A possible parameter for gait clinimetric evaluation in Parkinson's disease patients

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Abstract: The strength and usefulness of a rating scale for describing disease evolution relies on the accurate determination of variations representing clinically relevant changes. In this sense, the habitually used Hoehn-Yahr (HY) Scale for Parkinson Disease (PD) in its modified version distinguishes between the 2 and 2.5 stages to explain if the bilateral involvement is or is not accompanied by body balance impairment. Nevertheless, this scaling does not allow for differentiating the symptoms and signs associated with each stage accurately. Considering this difference, this work aims at analyzing some gait parameters -stance and swing phase times and magnitude of the vertical component of ground reaction force during the gait cycle- of PD patients classified as HY=2 and HY=2.5 in contrast with healthy subjects (HY=0), with the purpose of assessing whether there is a statistically significant difference among all these HY categories. For all gait parameters evaluated, the results indicated significant differences between HY=0 and HY=2.5. However, only the magnitude of the vertical component of ground reaction force presented relevant differences between HY=2 and 2.5. As expected, therefore, these results show the potential of such parameter to clinimetrically identify the level of gait impairment/disability in PD patients on the Hoehn-Yahr Scale.

1. Introduction

Parkinson's disease (PD) is a progressive disorder of the nervous system that affects human body movement, among other functions. Worldwide, approximately 7 to 10 million people have PD [1], and in Argentina the disease is the second most common chronic neurodegenerative disorder after Alzheimer's disease, with around 70,000 individuals affected [2]. PD can occur in different age groups, including patients less than 20 years old, though its prevalence is about of 1-2% in those over 65 years. Also, it is known that men are one and a half times more likely to have PD than women [3].

Classical research indicates that PD is gradually developed as the result of a defect in dopamine production, though today the involvement of many other neurotransmitters is recognized, such as norepinephrine, acetylcholine, glutamate and GABA [1, 3]. While PD cannot be cured at this moment, early diagnosis and medical intervention with levodopa (L-dopa) therapy may markedly improve its symptoms [1-3, 4], thus displaying the importance of accurately recognizing the early manifestations of this disease, as well as the symptoms and signs characteristic of its progressive evolution.

In this sense, it is well established that in the early stages of Parkinson's disease, a patient's face may show little or no expression and his arms may not swing when he walks. In addition, his speech may become soft or slurred. Among the most common PD features that worsen over time, we find bradykinesia (i.e., slowed movement), hypokinesia (small amplitude movements), resting tremors and

rigidity, though these may not all be present, which can be accompanied by postural instability and another features described as "no-motor symptoms" [3, 5, 6].

As regards clinical features of PD related to locomotion disorder development, in addition to a decrease in arm movement (hypokinesia), symptoms in the lower limbs include: temporal / spatial variability of gait patterns and shortening step length, little foot-lifting off the ground with consequent shuffling, and gait speed decrease or increase at the expense of a cadence rise greater than the step length. It is also possible that at a given moment, the patient may have difficulty starting up his gait or making turns, an episode known as freezing [7, 8].

In order to describe and classify this complexity of signs and symptoms related with PD evolution, different scales have been developed, such as the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn-Yahr (HY) Scale [9, 10]. The first assesses various patient features: mental status, daily life activities, motor status, complications of therapy, etc. In contrast, the HY Scale focuses on motor disorders caused by PD and their functional consequences. It was originally designed to be a simple descriptive scale divided into five-point stages (Table 1, left), providing a general estimate of clinical function in PD by combining functional deficit (disability) and objective signs (impairment) [9].

Additionally, the HY Scale is based on the two-fold concept that the severity of overall parkinsonian dysfunction relates to bilateral motor involvement and balance/gait compromise. Consequently, parkinsonian motor impairment can be charted from a unilateral (Stage 1) to a bilateral disease without balance difficulties (Stage 2), to the presence of postural instability (Stage 3), the loss of physical independence (Stage 4), and being wheelchair- or bed-bound (Stage 5) [9].

A more detailed analysis of this gradation system shows that the definition of Stage 1 as "unilateral involvement only, usually with minimal or no functional disability," combines two concepts that are not truly equivalents. Stage 2 is defined by the lack of "impairment of balance," but this wording does not use the same descriptive wording as in Stage 1. Besides, the progressive stages of the HY scale are based on two different indices of severity: unilateral versus bilateral signs, and absence or presence of gait and balance impairments. As such, the HY scale is a categorical scale describing clinical status, but each increment does not really represent a higher degree of overall motor dysfunction [9, 10].

Table 1. Comparison between the original and modified Hoehn and Yahr Scale.

Stage	Hoehn−Yahr Scale	Modified Hoehn−Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only
1.5	-	Unilateral and axial involvement
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
2.5	-	Mild bilateral disease with recovery on pull test
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided

Despite these weaknesses and the scale's development in the pre-L-dopa era, the use of the HY Scale has continued to be widely used for the description of large populations of PD patients. As an example, studies from both the pre-L-dopa and L-dopa eras involving large cohorts of PD patients have found similar percentages of cases assigned to the different stages of the HY Scale. In these studies, Stage 1 and Stage 5 account for the smallest number of subjects, followed by Stage 4, with the bulk of patients, ranging from 52 to 77%, falling into Stages 2 or 3 [11].

Among the gait variability measures considered for PD patients, the following temporal parameters calculated for each gait cycle were used [13]: 1− stride time or duration of the gait cycle (time from initial contact of one foot to subsequent contact of same foot); 2− swing time (amount of time one foot is in the air); 3− percentage swing time (100 x swing time/stride time); 4− double stance time (time of

bilateral foot contact); 5− percentage double stance time (100 x double stance time/stride time); and 6− step time (time from initial contact of one foot to initial contact of the other foot).

While this research group has not evaluated these gait variability measures for PD patients classified in each stage of the HY Scale, further studies on the subject led these investigators to conclude that gait variability is a quantifiable feature of walking that is altered (both in terms of magnitude and dynamics) in clinically relevant syndromes, such as falling and neuro-degenerative diseases (e.g., Parkinson's and Alzheimer's disease [15, 16]. Additionally, gait instability measures [14, 17] directly related to body balance impairment signalled by a score of 2.5 on the modified HY Scale, apparently would predict falls in idiopathic elderly fallers and other populations who share an increased fall risk.

With regard to the variability analysis of gait kinetic parameters as possible indicators of PD evolution, a previous work by our research group showed that the vertical component of ground reaction force (VGRF) can be used for automatic classification of PD patients from clustering techniques based on artificial neural networks [18, 19]. In this case, the gait variability measures utilized were: 1− mean maximum value of VGRF; 2− mean standard deviation of VGRF; 3− mean coefficient of variation of VGRF and 4− mean sum of VGRF over successive stance phases. The preliminary results of our study indicated that the VGRF contains relevant information to differentiate objectively normal and PD gait patterns, thus displaying that this parameter could be a predictor of the degree of gait impairment/disability for PD.

According to all these studies, we therefore hypothesize that gait data analysis can provide sensitive and clinically relevant information in the evaluation of PD regarding morbidity, fall risk and the response to therapeutic interventions in general terms and particularly, in the assessment of significant statistical differences between patients included in the HY=2 and HY=2.5 stages.

In order to evaluate the viability of our hypothesis and based on this background, the aim of this work was to analyze gait data of PD patients classified as HY=2 and HY=2.5 with respect to normality (HY=0), with the purpose of assessing whether there are statistically significant differences between these HY categories. In the following sections, the methodology utilized to fulfill this objective is described. Firstly, the materials and methods used to evaluate gait data variability for PD patients belonging to HY=2 and HY=2.5 are detailed. Then, the results of a statistical analysis of different gait parameters among the considered Hoehn-Yahr categories are presented. Finally, a brief discussion and conclusions are provided, in the search for clues to assess the level of gait impairment/disability in PD patients on the HY Scale from a clinimetrically consistent gait parameter.

2. Materials and Methods

2.1 Human Gait Database

To evaluate whether there are significant differences of gait disorders between the analyzed PD patient groups (HY=2 and HY=2.5) and among them and the control group (HY=0), a database of 20 patients with idiopathic PD and 20 healthy control subjects of similar age was used. This database, freely available on the *Physionet* website [20], contains clinical and demographic information of the considered subjects, besides the corresponding value of the modified Hoehn-Yahr Scale (Table 2).

Table 2. Clinical and demographic data, expressed as average values and standard deviation

	Healthy subjects	Parkinson's disease patients	
Interest-factor level	HY=0	HY=2	HY=2.5
Age	67.4±8.6	71.8±10.5	73.8±7.38
Height [m]	1.64±0.08	1.70±0.08	1.66±0.08
Weigth [Kg]	70.1±12.52	73.7±9.79	70.4±11.86
Gait Speed [m/s]	1.18±0.14	1.01±0.15	0.96±0.23
Study made by:	Yogev *et al.*, 2005; Toledo *et al.*, 2005; Hausdorff *et al.*, 2007 [20].	Yogev *et al.*, 2005; Hausdorff *et al.*, 2007 [20]	

In contrast to normal cases (HY=0), pathological cases analyzed here correspond to 10 PD cases of both Stages HY=2 and HY=2.5 based on the modified version of the Hoehn-Yahr Scale. As was previously mentioned, these Stages are related to patients that exhibit an altered gait with bilateral symptoms, differentiated by the lack or presence of body balance impairment [9, 12].

Also, the database includes kinetic data for both feet that were previously acquired with the F-Scan insole system [21]. From an insole with 8 sensors underneath each foot, this system measures force (in Newtons, N) as a function of time, which together represent the plantar pressures distribution for every foot. The gait test was performed during about 2 minutes on level ground at a normal self-selected cadence for each analyzed subject, the data being then digitalized and recorded at 100 samples per second. Also, the database contains two signals that reflect the sum of the 8 sensor data for each foot, that is, equivalent to the VGRF for left and right feet, respectively [20]. Although this VGRF value is not exactly equivalent to the vertical component of the ground reaction force measured on force platforms [22, 23], the analysis on this value can still be done to obtain clinically relevant information.

Furthermore, for minimizing the effects of start-up and to match the length of the vector data for all samples, the first 5 seconds of data were discarded, opting finally for a vector length of 2700. Figure 1 shows the VGRF during a gait cycle for both feet, obtained from the mentioned database for a subject with a normal gait and a Parkinson's patient with HY=2.
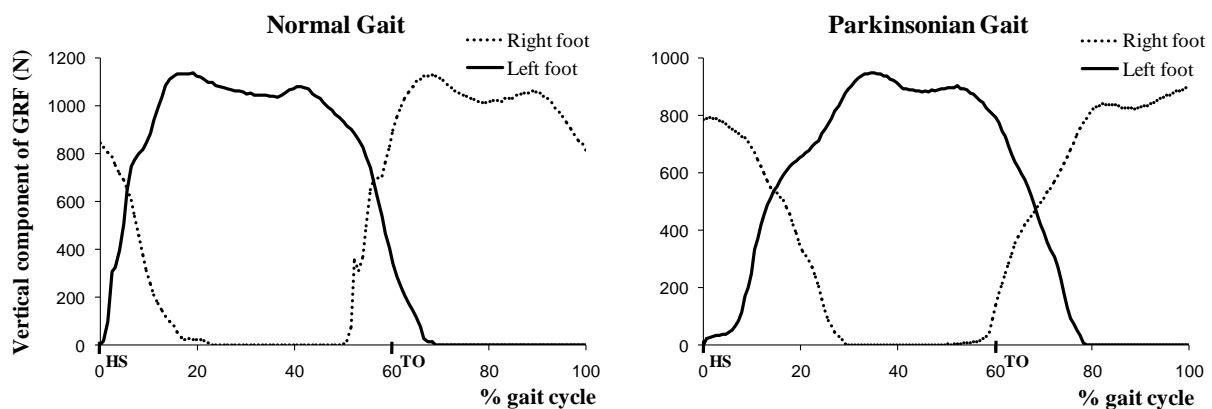

Figure 1. VGRF for both feet for a gait cycle. Left: normal gait. Right: parkinsonian gait, HY=2. For normal gait, stance phase (0-60% GC) begins at left heel strike (HS) and ends with toe off (TO). Swing phase takes between 60 and 100% GC. Notice how these percentages vary for PD gait.

2.2 Definition of Variables

The choice of variability parameters to analyze gait in PD is based on typical inter-subject differences observed in the size and shape of the curve representing the temporal variation of the VGRF. Indeed, as shown on the left in Figure 1 for a case of normal gait, the curve has two peaks. The first happens during heel strike with the ground at the beginning of the stance phase, while the second peak is caused by the upward force exerted by the ground during toe off at the end of the same phase [18-19, 24, 25]. Additionally, the stance and swing phases occur between 0-60% and 60-100% of gait cycle.

In contrast, the curve represented on the right side of Figure 1 for the case of the HY=2 PD patient, sometimes exhibits a reduction in the peak height of VGRF. Also of note is the variation of time taken for the stance and swing phases for PD patients as compared to control subjects (in this case 70% and 30% of gait cycle, respectively), so as to ensure body stability during locomotion. Later stages of this disease are characterized by a gait with small shuffling steps and a single narrow peak of VGRF, thus reducing the time required for the swing phase significantly [18-19, 26].

According to these observations and in order to select the most appropriate variables for differentiation of normal and parkinsonian gait patterns, distinct parameters were employed. Such parameters characterize the inter-subject gait variability throughout the temporal signal corresponding to consecutive gait cycles. Among them, the following were utilized: the stance phase (STPT) and swing phase (SWPT) times and the magnitude of the VGRF, as well as the respective variability

obtained by calculating their corresponding coefficients of variation (CV), defined as the ratio of the standard deviation to the mean. In each case, twenty gait cycles performed by the left limb were analyzed, from which the mentioned gait parameters were statistically analyzed [27].

Furthermore, prior to analysis, the VGRF signals were filtered using a moving average filter of 5 points. Then, from the filtered signals the stance phase and swing phase times (STPT and SWPT) were determined by applying the thresholding technique [28]. For this, the stance phase was defined for signal fractions above 10N and the swing phase as the time during which the foot is not in contact with the ground and hence, the VGRF falls below 10N. Also, the STPT and SWPT data were normalized by their respective gait cycle time for each considered subject. The same procedure was applied to the magnitude of VGRF, in this case normalized in regard to the body mass of each analyzed subject.

3. Results

3.1 Analysis of Stance Phase and Swing Phase Times

Gait data (STPT and SWPT) for the samples HY=0, HY=2 and HY=2.5 yielded values of standardized asymmetry and kurtosis coefficients outside the range (-2, +2), showing that such data does not come from populations with normal distribution. Thus, the non-parametric Kruskal-Wallis test to compare medians instead of means was applied using Statgraphics Centurion XVI.II [27]. The results indicated that there is a statistically significant difference (p <0.05) between the medians of the analyzed samples (Table 3). Still, when the results for STPT and SWPT were contrasted with the respective box and whisker plots (Figures 2 and 3), a significant difference was seen only between samples with HY=0 and HY=2.5, but neither between HY=0 and HY=2 nor between HY=2 and HY=2.5.

Tabla 3. Kruskal-Wallis test

		SWPT	STPT
HY	*Sample size*	*Rank*	*Rank*
0	400[a]	427,711	373,289
2	200[b]	408,668	392,332
2,5	200	337,91	463,09

Statistic= 20,4691   P Value = **0,0000359089**
[a]20 time series multiplied by 20 normal subjects.
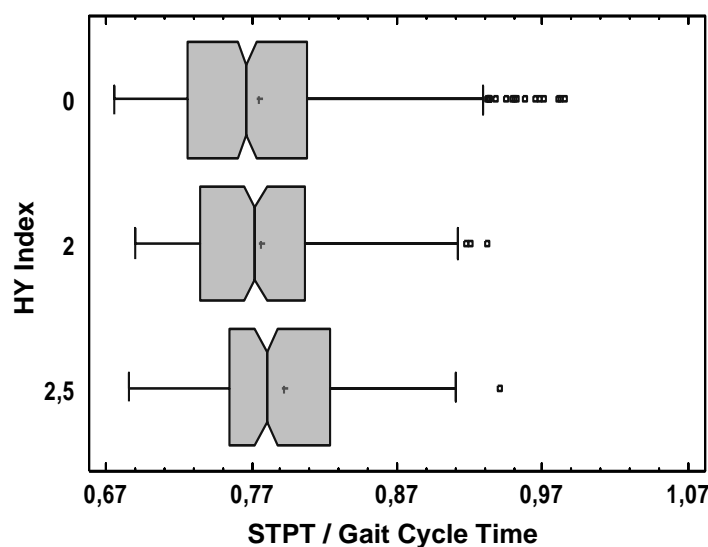[b]20 time series multiplied by 10 PD patients in each case (HY=2 and HY=2.5).

Figure 2: Box and whisker plot for stance phase time (STPT) during gait cycle for the analyzed HY categories.
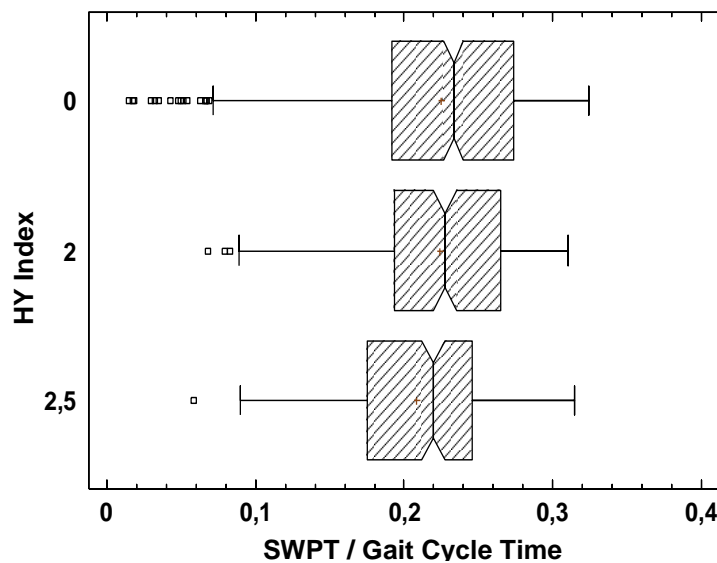
Figure 3: Box and whisker plot for swing phase time (SWPT)
during gait cycle for the analyzed HY categories.

In addition, using the temporal data, the coefficients of variation (CV) of the STPT and SWPT series were calculated. According to the obtained values for standardized asymmetry and kurtosis coefficients, it is possible that the achieved transformation through CV calculation comes from normal distribution, being valid to apply statistical tests that evaluate their respective standard deviations [27]. However, when the corresponding central tendency (mean and median) and standard deviation measures for these new considered variables were compared, no significant differences between samples were evidenced. Furthermore, the Kruskal-Wallis contrast confirmed that there is no significant difference between medians with a value of p = 0.487911 for a confidence level of 95%. Figure 4 represents the results of this analysis for the CV(SWPT) through the box and whisker diagram.
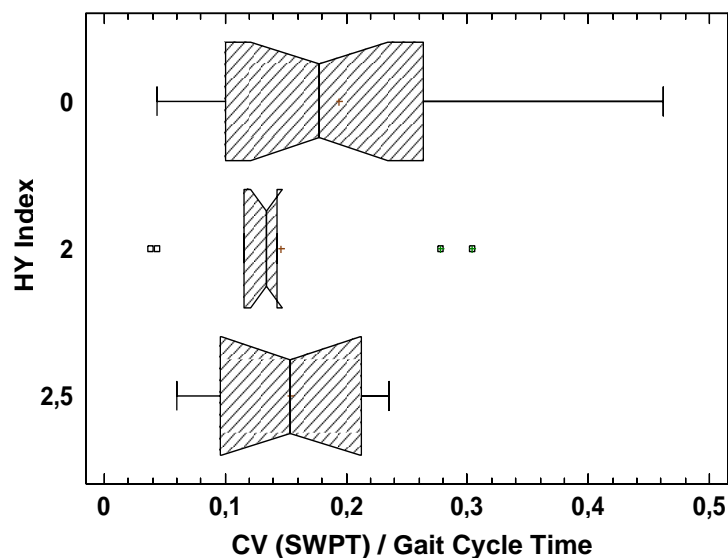

Figure 4. Box and whisker diagram for the coefficient of variation of swing phase time normalized by their respective gait cycle time for the HY categories analyzed.

Finally, Table 4 displays the mean, standard deviation, and maximum and minimum values obtained for the respective coefficients of variation (CV(SWPT)) of the analyzed HY samples.

Table 4. Statistical evaluation of CV(SWPT)

HY	Simple size	Mean value	Standard deviation	Minimum	Maximum
0	20	0,193536	0,113304	0,044103	0,461981
2	10	0,145837	0,0856172	0,0380525	0,304059
2,5	10	0,153885	0,064203	0,0596666	0,235273
Total	40	0,171698	0,0969254	0,0380525	0,461981

3.2 Analysis of the Magnitude of the Vertical Component of Ground Reaction Force
In order to find parameters that establish significant differences for the analyzed samples, three features of the VGRF were evaluated for each gait cycle:

-Maximum VGRF value normalized to respective body weight,

- Area under the VGRF curve during stance phase,

- Coefficient of variation of the maximum VGRF.

In the first two cases (maximum VGRF value and area value under the VGRF curve), the values of standardized asymmetry and kurtosis coefficients were out of range, and as such, the non-parametric Kruskal-Wallis test was applied [27]. In the case of the maximum VGRF, the obtained p value indicated that there is statistically significant difference between the medians of the analyzed HY samples (Table 5). Also, the box and whisker plot for the three samples exhibited differences between HY=0 and HY=2.5, and between HY=2 and HY=2.5. However, this difference is not significant when comparing the cases HY=0 and HY=2 (Figure 5).

Table 5. Kruskal-Wallis test

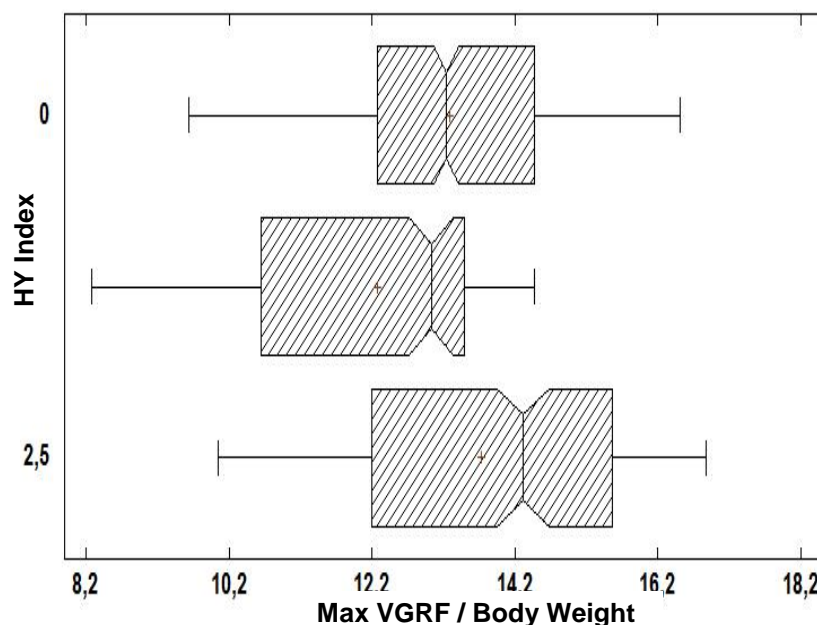|		Max VGRF/Body Weight
HY	Sample size	Rank
0	400	411,89
2	200	304,965
2,5	200	473,255

Statistic= 54,9801   P Value = **1,15141E-12**

Figure 5. Box and whisker diagram for the maximum value of VGRF normalized by the respective body weight, during gait cycle for the analyzed HY categories.

Similar results were achieved when the area under the VGRF curve during stance phase were analyzed, in this case with a value p=0.03 (<0.05). Finally, in regard to maximum VGRF variability, although data are from a population with normal distribution, the central tendency measures did not show statistically significant differences for the HY index [27]. As for the comparison of standard deviation, only significant differences between the HY=0 and HY=2.5 samples were found.

4. Discussion and Conclusions

In the literature, there are various examples of previous research analyzing the stride to stride fluctuations in PD patients from spatial-temporal parameters of gait patterns [7-8, 13-17]. On the one hand, through such research, both an increase of gait variability in PD in contrast to normal gait and a correlation between the degree of gait variability and PD severity [8, 13-14] are shown. On the other hand, this research also confirms that gait variability is a quantifiable feature that, specifically for PD, exhibits alterations in terms of both its magnitude and its dynamics [15-17].

With respect to the viability of using the magnitude of VGRF registered with insole systems for differentiating gait features between PD and control groups, some researchers object to its efficacy. As examples, Barnett and collaborators [22] have signalled that the VGRF measures obtained with an instrumented insole, such as the F-Scan system used for gait database acquisition [20-21], are lower than those achieved with a force platform. This is due to a threshold established in baropometric systems in order to reduce the noise during data collection. Other studies have demonstrated that although the F-Scan insole system could be a useful device to measure the VGRF during gait, care should be taken when interpreting the force data during the initial 21% and final 10% of the stance phase of gait cycle because of a delay in data acquisition with such system [23].

In this regard, our suggestion is that the comparison of VGRF data collected by different instruments should be avoided. Taking into account that the VGRF data for the PD and control groups in this study were acquired using the same insole system [20-21], it is valid to consider that only relative differences in force values between both groups are important. Our previous results based on the analysis of the VGRF measured with this insole system, in where an automatic classification of PD patients was achieved through the application of clustering techniques based on artificial neural networks [18-19], supports the argument that this measure of VGRF contains relevant information for objectively differentiating normal and PD gait patterns.

However, in all of these studies the gait variability has not been evaluated taking into account each progression stage of PD according to both the original and modified version of the HY Scale [9-10, 12]. In this sense, our present work shows possible ways to differentiate the gait alterations specifically for each HY stage. This proposal is based on the obtained results indicating that, for all temporal variables analyzed (stance phase time and swing phase time, referred to in the text as STPT and SWPT), there were significant differences between the HY=0 and HY=2.5 groups. In addition, although these differences were not evidenced between HY=0 and HY=2, this could indicate that in the early stages of Parkinson's disease, the temporal parameters of the gait cycle do not differ with respect to those for healthy subjects.

In relation to this issue, the analysis of Figure 2 indicates that the STPT achieved for the different levels of the factor of HY interest gradually increases as the HY level rises. The opposite occurs for SWPT. Such results support the theory regarding body balance impairment with PD progression [8, 16-17]. Furthermore, the differences observed between the HY=0 and HY=2.5 groups cannot be attributed to age because both analyzed PD groups (HY=2 and HY=2.5) are age-matched, having in addition similar ages to the normal group. A challenge for future studies is to better map these temporal gait parameters and their changes in response to PD evolution.

As regards the analysis of the magnitude of the VGRF from its features evaluated (maximum VGRF value and area under the VGRF curve), the results showed statistically significant difference between the cases HY=0 and HY=2.5, but not between the cases HY=0 and HY=2. However, relevant differences were obtained between the HY=2 and HY=2.5 groups in analyzing the median of maximum VGRF (Table 5 and Figure 5), thus showing the potentiality of the VGRF as a possible predictor of the level of gait impairment/disability in PD patients. In this way, these results confirm our hypothesis. Particularly, in further research, our objective will be to explore the strength and usefulness of the VGRF to quantify the lack or presence of body balance impairment that typically differentiate PD patients classified as HY=2 and HY=2.5.

Finally, as a general conclusion, we can say that this work constitutes an application example of gait analysis in the search for clues to clinimetrically identify the level of gait impairment/disability in PD patients on the Hoehn-Yahr Scale. This type of identification could be applied in our country as a routine study in clinical decision-making taking into account the lower cost of insole systems with respect to force platforms.

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