Sleep and Breathing (2019) 23:665–672
https://doi.org/10.1007/s11325-018-1754-z

BASIC SCIENCE • ORIGINAL ARTICLE

Postural and vestibular changes related to CPAP treatment in moderate-to-severe OSA patients: a 12-month longitudinal study

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Received: 3 May 2018 / Revised: 18 October 2018 / Accepted: 13 November 2018 / Published online: 19 November 2018

Abstract

Purpose To assess whether vestibulo-ocular reflex (VOR) gain, posturography parameters and related clinical outcomes can improve in OSA patients after 12 months of CPAP treatment, taking into consideration that a certain degree of vestibular dysfunction has been identified in these subjects.

Methods Vestibular, postural, clinical, and polygraphic parameters were assessed in 32 OSA patients before and after beneficial CPAP treatment by means of video head impulse test (vHIT), static posturography (SP), Dizziness Handicap Inventory (DHI), Epworth Sleepiness Scale (ESS), and Apnea–Hypopnea Index (AHI), respectively, and were compared by means of a "within-subject" ANOVA model and Spearman's rank correlation.

Results After the 12-month period of treatment, OSA patients demonstrated a significant reduction in AHI values, in both opened and closed eyes conditions of surface and length as well as in power spectra recorded in low, middle, and high frequency interval. Although a significant improvement was also recorded among DHI and ESS scores, VOR gain increase did not survive to post-hoc corrections. Finally, positive correlations between the differences between pre- and post-treatment AHI, ESS, and PS values were found.

Conclusions The present work highlighted that postural instability and dizziness-related conditions due to OSA may improve after 12 months of CPAP treatment. Although VOR gain did not demonstrate significant improvement, this study might open future perspectives directed to assessing VOR gain changes after longer periods of CPAP treatment.

Keywords Obstructive sleep apnea syndrome · Posturography · Vestibulo-ocular reflex · Video head impulse test · CPAP

Summary of abbreviated terms

AHI	Apnea–Hypopnea Index
ODI	Oxygen desaturation index
SaO_2	Oxygen saturation
lowest SaO_2	Time spent with $SaO_2 < 90\%$
vHIT	Video Head Impulse Testing
SPT	Static Posturography Testing
SP	Stiff platform
FC	Foam carpet
FFT	Fast Fourier transform
PS	Power spectra of body oscillations
DHI	Italian Dizziness Handicap Inventory
ESS	Epworth Sleepiness Scale
VOR	Vestibulo-ocular reflex

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Introduction

Subjects with obstructive sleep apnea (OSA) have recurrent episodes of upper respiratory tract obstruction causing intermittent hypoxia and fragmented sleep, which in turn have long-term effects on neurocognitive functions [1, 2]. Indeed, it has been suggested that sleep fragmentation and deprivation are mechanisms that determine cognitive deterioration, including impairments of memory, executive functioning, attention, and also of motor and balance coordination [2].

Balance is controlled by the online integration of vestibular, visual, and proprioceptive inputs so that this sensorial stream is re-weighted and processed in the brain stem and cerebellum, which makes it possible for postural muscle tensing to maintain the center of gravity [3].

According to studies using sleep deprivation models (that alter sleepiness/vigilance levels), the vestibular system is mainly affected by an increase in the length of awake time [4, 5]. Moreover, sleep deprivation in humans can provoke an alteration in the posterior parietal cortex [6] that is pivotally involved in processing vestibular inflow related to space representation and in controlling the vestibulo-ocular reflex (VOR) [6, 7]—and that more extensively, leads to impairment in central multisensory integration and consequently to poorer postural control [8–10].

In line with these assumptions, vestibular dysfunction has been shown to be more critically pronounced in moderate-to-severe than in mild OSA groups [1, 11–13]. The recent analyses of the VOR gain under physiological conditions (i.e., via video head impulse test; vHIT), functional brain imaging studies and spectral analysis of body sway have reinforced previous hypotheses suggesting that the impairment related to hypoxia in the brainstem and cortical level is the neurophysiological counterpart that leads to the deterioration of the top-down and bottom-up vestibular pathways and sensorial integration process [1, 4, 6, 11–15].

The standard treatment for patients with OSA is continuous positive airway pressure (CPAP) and its chronic application has been demonstrated to improve sleep quality and to reverse cortical and brainstem dysfunction in OSA subjects with subsequent neurocognitive and behavioral improvement [15–17].

Therefore, to evaluate how CPAP treatment might affect the vestibulo-ocular and vestibulo-spinal pathways that determine postural changes, this study aimed to assess VOR gain, posturography parameters, and related clinical outcomes in a group of moderate-to-severe OSA subjects before and also after 12 months of CPAP treatment.

Materials and methods

Participants and study design

Following the American Academy of Sleep Medicine criteria [18], 32 moderate-to-severe OSA patients previously studied by means of the home sleep apnea test at the Sleep Disorder Center of the University of Rome "Tor Vergata" were included in this protocol [13]. Eligible OSA patients were required to be anamnestically negative for malignancy, head trauma, neuropsychiatric disorders, and metabolic, cardiovascular, endocrine, infectious, and neuro-otological illnesses. The common peripheral blood parameters were checked and neurological disorders were excluded using the Mini Mental State Examination and Magnetic Resonance Imaging. Finally, no patient was pregnant or breastfeeding and no participants on medications that might influence neuro-otological functions were included. The study adhered to the principles of the Declaration of Helsinki and all the participants gave written informed consent after receiving a detailed explanation of the protocol, which was approved by the Independent Ethical Committee of the University of Rome "Tor Vergata."

At baseline, OSA patients underwent the home sleep apnea test, carried out according to AASM criteria [18]. Apnea–Hypopnea Index (AHI) was determined as the sum of all apneas (> 90% reduction in airflow for > 10 s) and all hypopneas (> 30% reduction in airflow > 10 s) associated with ≥ 3% O_2 desaturation [18]. Moreover, also the following oxygen saturation (SaO_2) parameters were ascertained: mean SaO_2, lowest SaO_2, time spent with SaO_2 < 90% (T < 90), and oxygen desaturation index (ODI) (number of oxygen desaturations ≥ 3% per hour). All patients were followed up at our Sleep Medicine Center and had to meet three specific inclusion criteria for this study: 1 year of CPAP therapy, good compliance to CPAP therapy used ≥ 4 h per night and of > 5 nights per week, and efficacy of the CPAP treatment supported by the ventilator software report (AHI < 5 per hour) [19].

After an in-depth clinical otoneurological examination [20] and in order to comply with the longitudinal approach of the study, 1 week before and 1 week after the 12-month period of treatment, all OSA patients underwent the following tests:

- Follow-up visits at the Sleep Medicine Center, with the evaluation of compliance and effectiveness of CPAP treatment by analyzing the ventilator software report [21];
- Otoneurological testing, consisting of:

Video head impulse testing (vHIT) For vHIT evaluations, the EyeSeeCam™ System and the procedure recommended in previous studies were used [20, 22]. According to the software manufacturer (OtoAccess™, Interacoustics, Middelfart, Denmark), right and left side median values registered at 60 ms were transferred on .xls file for raw analysis. Following previous experiences [13, 20] and in agreement with quantitative studies [13, 22], an average gain-reference range [$mean_{normal} \pm 2$(standard deviations; SD)]—incorporating 95% of the healthy population, age and gender matched with the current sample of patients and concerning the previously described 32 healthy volunteers in our laboratory—was set at 1.05 ± 0.32 [13];

Static posturography testing (SPT) Subjects were instructed to maintain an upright position on a standardized platform for static posturography (EDM Euroclinic®, MEDI-CARE Solutions, Bologna, Italy). The recording interval was 60 s for each test (eyes closed or opened while standing on the stiff

platform [SP] or foam carpet [FC]) and the sampling frequency was 25 Hz [23]. The posturography parameters were the trace length, the surface of the ellipse of confidence and the fast Fourier transform (FFT) elaboration of oscillations on both the X (right-left) and Y (forward-backwards) planes [23]. According to previous experiences [20, 23, 24] and FFT core function analysis implemented in Matlab (MathWorks, Natick, MA, USA) space [13, 20], spectral values (power spectra, PS) of body oscillations were gained and were split into three groups: 0.01–0.70 Hz (low frequency interval), 0.70–1.00 Hz (middle frequency interval), and 1.00–5.00 Hz (high frequency interval). Normative data for posturography parameters and FFT results gained by means of the present procedure in age- and gender-matched healthy population are reported in a previous study [13];

The following validated questionnaires:

- The Italian Dizziness Handicap Inventory (DHI) version, consisting of 25 items aimed at evaluating patients' functional (nine questions), emotional (nine questions), and physical (seven questions) restrictions with multiple choice answers as follows: "yes" (4 points), "sometimes" (2 points), and "no" (0 points) [25];
- The Epworth Sleepiness Scale (ESS), which is a validated questionnaire, extensively employed to explore daytime sleepiness [26, 27].

Data handling and statistical analysis

Mean and standard deviations (SDs) of all variables were calculated in OSA groups. In order to verify that data were of Gaussian distribution, the D'Agostino K-squared normality test was adopted (where the null hypothesis is that the data are distributed normally). A within-subjects analysis of variance (ANOVA) was performed for AHI and each otoneurological and VQ variable. Age and gender were managed as continuous and categorical predictors, respectively. The significant cut-off level (a) was fixed at a p value of 0.01. Bonferroni correction for multiple comparisons was applied to test post-hoc significant main effects. Spearman's rank correlation was performed between significant pre–post-treatment differences (Δ) in otoneurological, home sleep apnea test, and VQ scores. A significant cut-off level (a) was set at a p value of 0.01 (STATISTICA version 7 for Windows).

Results

OSA patients demonstrated a significant ($p < 0.001$) decrease in AHI values after 12 months of CPAP treatment (Table 1). The recorded CPAP usage was 5.32 ± 1.05 h per day and 5.9 ± 0.53 days per week and no significant changes were demonstrated in BMI within the treatment period ($p > 0.01$) (Table 1).

Table 1 Pre- and post-treatment clinical aspects of moderate-to-severe OSA patients

	Pre-treatment		Post-treatment		Significance
	Mean	SD	Mean	SD	
BMI	28.11	3.76	27.78	3.78	$F(1, 31) = 30.536$, $p > 0.01$
ESS	*10.68*	*3.02*	*7.62*	*2.25*	$F(1, 31) = 150.37$, $p < 0.01$
AHI	*38.92*	*14.94*	*4.3*	*1.44*	$F(1, 31) = 171.74$, $p < 0.01$
DHI-P	*16.37*	*2.75*	*13.62*	*2.56*	$F(1, 31) = 197.42$, $p < 0.01$
DHI-E	*27.5*	*3.44*	*23.75*	*3.43*	$F(1, 31) = 225.00$, $p < 0.01$
DHI-F	*27*	*3.96*	*22.81*	*4.12*	$F(1, 31) = 647.25$, $p < 0.01$
Total DHI	*70.87*	*5.07*	*60.18*	*5.38*	$F(1, 31) = 1220.0$, $p < 0.01$

In italics are highlighted significant main effects of clinical scores before and after 12 months of CPAP treatment in OSA patients. *BMI*, body mass index; *ESS*, Epworth Sleepiness Scale; *AHI*, Apnea–Hypopnea Index; *DHI*, Dizziness Handicap Inventory; *P*, physical, *E*, emotional; *F*, functional; *SD*, standard deviation. Exact p values are given in the text

On the other hand, a significant reduction of surface values was found in post-treatment opened eyes condition on both SP ($p = 0.0034$) and FC ($p = 0.0041$) and in closed eyes condition on SP ($p = 0.0045$) when compared to pre-treatment scores (Table 2). Accordingly, post-treatment length values in opened eyes condition on SP demonstrated to be significantly ($p = 0.0039$) reduced after 12 months of CPAP treatment (Table 2).

Concerning the FFT analysis, a significant reduction of PS post-treatment values was found in closed eyes condition on X and Y planes on both SP and FC within low ($p = 0.0018$, 0.0024, 0.0022, and 0.0037, respectively) and middle frequency ($p = 0.0012$, 0.0021, 0.00087, and 0.00076, respectively) interval when compared with pre-treatment scores. In line, post-treatment PS values in closed eyes condition on X and Y planes on FC within high frequency interval demonstrated to significantly ($p = 0.0036$ and 0.0029) be reduced after 12 months of CPAP treatment (Fig. 1, Table 2).

Although the within-subject ANOVA found a significant main effect when comparing pre- and post-treatment VOR gain values, such a comparison did not survive the Bonferroni correction ($p = 0.0086$) (Table 2).

Furthermore, a significant reduction was found in post-treatment DHI-P ($p = 0.0034$), DHI-E ($p = 0.0031$), DHI-F ($p = 0.0036$), and DHI total score ($p < 0.001$) as well as in ESS ($p = 0.0028$) outcomes (Fig. 2, Table 1).

Finally, positive correlations between the Δ AHI and Δ PS values in closed eyes condition on the Y plane within the low frequency interval on SP ($r = 0.75$) and between Δ ESS and Δ PS values in closed eyes condition on the X plane on FC within the high frequency interval ($r = 0.72$) were found (Fig. 3).

Table 2 Otoneurological main effects in pre and post-treatment OSA patients

	Pre-treatment		Post-treatment		Significance
	Mean	SD	Mean	SD	
Low frequency interval PS					
CE X	*8.26*	*1.83*	*6.01*	*1.81*	$F(1, 31) = 2909.8$, $p < 0.01$
CE Y	*8.1*	*1.71*	*5.87*	*1.79*	$F(1, 31) = 1118.0$, $p < 0.01$
OE X	5.55	0.46	5.23	0.47	$F(1, 31) = 365.12$, $p > 0.01$
OE Y	4.67	0.42	4.37	0.43	$F(1, 31) = 319.7$, $p > 0.01$
FC-CE X	*11.63*	*1.02*	*10.35*	*1.08*	$F(1, 31) = 808.86$, $p < 0.01$
FC-CE Y	*9.55*	*1.63*	*7.52*	*1.6*	$F(1, 31) = 5614.1$, $p < 0.01$
FC-OE X	8.68	0.8	8.04	0.84	$F(1, 31) = 228.9$, $p > 0.01$
FC-OE Y	7.3	0.45	6.94	0.47	$F(1, 31) = 191.6$, $p > 0.01$
Middle frequency interval PS					
CE X	*0.57*	*0.04*	*0.5*	*0.05*	$F(1, 31) = 206.06$, $p < 0.01$
CE Y	*0.5*	*0.01*	*0.47*	*0.02*	$F(1, 31) = 163.30$, $p < 0.01$
OE X	0.31	0.02	0.3	0.01	$F(1, 31) = 74.291$, $p > 0.01$
OE Y	0.22	0.01	0.2	0.01	$F(1, 31) = 31.23$, $p > 0.01$
FC-CE X	*1.76*	*0.04*	*1.69*	*0.04*	$F(1, 31) = 369.00$, $p < 0.01$
FC-CE Y	*1.78*	*0.03*	*1.72*	*0.03*	$F(1, 31) = 721.19$, $p < 0.01$
FC-OE X	0.23	0.01	0.22	0.01	$F(1, 31) = 38.14$, $p > 0.01$
FC-OE Y	0.31	0.02	0.3	0.02	$F(1, 31) = 29.63$, $p > 0.01$
High frequency interval PS					
CE X	1.12	0.13	1.1	0.13	$F(1, 31) = 90.251$, $p > 0.01$
CE Y	1.06	0.1	1.06	0.1	$F(1, 31) = 33.86$, $p > 0.01$
OE X	1.02	0.14	1.02	0.14	$F(1, 31) = 61.00$, $p > 0.01$
OE Y	0.8	0.19	0.8	0.19	$F(1, 31) = 45.61$, $p > 0.01$
FC-CE X	*1.87*	*0.12*	*1.72*	*0.12*	$F(1, 31) = 426.1$, $p < 0.01$
FC-CE Y	*1.91*	*0.13*	*1.75*	*0.13*	$F(1, 31) = 454.7$, $p < 0.01$
FC-OE X	0	0	0	0	$F(1, 31) = 28.5$, $p > 0.01$
FC-OE Y	0.73	0.31	0.72	0.31	$F(1, 31) = 21.85$, $p > 0.01$
Surface					
OE	*710.58*	*236.88*	*485.66*	*216.66*	$F(1, 31) = 1123.6$, $p < 0.01$
CE	*1681.1*	*472.67*	*1214.91*	*460.62*	$F(1, 31) = 2057.3$, $p < 0.01$
FC-OE	*1318.69*	*366.79*	*932.74*	*363.6*	$F(1, 31) = 19{,}302.0$, $p < 0.01$
FC-CE	3956.48	855.9	3349.98	853.3	$F(1, 31) = 629.32$, $p > 0.01$
Length					
OE	*649.98*	*108.66*	*527.7*	*113*	$F(1, 31) = 1498.0$, $p < 0.01$
CE	964.78	171.62	830.64	166.28	$F(1, 31) = 504.9$, $p > 0.01$
FC-OE	1099.39	292.18	870.38	295.77	$F(1, 31) = 549.6$, $p > 0.01$
FC-CE	2383.94	516.81	1995.94	515.36	$F(1, 31) = 887.0$, $p > 0.01$
Average VOR gain	*0.42*	*0.06*	*0.48*	*0.09*	$F(1, 31) = 1344.7$, $p < 0.01$

In italics are reported significant main effects of static posturography and video head impulse test when comparing pre- and post-CPAP treatment values. Acronyms represent tags for surface, length, and spectral values of body oscillations (PS) on X plane (X) and Y plane (Y) within low, middle, and high frequency interval recorded on platform or foam carpet (FC) and during closed eyes (CE) and opened eyes (OE) conditions. *VOR*, vestibulo-ocular reflex; *SD*, standard deviation. Exact *p* values are given in the text

Discussion

One result of this study is the significant reduction in both classical as well as PS posturography parameters after 12 months of CPAP treatment (Table 2). This aspect highlights the fact that using static posturography (and its related implementations) is of great value in assessing the impact of CPAP treatment on vestibular, visual, and somatosensory

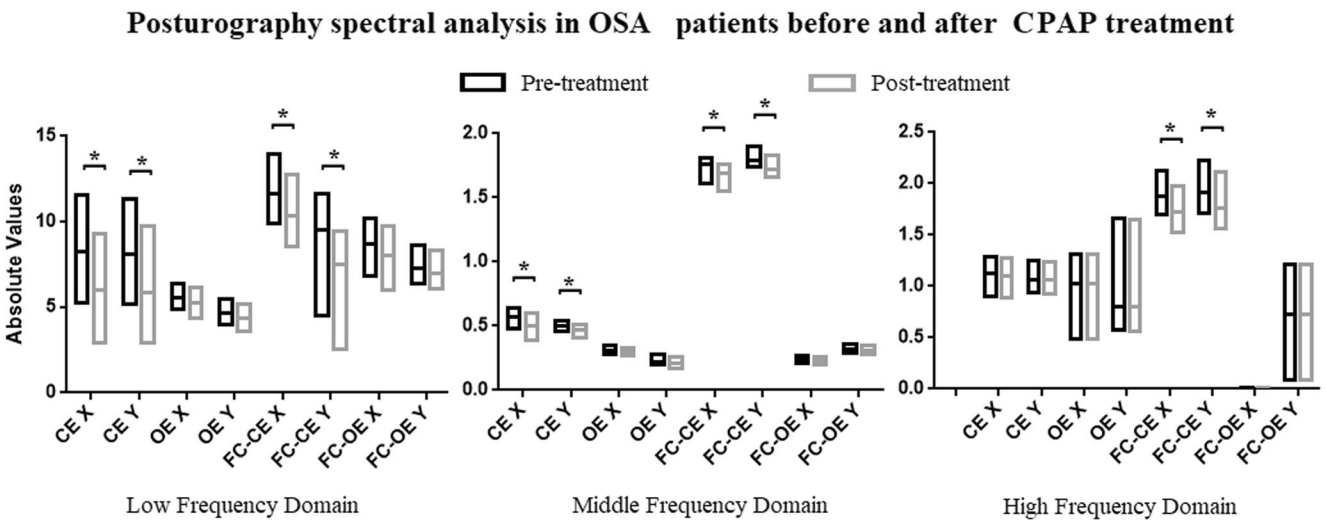

Fig. 1 Box plot representing mean and standard deviation of spectral values of body oscillations on X plane (X) and Y plane (Y) within low, middle, and high frequency domain recorded on platform or foam carpet (FC) and during closed eyes (CE) and opened eyes (OE) conditions in obstructive sleep apnea (OSA) patients before and after continuous positive airway pressure (CPAP) treatment. Asterisk indicates significance within-subjects differences

contributions to postural control and their connection with the circadian rhythm [3, 4]. In particular, CPAP treatment significantly reduced the postural parameters which have been found to be more related to vestibular discharge, especially during blind vision (closed eyes condition) and challenging situations (i.e., upright position on FC). These assumptions are confirmed by the fact that body sways within low frequency intervals and surface are mainly under vestibular control [23, 28, 29], and patients suffering from peripheral vestibular impairments (i.e., vestibular neuritis, Meniere's disease) as well as moderate-to-severe OSA had more increased values than normal subjects [13]. Furthermore, post-treatment OSA patients demonstrated a PS reduction in those blind vision and challenging conditions involving middle and high frequency interval related to somatosensory, proprioceptive, and central nervous systems discharge [23, 30] (Fig. 1, Table 2). Increased body sway within these intervals was described as resulting in a poorer ability to adapt to balance perturbations under sleep reduction [5, 30]. Although previous research demonstrated vestibular-related frequency domain as the most vulnerable in both sleep deprivation paradigm and OSA [5, 13, 30], this study has highlighted for the first time that PS values within both low and middle/high frequency domain are similarly influenced by CPAP treatment, moving close to the outcomes highlighted in matched healthy subjects [13]. This aspect indirectly reflects the complexity of postural reweighting after sleep reduction and—conversely—CPAP treatment, especially considering that (i) lack of attention and vigilance are thought to affect the integration of information from the visual, vestibular, and somatosensory organs and motor coordination [4] and (ii) previous neuroimaging studies found that lower metabolic rates and gray matter reduction in the temporal lobes and

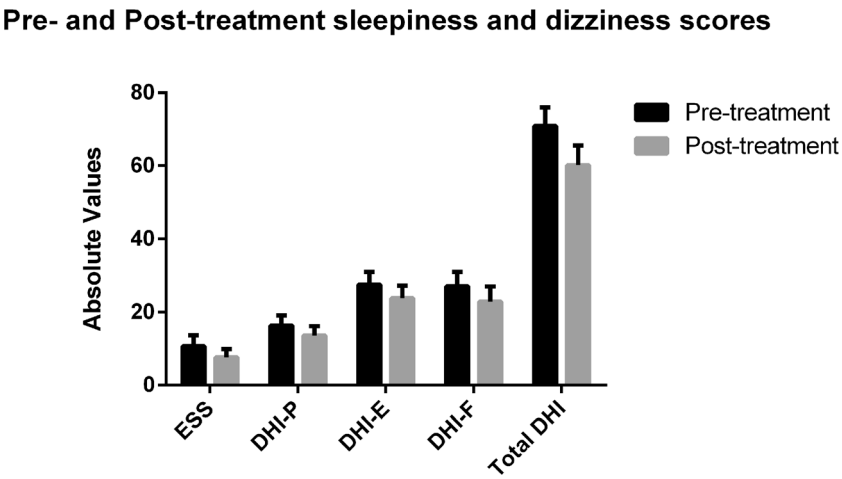

Fig. 2 Histogram representing mean and standard deviation recorded in Epworth Sleepiness Scale (ESS) and Dizziness Handicap Inventory (DHI) before and after 12 months of CPAP treatment. P physical, E emotional, F functional

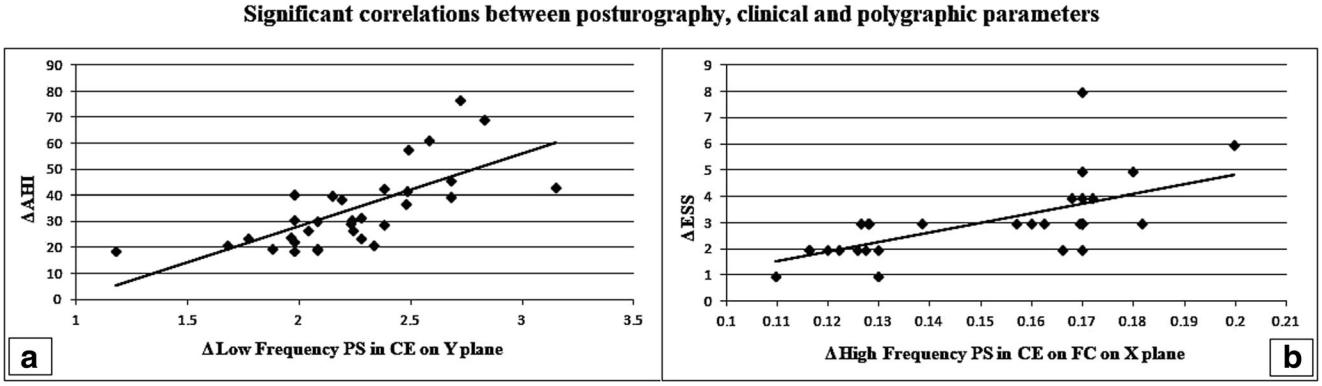

Fig. 3 Scatterplot representing in **a** significant positive correlation between pre- and post-treatment differences (Δ) measured in Apnea–Hypopnea Index (AHI) and spectral values of body oscillations (PS) on Y plane within low frequency interval during closed eyes (CE) condition and in **b** significant positive correlation between Δ measured in Epworth Sleepiness Scale (ESS) and PS on X plane within high frequency interval during CE on foam carpet (FC). *r* values are given in the text

insular cortex (vestibular system), thalamus, basal ganglia, white matter, and cerebellum (proprioceptive system) may be induced by sleep reduction and OSA [31, 32].

In this light, it has been demonstrated that cross-talking phenomena between vestibular and neurovegetative systems exist in the brainstem and that long-term CPAP treatment may induce neuronal restoring effects at this level [14]. Thus, present outcomes in surface and PS values in both vestibular and proprioceptive-related frequency domains could reflect the overall improvement related to alertness, daytime sleepiness, cognitive function, and fatigue reduction known to be induced by CPAP treatment [33]. This aspect appears more evident when taking into account the positive correlations between the Δ AHI and Δ PS values found in closed eyes condition on the Y plane within the low frequency interval on SP ($r = 0.75$) and between Δ ESS and Δ PS values found in closed eyes condition on the X plane on FC within the high frequency interval ($r = 0.72$) (Fig. 3). Such findings may reflect that the AHI significant reduction due to CPAP treatment is involved in a decreasing effect of the chronic hypoxic state involving the cross-talking pathways between brainstem nuclei and vestibular system and thus resulting in a reduction of PS values within vestibular-related domain [14]. On the other hand, the reduction in the ESS scores—which is intrinsically related to daytime alertness and vigilance [33]—may be correlated with the phenomena of sleep improvement that induce the activation of those cerebral regions mediating attention and also of the areas involved in the integration of information from somatosensory receptors [4].

Interestingly, although the within-subject ANOVA model highlighted a post-treatment VOR gain increase, this parameter did not survive the Bonferroni correction. It was previously considered that VOR gain could be progressively reduced by sleep deprivation, affecting the neural inflow at different stages [7]. This consequence could be the pathophysiological counterpart of the hypoxia-related processes that affect vestibular pathways both in the brainstem and in the temporo-parietal joint cortex, and is also involved in regulating VOR gain and its activity during tasks requiring attention is modified by sleep deprivation [1, 6, 7, 11–13]. This VOR gain reduction only became evident with long-lasting deprivation because of the covert effect related to the activation of those phenomena for redirecting attention when the sleep deprivation does not last long [7]. Moreover, findings of this study and the amount of evidence related to the sudden changes in posturography parameters [4, 5, 7, 13] may induce one to hypothesize that VOR gain—with respect to the vestibular frequency domain—reacts more leniently to both short sleep deprivations and those treatments directed to reduce hypoxic processes in the central nervous system, which may require long-lasting CPAP treatment [13].

Finally, this is the first study in which OSA patients referred an overall improvement in dizziness-related quality of life, when tested by means of DHI after a long-term CPAP treatment (Fig. 2). This finding could be subserved by those changes respectively found in posturography and VOR gain scores, as a possible expression of oxidative restoring phenomena occurring along the cognitive and multisensory neural streams involved in balance control [15].

In conclusion, this study highlighted that postural instability related to OSA condition may be enhanced after 12 months of CPAP treatment. Although VOR gain did not demonstrate such strong behavior, further studies would make it possible to evaluate whether a longer period of CPAP treatment could significantly restore VOR gain and how these aspects could reflect on daytime quality of life.

Limitations of the study

The findings of this study should be evaluated in the light of some possible limitations. Among these, the first limitation could be represented by the Bonferroni multiple correction applied as post-hoc test, which may increase the likelihood

of type II statistical errors. Secondly, no OSA group undergoing sham CPAP treatment—unethically achievable for these long-term protocols—was investigated. This procedure could have respectively disclosed and/or tempered not significant and significant results of the present study.

Author contributions MA, AM, CL, and AV conceived and designed the experiment; AM, MA, AV, FP, FI, CL, and AL performed the experiment; AM, MA, CL, AV, and NBM analyzed the data; MA, FI, AM, CL, FP, DC, AL, and NBM contributed clinical data/materials/analysis tools; AM, MA, CL, and AV wrote the paper.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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