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Effects of continuous positive airway pressure on comprehensive geriatric assessment and cognitive function in elderly patients with obstructive sleep apnea syndrome

Valentino Condoleo[1] · Leonilde Bonfrate[2] · Giuseppe Armentaro[1] · Corrado Pelaia[1] · Velia Cassano[1] · Mario De Marco[1] · Giandomenico Severini[1] · Carlo Alberto Pastura[1] · Sofia Miceli[1] · Raffaele Maio[1] · Maria Perticone[1] · Franco Arturi[1] · Giorgio Sesti[3] · Angela Sciacqua[1]

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Abstract

Obstructive sleep apnea syndrome (OSAS) can lead to cognitive impairment and depression affecting memory, attention, and executive functions. Continuous positive airway pressure (CPAP) treatment seems to be able to revert changes in brain networks and neuropsychological tests correlated to OSAS. The aim of the present study was to evaluate the effects of a 6-month treatment with CPAP on functional, humoral and cognitive parameters in a cohort of elderly OSAS patients with several comorbidities. We enrolled 360 elderly patients suffering from moderate to severe OSAS and indication for nocturnal CPAP. At baseline the Comprehensive Geriatric Assessment (CGA) revealed a borderline Mini-Mental State Examination (MMSE) score that improved after 6-month treatment with CPAP (25.3 ± 1.6 vs 26 ± 1.5; $p < 0.0001$), as well as the Montreal Cognitive Assessment (MoCA) showed a mild improvement (24.4 ± 2.3 vs 26.2 ± 1.7; $p < 0.0001$). Moreover, functionality activities increased after treatment, as documented by a short physical performance battery (SPPB) (6.3 ± 1.5 vs 6.9 ± 1.4; $p < 0.0001$). Reduction of the Geriatric Depression Scale (GDS) from 6.0 ± 2.5 to 4.6 ± 2.2 ($p < 0.0001$) was also detected. Changes of homeostasis model assessment (HOMA) index, oxygen desaturation index (ODI), sleep-time spent with saturation below 90% (TC90), peripheral arterial oxyhaemoglobin saturation (SpO_2), apnea–hypopnea index (AHI) and estimation of glomerular filtration rate (eGFR), contributed, respectively, to 27.9%, 9.0%, 2.8%, 2.3%, 1.7% and 0.9% of MMSE variability for a total of 44.6% of MMSE variations. GDS score changes were due to the improvement of AHI, ODI and TC90, respectively, for 19.2%, 4.9%, 4.2% of the GDS variability, cumulative responsible for 28.3% of GDS modifications. The present real-world study shows that CPAP treatment is able to improve cognition and depressive symptoms in OSAS elderly patients.

Keywords Obstructive sleep apnea syndrome · Cognitive impairment · Comprehensive geriatric assessment · Continuous positive airway pressure · Endothelial function

Introduction

Obstructive sleep apnea syndrome (OSAS) is a respiratory disorder characterized by repeated events of upper airway collapse which leads to airflow limitation. Upper airway obstructions are defined as airflow decreases ≥ 90%, lasting more than 10 s; hypopneas take place when airflow reductions reach almost 30%, with consequent drops of haemoglobin saturation [1]. The consequent sleep fragmentation causes daytime symptoms featured by excessive sleepiness, lack of concentration and decreased attention, which impair daily activities and quality of life [2, 3]. About 4% of males and 2% of females complain of OSAS, which is characterized by a disease risk that progressively increases with age

Valentino Condoleo and Leonilde Bonfrate have contributed equally to the elaboration of this manuscript.

✉ Giuseppe Armentaro
peppearmentaro@libero.it

[1] Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Campus Universitario "S. Venuta", Viale Europa – Località Germaneto, 88100 Catanzaro, Italy

[2] Clinica Medica "A. Murri", Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy

[3] Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

for both genders [4]. Some epidemiological studies estimate that in Europe and the United States a prevalence of an apnea–hypopnea index (AHI) ≥ 5 without other symptoms occurs in 24% of men and 9% of women aged between 30 and 60 years [5]. It is well known that OSAS complications go far beyond the respiratory system, favouring and worsening other disorders such as insulin-resistance and diabetes mellitus, endothelial dysfunction, arterial hypertension and cerebrovascular diseases, possibly being responsible for an increased risk of all-cause mortality [6–8]. Moreover, a large body of evidence suggests that OSAS leads to significant cognitive impairment [9, 10]. Further studies suggested the presence of mild deficits in global intellectual function [11, 12], even if more recent meta-analyses reported no significant impairment [13]. OSAS patients experience frequently impairment in verbal memory [14, 15], and both short-term and long-term types of memory are affected [16, 17]. There is also strong evidence for attention impairment in OSAS, given by several studies conducted through classical neuropsychological and simulation tests [18, 19]. All these findings were also confirmed by specific meta-analyses [13, 20, 21]. According to the above literature data, the most important domains which seem to be impaired in OSAS patients include attention and executive functions, whereas memory is partially affected in a few subdomains, and global intellectual function is spared. Two longitudinal studies showed that OSAS represents an independent risk factor for the development of depression [22–25]. Indeed, the prevalence of depression is higher in patients with OSAS than in the general population [26]. Several different mechanisms can underlie cognitive impairments occurring in OSAS patients. An important pathogenic factor is chronic intermittent hypoxemia (CIH), resulting from haemoglobin desaturation due to upper airway collapse. This mechanism is responsible for repeated cycles of hypoxemia and reoxygenation in cerebral vessels, causing ischemia–reperfusion injury with the production of reactive oxygen species (ROS) [27–29], which induce vascular damage, inflammation and endothelial dysfunction. Sleep fragmentation is another cause of brain injury in OSAS patients. It is responsible for daytime symptoms such as excessive somnolence and attention deficits. The fragmentation of sleep architecture is also involved in brain damage through the disruption of sleep-active and wake-active neurons networks, leading to the release of several interleukins (IL), such as IL-1β, IL-4, IL-10 and as tumor necrosis factor alpha (TNF-α), that amplify the pathogenic cascade underlying endothelial dysfunction [30–33]. Moreover, different brain regions appear to be impaired, being characterized by a quantitative reduction of grey matter volume in the left posterior parietal cortex, right superior frontal gyrus, and in the cytoarchitecture of hippocampus [34]. Widespread white matter alterations are also present, featured by changes in brain networks and neuropsychological tests, that seem to be reversible after continuous positive airway pressure (CPAP) treatment [35]. The positive pressure maintains the patency of upper airways, thereby avoiding their collapse [1]. CPAP use improves nocturnal and daytime symptoms of OSAS so that it can be argued that CPAP also improves cognitive impairment in OSAS patients.

On the basis of the above considerations, the aim of this study was to evaluate the effects of a 6-month treatment with CPAP on functional, humoral and cognitive parameters in a cohort of elderly patients with moderate to severe OSAS and different comorbidities.

Materials and methods

Patients

Between March 2018 and December 2020, 360 consecutive outpatients, referring to the Sleep Disorder Unit of the Geriatrics Division, "Mater Domini" University Hospital of Catanzaro, Italy, were enrolled. Inclusion criteria were the following: moderate to severe OSAS with or without respiratory failure and indications of nocturnal CPAP, eventually enriched with oxygen therapy, ability to give a written consensus, age ≥ 70 years, ability to understand and submit psychometric tests. Exclusion criteria were the presence of severe dementia or Alzheimer disease, central or mixed apnea syndrome, atrial fibrillation, prior ischemic or haemorrhagic major stroke, psychiatric comorbidities or drug therapy that may affect the cognitive function or sleep (i.e. Selective Serotonin Reuptake Inhibitors, buspirone, ondasentron); and contraindications to nocturnal CPAP: recent facial or esophagogastric surgery, anatomical alterations or facial trauma and difficulty swallowing, evaluated by medical history [36–40].OSAS diagnosis was made after one-night home polygraphy. The report was analyzed with the dedicated software by two expert operators blinded to patients' characteristics, according to the American Academy of Sleep Medicine (AASM) guidelines [1]. During the enrolment visit, all patients underwent a through medical history anamnesis and a complete physical examination, measuring anthropometric and hemodynamic parameters. In particular, weight, height, and body mass index (BMI) were assessed. The Comprehensive Geriatric Assessment (CGA), blood tests, and evaluation of endothelial function with EndoPat were performed and explained below. After these preliminary evaluations, patients started nocturnal CPAP therapy using ResMed Airsense 10 Autoset (Resmed, Sydney, Australia), reaching a mean use time > 4 h per night. Follow-up visits were scheduled after 6 months after CPAP initiation.

Blood pressure measurement

Blood pressure (BP) measurements were obtained on the non-dominant arm in a seated patient, after five minutes of rest. At least three measurements were performed in three different visits, approximately two weeks apart. Systolic (SBP) and diastolic (DBP) values of BP were recorded, respectively, at the first (phase I) and at the last (phase V) Korotkoff tones. Baseline BP values were obtained from the average of three measurements performed at three-minute intervals [41].

Laboratory measurements

All laboratory measurements were carried out on peripheral blood samples after at least 12 h of fasting. Glycemia was determined by the glucose oxidase method (glucose analyzer, BeckmanCoulter, Milan). Creatinine levels were measured using the Jaffe method. The estimation of glomerular filtration rate (eGFR) was based on the new CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [42]. Serum uric acid (UA) levels were assessed using URICASE/POD method (Boehringer Mannheim, Mannheim, Germany). Serum levels of high-sensitivity C-reactive protein (hs-CRP) were measured by immunoturbidimetric method automated system (Cardio Phase hs-CRP, Milan, Italy). In addition, glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography certified by the national glycohemoglobin standardization program (NGSP) and using an automatic analyzer (Adams HA-8160 HbA1c analyzer, Menarini, Italy). Analytical determinations were taken using an automatic particle counter (Siemens Healthcare Diagnostics, ADVIA 120/2120 Haematology System, Milan, Italy) to measure haemoglobin, haematocrit, and white blood cell count. Plasma concentrations of insulin were determined by chemiluminescence test (Roche Diagnostics). Insulin resistance was determined by the homeostasis model assessment (HOMA) index [43].

Comprehensive geriatric assessment

In the Comprehensive Geriatric Assessment (CGA), the following tests were administered at baseline and at 6 months follow-up:

- Mini-Mental State Examination (MMSE) is a test for assessing intellectual efficiency disorders and for identifying cognitive impairment. It is made of 30 items that refer to seven different cognitive areas: orientation in time, orientation in space, recording of words, attention and calculation, evocation, language, constructive practice. The total score is between 0 and 30. A score of 18 or less indicates severe cognitive impairment; a score between 18 and 24 indicates moderate and mild cognitive impairment; a score of 25 represents a limit value; a score between 26 and 30 indicates cognitive normality [44].
- Montreal Cognitive Assessment (MoCA) is a brief screening tool used to detect early mild cognitive impairment (MCI). This one-page 30-point test can be administered to the patient in at last 10 min. Several cognitive domains are assessed in the test. The short-term memory recall task (5 points) involves two learning trials of five nouns, followed by a delayed recall after 5 min. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), then repetition of two syntactically complex sentences (2 points), and the fluency task. Finally, orientation to time and place is evaluated (6 points). Using a cut-off score of 26, MoCA has a sensitivity of 90% to detect MCI patients [45].
- Geriatric Depression Scale (GDS) is a self-assessment measure of depression in the elderly. The short form (GDS-S) consists of 15 items. Of the 15 elements, 10 indicate the presence of depression when responding positively, while the other 5 are indicative of depression when responding negatively, moreover > 5 points suggest depression and require follow-up evaluation, ≥ 10 points almost always indicate depression [46].
- Short physical performance battery (SPPB) or test to evaluate the functionality of the lower limbs. In this test there are three different sections: evaluation of balance in 3 tests, including maintaining the position with feet together for 10 min, maintaining the position of semi-tandem for 10 min (big toe on the side of the heel), maintaining the tandem position for 10 min (big toe behind the heel). The score varies from a minimum of 0 if the patient is unable to maintain the position with feet together for at least 10 min to a maximum of 4 if he is able to complete all three tests. Then we have the evaluation of the gait on 4 linear meters, where the score of the section varies on the basis of the time needed to complete the task. Finally, the assessment of the ability to perform, 5 consecutive times, the sit to stand from a chair without using the upper limbs that must be crossed in front of the chest. The score varies from 0 if unable to

4 if the test is carried out in less than 11.2 min. The total score on the scale has a range from 0 to 12 [47].

- Epworth Sleepiness Scale (ESS) is a self-administered questionnaire with 8 questions that last 2–3 min to be completed. Patients have to rate, on a 4-point scale (0–3), their usual chances of dozing off or falling asleep while engaged in eight different activities (sitting and reading; watching TV; sitting inactive in a public place as a theater or a meeting; as a passenger in a car for an hour without a break; lying down to rest in the afternoon when circumstances permit; sitting and talking to someone; sitting quietly after a lunch without alcohol; in a car, while stopped for a few minutes in the traffic). The ESS score ranges from 0 to 24, and the higher the ESS score, the higher that person's average sleep propensity in daily life. A score ≥ 16 indicates severe daily sleepiness and may relate to OSA diseases [48].

Polygraphy

OSAS diagnosis was made through a one-night home polygraphy registration using Vitalnight 7 (VitalAire GmbH, Norderstedt, Germany) equipped with a nasal cannula used to detect the flow-meter trace, two piezoelectric belts measuring thoraco-abdominal movements, a digital pulse oximeter assessing peripheral arterial oxyhaemoglobin saturation (SpO_2). Obstructive apnea was defined as a complete or sub-complete reduction in the airflow for almost 10 s with thoracic and abdominal respiratory efforts, while obstructive hypopnea was defined as a reduction in the airflow $\geq 30\%$ for almost 10 s, with associated desaturation $\geq 3\%$ and thoracic and abdominal respiratory efforts. Apnea–hypopnea index (AHI), oxygen desaturation index (ODI), sleep-time spent with saturation below 90% (TC90), mean value of sleep-time SpO_2, and the lowest saturation registered. AHI was used to classify the presence and the severity of OSAS ($5 \leq$ AHI < 15, mild; $15 \leq$ AHI < 30, moderate; AHI ≥ 30, severe) [1]. Only good-quality records were reviewed.

Endothelial function

Endothelial functionality was assessed using EndoPAT (Itamar Medical, Caesarea, Israel), a non-invasive device that use the peripheral response to reactive hyperemia to evaluate endothelial function. The device records endothelium-mediated changes in the digital pulse waveform known as the PAT (Peripheral Arterial Tone) signal, measured through a special finger-probe in the index of the two hands after that hyperemia was induced by occluding blood flow through the brachial artery for 5 min using an inflatable cuff on one hand. The occlusion in the brachial artery is followed by a hyperemia endothelial mediated, and the amplitude of the hyperemia is used to calculate a PAT ratio and the Reactive Hyperemia index (RHi). The same procedure was repeated for the contralateral arm, which serves as a control for non-endothelial dependent systemic effects [49].

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) (normally distributed data), or as the median and interquartile range (data not normally distributed). Normally distributed data were analyzed using t test for paired data, instead data not normally distributed were analyzed by the Wilcoxon test for paired data. Subsequently, a simple linear regression model was built with delta (Δ) as the dependent variable, i.e., changes in CGA variables between follow-up and baseline, and deltas of different variables that differed in a statistically significant manner between follow-up and baseline as independent variables. Therefore, changes in the variables that correlated significantly with changes in the dependent variable were entered into a stepwise multivariate linear regression model. Statistical analysis was carried out using SPSS V20.0 program for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

From an initial cohort of 512 patients, 12 were excluded because did not sign the informed consent, 54 because suffered from atrial fibrillation, 23 complained of Alzheimer's disease, 63 because had central apnoea syndrome (Fig. 1). The final cohort included 360 patients (252 men and 108 women) (mean age 75.2 ± 4.3 years). Table 1 shows the baseline anthropometric, clinical, and biochemical characteristics of the study population. In particular, 57.2% of patients suffered from type 2 Diabetes mellitus (T2DM), 5.8% from Heart Failure (HF), 21.4% from Chronic Ischaemic Cardiopathy and 34.7% from Chronic Obstructive Pulmonary Disease (COPD) or Asthma. When compared to baseline, 6-month data revealed correction of AHI (35.4 ± 19.1 vs

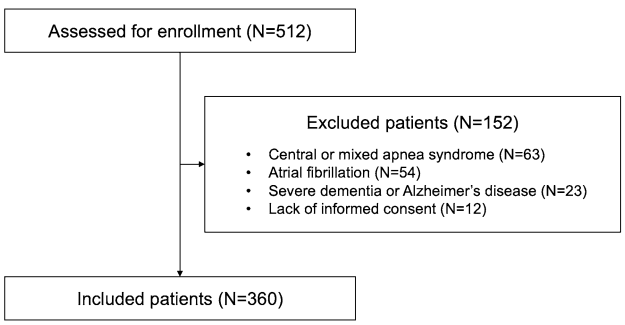

Fig. 1 Flowchart of the recruitment process of the study

Table 1 Baseline clinical characteristics of the overall study population

Age, years	75.2 ± 4.3
Sex, m/f (%)	252/108 (70/30)
Obesity, *n* (%)	226/360 (62.8)
Type 2 diabetes mellitus, *n* (%)	206/360 (57.2)
NAFLD, *n* (%)	62/360 (17.2)
Dyslipidaemia, *n* (%)	236/360 (65.6)
TIA, *n* (%)	88/360 (24.4)
Arterial hypertension, *n* (%)	270/360 (75)
Ischaemic heart disease, *n* (%)	77/360 (21.4)
Heart failure, *n* (%)	21/360 (5.8)
Chronic kidney disease, *n* (%)	171/360 (47.5)
COPD/asthma, *n* (%)	125/360 (34.7)
Smokers, *n* (%)	68/360 (17.8)
Ex smokers, *n* (%)	139/360 (38.6)
Severe Sleep Apnoea, *n* (%)	175/360 (48.6)
Moderate Sleep Apnoea, *n* (%)	186/360 (51.7)
CPAP, *n* (%)	360/360 (100)
CPAP and Oxygen therapy, *n* (%)	75/360 (20.8)

NAFLD nonalcoholic fatty liver disease, *TIA* transient ischemic attack, *COPD* chronic obstructive pulmonary disease, *CPAP* continuous positive airway pressure

9.5 ± 5.9 e/h; < 0.0001) and improvement of oxyhaemoglobin desaturation with an increase of mean nocturnal SpO_2 (92.0 ± 3.2 vs 94.9 ± 1.5%; $p < 0.0001$), TC90 [11.0 (2.5 – 32.8) vs 1.7 (0.3 – 9.1) %; $p < 0.0001$], and ODI [30.9 (18.7 – 47.0) vs 5.9 (4.4 – 11.9) e/h; $p < 0.0001$] (Fig. 2). Relevant improvements of hemodynamic and clinical parameters were observed, such as reduction in daytime heart rate (68.4 ± 9.9 vs 64.5 ± 8.7 bpm; $p < 0.0001$), in particular during the nocturnal period (68 ± 12.1 vs 61.5 ± 9.2 bpm; $p < 0.0001$), associated with a decrease of SBP (139 ± 13 vs 128.6 ± 9.3 mmHg; $p < 0.0001$) and DBP (78.2 ± 9.9 vs 72.8 ± 7.9 mmHg; $p < 0.0001$) (Table 2). Endothelial function showed a significant improvement, confirmed by the enhance of RHi values (1.57 ± 0.4 vs 2.2 ± 0.4; $p < 0.0001$) (Table 2). A significant improvement was detected also for the glycometabolic profile, with the reduction of HbA1c [6.6 (6.2 – 7.7) vs 6.1 (6.0 – 6.4) %, $p < 0.0001$], HOMA index [5.6 ± 3.2 vs 3.4 ± 1.5; $p < 0.0001$], uric acid [6.7 ± 1.3 vs 6.1 ± 0.4 mg/dl; $p < 0.0001$], and hs-CRP [3.7 ± 4.9 vs 2.3 ± 3.2 mg/dl; $p < 0.0001$] (Table 2). Renal function improved, with a reduction of creatinine values (1.17 ± 0.38 vs 0.99 ± 0.36 mg/dl; $p < 0.0001$) and an increase of eGFR (60.7 ± 17.3 vs 71.9 ± 17.8 ml/min/1.73 m^2; $p < 0.0001$) (Table 2). CGA revealed a borderline baseline MMSE score that improved during follow-up [25.3 ± 1.6 vs 26 ± 1.5; $p < 0.0001$], and MoCA showed a mild improvement in the same period [24.4 ± 2.3 vs 26.2 ± 1.7; $p < 0.0001$] (Table 2). Functionality and home daily activities increased, as documented by SPPB [6.3 ± 1.5 vs 6.9 ± 1.4; $p < 0.0001$] (Table 2). Reductions of ESS [11 ± 4.7 vs 3.7 ± 2.1; $p < 0.0001$] and GDS [6.0 ± 2.5 vs 4.6 ± 2.2; $p < 0.0001$] were observed (Table 2). Linear regression analysis revealed relationships between changes in CGA and the major considered clinical variables (Table 3). By using variations of MMSE score (Δ MMSE) as a dependent variable, linear regression analyses confirmed that MMSE changes were significantly associated with variation of AHI, TC90, ODI, mean SpO_2, HOMA index and eGFR. The same parameters, excepted for eGFR, but with also RHi, were significantly associated with Δ MoCA. GDS variations were significantly correlated with changes of AHI, ODI, TC90, and RHi. With regard to functional tests, Δ SPPB was significantly associated with variations of AHI, ODI, TC90, and HOMA index. Moreover, variables correlated to CGA changes were inserted in a multivariate linear regression model to define the independent predictors of CGA changes. We observed that changes in the HOMA index, ODI, TC90, SpO_2, AHI and eGFR, contributed, respectively, to 27.9%, 9.0%, 2.8%, 2.3%, 1.7% and 0.9% of MMSE variability, and the whole model accounted for a 44.6% of MMSE variations (Table 4). However, the variations of AHI, ODI, HOMA index and RHi explained, respectively, 25.0%, 7.4%, 4.8% and 2.4% of MoCA changes, overall contributing for 39.6% of Δ MoCA

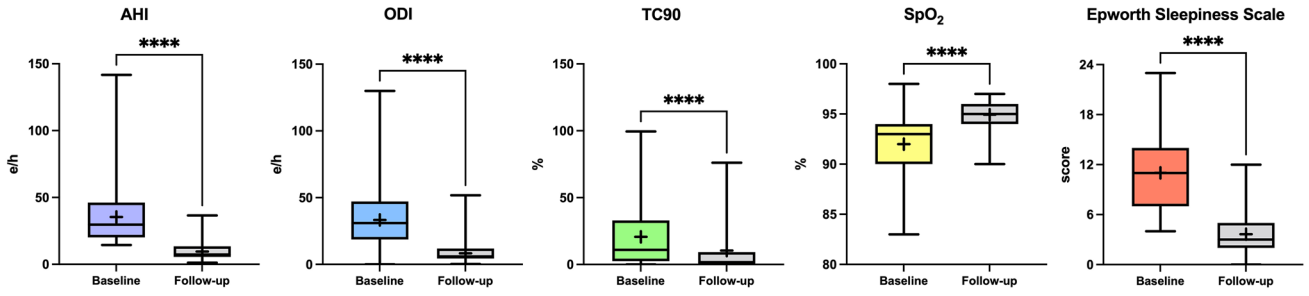

Fig. 2 Mean values of Apnea–Hypopnea index (AHI) (e/h), Oxygen desaturation index (ODI) (e/h), sleep-time spent with a saturation below 90% (TC90) (%), peripheral arterial oxyhaemoglobin saturation (SpO2) (%), Epworth Sleepiness Scale (ESS) (pt), at baseline and at six month of follow-up

Table 2 Variations between baseline and follow-up of the main study variables in the overall population

	Baseline	Follow-up	*p**
BMI, kg/m^2	32.7 ± 6.2	31.7 ± 5.8	< 0.0001
Waist circumference, cm	109.2 ± 13.9	107.0 ± 13.0	< 0.0001
SBP, mmHg	139 ± 13	128.6 ± 9.3	< 0.0001
DBP, mmHg	78.2 ± 9.9	72.8 ± 7.9	< 0.0001
MBP, mmHg	98.5 ± 9.8	91.4 ± 7.2	< 0.0001
Diurnal HR, bpm	68.4 ± 9.9	64.5 ± 8.7	< 0.0001
Nocturnal HR, afm	68 ± 12.1	61.5 ± 9.2	< 0.0001
MMSE, pt	25.3 ± 1.6	26 ± 1.5	< 0.0001
MoCA, pt	24.4 ± 2.3	26.2 ± 1.7	< 0.0001
GDS, pt	6 ± 2.5	4.6 ± 2.2	< 0.0001
SPPB, pt	6.3 ± 1.5	6.9 ± 1.4	< 0.0001
Glycaemia, mg/dl	128 ± 41.5	106.1 ± 20.6	< 0.0001
Insulinemia, mg/dl	17.7 ± 7.3	13 ± 5.1	< 0.0001
HOMA	5.6 ± 3.2	3.4 ± 1.5	< 0.0001
HbA1c, %	6.6 (6.2–7.7)	6.1 (6.0–6.4)	< 0.0001
Creatinine, mg/dl	1.17 ± 0.38	0.99 ± 0.36	< 0.0001
e-GFR, ml/min/m^2 (CKD-EPI)	60.7 ± 17.3	71.9 ± 17.8	< 0.0001
Uric acid, mg/dl	6.7 ± 1.3	6.1 ± 0.4	< 0.0001
Hb, g/dl	13.9 ± 1.7	13.8 ± 1.3	0.353
HCT, %	43.3 ± 5.4	42.8 ± 4.3	< 0.0001
hs-CRP, mg/l	3.7 ± 4.9	2.3 ± 3.2	< 0.0001
RHi	1.57 ± 0.4	2.2 ± 0.4	< 0.0001

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *HR* heart rate, *MMSE* mini mental state examination, *MoCA* Montreal cognitive assessment, *GDS* geriatric depression scale, *SPPB* short performance physical battery, *HOMA* homeostatic model assessment, *HbA1c* glycated haemoglobin, *eGFR* estimated glomerular filtration rate, *Hb* haemoglobin, *HCT* haematocrit, *hs-CRP* highly sensitive c-reactive protein, *RHi* reactive hyperemia index

(Table 4). GDS score changes were due to the improvement of AHI, ODI and TC90, respectively for 19.2%, 4.9%, 4.2% of the GDS variability, cumulative responsible for 28.3% of GDS modifications (Table 5). Changes in SPPB could be referred to HOMA index, ODI, TC90 and AHI variations for 19.9%, 7.5%, 2.4%, 1.4%, respectively, and considered together were responsible for 31.2% of SPPB variations (Table 5).

Discussion

In a large geriatric cohort, we observed that subjects with OSAS showed a significant improvement in cognitive function and depressive symptoms after standard treatment with CPAP. Moreover, a significative improvement in markers of inflammation and endothelial dysfunction, as well as in metabolic and renal function, were detected after six months of positive pressure therapy.

In particular, we found a significative statistical association between the treatment of sleep respiratory events and the improvement in cognitive function, measured through two widely used neuropsychological screening tests. More specifically, linear and multivariate regressions showed that improvements in the main indices of hypoxia might explain in a large amount the higher scores of MoCA and MMSE during follow-up. As described above, MoCA was shown to be most sensible in early MCI, and plausibly, this is the reason because we found a worse score at baseline with respect to MMSE. However, the correction of AHI and ODI events determined 32.4% of the MoCA changes, while the correction of mean nocturnal SpO_2, TC90, ODI, and AHI events were responsible for 15.8% in MMSE improvement. Furthermore, considering AHI and ODI events as direct markers of nocturnal chronic intermittent hypoxemia, we argue that the enhancements in cognitive function were due to CPAP-induced interruption of CIH and to the consequent blockade of ROS cascade [50]. In particular, ROS damage blood vessel walls, thus triggering endothelial dysfunction and the production of C reactive protein (CRP) and pro-inflammatory cytokines such as TNF-α and IL-6 [51, 52]. These cytokines are responsible for the reduction of nitric oxide (NO) production and disruption of cerebral vessels autoregulation, expression of adhesion molecules on the endothelial cells and permeability of the blood–brain barrier (BBB) [53, 54]. Endothelial leaks and expression of adhesion molecules on the BBB allow the passage of plasma proteins and macrophages leading to fibrosis and neuronal/microglia damage, causing lacunar infarction and chronic vessel disease [55–57]. CIH is also a potent trigger of sympathetic system hyperactivity, through baroreflex and autonomic pathways that lead to sympathetic overactivity that contributes to endothelial dysfunction and systemic hypertension [58, 59]. In normal subjects, intracranial haemodynamic homeostasis is maintained by autoregulation even during arterial hypertension. In OSAS patients, the small vessel disease results in increased stiffness of vessel walls, associated with an impaired ability to respond to haemodynamic changes, thus exposing the brain to damage during hypertension or hypoperfusion [60, 61]. Therefore, during apnoic or hypopnoic events, increased blood flow may not be able to guarantee an adequate amount of oxygen. This is particularly true for the terminal arteriolar territory with poor collateral circulation, and intrinsic hypoxic vulnerable brain regions such as frontal and pre-frontal lobes, basal ganglia, and hippocampus [62–66]. Notably, mean nocturnal SpO_2 and TC90 are not markers of intermittent hypoxemia events, but only reflect the rate of oxyhemoglobin saturation during sleep time [1], and they did not statistically correlate

Table 3 Linear regression analysis between Δ of MMSE, MoCA, GDS, SPPB as dependent variables and Δ of different covariates in the study population

	Δ MMSE	Δ MoCA	Δ GDS	Δ SPPB
	R/P	R/P	R/P	R/P
Δ AHI, *e/h*	− 0.138/0.003	− 0.266/ < 0.0001	0.265/ < 0.0001	− 0.134/0.010
Δ TC90, %	− 0.126/0.004	− 0.096/0.037	0.203/ < 0.0001	− 0.128/0.009
Δ ODI, *e/h*	− 0.223/ < 0.0001	− 0.244/ < 0.0001	0.211/ < 0.0001	− 0.214/ < 0.0001
Δ SpO2, %	0.286/0.035	0.115/0.420	− 0.018/0.907	0.072/0.629
Δ SBP, *mmHg*	− 0.047/0.275	− 0.041/0.359	0.005/0.911	− 0.086/0.071
Δ DBP, *mmHg*	− 0.069/0.115	− 0.028/0.548	0.031/0.534	− 0.064/0.186
Δ HOMA,	− 0.326/ < 0.0001	− 0.176/0.023	0.087/0.295	− 0.197/0.016
Δ eGFR, *ml/min/1.73 m²*	0.311/0.029	0.165/0.268	− 0.187/0.243	0.164/0.298
Δ Uricemia, *mg/dl*	− 0.013/0.734	0.032/0.440	0.017/0.708	− 0.0001/0.991
Δ hs-CRP, *mg/l*	− 0.037/0.505	0.035/0.545	0.059/0.338	− 0.026/0.671
Δ RHi,	0.104/0.068	0.139/0.020	− 0.051/0.424	0.093/0.138

Δ variation between baseline and six months follow-up, *MMSE* mini-mental state examination, *MoCA* Montreal cognitive assessment, *GDS* geriatric depression scale, *SPPB* short performance physical battery, *AHI* apnea-hypopnea index, *TC90* percentage time of saturation below 90%, *ODI* oxygen desaturation index, SpO_2 peripheral arterial oxyhemoglobin saturation, *SBP* systolic blood pressure, *DBP* dyastolic blood pressure, *HOMA* homeostatic model assessment, *eGFR* estimated glomerular filtration rate, *hs-CRP* highly sensitive c-reactive protein, *RHi* reactive hyperemia index

Table 4 Stepwise multivariate linear analysis between Δ of MMSE and Δ of MoCA as dependent variable, and Δ of different covariates

Δ of MMSE as dependent variable				Δ of MoCA as dependent variable			
All	R^2 partial	R^2 total	*p*	All	R^2 partial	R^2 total	*p*
Δ HOMA	27.9%	27.9%	< 0.0001	Δ AHI, *e/h*	25.0%	25.0%	< 0.0001
Δ ODI, *e/h*	9.0%	36.9%	< 0.0001	Δ ODI, *e/h*	7.4%	32.4%	< 0.0001
Δ TC90, %	2.8%	39.7%	< 0.0001	Δ HOMA	4.8%	37.2%	< 0.0001
Δ SpO_2, %	2.3%	42.0%	0.001	Δ RHi	2.4%	39.6%	< 0.0001
Δ AHI, *e/h*	1.7%	43.7%	0.010	–	–	–	–
Δ eGFR, *ml/min/1.73 m²*	0.9%	44.6%	< 0.0001	–	–	–	–

MMSE mini-mental state examination, *MoCA* Montreal cognitive assessment, *HOMA* homeostatic model assessment, *ODI* oxygen desaturation index, *TC90* percentage time of saturation below 90%, SpO_2 peripheral arterial oxyhemoglobin saturation, *AHI* apnea-hypopnea index, *eGFR* estimated glomerular filtration rate *RHi* reactive hyperemia index

Table 5 Stepwise multivariate linear regression analysis between Δ of GDS and Δ of SPPB as dependent variable and Δ of different covariates

Δ of GDS as dependent variable				Δ of SPPB as dependent variable			
All	R^2 partial	R^2 total	*p*	All	R^2 partial	R^2 total	*p*
Δ AHI, *e/h*	19.2%	19.2%	< 0.0001	Δ HOMA	19.9%	19.9%	< 0.0001
Δ ODI, *e/h*	4.9%	24.1%	< 0.0001	Δ ODI, *e/h*	7.5%	27.4%	< 0.0001
Δ TC90, %	4.2%	28.3%	< 0.0001	Δ TC90, %	2.4%	29.8%	< 0.0001
–	–	–	–	Δ AHI, *e/h*	1.4%	31.2%	0.005

GDS geriatric depression scale, *SPPB* short performance physical battery, *AHI* apnea hypopnea index, *ODI* oxygen desaturation index, *TC90* percentage time of saturation below 90%, *HOMA* homeostatic model assessment

with MoCA improvement, accounting only for a 5.1% of MMSE change.

Literature data include inconsistent results about cognitive functions in OSAS patients and their improvement after CPAP therapy. Several studies suggested a correlation between OSAS and MCI detected through MMSE or MoCA [67], as well as the association of sleep respiratory events such as ODI and TC90 with lower neuropsychological test scores [68], or with the nocturnal nadir of SpO_2 [69]. The treatment with CPAP was able to improve cognitive

function, but currently available data are discordant about the time treatment needed to obtain improvement or the cognitive domain and subdomain that are restored by treatment [70]. Several reasons make it difficult to assess a direct comparison between our results and those previously published, such as relevant differences in sample characteristics, and in tests used to assess cognitive domains and subdomains. However, the current bulk of evidence is consistent with the positive CPAP effects on daytime sleepiness, attention, executive function and memory [71], and it is conceivable that these same factors are responsible for the improvement that we observed in the cohort of our patients.

In the present investigation, we found that with respect to baseline, mild depressive symptoms significantly improved upon CPAP treatment. In fact, the association between OSAS and mood disorders is well known [25, 72, 73]. Several mechanisms underlie the relationship between sleep disorders and depressive conditions. Firstly, there is a certain degree of overlap between the diagnostic criteria of depressive disorders and the characteristic daytime symptoms such as fatigue and loss of energy [74], so that it is conceivable that the used scores for mood and OSAS can arise from the same symptom pattern. Further common predisposing conditions include obesity and inflammation, which are both related to OSAS and depression [75–77]. The association between depression and OSAS was also corroborated by neuroimaging studies, which showed that the impairment in the insula cortex of OSAS patients was associated with depression and anxiety [78]. According to our evaluations, we found that the improvement in depressive symptoms was consistent with the correction of hypoxic events, including AHI, ODI and TC90. Differently from our predictions, inflammation and endothelial dysfunction markers did not correlate with GDS score improvement. Hence, we argue that the reversal of daytime symptoms may explain mood improvements. Moreover, SPPB changes were also associated with the reported decreases in apnoic and oxygen desaturation events. In this regard, several previous studies found in OSAS patients a relationship between fatigue reduction and the correction of daytime symptoms due to CPAP treatment [79–82]. It is reasonable that the relief of sleepiness and fatigue improves the functionality of elder patients complaining of OSAS.

The main limitation of this study depends on OSAS diagnosis, which was made using a one-night home polygraphy that did not record electroencephalographic channels so that in our model we could not analyse the contribution on cognition of arousals, respiratory effort-related arousal (RERA), and fragmentation of sleep architecture. In addition, we excluded from our study patients with psychiatric conditions or with a drug therapy that could induce effects on sleep and cognition. Therefore, we routinely excluded patients with moderate to severe depressive episodes and enrolled only elderly subjects affected by mild depressive symptoms. Similar to all real-world experiments, it is a single-center study and not a randomized controlled clinical trial, therefore, biased selection cannot be ruled out; moreover, a matched control group is missing.

Conclusions

OSAS was associated with cognitive impairment in geriatric patients, and the MoCA test was more reliable when compared to MMSE, to detect initial cognitive deficits. In particular, OSAS represents a systemic disease that involves the cardiovascular system, metabolism, renal activity and functionality in the elderly. Within this context, we herein demonstrated in OSAS patients that CPAP treatment was able to improve cognition and depressive symptoms.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The local Ethical Committee (Comitato etico Regione Calabria "Area Centro") approved the protocol (code protocol number 2020.161). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Informed written consent was obtained from all participants.

Consent for publication Not applicable.

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