

Manuscript Number:	NEUS-D-18-00066R1
Full Title:	Romberg ratio coefficient in quiet stance and postural control in Parkinson disease
Article Type:	Original Article
Keywords:	balance, posture, stabilometry, visual , rehabilitation
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Abstract:	<p>The aim of this study was to determine the function of visual afference in postural control in Parkinson patients. We enrolled 29 patients and 30 healthy controls. The stabilometry test was performed for posture and balance and Romberg ratio coefficients were calculated. In addition, the Berg scale and the 6-Minute Walking test were administered to assess balance and functional exercise capacity; the Unified Parkinson's Disease Rating Scale was used to determine the stage of the disease; and the Short Form (SF)-36 Health Survey was given to collect information on quality of life. Results: significantly longer Center of Pressure (CoP) sway lengths were observed in the Parkinson group. The Romberg index for CoP length of sway in parkinson patients was $94.3 \pm 19.3\%$, versus $147.4 \pm 120.6\%$ for the Control Group. ($p=0.025$). Conclusion: Parkinson patients use the increase in CoP sway length and ellipse area to stabilize their balance and sight does not facilitate static postural control as in healthy subjects.</p>
Response to Reviewers:	<p>We would like to thank the Editor and the Reviewer for their positive general judgments about our work and for their qualified and constructive comments that helped us in improving our work. In the following we have reported all our point-by-point responses to reviewer's comment.</p> <p>Reviewer #1: In present article authors investigated Romberg ratio coefficient in quiet stance and postural control in Parkinson's disease. Hypothesis sounds good; I have some comments followings;</p>

1. English of manuscript is quite poor; thus manuscript must be edited in terms of English.

AUTHORS: We performed a careful English revision of the entire manuscript

2. Description of statistical method is also insufficient; it must be reconsidered.

AUTHORS: We have rewritten the description of statistical methods used in this study. We have now written as follows:

“Statistical analysis

Data are reported in terms of mean \pm standard deviation. A Mixed analysis of variance (Anova) was used to compare stabilometric parameters (length of sway path and ellipse area), using as within subject factor the condition open eyes vs. closed eyes and as between subject factor the group (PD vs. CG). The results of Mixed-Anova are reported in terms of F, p-value and effect size evaluated computing the eta-squared (ES). For the parameters with a statistically significant difference highlighted by mixed analysis of variance, post hoc analysis was also performed within groups using paired t-test. The Romberg Index evaluated for the above two stabilometric parameters was compared between the two groups using unpaired Student’s t-test. Other data were compared between subjects with Parkinson’s disease (PD) and control healthy subjects (CG) using unpaired Student’s t-tests. The alpha level for all was set to 0.05, but that of the post hoc comparison was 0.025 for the Bonferroni correction.”

3. The tables of present study are not well designed and must be revised; abbreviations are also insufficient.

AUTHORS: We have revised the tables of the manuscript. The new tables are reported in the text:

Table 1. Demographics and clinical descriptions of the group with Parkinson’s disease and the group of control healthy subjects (PD vs. CG, mean \pm standard deviation, compared using t-test). UPDRS: Unified Parkinson’s Disease Rating Scale; 6MWT: Six minute walking test; H&Y: Hoehn and Yahr scale.

Table 2. Mean \pm standard deviation of quality of life domains of SF-36 (Short Form Health Survey with 36 items) for our patients compared between healthy aged-matched Italian reference population (PF: physical function; PR: physical role; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: role emotional; MH: mental health). N.S. stands for not significant.

Title page

Title: Romberg ratio coefficient in quiet stance and postural control in Parkinson's disease

Running head: postural control in Parkinson disease

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Acknowledgments We would like to thank the Physiotherapy School of S. Filippo Neri Hospital "Sapienza" University of Rome. The authors would like to thank all patients who participated in this study.

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

Abstract:

The aim of this study was to determine the function of visual afference in postural control in Parkinson patients. We enrolled 29 patients and 30 healthy controls. The stabilometry test was performed for posture and balance and Romberg ratio coefficients were calculated. In addition, the Berg scale and the 6-Minute Walking test were administered to assess balance and functional exercise capacity; the Unified Parkinson's Disease Rating Scale was used to determine the stage of the disease; and the Short Form (SF)-36 Health Survey was given to collect information on quality of life. Results: significantly longer Center of Pressure (CoP) sway lengths were observed in the Parkinson group. The Romberg index for CoP length of sway in parkinson patients was $94.3 \pm 19.3\%$, versus $147.4 \pm 120.6\%$ for the Control Group. ($p=0.025$). Conclusion: Parkinson patients use the increase in CoP sway length and ellipse area to stabilize their balance and sight does not facilitate static postural control as in healthy subjects.

Keywords balance, posture, stabilometry, visual , rehabilitation

Text

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Introduction

In addition to such symptoms as shaking, rigidity, slowness of movement, and difficulty with walking in its early stages, patients with Parkinson disease (PD) experience impairments to balance one of the most important elements that must be considered in rehabilitation. As a major axial disorder in PD, postural instability, including imbalance, is the most disabling long-term problem and fails to respond to pharmacological agents, increasing the risk of falls [1-2].

Balance impairments in PD can be related to disorders that are linked to movement, motor planning, and the integration of various sensorial inputs, such as perception and vision [3].

PD patients have less adaptive capacity in using visual stimuli to effect correct postural control with an "en block" body movement strategy. The frequency, duration, and mean and maximum amplitudes of postural oscillations, reflecting the influence of vision, differ in patients with various neurological diseases compared with healthy subjects [4].

Further, in patients with unilateral PD, balance control has greater reliance on vision input, possibly to compensate for somatosensory system impairments. In the stabilometry test, subjects whose dominant side is affected experience significantly greater variations in center of pressure (CoP) versus the non dominant side, primarily under conditions in which the eyes are closed [5].

In PD, the visual postural loop apparently becomes hyperactive, and its influence cannot be de-emphasized easily when the visual information is misleading. The participation of basal ganglia in posture is concerned with the reweighting of various sensor-motor loops that control posture during adaptation to novel situations [6]. These patients might have a deficit in reorganizing sensory priorities due to the damage to basal ganglia affecting the integration of sensory information for postural control [7].

Impaired proprioception, visual sense, and a smaller base of support cause postural instability in PD patients, correlating with a quantitative reduction in muscle strength in the spine, hip, and ankle. In particular, several studies support the hypothesis regarding the influence of changes in visual information in triggering balance control disorders in PD [8,9]. Further, postural sensory deficits that involve specific sensory modalities are strongly associated with the freezing of

gait [10]. Certain pharmacological treatments improve muscle strength, gait speed, and the use of ankle strategy but do not worsen proprioceptive sense [8,11].

Stabilometry is a reliable tool in assessing postural stability in PD [4]. Our study aims to determine whether patients with PD, even in its early stages, have decreased limits of stability and whether changes in visual input impair their postural control by stabilometric analysis.

Material and Methods

We conducted a case-control observational study in patients who had had a diagnosis of idiopathic PD for at least 1 year at the Physical Medicine and Rehabilitation Outpatient Clinic, XXX of XXX University, from July 2015 to January 2017. The inclusion criteria were a diagnosis of idiopathic PD with scores of ≤ 3 and > 1 on the Hoehn and Yahr scales, respectively (in the “*On*” phase medication: 45-90 minutes after the morning dose of anti-Parkinson drug therapy) [12]; age between 40 and 80 years; Mini-Mental State Examination Score (MMSE) > 27 [13,14]; visual analog scale (VAS) score < 3 [15]; other disabling diseases that affected movement and gait; and steady pharmacological treatment with anti-Parkinson agents for at least 1 month.

The exclusion criteria comprised cognitive and visual impairments that could prevent one from understanding and executing the tasks; engagement in another rehabilitative study protocol; participation in a conflicting research study; previous treatment with deep-brain stimulation for symptom management; significant neck, shoulder, or back injuries; uncontrolled hypertension; fall fractures in the past year; lack of sensitivity in the lower limbs; vestibular disorders; symptomatic orthostatic hypotension; and the presence of clinically documented dementia.

The control group included age- and sex-matched healthy subjects who were recruited from a pool of volunteers who did not have acute algic disease or balance deficits; comorbidities, such as diabetes, hypertension, rheumatic, and oncological diseases; vision problems; or endocrinological or neurological disease and did not use antidepressants or anxiolytic drugs.

This study was approved by the ethical committee of XXX University of XXX. All participants signed informed consent forms after receiving detailed information about the study’s aims and procedures per the Declaration of Helsinki. Eligible individuals were referred to a physiatrist who was uninvolved in the study and who provided them with details on the experimental protocol. All tests were performed during the *on* pharmacological phase.

Sociodemographic and clinical data were collected. The following scales were administered to the PD group:

Evaluation Scales

The Berg Balance Scale (BBS), for determining the risk of falls, is a widely used instrument that measures static and dynamic balance by assessing one's performance on functional tasks. It comprises a series of 14 simple tasks, each of which is scored from 0 (lowest level of function) to 4 (highest function). The maximum score is 56 (41-56 = low risk of falls; 21-40 = moderate risk; 0-20 = high risk) [16].

The VAS [15] is a simple and sensitive instrument that enables patients to express their pain intensity as a numerical value. Patients were asked to mark the point that corresponded to their perceived pain intensity on a 10-cm line (0 = absence of pain, 10 = most severe pain).

The UPDRS is the most commonly used scale for monitoring the course of disease in PD patients, consisting of 6 parts, posing questions on mental state, behavior and mood, ADL, motor functions, complications of advanced disease, stage of disease per the Hoehen and Yahr scale, and everyday life activities per the Schwab and England scale. The UPDRS is a metric scale, ranging from 0 (no disability) to 147 points (severe disability). In this study, we measured scores for UPDRS PART I: Mentation, Behavior, and Mood; UPDRS PART II: Activities in Daily Living; UPDRS PART III: Motor Examination; and UPDRS PART IV: Complications of Therapy and Total [17].

Functional exercise capacity was measured using the 6-minute walk test (6MWT), a practical, simple task that measures the maximum distance that a patient can walk quickly on a flat, hard surface in 6 minutes [18].

The Short Form (SF)-36 Health Survey was administered to collect information on health status and quality of life. SF-36 is a generic multidimensional health questionnaire that records practical, reliable, and valid information about a patient's functional health and well-being. It comprises 36 items, divided into 2 general indices that summarize physical and mental health. The physical health category includes 4 domains: physical function (PF), physical role (PR), bodily pain (BP), and general health (GH). Emotional health covers domains on mental health (MH), social function (SF), emotional role (RE), and vitality (VT). Each scale ranges from 0 to 100 (worst and best health state, respectively). The questionnaire has been validated in Italian. [19]. For this observational study, the Strobe guidelines were followed [20].

Assessment of Stabilometry - Romberg Ratio

Data were collected on a baropodometric platform (Milletrix software-XXX) to measure oscillations in terms of the elliptical area that contained 95% of sway points, center of pressure length, and velocities with eyes closed (EC) and open (EO). The stabilometry test was performed, recording the position of the CoP for 51.2 seconds during quiet standing.

After receiving information about the test procedure, the patients and healthy controls were instructed to stand erect, but not at attention, with their arms along the trunk, their feet open at an angle of approximately 30 degrees, and their heels approximately 3 cm apart. All tests were performed by the same examiner; thus, the participants were supplied with the same instructions prior to each test. Three tests were conducted for each trial condition (EO and EC), for which we have reported the median scores. In the EO condition, subjects fixated on a mark on a wall 1.5 m away at eye level. The test order, EO-EC, was randomized. To minimize external disturbances and cues for the test subjects, the environment was naturally brightly lit and quiet.

We analyzed the Romberg ratio for CoP length of sway (ie, the length of sway with the closed eyes, divided by that measured with the eyes open and expressed as a percentage) [21]. Higher Romberg ratios reflect greater instability with closed eyes, whereas a ratio < 1 indicates higher stability in the EC versus EO condition.

Statistical analysis

The data were reported as mean \pm standard deviation. Mixed analysis of variance (ANOVA) was used to compare stabilometric parameters (length of sway path and elliptical area), with the condition open eyes versus closed eyes as the within-subject factor and the group (PD vs. CG) as the between-subject factor. The results of the mixed ANOVA are reported as F, p-value, and effect size, based on eta squared (ES). For parameters with a statistically significant difference in the mixed ANOVA, post hoc analysis was performed within groups by paired t-test. The Romberg Index, evaluated for the 2 stabilometric parameters above, was compared between the 2 groups by unpaired student's t-test. Other data were compared between subjects with Parkinson disease (PD) and control healthy subjects (CG) by unpaired student's t-test. The alpha level was set to 0.05, but that of the post hoc comparison was 0.025, based on Bonferroni correction.

Sample size calculation

Manabe et al. [22] showed significant differences in stabilometric parameters between 15 PD patients and 15 healthy subjects. Using the data of Blaszczyk and Orawiec [4] on EC, setting the power of the analysis to 90% (corresponding to a beta level at 10%) and the alpha level to 5%, significant differences between patients and healthy subjects could be detected by enrolling at least 27 subjects per group.

Results

A total of 43 PD patients were screened, 28 of whom were enrolled; 30 subjects formed the healthy group. The demographics and clinical descriptions of the 2 groups are reported in **Table 1**. The 28 PD patients were compared with an age-matched healthy Italian population by t-test. We observed significant differences in the General Health and Physical Role items on the SF-36 scale [19] (**Table 2**).

There were no significant differences in age, weight, stature, or body mass index between groups. **Figure 1** shows the length of sway path of the center of pressure (CoP) for the 2 groups. CoP lengths were significantly longer in the PD group [$F(1,56)=14.825$, $p<0.001$, $ES=0.209$]. In contrast, there was no main effect of sight by ANOVA [$F(1,56)=1.227$, $p=0.273$, $ES=0.021$]. Notably, the effect of the interaction between pathology and condition was significant [$F(1,56)=13.474$, $p=0.001$, $ES=0.194$]. In the within-subject post hoc analysis, the length of CoP sway was lower in the CG with open versus closed eyes ($p=0.002$). Conversely, in PD subjects, the effect of sight was not significant ($p=0.079$).

Similar results were observed for the main factors “group” and “sight” by ANOVA of the elliptical area data; a significant effect was seen for group [$F(1,56)=7.114$, $p=0.010$, $ES=0.113$] but not sight [$F(1,56)=0.352$, $p=0.555$, $ES=0.006$]. In this case, the interaction group x sight approached the threshold of significance for the higher data variability [$F(1,56)=2.822$, $p=0.099$, $ES=0.048$] but trended similarly as length of sway.

The Romberg Index for CoP length of sway (ie, the length of sway with the eyes closed, expressed as a percentage of that with the eyes open) was $94.3\pm 19.3\%$ in PD patients versus $147.4\pm 120.6\%$ in CG subjects ($p=0.025$).

Discussion

The aim of this study was to determine the function of visual afference in postural control in patients with PD.

Unexpectedly, we found that for patients with PD, the effect of sight was not statistically significant in increasing their stability, whereas it was in the control group. Vision helped healthy subjects maintain their stability, but this effect was not observed in patients with PD, in contrast to previous results [4] in which patients with PD benefited from vision during postural assessment. This difference could be attributed to several factors. For example, the reduced sample size ($n=28$ in experimental group) versus that in the previous study ($n=55$) could have affected the significance. However, even the trend in stability in our study was opposite to that of the other study, for which we noted increased stability with EC. Another reason could be the differences in the clinical features of the sample: our patients were more severely affected by these symptoms (higher score of UPDRS: 36.8 ± 16.1 vs. 23.3 ± 12.1) and developed them in a shorter time (average 4 vs. 5.5 years). Also, in our study, the postural analysis lasted 51.2 s—longer than the 30-s analysis in Błaszczyk and Orawiec [4].

The interactions between sensory and proprioceptive inputs have been studied extensively with regard to motor dysfunction in PD patients [23], but the importance of visual afference in postural control and motor skills remains unknown, especially in the early and mild stages of PD. We observed significantly longer CoP lengths in the PD group [$F(1,56)=14.825$, $p<0.001$, $ES=0.209$] (**Figure 1**).

We hypothesize that PD patients can not use visual afference as a positive reinforcement feedback element for static postural control. Difficulties in using visual afference in PD can be confirmed by their vulnerability to incongruent stimuli of visual information compared with healthy subjects, who are able to adapt to a certain amount of visual incongruity [24]. This pattern is critical, especially in rehabilitation, in which the use of external cues as visual and auditory biofeedback is recommended—for example, to improve fluidity and cadence during walking. In rehabilitation for PD, visual cues appear to increase compensatory steps during gait [25]. Notably, the interaction between pathology and condition was significant in the within-subject analysis, in which the length of CoP sway was lower in the CG under the open versus closed eyes condition, but in PD patients, the effect of sight was not significant ($p=0.079$).

Our results contradict the common physiological model in which vision helps stabilize posture [26,27] and improve walking performance (upper body stability and harmony) in healthy subjects [28] and persons who are affected by subclinical Parkinson, as demonstrated by Panyakaew and colleagues [29]. We hypothesize that visual cues have varying functions, depending on disease severity; for example, attentional shifting is compromised in PD but should be preserved in those with very mild PD and slight motor symptoms, as reported in 2 studies [29,4]. Normal body oscillation was only observed in patients without clinical evidence of postural instability (HY stage 2 and UPDRS motor score <20) [26]. However, this model should be tested in a specific and dedicated experiment. Patients with PD have difficulties organizing and using visual information when receiving visual cues for rehabilitation; thus, they should be contextualized and refer to specific tasks by exploiting attention processes [30].

Preliminary findings also support the hypothesis that cognitive load is an important aspect of postural control: Barbosa et al. demonstrated that balance in a dual task is significantly poorer than balance with the eyes closed [31]. Exteroceptive information is not critical for achieving step length and improving overall gait with visual cues in PD, but it is necessary for the accuracy and precision of foot placement on targets [32]. Also, the presence of visual cues significantly reduces bradykinesia during motor imagery training [33]; thus, it is important to avoid inhibition of overlearned and contextually compatible reactions with visual distracters. Schlick and colleagues found that visual cues, combined with treadmill training, have greater beneficial effects on gait in PD patients [30].

We hypothesize that patients with PD use the increase in CoP sway length and elliptical area to stabilize their postural balance during initial postural bradykinesia: we did not observe any differences in oscillation velocity between groups. The increase in support of the CoP area allows the patient to continue to perform normal activities of daily life without any particular risk of falling.

These results increase our understanding of the function of visual input in static postural control of a mild-grade Parkinson patient. However, one limitation of the study was that we did not stratify patients by severity of disease in evaluating the influence of sight, even in relation to dynamic postural control or cognitive problems, such as difficulty in maintaining attention.

Conclusion: Our findings suggest that the relationship between visual integration and postural control is not linear, even in mild-grade PD. Visual integration in a PD patient remains paramount in the management of postural stability—an aspect that should be taken into account in planning the rehabilitation program—necessitating further research into these areas.

Funding: The authors declare that they have no source of funding for the research reported.

Conflicts of interest: The authors declare no conflicts of interest.

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Legends:

Figure 1. Mean and standard deviation of center of pressure (CoP) length of sway in the open vs. closed eyes condition for patients with PD (white bars) and the control group (CG), formed of healthy elderly persons (grey bars). PD = Group with Parkinson disease, CG = Control group of healthy elderly, CoP = center of pressure

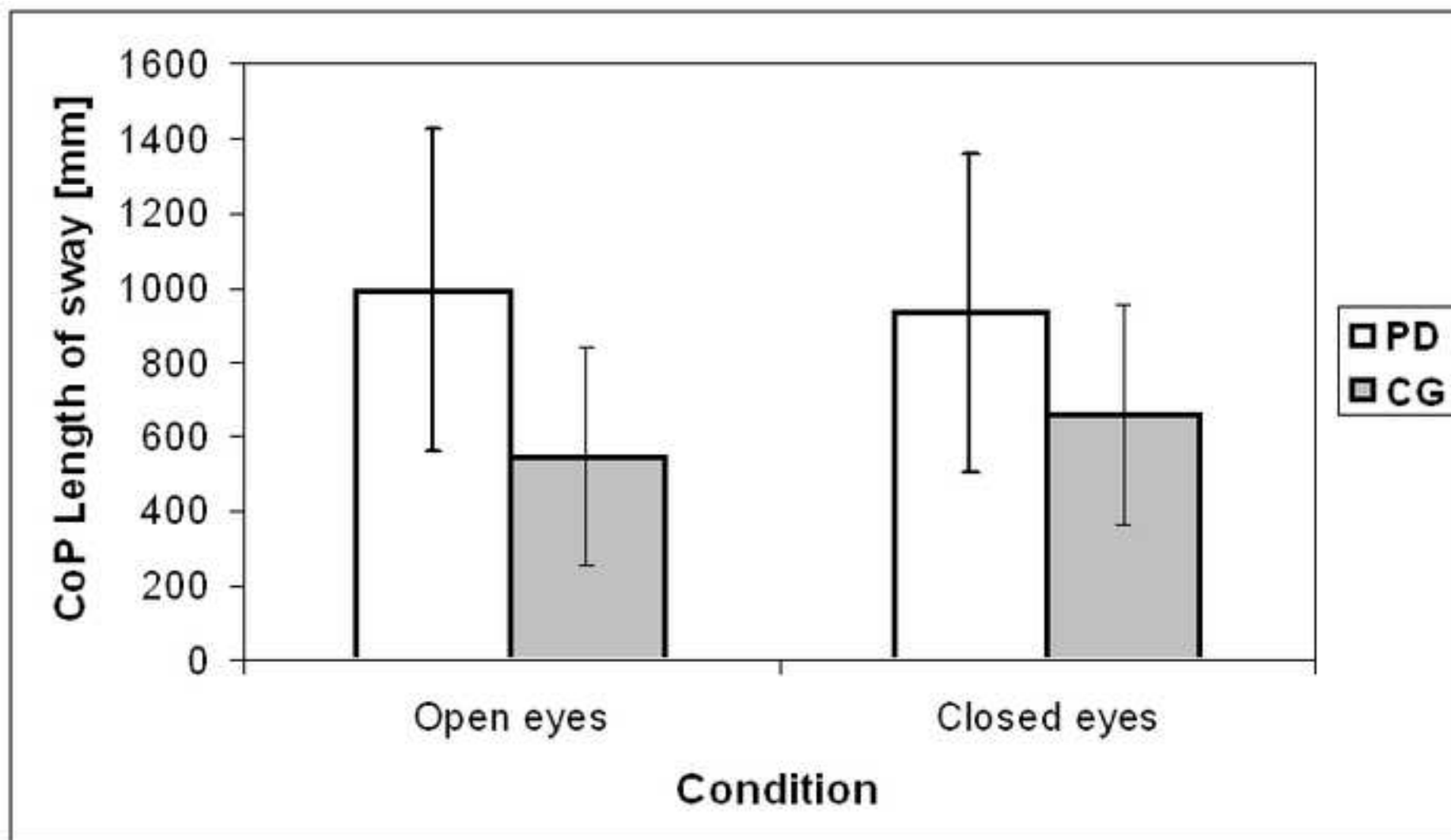


Table 1. Demographics and clinical descriptions of the group with Parkinson's disease and the group of control healthy subjects (PD vs. CG, mean \pm standard deviation, compared using t-test). UPDRS: Unified Parkinson's Disease Rating Scale; 6MWT: Six minute walking test; H&Y: Hoehn and Yahr scale.

Factors	PD N=29	CG N=30	p-value
Age (years)	66.1 \pm 8.9	65.7 \pm 7.1	0.547
Weight (kg)	74.5 \pm 15.0	75.4 \pm 16.4	0.694
Stature (m)	1.66 \pm 0.09	1.66 \pm 0.08	0.487
Body Mass Index (kg/m ²)	26.5 \pm 4.3	27.1 \pm 4.7	0.286
Berg Balance Scale	48.4 \pm 4.7	-	-
UPDRS	36.8 \pm 16.1	-	-
6MWT (m)	496 \pm 121	-	-
Faller (in the last year)	28%	-	-
H&Y stage	2 \pm 0.6	-	-
Duration of illness (years)	4.0 \pm 2.1	-	-

Table 2. Mean \pm standard deviation of quality of life domains of SF-36 (Short Form Health Survey with 36 items) for our patients compared between healthy aged-matched Italian reference population (PF: physical function; PR: physical role; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: role emotional; MH: mental health). N.S. stands for not significant.

SF-36	Patients Group (PG) N=29 Mean age: 66.1\pm8.9 years	Reference data of aged-matched healthy population N=367 Age range: 55-64	p-value
PF	65 \pm 27	67 \pm 20	N.S.
PR	70 \pm 35	48 \pm 37	<0.05
BP	62 \pm 20	44 \pm 22	N.S.
GH	49 \pm 17	60 \pm 15	<0.01
VT	51 \pm 14	51 \pm 22	N.S.
SF	78 \pm 20	70 \pm 23	N.S.
RE	72 \pm 42	56 \pm 42	N.S.
MH	66 \pm 15	61 \pm 23	N.S.



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