correlation (r = .71). In this previous study, the reliability of IPAQ was determined after 7 days, and the Spearman correlation was significant and high (rho = .69–.71, P < .01).

In the current study, patients with a physical activity time < 30 min/wk were considered insufficiently active so were included in the sedentary (SED) group, and patients with physical activity time ≥ 150 min/wk including moderate or vigorous physical activity (≥ 3 d/w and ≥ 30 min/exercise session) were included in the physically active (ACTIVE) group.

Experimental Protocol

The study was performed in a quiet, temperature-controlled room (21°C to 22°C), with the subjects in the supine position

Table 1—Baseline characteristics and physical activity level in sedentary and physically active patients with obstructive sleep apnea.

	SED (n = 21)	ACTIVE (n = 19)	*P*
Sex (male/female)	16/5	8/11	.06
Age, years	48 ± 1	52 ± 1	.08
Weight, kg	85 ± 2	77 ± 2	.08
Body mass index, kg/m^2	29 ± 0.81	29 ± 0.70	.53
Fat mass, %	26 ± 1	26 ± 1	.94
Education, years	13 ± 1	12 ± 0.8	.46
Leisure time physical activity, min/week	20 ± 8	239 ± 32	.01*
Cardiovascular parameters			
Heart rate, beats/min	81 ± 3	83 ± 2	.57
Systolic BP, mmHg	120 ± 2	118 ± 2	.49
Diastolic BP, mmHg	78 ± 1	78 ± 1	.97
Mean BP, mmHg	102 ± 2	98 ± 1	.19
FBF, mL/min/100 mL	1.74 ± 0.08	2.47 ± 0.19	.01*
FVC, U	1.70 ± 0.07	2.53 ± 0.30	.01*

Values are means ± standard error. * = *P* < .05, SED versus ACTIVE. Sex was tested by χ^2 test; other values were tested by unpaired Student *t* test. Sex was not significantly different among groups. There was no significant difference in age, weight, body mass index, body fat, and education. Leisure time physical activity was higher in the ACTIVE compared with the SED group. Heart rate and brachial systolic and diastolic BP were not significantly different among groups. The baseline FBF and FVC were higher in the ACTIVE group compared with the SED group. ACTIVE = physically active group, BP = blood pressure, FBF = forearm blood flow, FVC = forearm vascular conductance, SED = sedentary group.

in the morning at approximately the same time each day. The variables described below were continuously measured during 4 minutes at rest followed by 3 minutes of a mental stress test.

Hemodynamic Variables

Heart rate (HR) was continuously measured by electrocardiography. BP was monitored noninvasively with an automatic BP cuff on the nondominant ankle with an automatic oscillometric device (DX 2022, Dixtal Biomédica e Tecnologia, Manaus, Amazonas, Brazil). The systolic, diastolic, and mean BP was recorded every minute of the mental stress test.

Forearm Blood Flow

Venous occlusion plethysmography (AI6, Hokanson, Bellevue, Washington, United States) was used to determine forearm blood flow, as previously described.[21] Briefly, the nondominant arm was elevated above the heart level. A suitable strain gauge (Hokanson) was placed around the forearm and connected to a plethysmograph. An inflating cuff (SC12D, Hokanson) was placed around the participant's bicep to occlude venous blood flow and connected to a rapid cuff inflator (Hokanson). To exclude hand circulation, which contains a large number of arteriovenous shunts, a segmental pressure cuff (TMC7, Hokanson) was placed around the wrist and inflated to supra-arterial pressure immediately before testing commenced. At 20-second intervals, the upper arm cuff was inflated above venous pressure for 10 seconds. Baseline forearm blood flow (FBF) was then recorded continuously for 4 minutes at baseline and during the 3-minute period of the Stroop Color Word Test (SCWT). Each minute of the FBF was determined based on three separate readings. Forearm vascular conductance (FVC) was calculated (FBF / mean BP × 100).

Mental Stress Test

The mental stress test was performed after resting baseline using a modified version of the SCWT conducted for 3 minutes. Briefly, during the SCWT, patients were shown a series of names written with different colors of the specified word. The subjects were asked to identify the color of the ink and not read the written word. If the patient took more than 3 seconds to speak the next word, the subject received a standard verbal incentive to continue the test. At the conclusion of the protocol, each participant was asked about a perception of the stress experienced, using a scale from 0 to 5 (0: not stressful, 1: very mild stress, 2: mild stressful, 3: moderately stressful, 4: very stressful, and 5: extremely stressful).[10]

Statistical Analysis

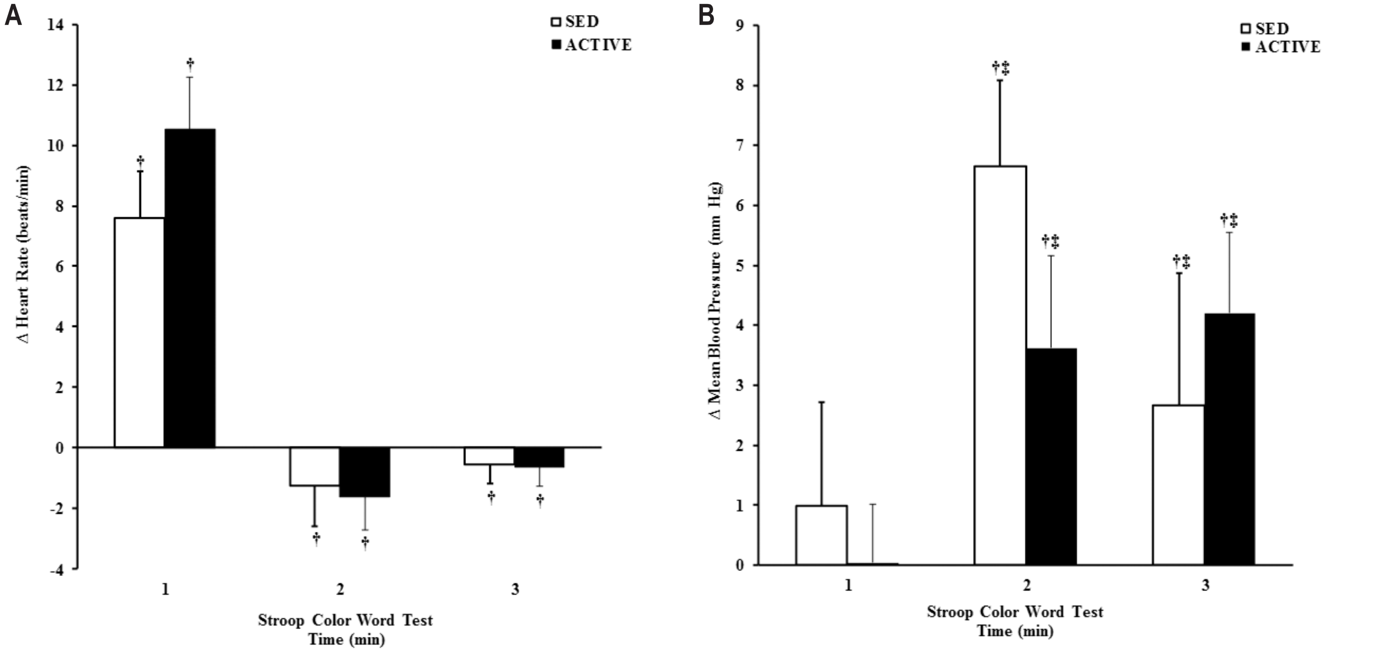
Data are presented as mean ± standard error. An unpaired Student *t* test (years, BMI, left ventricular ejection fraction, cardiovascular parameters, AHI, minimum O_2 saturation) of SED and ACTIVE groups was performed. The difference between sexes was tested by the χ^2 test. The Kolmogorov-Smirnov and Levine tests were used to assess the normality and homogeneity of distribution of each variable studied. The FBF responses to SCWT were analyzed by relative and absolute differences (each minute of the SCWT – mean baseline) for the group. In the case of significance, *post hoc* comparisons were performed by Tukey honest significant difference test. The correlations between the level of physical activity and clinical variables were performed using Pearson correlation analysis. In all analyses, a value of *P* < .05 was considered statistically significant. All statistical analyses were performed using Statistica 12 software (StatSoft, Tulsa, Oklahoma, United States).

Table 2—Sleep parameters in sedentary and physically activity patients with obstructive sleep apnea.

	SED (n = 21)	ACTIVE (n = 19)	*P*
TRT, min	458 ± 8	440 ± 6	.10
TST, min	384 ± 13	377 ± 10	.69
Stage N1, %TST	9 ± 1	8 ± 1	.72
Stage N2, %TST	59 ± 2	53 ± 2	.06
Stage N3, %TST	13 ± 2	15 ± 1	.46
Stage R, %TST	17 ± 1	22 ± 1	.02*
Arousal index, events/h	33 ± 4	23 ± 2	.05*
Apnea index, events/h	17 ± 6	14 ± 4	.71
Hypopnea index, events/h	26 ± 3	28 ± 6	.71
AHI, events/h	43 ± 5	37 ± 5	.50
ODI, events/h	33 ± 5	36 ± 5	.73
T90, %	6 ± 2	9 ± 4	.66

Values are means ± standard error. * = $P < .05$, SED versus ACTIVE. Values were tested by unpaired Student *t* test. There was no significant difference in TRT, TST, or sleep stages (N1, N2, and N3). Arousals index was higher in the SED than in the ACTIVE group. REM sleep was higher in ACTIVE than in the SED group. Apnea index, hypopnea index, ODI, and T90 did not differ between groups. ACTIVE = physically active group, ODI = oxygen desaturation index, REM = rapid eye movement, SED = sedentary group, T90 = recording time with $SaO_2 < 90\%$, TRT = total recording time, TST = total sleep time.

Figure 1—Hemodynamic response during the Stroop Color Word Test in sedentary and physically active patients with obstructive sleep apnea.

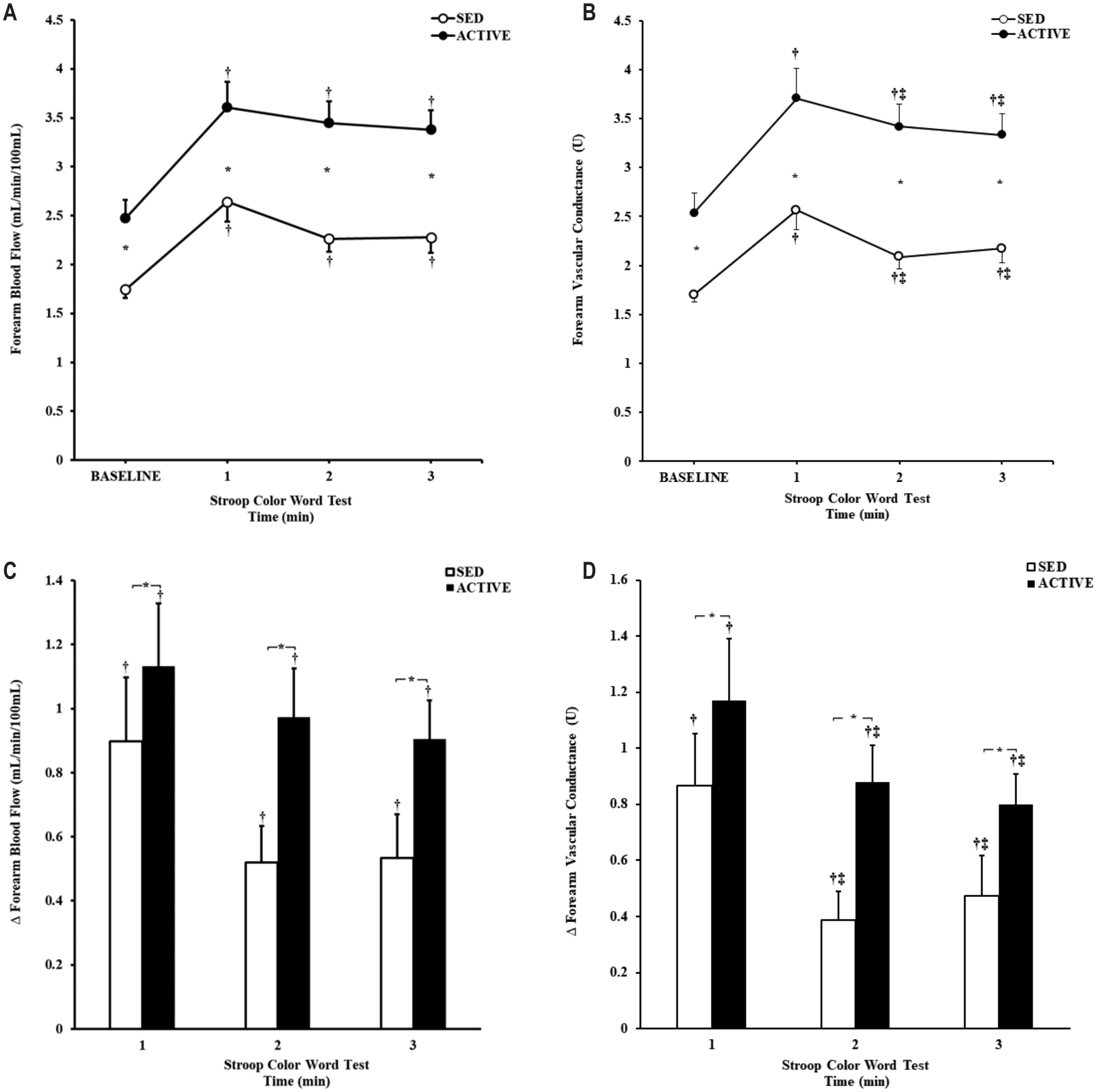


(A) Heart rate and **(B)** ankle mean blood pressure. Dagger indicates versus baseline, $P < .05$ (within groups). Double daggers indicate versus first minute, $P < .05$ (within groups). ACTIVE = physically active group, SED = sedentary group.

RESULTS

From a total of 44 subjects who were initially selected to participate in the study, 4 were excluded because of the inadequate FBF recording obtained. Thus, 40 patients with moderate to severe OSA completed the study. The patients were classified into SED (n = 21) and ACTIVE (n = 19) groups through the IPAQ. The SED and ACTIVE groups were similar regarding sex distribution, age, weight, BMI, fat mass, and years of education (**Table 1**). As expected, the leisure time physical activity was significantly different between groups ($P < .05$). Baseline HR and BP were also similar between groups. The baseline FBF and FVC were significantly lower in the SED compared to the ACTIVE subjects ($P < .05$). For instance, in our previous study[16] the FBF and FVC were 2.50 ± 0.30 and 3.10 ± 0.40, respectively in normal healthy subjects without sleep apnea and a similar age as subjects in the current study.

Figure 2



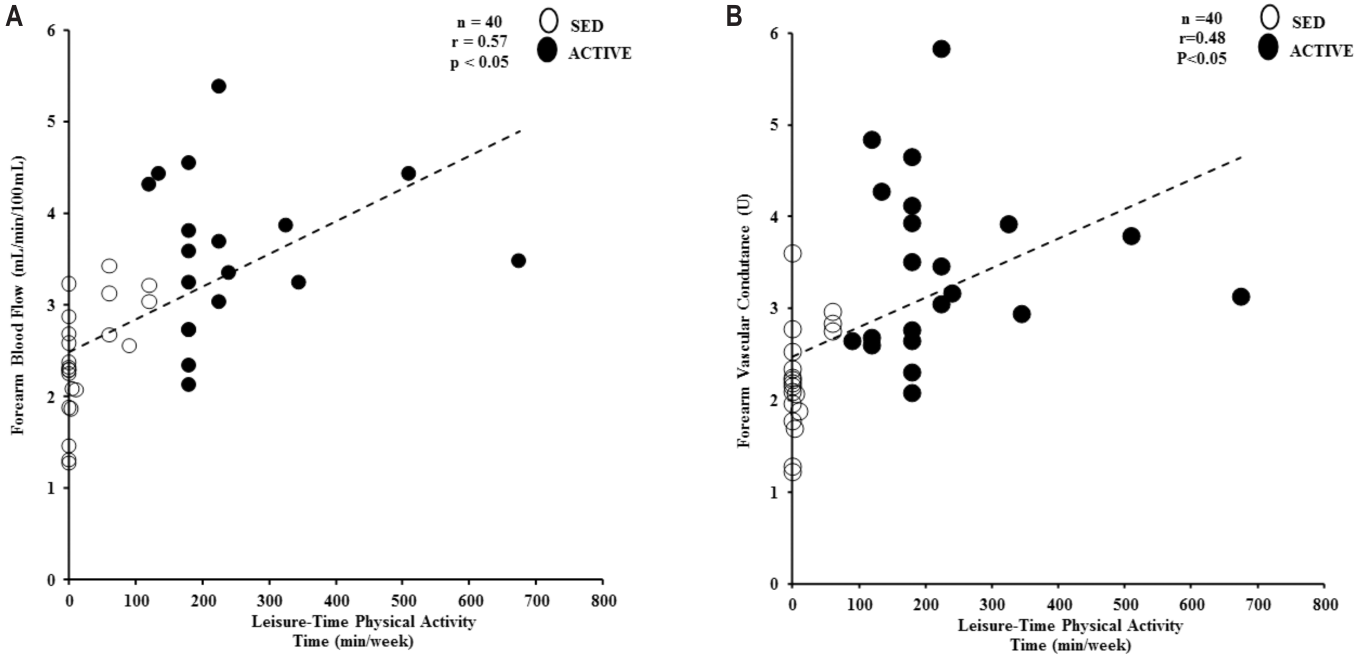
(A) Forearm blood flow and **(C)** forearm blood flow response during the Stroop Color Word Test in patients with obstructive sleep apnea. **(B)** Forearm vascular conductance and **(D)** forearm vascular conductance response during the Stroop Color Word Test in patients with obstructive sleep apnea. Asterisk indicates ACTIVE versus SED, $P < .05$. Dagger indicates versus baseline, $P < .05$ (within groups). Double daggers indicate versus first minute, $P < .05$ (within groups). ACTIVE = physically active group, SED = sedentary group.

Regarding sleep patterns, no differences were noted in total recording time, total sleep time, percentage of sleep stages (N1, N2, and N3). Percentage rapid eye movement (REM) was greater in the ACTIVE compared with the SED group. The arousal index was higher in the SED compared with the ACTIVE group. Apnea index, hypopnea index, oxygen desaturation index, and percentage of recording time with SaO_2 of < 90% did not differ between groups (**Table 2**).

Responses to Mental Stress

The stress perception after SWCT did not differ between the SED and the ACTIVE groups (2.9 ± 0.3; 2.7 ± 0.35; $P = .63$), respectively. The HR response showed the greatest increase ($P > .05$) in the first minute of SWCT compared with baseline in both SED and ACTIVE groups (**Figure 1A**), with further decreases in the second and third minute. The mean BP significantly increased during the second and third minute of SWCT

Figure 3



Group data correlations between forearm blood flow and leisure time physical activity **(A)** and forearm vascular conductance and leisure time physical activity **(B)**. Open circles indicate sedentary (SED) and dark circles indicate physically active (ACTIVE) patients with obstructive sleep apnea.

in both SED and ACTIVE groups compared with baseline and the first minute of SWCT (**Figure 1B**).

The absolute values of FBF and FVC increased significantly during 3 minutes of SWCT in both groups (**Figure 2A, 2B**). The FBF and FVC responses (each minute of SWCT – baseline) increased in both SED and ACTIVE groups during 3 minutes of SWCT compared to baseline (**Figure 2C, 2D**). However, there was a significant difference between groups in the first, second, and third minute of SWCT. Exploratory analysis including sex as a covariate did not alter the results. In addition, a significant correlation was found between FBF during SWCT ($r = .57$; $P < .05$; **Figure 3A**) and FVC during SWCT ($r = .48$; $P < .05$; **Figure 3B**) with the time spent in leisure physical activity.

DISCUSSION

In this study we found that among a homogeneous group of patients with OSA with no other comorbidities, ACTIVE patients had better vascular function at rest and during mental stress compared with the SED patients. The main findings that support this observation are as follows: ACTIVE compared with SED patients had 37% higher FBF and 33% higher FVC at rest. The ACTIVE group compared with SED group had a better vascular response to mental stress, as observed by a significantly higher change in FBF (32%) and FVC (35%). In addition, there was a positive correlation between mean FBF and FVC during mental stress and leisure time physical activity.

There is consistent evidence indicating that OSA may affect endothelial function.[22] OSA has been independently associated with lower nitric oxide bioavailability[23] and increased vasoconstrictor tone.[24] Consistent with the literature, the baseline mean values of FBF and FVC in our SED group were similar to those of a previous study that evaluated patients with OSA and congestive heart failure. The baseline mean values of FBF and FVC in our ACTIVE group were similar to those in healthy control subjects with similar mean age but without OSA.[16] Therefore, our finding of better baseline vascular function in ACTIVE than SED patients with OSA is consistent with previous studies in other populations.[17,18]

Our study extends these previous findings by investigating the possible effect of physical activity level on vascular function in patients with OSA without other comorbidities. Aerobic exercise improves endothelial function in healthy adults,[25] obese subjects,[26] patients with hypertension,[27] and patients with heart failure.[28] In addition, cross-sectional studies that evaluate the level of physical activity in real-world conditions have shown that compared with sedentary subjects, regular physical activity is associated with better vascular function.[29] In our study, the mean leisure physical activity level in the ACTIVE group was moderate and corresponded to approximately 4 h/week of moderate to vigorous activities. This amount of physical activity is similar to that reported in a recent study that showed that moderate physical activity levels (≥ 4 h/wk) is sufficient to obtain health benefits, reduction in mortality, and development of cardiovascular diseases in older adults independently of associated risk factors.[30]

In the current study we also evaluated vascular functional response to mental stress tests that have been extensively used to evaluate endothelial function in distinct groups with cardiovascular risk.[13,18] Studies have shown that vascular functional response to stress is a marker of endothelial dysfunction or atherosclerosis as reflected by increased carotid intima media thickness[14] and decreased flow-mediated dilation.[17,31]

The HR and BP response to mental stress was similar in SED and ACTIVE groups. HR peak at the first minute of mental stress is caused by a β-adrenergic receptor stimulation[32] and probably represents a defensive reaction of the body preparing the body for a fight or flight response[33] to the mental stress. Elevation in BP may occur mainly because of an increase in cardiac output and increased sympathetic activity.[10]

In the current study, ACTIVE and SED groups significantly increased FBF and FVC during mental stress. However, the level of vasodilation was significantly higher in the ACTIVE than in the SED group. Our results are in line with the observation that regular physical activity is effective in preventing endothelial dysfunction during mental stress in subjects with metabolic syndrome[17] and obesity.[18] Thus, it might be speculated that the increased forearm vasodilation during mental stress in our ACTIVE group may be related to a protective factor of some of the vascular pathophysiology observed in patients with moderate to severe OSA. Physical exercise improves nitric oxide-mediated endothelial function,[34] promotes metabolic vasodilation that is partly dependent on the release of nitric oxide[35] and its greatest importance is in autonomic control during mental stress.[36,37]

The observation of the increased percentage of REM and reduced arousals in the ACTIVE compared with the SED group demonstrate that regular physical activity improves sleep pattern in patients with OSA. These findings are in line with a previous study in which regular exercise improved sleep parameters in OSA patients with heart failure.[15] Cooper et al.[38] also indicate an association between impaired vasodilatory capacity and decreased percentage of REM, suggesting that diminished vascular function in OSA could be a mechanism also linking poor sleep parameters.

This study has limitations that should be noted. We only studied patients with OSA; no healthy control patients were included. However, a previous study has shown that patients with OSA have impaired vascular function compared with healthy control patients.[39] Our study design allowed us to isolate one single variable (level of physical activity) in an otherwise homogenous group of patients with OSA with no other comorbidities. This was a cross-sectional study and therefore the association found between FBF and FVC with leisure time physical activity level does not necessarily imply a causal relationship. The evaluation of FBF by venous occlusion plethysmography calculates the total amount of blood in the forearm muscle. Further studies using pharmacological blockade of adrenergic and cholinergic receptors are needed to explain the endothelial dependent and neuronal mechanisms associated with the level of physical activity among patients with OSA.

In summary, active patients with OSA have increased resting and vasodilator response during mental stress than do sedentary patients. Our results reinforce the importance of regular physical activity, especially in leisure time, as a potential nonpharmacologic preventive measure for vascular dysfunction in patients with moderate to severe OSA. Our study also indicates that the level of physical activity must be clearly determined in future studies that evaluate cardiovascular function in patients with OSA.

ABREVIATIONS

ACTIVE, active group
AHI, apnea-hypopnea index
BMI, body mass index
BP, blood pressure
FBF, forearm blood flow
FVC, forearm vascular conductance
HR, heart rate
IPAQ, International Physical Activity Questionnaire
OSA, obstructive sleep apnea
SCWT, Stroop Color Word Test
SED, sedentary group

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