CLINICAL SCIENCE

Oxidative stress and quality of life in elderly patients with obstructive sleep apnea syndrome: are there differences after six months of Continuous Positive Airway Pressure treatment?

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OBJECTIVES: This study evaluated the effect of Continuous Positive Airway Pressure treatment on oxidative stress parameters and the quality of life of elderly patients with obstructive sleep apnea syndrome.

METHODS: In total, 30 obstructive sleep apnea syndrome patients and 27 subjects without obstructive sleep apnea syndrome were included in this study. Both groups underwent quality of life and oxidative stress evaluations at baseline and after six months. Polysomnography was performed in both groups at baseline and a second time in the obstructive sleep apnea syndrome group after six months of Continuous Positive Airway Pressure treatment. All of the variables were compared between the control and obstructive sleep apnea syndrome groups in this prospective case-control study.

RESULTS: The baseline concentrations of the antioxidant enzyme catalase were higher in the obstructive sleep apnea syndrome group than the control group. After Continuous Positive Airway Pressure treatment, the obstructive sleep apnea syndrome group exhibited a reduction in the level of oxidative stress, as indicated by a decrease in the level of lipid peroxidation measured by the malondialdehyde (MDA) concentration [pre: 2.7 nmol malondialdehyde/mL (95% 1.6-3.7) *vs.* post: 1.3 nmol MDA/mL (0.7-1.9), $p<0.01$]. Additionally, improvements were observed in two domains covered by the SF-36 questionnaire: functional capacity [pre: 77.4 (69.2-85.5) *vs.* post: 83.4 (76.9-89.9), $p=0.002$] and pain [pre: 65.4 (52.8-78.1) *vs.* post: 77.8 (67.2-88.3), $p=0.004$].

CONCLUSION: Our study demonstrated that the use of Continuous Positive Airway Pressure to treat obstructive sleep apnea syndrome in elderly patients reduced oxidative stress and improved the quality of life.

KEYWORDS: Continuous Positive Airway Pressure; Elderly; Obstructive Sleep Apnea Syndrome; Oxidative Stress; Quality of Life.

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) manifests as a reduction (hypopnea) or complete cessation (apnea) of airflow, which causes an increase in inspiratory effort that often culminates in arousal (1). OSAS is characterized by the collapse of the extrathoracic airway (2,3), a transient decrease in oxyhemoglobin saturation, hypercapnia, and consequent hyperventilation. These symptoms affect the objective and subjective qualities of sleep and trigger characteristic clinical symptoms, such as excessive daytime sleepiness (4,5). Several factors, including male gender, older age, obesity, alcohol use, otorhinolaryngological changes (6,7) and heredity, are associated with the prevalence, increased risk, and severity of OSAS (8,9).

The consequences of OSAS, such as accidents caused by excessive daytime sleepiness (10), increased risk of cardiovascular diseases (11) and mood and metabolic alterations (12,13), have been widely studied. OSAS also increases the generation of reactive oxygen species (ROS). The overproduction of ROS results in oxidative stress (OS), which results in damage to cellular structures, including lipids, membranes, proteins and DNA (14). OS produces a cascade

No potential conflict of interest was reported.

of events that trigger inflammation, an increase in sympathetic tonus, vascular endothelial dysfunction, metabolic alterations, and/or increased platelet aggregation (15,16). The chronic intermittent hypoxia, sleep loss and fragmentation experienced by OSAS patients may be related to endothelial dysfunction due to the increases in the levels of inflammatory mediators, OS and coagulant activity. Endothelial dysfunction contributes to the development of atherosclerosis and OSAS-associated cardiovascular disorders. However, OSAS comorbidities and metabolic syndrome are also associated with endothelial dysfunction. OSAS may also induce or exacerbate various aspects of metabolic syndrome, such as glucose metabolism, cholesterol, inflammatory markers, and nonalcoholic fatty liver disease (17-21).

The use of Continuous Positive Airway Pressure (CPAP) is an effective treatment for OSAS because CPAP normalizes the sleep architecture, reduces subjective excessive daytime sleepiness and reverses other OSAS symptoms (22). CPAP treatment prevents hypoxia and oxygenation injury, decreases OS and inhibits the cascade of deleterious OSAS-induced consequences (23,24). Patients with severe OSAS and metabolic syndrome who exhibit good compliance with CPAP treatment may exhibit improved insulin sensitivity and reduced systemic inflammation, OS, and global cardiovascular disease risk (25).

Aging predisposes people to OSAS. The prevalence of OSAS is higher in elderly populations than in young adults (26). The prevalence of an apnea hypopnea index (AHI) >15 events per hour among 60- to 69-year-old males was 52.3% in São Paulo city, Brazil, and this frequency increased to 84.7% among 70- to 80-year-old males (27).

The literature highlights the positive effects of CPAP on excessive daytime sleepiness in adults and reports variable responses with respect to cardiovascular and cognitive functions; however, the impact of OSAS on the cardiovascular system in the elderly population is controversial (28,29).

The aims of this study were to compare OS parameters and the quality of life in elderly patients between individuals with and without OSAS and to evaluate the effect of CPAP treatment on OSAS patients.

METHODS

This study was approved by the ethics committee of the Universidade Federal de São Paulo (CEP: 1977/09). All of the patients signed an informed consent form.

Patients and Study Design

This prospective case-control study evaluated consecutive patients with suspected OSAS who were seen at the outpatient sleep clinic. The diagnosis of OSAS was confirmed using polysomnography (PSG) if the AHI was ≥20. Patients were compared with age-matched subjects without OSAS (AHI≤10). These cut-off values were based on previous publications on OSAS in elderly patients (30,31).

The inclusion criteria were as follows: age between 60 and 75 years (32,33), male gender, and a body mass index (BMI) less than 35 kg/m^2. Subjects in the OSAS group exhibited clinical criteria of this syndrome (34) and an AHI of ≥20 events per hour; the AHI was ≤10/h in the control group. The protocol excluded individuals who had neurological or psychiatric diseases, sleep disorders other than OSAS, alcohol abuse and/or psychoactive drug use. Patients who had previously received treatment for OSAS were also excluded.

Subjects underwent an assessment protocol at baseline that used the following tools: a questionnaire that is routinely used in our sleep laboratory (35), the Epworth Sleepiness Scale (ESS) (36), a quality of life questionnaire (SF – 36) (37), laboratory tests and PSG. The PSG results and clinical symptoms divided the subjects into two groups (i.e., the presence or absence of OSAS). The OSAS group received six months of CPAP treatment, and the control subjects received no intervention. The OSAS group was submitted to PSG with CPAP at the end of the study. Both groups completed all of the other assessments at baseline at the end of the study (Figure 1).

Polysomnography

Full-night PSG was performed using a digital system (Embla® S7000, Embla Systems, Inc., Broomfield, CO, USA), and the following parameters were measured: electroencephalography, electromyography, electrocardiography, oral and nasal breathing (thermistor and pressure transducer), thoracic and abdominal respiratory effort (inductive plethysmography), snoring, oxyhemoglobin saturation, and body position. We used the Rechtschaffen and Kales criteria to score sleep (38). Respiratory events were assessed according to the American Academy of Sleep Medicine Task Force (1). Arousals (39) and periodic leg movements (40) were described according to the American Sleep Disorders Association criteria.

CPAP

All of the patients in the OSAS group underwent a full-night PSG to titrate the CPAP pressure. Each patient received a CPAP system (REMstar® Plus, Respironics, Inc., Murrysville, Pennsylvania, USA) after researchers determined the ideal pressure for treatment. The CPAP system had an hour meter to control the duration of the positive pressure.

The patients also participated in an educational program on CPAP use that included four visits by trained staff. Visits occurred one week and one, three, and six months after the initial treatment.

Laboratory Analysis

Venous blood for laboratory evaluations of OS parameters was collected in heparin-containing tubes in the morning after volunteers had fasted for twelve hours. Plasma and red blood cells were separated and properly stored for the evaluation of biochemical parameters (41). Spectrophotometry (Hitachi U-3900/3900H, Tokyo, Japan) was used to determine the levels of malondialdehyde (MDA, expressed in nmol MDA/mL),

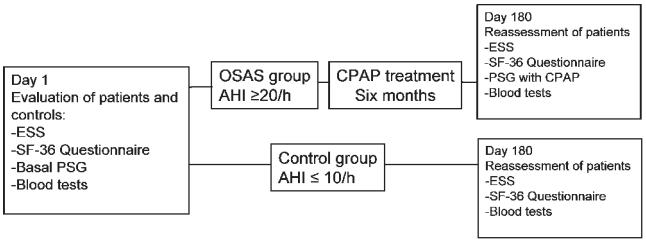

Figure 1 - Study Design.

erythrocyte catalase (CAT) activity (expressed in U/mg hemoglobin), and superoxide dismutase (SOD) activity in erythrocytes (expressed as U/mg Hb).

A competitive immunoassay using direct chemiluminescence was used to determine the vitamin B12 and folate concentrations (ADVIA Centaur®/Siemens Healthcare Diagnostics, Inc., Deerfield, Illinois, USA). The folate concentrations are expressed as nmol/L, and the vitamin B12 concentrations are expressed as pmol/L.

High-performance liquid chromatography (HPLC) (Shimadzu with fluorescence detector RF-10AXL, Kyoto, Japan) with fluorometric detection and isocratic elution was used to measure the levels of plasma homocysteine (Hcy) and cysteine (Cys) (both are expressed in μmol/L). The uric acid values were measured using the uricase-enzymatic colorimetric method (Advia® 1650/2400/Siemens Healthcare Diagnostics, Inc., Deerfield, Illinois, USA). The results are expressed as mg/dL. To determine the concentrations of vitamins C and E, we used an HPLC-UV system according to the Immundiagnostik method. The results are expressed in mmol/L.

Statistical Analysis

Statistical analysis was performed using SPSS version 13.0 for Windows. Descriptive analysis (means ± standard errors) was used to characterize the groups. The results of the PSG, the questionnaire answers and the OS parameters were assessed using a general linear model (GLM) with repeated measures. This analysis assessed the effects of time, independent groups and control variables of interest. BMI was a covariate in this analysis to prevent bias because an association among obesity, OSAS and OS has been demonstrated previously.

We standardized the data using the Z score. The nonparametric Mann-Whitney test was used to compare independent groups, and the Wilcoxon test was used for repeated measures. Effect sizes (Partial Eta Squared - Eta^2) and the observed power were also considered to prevent type I and type II errors. Statistical significance was set at 5% ($p<0.05$).

RESULTS

In total, 30 OSAS patients and 27 age-matched control subjects were included in this study. Both groups (control and OSAS) were homogeneous with respect to age (66.4 ± 0.7 years *vs.* 66.4 ± 0.7 years, respectively; $p = 0.97$), but the OSAS group had a higher mean BMI than the control group (25.1 ± 0.7 kg/m^2 (control) *vs.* 27.9 ± 0.7 kg/m^2 (OSAS); $p = 0.004$) (Table 1). The important comorbidities of both groups are presented in Table 2. No differences with respect to the frequencies of hypothyroidism, diabetes and dyslipidemia were observed between the groups; however, the prevalence of hypertension was higher in the OSAS group.

A multivariate analysis was used to evaluate the questionnaire responses at baseline, and the nonparametric Mann-Whitney test confirmed the results of this analysis. The OSAS group had a trend of higher ESS scores and worse quality of life, with lower scores for ''Functional Capacity'' (79.7 ± 3.1 *vs.* 89.8 ± 2.8; $p = 0.02$) and ''Pain'' (68.6 ± 5 *vs.* 82.7 ± 4.5; $p = 0.04$) compared with the control group. A tendency toward a lower score for ''General Heath'' was observed in the OSAS group (Table 3).

All of the factors exhibited overlapping confidence intervals in the repeated measures analysis of the two groups. However, because the groups were heterogeneous and because there was an insufficient number of cases, we used the Wilcoxon test and divided the level of significance by two. This test showed that there were improvements in ''Functional Capacity'' ($p = 0.002$) and ''Pain'' on the SF-36 ($p = 0.004$) (Table 3).

Table 1 - Baseline polysomnographic and clinical data for the control and obstructive sleep apnea syndrome (OSAS) groups.

	Control	OSAS	*p*-value
Age	66.4 ± 0.7	66.4 ± 0.7	0.97
BMI (kg/m^2)	25.1 ± 0.7	27.9 ± 0.7	<0.001
Sleep Lat (min)	23.8 ± 6.1	18.2 ± 6.6	0.53
REM Lat (min)	98.0 ± 11.7	81.2 ± 12.7	0.34
TST (min)	336.3 ± 15.5	327.6 ± 16.9	0.71
SE (%)	75.4 ± 3.0	75.4 ± 3.3	1.00
S1 (%)	8.9 ± 1.8	6.1 ± 1.9	0.30
S2 (%)	53.0 ± 2.3	60.3 ± 2.5	0.04
S3+4 (%)	18.6 ± 1.5	15.1 ± 1.6	0.13
REM Sleep (%)	19.7 ± 1.1	18.3 ± 1.2	0.44
Wake (min)	93.0 ± 12.1	103.3 ± 13.2	0.57
AI/h	11.8 ± 2.2	27.1 ± 2.4	<0.001
PLM/h	6.3 ± 3.3	8.4 ± 3.6	0.67
AHI/h	5.3 ± 2.1	37.8 ± 2.3	<0.001
Mean SpO_2 (%)	94.2 ± 0.8	91.2 ± 0.8	0.02
Min SpO_2 (%)	87.9 ± 1.8	76.7 ± 2.0	<0.001
SpO_2< 90% (min)	1.19 ± 3.3	22.91 ± 4.6	<0.001

Data are expressed as the mean ± standard error (SE). BMI: body mass index; Sleep Lat: sleep latency; REM Lat: REM sleep latency; TST: total sleep time; SE: sleep efficiency; S1: stage 1; S2: stage 2; S3: stage 3; S3+4: stage 3 and 4; REM Sleep: rapid eye movement sleep; Wake: minutes awake; AI: arousal index; PLM: periodic leg movements; AHI: apnea/hypopnea index; SpO_2: saturation of oxyhemoglobin; SpO_2<90%: cumulative time during which the saturation of oxyhemoglobin was below 90%. (GLM test).All of the OSAS patients of this study adhered to the CPAP protocol for at least four hours per night, and the pressures ranged from 8 to 15 cm H_2O.

Multivariate analyses of all of the PSG variables at baseline demonstrated a high effect size ($Eta^2 = 0.79$) and a strong observed power ($p = 1.00$). BMI was used as a covariant. Relative to the control group, the OSAS group exhibited significant differences with respect to variables related to light sleep (increased percentage in stage 2 of NREM sleep) (60.3 ± 2.5% *vs.* 53 ± 2.3%; $p = 0.04$) and higher arousal rates (27.1 ± 2.4 per hour *vs.* 11.8 ± 2.2 per hour; $p<0.01$). In addition, the OSAS group had a higher AHI (37.8 ± 2.3 per hour *vs.* 5.3 ± 2.1 per hour; $p<0.01$) and lower minimum and mean oxyhemoglobin saturation levels (76.7 ± 2% *vs.* 87.9 ± 1.8%; $p<0.01$ and 91.2 ± 0.8% *vs.* 94.2 ± 0.8%; $p<0.05$, respectively) than controls. The OSAS group also spent more time with oxyhemoglobin saturation levels below 90% (22.9 ± 4.6% *vs.* 1.19 ± 3.3%; $p<0.01$) (Table 1).

PSG was performed a second time in the OSAS group to evaluate the effect of the CPAP treatment. The PSG performance after treatment revealed a decrease in the percentage

Table 2 - Number of individuals with relevant comorbidities in both groups.

	Control	OSAS	*p*-value
Hypothyroidism	14	3	NS
Dyslipidemia	7	12	NS
Diabetes	11	12	NS
Hypertension	29	60	0.03

Chi-square test.

Table 3 - Baseline and final measures for sleepiness and quality of life for the control and obstructive sleep apnea syndrome (OSAS) groups.

	Control		OSAS	
	Baseline	Final	Pre	Post
ESS	**8.8** (5.0-12.6)	**7.9** (5.3-10.5)	**10.7** (8.0-13.3)	**7.4** (5.6-9.2) *
Functional Capacity	**86.3** (76.0-96.5)	**84.2** (76.0-92.3)	**77.4** (69.2-85.5) **	**83.4** (76.9-89.9)
Physical	**87.5 (**70.5-104.5)	**90.6** (71.1-110.1)	**81.6** (68.0-95.1)	**80.3** (64.8-95.8)
Pain	**83.3** (67.4-99.3)	**78.1** (64.8-91.4)	**65.4** (52.8-78.1) **	**77.8** (67.2-88.3) *
Healthy	**79.0** (68.2-89.8)	**78.6** (69.7-87.5)	**68.0** (59.4-76.6)	**76.2** (69.1-83.2)
Vitality	**71.7** (58.7-84.6)	**73.8** (62.6-84.9)	**70.1** (59.8-80.4)	**68.7** (59.8-77.5)
Social Function	**74.0** (58.8-89.1)	**80.2** (65.0-95.4)	**84.2** (72.2-96.3)	**81.8** (69.7-93.9)
Emotional	**63.8** (42.5-85.1)	**80.5** (56.4-104.6)	**80.1** (63.2-97.1)	**78.9** (59.8-98.1)
Mental Health	**70.3** (58.0-82.7)	**73.6** (61.6-85.6)	**80.0** (70.2-89.8)	**80.0** (70.5-89.5)

Data are expressed as the mean (95% confidence interval). Scores are from the Epworth Sleepiness Scale (ESS) and the SF-36 questionnaire (domains: Physical: role limitations due to physical problems; Pain: bodily pain; Health: general health perception; Vitality: energy/vitality; Social function: social functioning; Emotional: role limitations due to emotional problems; Mental health: mental health).* $p<0.05$ compared with the baseline values for the control group. ** $p<0.05$ compared with controls. (GLM, Mann Whitney and Wilcoxon tests).

of stage 1 NREM sleep (5.8±0.6% *vs.* 4.3±0.5%; $p<0.01$), a tendency toward an increase in the percentage of REM sleep (18.1±1.4% *vs.* 22±1.5%; $p=0.06$), a decrease in minutes spent awake (102.7±17.3 min *vs.* 65±11 min; $p=0.03$), a decrease in the rate of awakenings (25.6±2.9 per hour *vs.* 10.4±1.2 per hour; $p<0.01$), a reduction in the AHI to within the normal range (36.6±3.4 per hour *vs.* 4±0.9 per hour; $p<0.01$), and a reduction in the duration of oxyhemoglobin saturation levels below 90% (20.9±8.6% *vs.* 0.8±0.4%; $p<0.05$) compared with baseline values. These changes were associated with objective improvements in sleep quality (Table 4).

The CAT concentrations at baseline were higher in the OSAS group than the control group [115.3 U/mg Hb (95% 88-142) *vs.* 105.6 U/mg Hb (95% 67.8-143), respectively; $p=0.004$]. A significant increase in the vitamin C concentration was observed for the control group [pre 56.5 mmol/L (95% 50.4-62.7) *vs.* post 69.4 mmol/L (95% 63.2-75.7); $p<0.01$] and for the OSAS group [pre 51.6 mmol/L (95% 44.0-59.2) *vs.* post 62.4 mmol/L (95% 54.7-70.1); $p<0.01$] at the final examination. Higher CAT activity was observed in the OSAS group compared with the control group [140.3 U/mg Hb (95% 115.0-165.0) *vs.* 50 U/mg Hb (95% 15.1-85.0)] at the final evaluation. The use of CPAP treatment by the OSAS group decreased the level of lipid peroxidation, which was expressed in terms of the MDA concentration [pre: 2.7 nmol MDA/mL (95% 1.6-3.7) *vs.* post: 1.3 nmol MDA/mL (0.7-1.9); $p<0.01$] (Table 5).

No significant correlations between variables were observed.

Table 4 - Polysomnographic data before and after Continuous Positive Airway Pressure treatment in the obstructive sleep apnea syndrome (OSAS) group

	OSAS		
	Before	After	*p*-value
Sleep Lat (min)	20.5±5.8	12.6±2.6	0.21
REM Lat (min)	69.5±5.8	65.2±8.0	0.64
TST(min)	326.7±17.7	349.1±11.3	0.25
SE (%)	75.5±3.7	82.2±2.3	0.08
S1 (%)	5.8±0.6	4.3±0.5	<0.001
S2 (%)	59.6±2.2	54.8±2.4	0.12
S3+4 (%)	16.3±1.7	18.8±1.7	0.26
REM Sleep (%)	18.1±1.4	22.0±1.5	0.06
Wake (min)	102.7±17.3	65.0±11.0	0.05
AI/h	25.6±2.9	10.4±1.2	<0.001
PLM/h	10.1±5.5	10.8±4.5	0.91
AIH/h	36.6±3.4	4.0±0.9	<0.001
Mean SpO_2 (%)	91.5±1.4	94.7±0.2	0.04
Min SpO_2 (%)	76.9±3.1	88.7±0.5	<0.001
SpO_2< 90% (min)	20.9±8.6	0.8±0.4	0.04

Data are expressed as the mean±standard error (SE). Sleep Lat: sleep latency; REM Lat: REM sleep latency; TST: total sleep time; SE: sleep efficiency; S1: stage 1; S2: stage 2; S3: stage 3; S3+4: stage 3 and 4; REM Sleep: rapid eye movement sleep; Wake: minutes awake; AI: arousal index; PLM: periodic leg movements; AHI: apnea/hypopnea index; SpO_2: saturation of oxyhemoglobin; SpO_2< 90%: cumulative time during which the saturation of oxyhemoglobin was below 90%. (GLM test).

DISCUSSION

Our study demonstrated that the use of CPAP to treat OSAS in elderly male patients contributed to a reduction in OS and improved the quality of life. Oxidative damage and OSAS may be related to aging. Similarly, a relationship may exist between the reduction in antioxidant capacity and OSAS after CPAP treatment. We demonstrated that CPAP was able to reverse OS, as demonstrated by decreases in the MDA concentrations. We also found that the CAT concentration increased in the OSAS group after treatment. These results suggest that OSAS may overload a patient's antioxidant capacity, which increases CAT activity. However, this augmentation of the antioxidant enzyme activity was insufficient to cope with OSAS-induced OS, and the lipid peroxidation levels were elevated in the OSAS group prior to CPAP treatment. These results suggest that lipid peroxidation may be an important pathological event for these patients. Six months of CPAP treatment increased the level of catalase activity, which suggests that the antioxidant defense system was activated, and this mechanism was able to reduce the level of lipid peroxidation levels in OSAS patients during this period.

The association between aging and antioxidant capacity is not well established, and no consensus has been reached regarding the influence of aging on antioxidant capacity (42,43). The increased CAT activity and reduced lipid peroxidation observed in this study indicate the importance of evaluating OS markers in OSAS patients. Therefore, future studies should focus on improving the antioxidant capacity of these patients.

An increase in the vitamin C concentration was observed in both groups at the time of re-assessment relative to the

Table 5 - Baseline and final values of oxidative stress parameters for the control and obstructive sleep apnea syndrome (OSAS) groups.

	Control		OSAS	
	Baseline	Final	Pre	Post
Uric Acid mg/dL	**5.8** (5.2-6.3)	**5.6** (5.1-6.2)	**6.0** (5.4-6.5)	**6.2** (5.7-6.8)
Vitamin B12 pmol/L	**363.4** (284.6-442.0)	**329.9** (184.0-475.0)	**461.7** (376.1-547.0)	**483.7**(325.0-642.0)
Folic Acid pmol/L	**11.4** (9.7-13.2)	**12.0** (10.2-13.9)	**11.5** (9.6-13.5)	**10.8** (8.8-12.9)
Vitamin E μmol/L	**26.4** (23.0-29.8)	**27.53** (24.1-31.0)	**22.5** (18.4-26.7)	**25.1**(20.9-29.3)
Vitamin C μmol/L	**56.5** (50.4-62.7)	**69.4** (63.2-75.7) †	**51.6** (44.0-59.2)	**62.4** (54.7-70.1) #
SOD U/mg Hb	**10.2** (7.5-12.9)	**8.2** (5.8-10.7)	**10.5** (8.6-12.5)	**10.3** (8.5-12.1) ∞
CAT U/mg Hb	**105.6** (67.8-143.0)	**50.0** (15.1-85.0)	**115.3** (88.0-142.0) ¥	**140.3** (115.0-165.0) ∞
TBARS, nmol MDA/mL	**1.2** (0.1-2.4)	**1.4** (0.7- 2.1)	**2.6** (1.6-3.6)	**1.2** (0.6-1.8) #
Hcy μmol/L	**9.6** (7.8-11.4)	**11.0** (8.7-13.4)	**12.1** (11.0-13.2)	**12.1** (10.7-13.5)
Cys μmol/L	**507.3** (438.7-576.0)	**531.6** (473.0-590.0)	**552.3** (510.3-594)	**550.7** (515.0-587.0)

Data are expressed as the mean (95% confidence interval). TBARS: thiobarbituric acid-reactive substances; MDA: malondialdehyde; SOD: superoxide dismutase; CAT: catalase; Hcy: homocysteine; Cys: cysteine. † $p<0.05$ for the comparison between the final and baseline results for the control group, # $p<0.05$ for the comparison between the final and baseline results for the OSAS group, ¥ $p<0.05$ for the comparison between the baseline values for the control and OSAS groups, ∞ $p<0.05$ for the comparison between the final values for the control and OSAS groups. (GLM test).

baseline levels. However, the concentrations were within the normal range. These findings suggest that alterations in the observed OS parameters are not related to vitamin C availability.

The mean vitamin E concentrations in both groups (OSAS and controls) were within the normal range (15 to 40 μmol/L), which suggests that there is no effect of age on this parameter.

One reason for the controversy regarding OS in the literature may be that there are many protocols for assessing OS, and researchers do not frequently follow the same protocol. In addition to the variability in protocols, most of the measures of OS markers are indirect measures, which are less accurate (42-44).

The OSAS group exhibited a worse quality of life for two domains of the SF-36 (''Functional Capacity'' and ''Pain'') compared with the control group at baseline. The *p*-value (0.051) for the difference in the ''General Health'' domain was not statistically significant, but a trend toward improvement in this domain was observed. Therefore, repeating this study with a larger sample size may detect an improvement in this domain. CPAP treatment improved ''Functional Capacity'' and ''Pain''. Improvement reflected by the SF-36 after CPAP treatment has been reported previously in adults (45). However, OSAS did not sufficiently impact the quality of life in the elderly in a previous study (46). The improvement of pain as measured by the SF-36 in our study suggests an association between OSAS and the activation of inflammatory pathways and a reversal of OSAS by CPAP treatment (47).

The OSAS group exhibited fragmented sleep, increased light sleep, reduced slow-wave sleep, and reduced REM sleep on the PSG. These results are consistent with those reported in the literature (48).

CPAP treatment tended to decrease ESS scores, suggesting that this treatment is effective and supporting its probable association with the improvement in the quality of sleep observed in previous studies (36,49).

No differences in hypothyroidism, diabetes, and dyslipidemia were observed between the two groups; however, the prevalence of hypertension was higher in the OSAS group. All of our patients and control subjects received hypertension treatment, and blood pressure levels were controlled for as a comorbidity. This difference has been reported previously, and it highlights the association between OSAS and cardiovascular diseases (11). This association may influence OS. OS is associated with endothelial dysfunction and metabolic syndrome, which leads to cardiovascular diseases. However, OSAS is frequently complicated by metabolic syndrome (50). OSAS and metabolic syndrome may exert negative synergistic effects on the cardiovascular system through multiple mechanisms (e.g., intermittent hypoxia, sleep disruption, and activation of the sympathetic nervous system and inflammatory mediators) (51), which may be related to OS.

Our study demonstrated that elderly patients with OSAS may benefit from CPAP treatment, which improved sleep parameters, contributed to the reversal of OS and enhanced the patients' quality of life.

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AUTHOR CONTRIBUTIONS

Yagihara F, Lucchesi LM, D'Almeida V, de Mello MT, Tufik S, and Bittencourt LRA were responsible for the study concept and design, the analysis and interpretation of the data, the drafting of the manuscript, and the critical revision of the manuscript for important intellectual content; they had full access to all study data and take responsibility for the integrity and accuracy of the data analysis. Yagihara F, Lucchesi LM, and D'Almeida V were responsible for the acquisition of the data. Castro LS and Souza AL were responsible for the statistical analysis. Tufik S and Bittencourt LRA obtained the funding. D'Almeida V, de Mello MT, Tufik S and Bittencourt LRA were responsible for administrative, technical, and material support. Tufik S and Bittencourt LRA were responsible for the supervision of the study.

REFERENCES

1. American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement

techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667-89.
2. Hirata RP, Aguiar IC, Nacif SR, Giannasi LC, Leitao FS Filho, Santos IR, et al. Observational study on efficacy of negative expiratory pressure test proposed as screening for obstructive sleep apnea syndrome among commercial interstate bus drivers - protocol study. BMC Pulm Med. 2011;11:57, http://dx.doi.org/10.1186/1471-2466-11-57.
3. Romano S, Salvaggio A, Lo Bue A, Marrone O, Insalaco G. A negative expiratory pressure test during wakefulness for evaluating the risk of obstructive sleep apnea in patients referred for sleep studies. Clinics. 2011;66(11):1887-94, http://dx.doi.org/10.1590/S1807-59322011001100007.
4. Patil SP, Schneider H, Schwartz AR, Smith PL. Adult obstructive sleep apnea - Pathophysiology and diagnosis. Chest. 2007;132(1):325-37, http://dx.doi.org/10.1378/chest.07-0040.
5. Owens RL, Eckert DJ, Yeh SY, Malhotra A. Upper airway function in the pathogenesis of obstructive sleep apnea: a review of the current literature. Curr Opin Pulm Med. 2008;14(6):519-24, http://dx.doi.org/10.1097/MCP.0b013e3283130f66.
6. Romano S, Salvaggio A, Hirata RP, Lo Bue A, Picciolo S, Oliveira LV, et al. Upper airway collapsibility evaluated by a negative expiratory pressure test in severe obstructive sleep apnea. Clinics. 2011;66(4):567-72, http://dx.doi.org/10.1590/S1807-59322011000400008.
7. Cahali MB, Soares CF, Dantas DA, Formigoni GG. Tonsil volume, tonsil grade and obstructive sleep apnea: is there any meaningful correlation? Clinics. 2011;66(8):1347-52, http://dx.doi.org/10.1590/S1807-59322011000800007.
8. Young T. Sleep-disordered breathing in older adults: Is it a condition distinct from that in middle-aged adults? Sleep. 1996;19(7):529-30.
9. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population - The relative importance of risk factors in the development of sleep-disordered breathing. JAMA. 2003;289(17):2230-7, http://dx.doi.org/10.1001/jama.289.17.2230.
10. Pizza F, Contardi S, Mondini S, Trentin L, Cirignotta F. Daytime sleepiness and driving performance in patients with obstructive sleep apnea: comparison of the MSLT, the MWT, and a simulated driving task. Sleep. 2009;32(3):382-91.
11. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet. 2009;373(9657):82-93, http://dx.doi.org/10.1016/S0140-6736(08)61622-0.
12. Hattori M, Kitajima T, Mekata T, Kanamori A, Imamura M, Sakakibara H, et al. Risk factors for obstructive sleep apnea syndrome screening in mood disorder patients. Psychiatry Clin Neurosci. 2009;63(3):385-91, http://dx.doi.org/10.1111/j.1440-1819.2009.01956.x.
13. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med. 2002;165(5):677-82.
14. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39(1):44-84, http://dx.doi.org/10.1016/j.biocel.2006.07.001.
15. Greenberg H, Ye X, Wilson D, Htoo AK, Hendersen T, Liu SF. Chronic intermittent hypoxia activates nuclear factor-kappa B in cardiovascular tissues in vivo. Biochem Biophys Res Commun. 2006;343(2):591-6, http://dx.doi.org/10.1016/j.bbrc.2006.03.015.
16. Baldwin CM, Bootzin RR, Schwenke DC, Quan SF. Antioxidant nutrient intake and supplements as potential moderators of cognitive decline and cardiovascular disease in obstructive sleep apnea. Sleep Med Rev. 2005;9(6):459-76, http://dx.doi.org/10.1016/j.smrv.2005.04.004.
17. Tokuda F, Sando Y, Matsui H, Yokoyama T. N epsilon-(hexanoyl) lysine, a new oxidative stress marker, is increased in metabolic syndrome, but not in obstructive sleep apnea. Am J Med Sci. 2009;338(2):127-33.
18. Jun J, Polotsky VY. Metabolic consequences of sleep-disordered breathing. ILAR J. 2009;50(3):289-306.
19. Bonsignore MR, Zito A. Metabolic effects of the obstructive sleep apnea syndrome and cardiovascular risk. Arch Physiol Biochem. 2008;114(4):255-60, http://dx.doi.org/10.1080/13813450802307451.
20. Celec P, Hodosy P, Behuliak M, Pálffy R, Gardlík M, Halčák L, et al. Oxidative and carbonyl stress in patients with obstructive sleep apnea treated with continuous positive airway pressure. Sleep Breath. 2012;16(2):393-8, http://dx.doi.org/10.1007/s11325-011-0510-4
21. Lavie L. Oxidative stress–a unifying paradigm in obstructive sleep apnea and comorbidities. Prog Cardiovasc Dis. 2009;51(4):303-12, http://dx.doi.org/10.1016/j.pcad.2008.08.003.
22. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med. 1999;159(2):461-7.
23. Christou K, Kostikas K, Pastaka C, Tanou K, Antoniadou I, Gourgoulianis KI. Nasal continuous positive airway pressure treatment reduces systemic oxidative stress in patients with severe obstructive sleep apnea syndrome. Sleep Med. 2009;10(1):87-94, http://dx.doi.org/10.1016/j.sleep.2007.10.011.
24. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, et al. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. N Engl J Med. 2011;365(24):2277-86.
25. Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. Chest. 2008;134(4):686-92, http://dx.doi.org/10.1378/chest.08-0556.
26. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, et al. Sleep Heart Health Study Research Group. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002;162(8):863-900.
27. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441-6, http://dx.doi.org/10.1016/j.sleep.2009.10.005.
28. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med. 2009;7(6):e1000132, http://dx.doi.org/10.1371/journal.pmed.1000132.
29. Lavie P, Lavie L. Cardiovascular morbidity and mortality in obstructive sleep apnea. Curr Pharm Des. 2008;14(32):3466-73, http://dx.doi.org/10.2174/138161208786549317.
30. Pavlova MK, Duffy JF, Shea SA. Polysomnographic respiratory abnormalities in asymptomatic individuals. Sleep. 2008;31(2):241-8.
31. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea - A population health perspective. Am J Resp Crit Care. 2002;165(9):1217-39, http://dx.doi.org/10.1164/rccm.2109080.
32. Câmara dos Deputados C. Estatuto do idoso. In: Senado Federal, Secretaria Especial de Editoração e Publicações: Câmara dos Deputados, Centro de Documentação e Informação, Coordenação de Publicações; 2003.
33. Organização Pan-Americana da Saúde. Envelhecimento ativo: uma política de saúde. Brasília: OPAS; 2005.
34. International Classification of Sleep Disorders: diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy Of Sleep Medicine; 2005.
35. Bittencourt LRA, Silva RS, Conway SG. Laboratório do sono – Estrutura física e pessoal, técnica polissonográfica, questionário de sono e banco de dados. São Paulo: Associação Fundo de Incentivo a Psicofarmacologia – AFIP. 2005.
36. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.
37. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31(3):247-63.
38. Rechtschaffen A, Kales A. A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects. Los Angeles: Brain Information Service/Brain Research Institute. 1968.
39. Bonnet M, Carley D, Carskadon M, Easton P, Guilleminault C, Harper R, et al. EEG Arousals: Scoring Rules And Examples: A Preliminary Report From The Sleep Disorders Atlas Task Force Of The American Sleep Disorders Association. Sleep. 1992;15(2):173-84.
40. Chesson AL Jr, Wise M, Davila D, Johnson S, Littner M, Anderson WM, et al. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. Sleep. 1999;22(20):961-9.
41. Brandão LC, Hachul H, Bittencourt LR, Baracat EC, Tufik S, D'Almeida V. Effects of isoflavone on oxidative stress parameters and homocysteine in postmenopausal women complaining of insomnia. Biol Res. 2009;42(3):281-7.
42. Teramoto S, Yamaguchi Y, Yamamoto H, Hanaoka Y, Ishii M, Shinichiro H, et al. Increase in oxidative stress levels in elderly patients with obstructive sleep apnea syndrome: Effects of age and sex. J Am Geriatr Soc. 2008;56(3):569-71, http://dx.doi.org/10.1111/j.1532-5415.2008.01577.x.
43. Guemouri L, Artur Y, Herbeth B, Jeandel C, Cuny G, Siest G. Biological Variability of Superoxide-Dismutase, Glutathione-Peroxidase, and Catalase in Blood. Clin Chem. 1991;37(11):1932-7.
44. Barceló A, Barbé F, de la Peña M, Vila M, Pérez G, Piérola J, et al. Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment. Eur Respir J. 2006;27(4):756-60, http://dx.doi.org/10.1183/09031936.06.00067605.
45. Jing J, Huang T, Cui W, Shen H. Effect on quality of life of continuous positive airway pressure in patients with obstructive sleep apnea syndrome: a meta-analysis. Lung. 2008;186(3):131-44, http://dx.doi.org/10.1007/s00408-008-9079-5.
46. Martinez-Garcia MA, Soler-Cataluna JJ, Roman-Sanchez P, Gonzalez V, Amoros C, Montserrat JM. Obstructive sleep apnea has little impact on quality of life in the elderly. Sleep Med. 2009;10(1):104-11, http://dx.doi.org/10.1016/j.sleep.2007.11.009.
47. One SH, Onen F, Albrand G, Decullier E, Chapuis F, Dubray C. Pain tolerance and obstructive sleep apnea in the elderly. J Am Med Dir Assoc. 2010;11(9):612-6, http://dx.doi.org/10.1016/j.jamda.2010.04.003.

48. Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep-apnea. Eur Respir J. 1995;8(7):1161-78, http://dx.doi.org/10.1183/09031936.95.08071161.
49. Bittencourt LR, Silva RS, Santos RF, Pires ML, Mello MT. Excessive daytime sleepiness. Rev Bras Psiquiatr. 2005;27(Suppl 1):16-21, http://dx.doi.org/10.1590/S1516-44462005000500004.
50. Lurie A. Endothelial dysfunction in adults with obstructive sleep apnea. Adv Cardiol. 2011;46:139-70, http://dx.doi.org/10.1159/000325108.
51. Lurie A. Inflammation, oxidative stress, and procoagulant and thrombotic activity in adults with obstructive sleep apnea. Adv Cardiol. 2011;46:43-66, http://dx.doi.org/10.1159/000325105.