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Abstract

The literature on gait analysis in Vascular Parkinsonism (VaP), addressing issues such as variability, foot clearance patterns, and the effect of levodopa, is scarce. This study investigates whether spatiotemporal, foot clearance and stride-to-stride variability analysis can discriminate VaP, and responsiveness to levodopa.

Fifteen healthy subjects, 15 Idiopathic Parkinson's Disease (IPD) patients and 15 VaP patients, were assessed in two phases: before (Off-state), and one hour after (On-state) the acute administration of a suprathreshold (1.5 times the usual) levodopa dose. Participants were asked to walk a 30-meter continuous course at a self-selected walking speed while wearing foot-worn inertial sensors. For each gait variable, mean, coefficient of variation (CV), and standard deviations SD1 and SD2 obtained by Poincaré analysis were calculated. General linear models (GLMs) were used to identify group differences. Patients were subject to neuropshychological evaluation (MoCA test) and Brain MRI.

VaP patients presented lower mean stride velocity, stride length, lift-off and strike angle, and height of maximum toe (later swing) ($p<.05$), and higher %gait cycle in double support, with only the latter unresponsive to levodopa. VaP patients also presented higher CV, significantly reduced after levodopa. Yet, all VaP versus IPD differences lost significance when accounting for mean stride length as a covariate.

In conclusion, VaP patients presented a unique gait with reduced degrees of foot clearance, probably correlated to vascular lesioning in dopaminergic/non-dopaminergic cortical and subcortical non-dopaminergic networks, still amenable to benefit from levodopa. The dependency of gait and foot clearance and variability deficits from stride length deserves future clarification.

Keywords: Vascular Parkinsonism; Idiopathic Parkinson's disease; Toe and heel clearance; Short and long-term gait variability; Levodopa.

1. Introduction

Parkinsonian syndromes are manifested by bradykinesia, rigidity, gait impairment and postural instability, with heterogeneous etiologies, ranging from Idiopathic Parkinson's Disease (IPD) to atypical Parkinsonian syndromes, such as Vascular Parkinsonism (Obeso et al., 2017). Even IPD can manifest with different phenotypes, tremor, akinetic-rigid, postural instability, and gait disorder, with the last two sharing overlapping features with VPD. Although IPD has a higher prevalence of over 180/100 000 inhabitants (Ferreira et al., 2017), the differential diagnosis of Parkinsonian syndromes is not always straightforward.

Vascular Parkinsonism (VaP) is a less frequent Parkinsonian syndrome (3-5% of patients with Parkinsonism) (Zijlmans et al., 2004)). It is characterized by lower body Parkinsonism, marked gait difficulty, a relatively symmetrical distribution of bradykinesia and rigidity, less tremor but frequent pyramidal tract signs and dementia, and a poor response to levodopa (Zijlmans et al., 2004). The acute challenges of levodopa, especially in the case of suprathreshold doses, are used to estimate the maximum function of the dopaminergic nigro-striatal-thalamic-cortical circuits and to infer differential diagnosis (Albanese et al., 2001). Yet, there are no clear guidelines as to the quantity of levodopa which should be administered in IPD, and even less in VaP, with most authors defending individualized treatment based on clinical judgment. A greater challenge is presented by the rising body of evidence which indicates that cerebrovascular lesions alter the natural history of IPD, conditioning mixed or even overlapping syndromes with VaP (Rektor et al., 2018). Although the controversy surrounding the criteria for pure Vascular Parkinsonism is beyond the scope of this article (Vizcarra et al., 2015), the aforementioned difficulties clearly justify additional clinical biomarkers. As such, gait analysis may allow one to objectively quantify the benefit of levodopa on the several domains of gait and will aid in a

differential diagnosis.

The growing body of evidence suggests that gait stride-to-stride variability, often measured by using standard deviation and coefficient of variation, provides disease-specific information (Hausdorff, 2007). In fact, higher values of gait variability have been associated with the freezing of gait in IPD, greater instability, and the risk of falls (Bryant et al., 2011). Quantitative Poincaré plot analysis offers an additional descriptive method for the assessment of gait variability (Hollman et al., 2016). The Poincaré plot is a graphic representation of consecutive data points that can be used to quantify measures of short- and long-term variability (Golińska, 2013).

The effect of levodopa on gait variability is not altogether clear. Some studies have shown that levodopa can decrease the variability of only some of the gait variables (step time, swing time, stride length and stride velocity) (Bryant et al., 2011; Bryant et al., 2016). Others have reported no effect in the variability of double support time and postural control, which mirror the involvement of non-dopaminergic structures (Galna et al., 2015; Bryant et al., 2016). This is of special relevance in the case of VaP, where cerebrovascular lesions may heterogeneously impair dopaminergic and non-dopaminergic networks. Furthermore, gait analysis studies are scarce in VaP (Zijlmans et al., 1996), and none of which have investigated gait variability and foot clearance pattern.

IPD patients typically walk at a slower walking velocity, mostly due to reduced step length (Almeida et al., 2007; Alcock et al., 2018). Studies on foot clearance (toe and heel height during swing phase), as well as foot angles before (lift-off angle) or after (strike angle) the swing phase are relatively scarce. The strike angle (Ginis et al., 2017) and the step length (Alcock et al., 2018) were reported to be significant determinants of foot clearance. Foot clearance patterns are critical, as insufficient or higher fluctuations in swing

foot progression have been related to a higher risk of tripping and falling in the elderly population and IPD patients (Dadashi et al., 2014). In a novel study concerning the effect of levodopa on foot clearance (Cho et al., 2010), levodopa was shown to be ineffective in normalizing foot dynamics completely. Yet, this study must be replicated in other cohorts, mostly accounting to the heterogeneity of IPD, but also contemplating other parkinsonian syndromes such as VaP.

The primary objective of the present study is to evaluate spatiotemporal and foot clearance gait stride-to-stride variability in VaP in comparison to IPD, and to seek to identify discriminative variables. Furthermore, the effect of levodopa on different gait variables is also investigated. We hypothesized that VaP patients have a different gait profile, with a distinctive foot clearance pattern (lower lift-off and strike angle), with higher variability, with lower response to levodopa.

2.Methods

2.1. Subjects and clinical assessment

Fifteen VaP patients (fulfilling criteria for VaP (Zijlmans et al., 2004)), and 15 IPD age-matched patients (fulfilling MDS-PD criteria (Postuma et al., 2015)) with a predominant symmetric akinetic-rigid phenotype, were consecutively recruited from our Movement Disorder outpatient consultations. Of the different IPD clinical subtypes – including tremor, postural instability, gait disorder, and akinetic-rigidity – the latter revealed the most substantial overlap with VaP (Obeso et al., 2017), reinforcing the added value of gait analysis as a differentiator. Patients and healthy subjects were excluded if they had a history of an orthopedic, musculoskeletal or vestibular disorder, or alcohol abuse. Patients

presented independent, but impaired gait (UPDRS Subscore 3.10 - Gait > 1 point), and VaP patients displayed lower body Parkinsonism related to acute or chronic cerebrovascular disease (6 patients exhibited an acute presentation, and 9 had an insidious presentation of VaP) (Supplementary material 1). The severity of dementia was graded according to the Clinical Dementia Rating scale (CDR) (Morris, 1993), and VaP patients with moderate-severe dementia (CDR>1), resting tremor, neuroleptic therapy, brain trauma, supranuclear palsy, retrocollis, cerebellar signs, dystonic and/or alien limb, respiratory stridor, orthostatic hypotension (>30mmHg), or motor deficits, whether related or unrelated to strokes, were excluded. Re-confirmation of diagnosis and levodopa response was performed during a longitudinal follow-up (Table 1). Demographic, anthropometric and clinical data (years of disease duration, as well as the Levodopa Equivalent Daily Dose (Williams-Gray et al., 2007)), scores of MDS-Unified Parkinson's Disease (MDS-UPDRS-III) and the Hoenh-Yahr scale (M. D. S. T. F. on Rating Scale for Parkinson's Disease, 2003) were collected by a movement disorders specialist (second author, MG). A brief neuropsychological examination, the Montreal Cognitive Assessment test (MoCA) (Freitas et al., 2011), was performed. Patients were evaluated in the ''Off-state'', in the morning, after 12 hours without any dopaminergic medication. Afterward, they were given suprathreshold dopaminergic medication, 150% of their usual morning dose, and were re-examined 60 minutes later (''On-state''). The study protocol and consent forms were approved by the hospital local ethics committee, and all participants provided informed written consent.

2.2. Gait analysis

The participants were asked to walk a 30-meter continuous course at a self-selected walking speed. Two Physilog® sensors (GaitUp®, Switzerland), one on each foot, were fixed on the upper part of the shoe with an elastic strap. Physilog® is a standalone inertial

measurement unit with wireless synchronization, including a tri-axial accelerometer, a tri-axial gyroscope, a tri-axial magnetometer, and a barometric pressure sensor. Using the software provided by GaitUp® featuring a patented fusion algorithm based on gait events detection, signal de-drifting, strap down integration, and biomechanical modeling, the spatiotemporal and foot clearance (panel A of Figure 1) variables were assessed for each stride and subsequently extracted as previously described and validated (Dadashi et al. 2014; Mariani et al. 2010).

In order to evaluate straight walking alone, without any variations due to the initiation and termination of gait, the two strides for initiation and termination were discarded.

2.3. Measures of stride-to-stride variability

For each gait time series, the arithmetic mean ($\overline{X}$), the standard deviation (SD) and the standard deviation of the successive differences (SD_{sd}) were determined. Subsequently, the three measures of the variability coefficient of variation (CV) and the two measures used in quantifying Poincaré plot geometry - SD1 and SD2 - were calculated as:

$$CV = \frac{SD}{\overline{X}} \times 100,$$

$$SD1 = \frac{\sqrt{2}}{2} SD_{sd},$$

and

$$SD2 = \sqrt{2[SD]^2 - \frac{1}{2}[SD_{sd}]^2}.$$

The Poincaré plot is a geometrical representation of a time series,x_0,x_1,x_2,x_3,..., on a Cartesian plane, where the values of each pair of successive elements of the time series, (x_0,x_1)

, (x_1,x_2),..., define a point in the scatter plot (Golińska, 2013) (panels B and C of Figure 1). A shape of the plot shows element-to-element variability as well as overall variation. SD1 and SD2 measures corresponded to the length of the minor and the major semi-axes, respectively, of an imaginary ellipse that is fitted to the Poincaré plot. The major axis of this ellipse is along a line beginning at the origin, with a slope of 1; the minor axis is perpendicular to the major axis, and the intersection of these two axes is given by ($\overline{X}$,$\overline{X}$) (ellipse center), where $\overline{X}$ is the arithmetic mean of the time series. Therefore, SD1 is the standard deviation of the distances of points from the minor axis and represents short-term variability; SD2 is the standard deviation of the distances of points from the major axis and represents long-term variability (Golińska, 2013).

2.4. Statistical analysis

2.4. Statistical analysis

The normality of the data distribution for each parameter was tested using the Shapiro–Wilk test, visual inspection of the histograms and evaluation of skewness. Demographic, anthropometric, clinical scores and gait measures in the Off-state were statistically compared using one-way ANOVA with Tukey's HSD as post-hoc test, Independent t-test or Mann-Whitney U test (intergroup analysis), and Paired t-test (intragroup analysis).

A series of general linear models (GLMs) was used to identify group differences in gait measures with the influence of different covariates and/or of the state: 1) In order, to explore group differences regarding the possible influence of demographic, anthropometric and clinical characteristics, which were significantly different in the intergroup analysis, different GLMs using each of these variables as a covariate on gait measures in the Off-state were performed. 2) GLMs were constructed in patients to identify the main and

interaction effects which ensued from the pathology itself (IPD versus VaP) and the state (Off versus On). When a statistical difference was found in the state factor, a Paired t-test was performed for each group of patients so as to analyze the differences between the Off- and On-states per group. 3) Pearson's correlation analysis was performed between mean stride length and the other gait measures. When significant correlation was observed, the GLMs were re-run, using stride length as a covariate. Testing of the assumptions was undertaken before conducting the GLM analyses. Data that were not normally distributed were subjected to log transformation. A p-value<.05 was considered statistically significant. Statistical analysis was performed using SPSS (v.24.0, IBM).

3. Results

3.1. Clinical characteristics

VaP patients were slightly older (Table 1), in concordance with the age-dependent onset of cerebrovascular events (Kalra et al., 2010), and presented a shorter disease duration, since an acute and insidious subtype of VaP usually presents an earlier burden of axial impairment when compared to IPD (Kalra et al., 2010). Moreover, VaP patients had significantly lower MoCA scores, possibly due to age and vascular lesions (Oren et al., 2015).

Concerning motor scores, in the Off-state there were no differences between VaP and IPD patients, reflecting substantial overlapping clinical features and the potential added value of Gait Analysis as a new biometric tool. Even so, the magnitude of response to levodopa was higher in IPD.

3.2. Gait variables

The time series sizes are different, depending on the number of strides needed by each person to complete the course (panel B of Figure 1). VaP needed the highest number

of strides In Off-state, the number of strides Median[Minimum,Maximum], were: 42[29,85] for VaP; 29[22,45] for IPD; and 24[17,27] for Control Group.

Group differences in the Off-medication, as well as the evaluation of within-group (state) and between-group (VaP vs. IPD) differences in gait characteristics, are summarized in Table 2 (right foot (RF)) and Supplementary material 2 (left foot (LF)).

3.2.1. Intergroup comparisons (Off medication)

In comparison to Control, both IPD and VaP patients presented lower stride velocity and stride length ($p<.001$), clearly more impaired in VaP; and a higher %gait cycle spent on double support ($p<.021$). Concerning foot clearance, both groups of patients exhibited lower lift-off angle ($p<.030$), strike angle ($p<.006$), lower maximum toe LSW (late swing) ($p<.001$), also clearly more impaired in VaP.

Concerning variability, VaP patients presented higher variability (CV) in stride velocity, stride length, lift-off angle, maximum heel, and strike angle ($p<.05$) in comparing to both Control and IPD groups. For the variability measured by SD1 and SD2, both VaP and IPD presented higher variability in stride length, %gait cycle spent on double support, lift-off angle, and maximum heel ($p<.031$), but without discriminative value between different groups of patients.

Group differences were found for sex, age, and MoCA. Therefore, GLMs with group as a fixed factor with each one of these variables as a covariate were analyzed. Group differences, previously described, were retained when sex, age or MoCA was used as a covariate (Table 2). Only the variable mean value of maximum heel lost statistical inter-group significance when controlling for age ($p=.129$ (RF) and $p=.069$ (LF)) or for MoCA ($p=.061$ (RF) and $p=.058$ (LF)).

3.2.2. The effect of levodopa

Suprathreshold levodopa improved gait impairments in both groups of patients in features such as stride velocity, stride length, and lift-off angle ($p<.001$). A significant interaction was observed for stride velocity ($p<.041$), highlighting that IPD patients increased walking velocity from Off to On-state, more than in VaP. Interestingly, in contrast to IPD, levodopa was ineffective in VaP in improving %gait cycle spent on double support, maximum heel, maximum toe LSW and strike angle. Concerning variability, levodopa reduced CV values of stride velocity, stride length, lift-off angle, and maximum heel features in VaP Group ($p<.05$), and CV value of the strike angle ($p<.006$) in IPD Group.

3.3.3 Influence of stride length

Correlations between mean stride length and the other gait measures (Supplementary material 3) revealed that moderate to strong associations were found for mean values of stride velocity (r=.79-.97), lift-off angle (r=.53-.96) and maximum toe LSW (r=.61-.84) in all groups for both feet. Additionally, except for the control group in the right foot, higher correlations were found for the mean value of strike angle (r=.59-.86). GLMs with the group as fixed factor (Table 2) were re-run for these four variables, using stride length as a covariate. Group differences were only retained in stride velocity, for IPD versus Control, and for VaP versus Control ($p<.001$) but were non-significant for IPD versus VaP ($p>.446$).

Concerning both groups of patients, higher correlations ($|r|= .60-.97$) were also found for the mean of stride velocity, mean of maximum toe LSW and mean and CV values of lift-off angle; maximum heel; and strike angle in both states. Additionally, except for IPD group in On-state, the CV of stride length and stride velocity, and the mean of %gait cycle spent on double support, also presented higher correlations ($|r|=.60-.80$). We re-run

the GLM controlling for state (Table 2) for these eleven variables, using stride length (average of On and Off state stride length) as a covariate. Group differences (IPD versus VaP) were found to be non-significant ($p>.138$) for all measures.

4.Discussion

In our work, we have shown that VaP patients presented a different gait profile, evident in a slower stride velocity, shorter stride length, reduced angles of freedom of foot clearance, higher stride-to-stride variability, with a lower response to levodopa.

4.1 Intergroup comparisons (Off-state)

Our findings are in accordance with earlier works (Alcock et al., 2016; Alcock et al., 2018; Almeida et al., 2007; Cho et al., 2010; Ginis et al., 2017), with IPD presenting slower walking velocity, reduced stride length, with increased time spent on double limb support as a marker of poor postural stability (Galna et al., 2015; Bryant et al., 2016; Moon et al., 2016). As hypothesized, all these spatiotemporal variables were severely impaired in VaP, in line with previous work (Zijlmans et al., 1996).

Humans modify stride length and/or cadence, which indirectly influences the pattern of foot clearance (Cho et al., 2010), in order to choose a walking velocity that is suited to the surrounding environment. Several hypotheses can be raised to explain our observations. Reduced angles of freedom of foot clearance in VaP may be due to lower hip and knee flexion throughout the gait cycle (Zijlmans et al., 1996). Furthermore, VaP presented either vascular lesions (Supplementary material 1), affecting cortical areas (supplementary and premotor cortex) (e.g. pre-frontal cortical stroke) or cerebro-pontine-cerebellum tracts (e.g. frontal-subcortical leucoencephalopathy), both having an important role in limb tonus and locomotion (Takakusaki, 2017).

Loss of automaticity and compensatory strategies, as well as the influence of cognition, may explain the increased variability in our cohort of IPD and VaP patients. To overcome the loss of automaticity in IPD, there is a compensatory increase in the activity in cerebellar locomotor areas, superior frontal gyrus, and cingular cortex, ultimately increasing variability (Hanakawa et al., 1999; Wu et al., 2013). In 20 patients with subcortical arteriosclerotic encephalopathy (using a length-voltage transducer linked to each foot) (Ebersbach et al., 1999), it was shown that, besides a slower gait, the increased variability of the amplitude and timing of steps was probably related to mild signs of dementia secondary to multiple subcortical white matter lesions. Thus, the higher variability observed in VaP, may be due to vascular lesioning of the non-dopaminergic networks and higher cognitive impairment.

4.2 The effect of levodopa

Unsurprisingly, levodopa improved stride velocity and stride length in IPD (Bryant et al., 2011; Bryant et al., 2016; Galna et al., 2015). This improvement was also evident in the initial and terminal phases of the swing, similar to a previous study (Cho et al., 2010) where levodopa (150% of usual morning dose) also improved foot dynamics. However, it still fell short of normality, especially in the terminal phase. Concerning the effect on variability, our results are in line with previous work (Galna et al., 2015), where at 18 months of follow-up and administration of levodopa (equivalent daily dosage), IPD patients did not show an improvement of the variability of the spatiotemporal domains. Conversely, in a transversal study where the equivalent of a daily dosage of levodopa was administered, only the variability of double support time was not responsive (Bryant et al., 2016).

The observation that some gait impairments in VaP (albeit with a lower magnitude when

compared to IPD), are still responsive to levodopa, reinforces the hypothesis – already presented by (Zijlmans et al., 2004) and recently updated by (Rektor et al., 2018) – that some VaP subtypes (acute/subacute post-stroke), with vascular lesions in the nigrostriatal pathways, are likely to benefit from levodopa.

4.3 Influence of stride length

In IPD, disturbed toe clearance and the terminal phase of the swing may be due to reduced step length (Alcock et al., 2018), or instead to abnormal cadence (Cho et al., 2010). Although this pending question is beyond the scope of this article, we re-ran our GLMs using stride length as a covariate. The results revealed that stride length significantly determined variability (CV) and foot clearance in IPD and VaP. Additionally, no differences were found in SD1 and SD2, confirming that stride-to-stride variability differences in IPD and VaP are influenced by the stride length.

4.4 Study limitations

Our work presents several limitations, which must be appraised. Despite compliance with published clinical criteria for VaP (Zijlmans et al., 2004), the diagnosis of VaP was purely supported by retrospective longitudinal clinical history. Yet, the clinical features of our VaP cohort would be considered as exclusion criteria (e.g., Parkinsonian features restricted to the lower limbs for more than 3 years, poor levodopa response) or even red flags (substantial gait and postural instability in an early phase, without clinical progression) in the diagnosis of IPD (Postuma et al., 2015). Elderly subjects show increased variability of toe clearance and increased risk of falling due to the use of multifocal spectacles (Johnson et al.,2007). Also, patients with late loss of vision present a similar gait profile as congenital blind, with slower walking speed and stride length, presumably reflecting a

compensatory use of non-visual sensory input and adaptation to egocentric and environmental restrictions, maintaining a safe gait (Nakamura,1997). As such, our data deserves re-observation, and future studies should contemplate these variables.

5.Conclusion

Gait stride-to-stride analysis, in particular, foot clearance patterns and variability, assist in the objectivation of clinical changes, reproducing the phenomenological observation in which VaP patients drag their feet and walk with a more extended body posture of the legs, hip, and trunk.

Moreover, in VaP, the increased variability of several gait parameters, which was related to reduced stride length, may also reflect worst cognition as also vascular lesioning in non-dopaminergic cortical and subcortical non-dopaminergic networks, less responsive to levodopa. These observations call for further studies in VaP, which should converge gait analysis with structural and functional neuroimaging, thus clarifying heterogeneity in VaP (acute/subacute versus chronic subtypes) and improving our knowledge of the role of vascular pathology in gait performance.

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Conflict of interest

The authors of the manuscript “Gait stride-to-stride variability analysis and foot

clearance pattern in Idiopathic Parkinson's Disease and Vascular Parkinsonism" declare that there are no conflicts of interest associated with this work.

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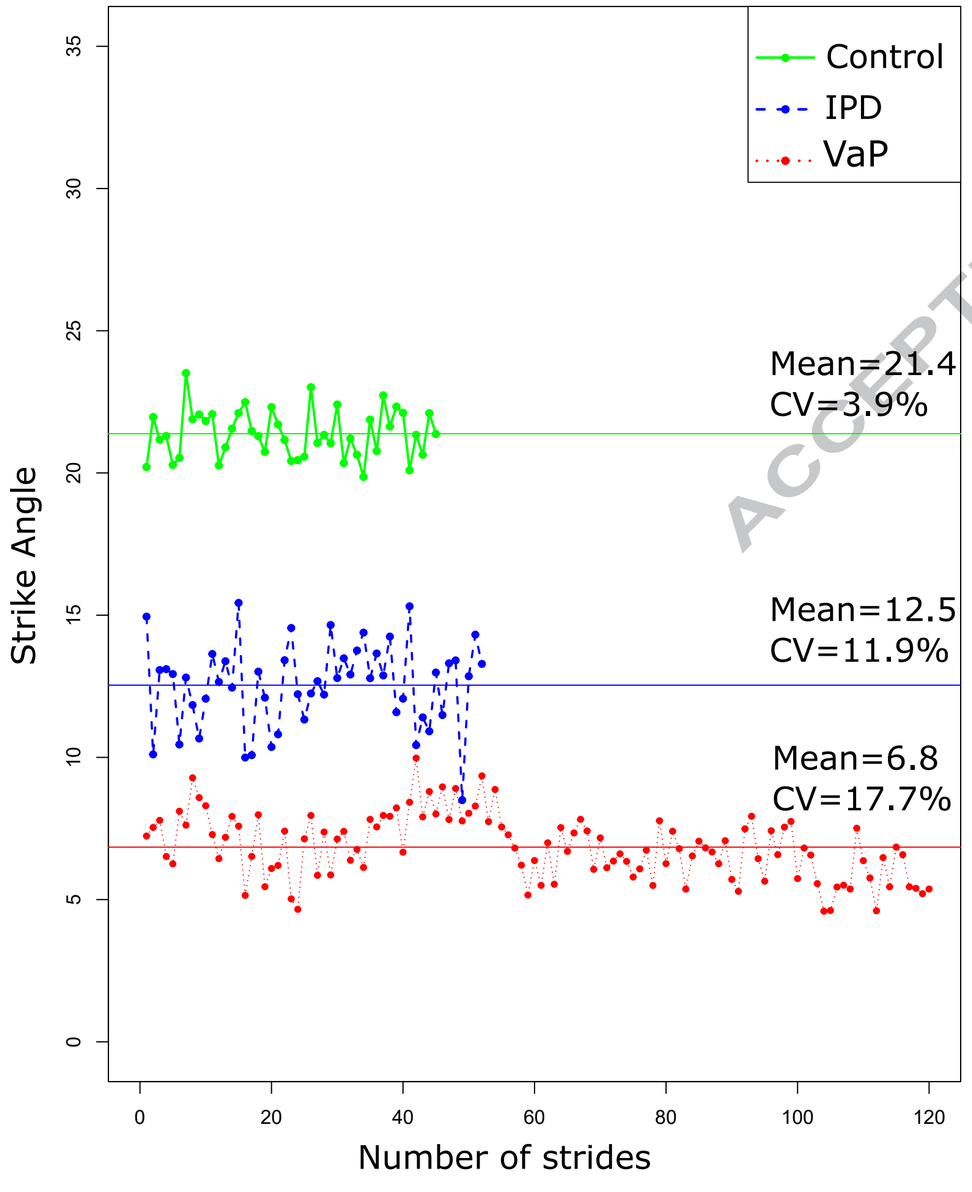
Figure Legend

Figure 1. Toe and heel height during swing phase as well as angles between the foot and the ground when the toe leaving the ground (lift-off angle) and when the heel hits the ground (strike angle) (A) (Adapted from GaitUp® document support. Used with permission.). Representative times series (B) and Poincaré plots (C) of strike angle over a continuous course for a healthy subject (green line), an Idiopathic Parkinson's disease (IPD) (blue line) and a Vascular Parkinsonism Disease (VaP) patient (red line). Each Poincaré plot represents data from each individual stride during a gait walk, x(n), on the x-axis, and the subsequent stride, x(n+1), on the y-axis SD1 (short-term variability) and SD2 (long-term variability) represents the dispersion along minor and major axis of the fitted ellipse. VaP patient presents a different clearance foot pattern (lower strike angle) and higher variability over the mean (coefficient of variation) (*CV*=17.7%). IPD patient presents the higher short-(SD1) and long-term (SD2) variability values. ESW, LSW denote early and late swing, respectively.

(A)

(B)



(C)

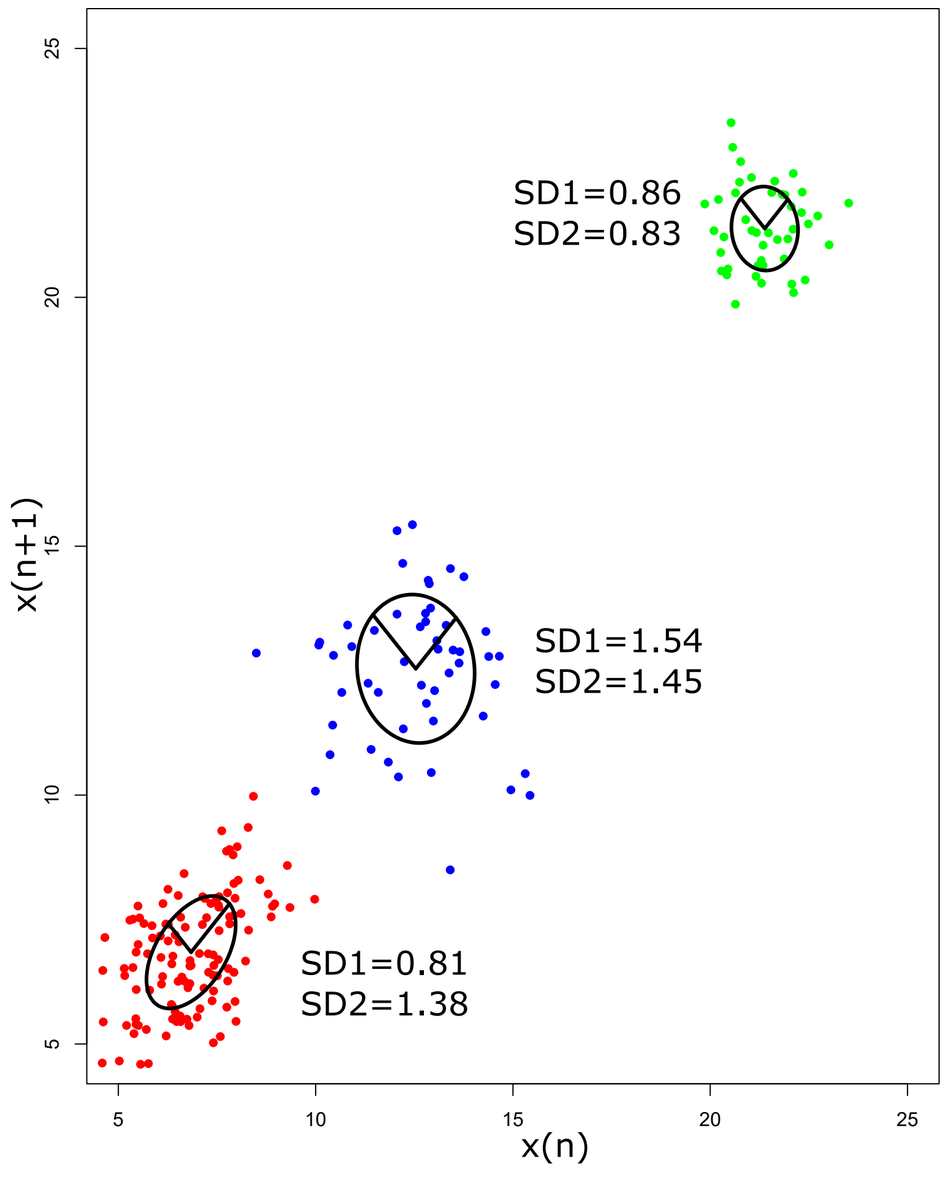


Table 1

Demographic, anthropometric and clinical variables.

	VaP (n=15)	**IPD** (n=15)	**Control** (n=15)	**All Groups**	**VaP vs. IPD**	**IPD vs. Control**	**VaP vs. Control**
Sex (percent male)	60%	80%	33%	---	---	---	---
Age	79.5[73,90]	78[67,83]	77[65,85]	***p*=.017**[a]	*p*=.085[b]	***p*= .018**[b]	*p*=.783[b]
Weight (*kg*)	65.1[50.6,85.0	68.0[57.0,95.0]	68.0[57.8;81.4]	*p*=.175[a]	---	---	---
Height (*m*)	1.63[1.44;1.76	1.66[1.52;1.79]	1.63[1.53,1.77]	*p*=.182[a]	---	---	---
Body Mass Index (*kg/m*^{2})	26.1[19.6,31.8	27.2[21.2,31.4]	25.5[23.1,29.5]	*p*=.655[a]	---	---	---
MoCA	12[4,21]	17[4,22]	21[16,29]	***p*< .001**[a]	*p*=.046[b]	***p*< .001**[b]	*p*=.044[b]
Disease duration (years)	3[2,5]	4[2,11]	---	---	***p*=.034**[c]	---	---
Levodopa total dose	550[345,1100]	675[400,1815]	---	---	*p*=.077[c]	---	---
Levodopa challenge dose	300[200,375]	300[200,1064]	---	---	*p*=.436[c]	---	---
UPDRS-III, Off-state	44[22,70]	47[28,73]	---	---	*p*=.904[d]	---	---
UPDRS-III, On-state	38[17,67]	22[9,47]	---	---	***p*< .001**[d]	---	---
Off vs On	***p*< .001**[e]	***p*< .001**[e]	---	---	---	---	---
Bradykinesia, Off-state	21[9,34]	24[12,35]	---	---	*p*=.590[d]	---	---
Bradykinesia, On-state	21[6,33]	12[3,22]	---	---	***p*=.005**[d]	---	---
Off vs On	***p*=.001**[e]	***p*< .001**[e]	---	---	---	---	---
Rigidity, Off-state	11[9,19]	11[6,15]	---	---	*p*=.393[d]	---	---
Rigidity, On-state	9[4,15]	6[2,12]	---	---	***p*=.005**[d]	---	---
Off vs On	***p*< .001**[e]	***p*< .001**[e]	---	---	---	---	---
PIGD, Off medication	8[4,15]	6[1,11]	---	---	***p*=.041**[d]	---	---
PIGD, On medication	3[1,12]	3[1,8]	---	---	*p*=.723[d]	---	---
Off vs On	***p*< .001**[e]	***p*< .001**[e]	---	---	---	---	---

Data is presented as median [minimum, maximum]. [a] One-Way ANOVA test. [b] Tukey HSD correction as Post hoc. [c] Mann-Whitney U test. [d] Paired t-test. [e] Independent t-test.

Bradykinesia, rigidity, and PIGD were calculated from the specific MDS-UPDRS items as follow: bradykinesia (sum of items 3.4 (finger tapping), 3.5 (hand movements), 3.6 (pronation-supination movements), 3.7 (toe tapping), 3.8 (leg agility) and 3.14 (global spontaneity of movements); rigidity (item 3.3 (rigidity)) and PIGD (sum of items 3.9 (arising from the chair), 3.10 (gait), 3.11 (freezing of gait), 3.12 (postural stability), 3.13 (posture) and 3.14 (global spontaneity of movements)).

Table 2
Statistical differences in spatiotemporal, foot clearance characteristics, stride-to-stride variability and symmetry outcomes for the right foot

	Off-state		Control	One-way ANOVA	Post-hoc Tukey's HSD test		On-state		General linear model		
	VaP	IPD		Group	VaP vs. IPD	Control vs. VaP	Control vs. IPD	VaP	IPD	Group	State	Group × State
Stride Velocity (m/sec)												
Mean	0.6 (0.39)	0.8 (0.36)	1.3 (0.18)	< .001 [a, b, c]	.016	< .001	< .001	0.7 (0.39)	0.9 (0.32)	< .001	< .001 [e, f]	.041
CV*	7.0 (5.89)	5.7 (3.75)	3.6 (1.16)	< .001 [a, b, c]	.018	< .001	< .001	6.6 (4.90)	4.8 (1.86)	.023	.008 [e]	.590
SD1*	0.03 (0.011)	0.03 (0.016)	0.03 (0.008)	.483	---	---	---	0.03 (0.013)	0.03 (0.010)	.391	.748	.645
SD2*	0.06 (0.035)	0.06 (0.015)	0.06 (0.026)	.472	---	---	---	0.06 (0.026)	0.07 (0.035)	.755	.874	.289
Symmetry	1.00 (0.013)	0.99 (0.008)	1.00 (0.008)	.515	---	---	---	1.00 (0.009)	0.99 (0.009)	.061	.460	.642
Stride length (m)												
Mean	0.7 (0.44)	1.0 (0.42)	1.3 (0.14)	< .001 [a, b, c]	.004	<.001	<.001	0.8 (0.41)	1.0 (0.33)	< .001	< .001 [e, f]	.223
CV*	6.1 (7.55)	4.4 (4.02)	2.4 (0.90)	< .001 [a, b, c]	.047	< .001	< .001	5.4 (5.73)	4.1 (2.26)	.030	.020 [e]	.956
SD1*	0.03 (0.015)	0.03 (0.022)	0.02 (0.008)	< .001 [a, b, c]	.945	.004	.002	0.03 (0.018)	0.03 (0.010)	.819	.149	.852
SD2*	0.06 (0.044)	0.06 (0.036)	0.04 (0.016)	.002 [a, b, c]	.773	.003	.018	0.06 (0.039)	0.06 (0.031)	.624	.421	.682
Symmetry	1.00 (0.012)	1.00 (0.010)	0.99 (0.005)	.902	---	---	---	1.00 (0.009)	0.99 (0.015)	.123	.732	.342
Double Support (% gait cycle)												
Mean	29.2 (6.89)	25.9 (4.86)	20.7 (7.24)	< .001 [a, b, c]	.088	< .001	.021	29.1 (7.78)	22.0 (6.15)	.009	.002 [f]	.068
CV*	9.5 (5.80)	9.9 (6.18)	6.1 (4.90)	.007 [a, b, c]	.866	.009	.032	10.4 (5.86)	9.2 (5.98)	.564	.715	.979
SD1*	2.99 (2.615)	2.08 (1.81)	1.19 (0.759)	< .001 [a, b, c]	.577	< .001	.003	2.91 (2.187)	2.00 (2.059)	.226	.703	.868
SD2*	3.79 (3.244)	2.97 (2.522)	1.65 (0.923)	< .001 [a, b, c]	.393	< .001	.001	3.91 (3.973)	2.39 (1.761)	.098	.098	.502
Lift-off angle (deg)												
|Mean|	44.4 (19.68)	53.6 (11.97)	60.6 (12.90)	< .001 [a, b, c]	.005	< .001	.030	46.7 (15.82)	54.8 (7.47)	< .001	< .001 [e, f]	.200
|CV|*	9.6 (5.81)	4.8 (1.88)	2.2 (1.13)	< .001 [a, b, c]	.009	<.001	<.001	5.6 (5.70)	3.9 (2.51)	.015	.015 [e]	.639
SD1*	2.22 (0.861)	2.31 (0.958)	1.2 (0.585)	< .001 [a, b, c]	.801	<.001	<.001	2.25 (1.277)	1.85 (1.152)	.644	.146	.794
SD2*	3.39 (2.213)	3.08 (1.747)	1.7 (0.70)	<.001 [a, b, c]	.142	< .001	< .001	2.93 (2.556)	2.86 (1.872)	.755	.874	.289
Symmetry	1.00 (0.104)	1.00 (0.066)	0.98 (0.045)	0.107	---	---	---	0.96 (0.085)	0.99 (0.038)	.139	.075	.953
Maximum Heel (m)												
Mean*	0.21 (0.094)	0.23 (0.054)	0.24 (0.054)	.020 [a]	.044	.028	.977	0.21 (0.072)	0.25 (0.059)	.030	.008 [e]	.529

CV*	7.4 (13.54)	4.3 (2.99)	2.8 (0.86)	< .001 [a, b, c]	.035	< .001	.036	5.1 (4.25)	3.4 (2.88)	.041	.047 [e]	.512
SD1*	0.013 (0.0076)	0.008 (0.0044)	0.006 (0.0022)	.002 [a, b, c]	.470	.002	.031	0.009 (0.0071)	0.008 (0.0037)	.421	.141	.300
SD2*	0.020 (0.0189)	0.013 (0.0074)	0.007 (0.0032)	< .001 [a, b, c]	.081	< .001	.020	0.013 (0.0130)	0.012 (0.0077)	.132	.140	.385
Symmetry	0.99 (0.158)	1.02 (0.103)	0.99 (0.120)	0.177	---	---	---	0.99 (0.035)	1.00 (0.130)	.168	.735	.350
Maximum Toe Early Swing (ESW) (m)												
Mean*	0.07 (0.020)	0.07 (0.040)	0.07 (0.023)	.771	---	---	---	0.07 (0.022)	0.07 (0.048)	.529	.736	.913
CV*	9.5 (6.44)	7.5 (2.37)	7.0 (3.06)	.066	---	---	---	6.5 (4.87)	6.1 (3.16)	.280	.055	.667
SD1*	0.005 (0.0018)	0.005 (0.0027)	0.004 (0.0023)	.621	---	---	---	0.005 (0.0031)	0.005 (0.0011)	.573	.152	.658
SD2*	0.009 (0.0068)	0.006 (0.0052)	0.005 (0.0034)	.195	---	---	---	0.006 (0.0039)	0.005 (0.0029)	.747	.068	.614
Symmetry	0.99 (0.254)	1.03 (0.323)	1.02 (0.181)	.285	---	---	---	1.00 (0.249)	1.10 (0.434)	.295	.999	.666
Minimum Toe (m)												
Mean*	0.03 (0.010)	0.03 (0.007)	0.04 (0.008)	.601	---	---	---	0.03 (0.008)	0.04 (0.012)	.426	.532	.676
CV*	7.5 (5.38)	9.4 (4.27)	8.0 (3.92)	.520	---	---	---	7.3 (3.37)	9.8 (3.85)	.158	.228	.513
SD1*	0.002 (0.0014)	0.003 (0.0012)	0.003 (0.0019)	.275	---	---	---	0.003 (0.0011)	0.003 (0.0012)	.009	.876	.122
SD2*	0.004 (0.0022)	0.004 (0.0012)	0.004 (0.0026)	.401	---	---	---	0.004 (0.0030)	0.004 (0.0011)	.069	.108	.070
Symmetry	1.07 (0.374)	0.95 (0.209)	0.93 (0.183)	.194	---	---	---	1.08 (0.212)	1.00 (0.212)	.318	.593	.512
Maximum Toe Late Swing (LSW) (m)												
Mean	0.06 (0.053)	0.10 (0.073)	0.13 (0.036)	< .001 [a, b, c]	.004	< .001	.163	0.07 (0.054)	0.12 (0.053)	.005	.007 [f]	.071
CV*	11.0 (8.81)	9.3 (4.38)	5.7 (1.39)	< .001 [a, b, c]	.297	< .001	< .001	10.6 (5.80)	7.9 (4.25)	.065	.110	.267
SD1*	0.007 (0.0052)	0.008 (0.0036)	0.007 (0.0031)	.073	---	---	---	0.008 (0.0058)	0.009 (0.0025)	.066	.356	.512
SD2*	0.010 (0.0076)	0.013 (0.0056)	0.009 (0.0027)	.056	---	---	---	0.009 (0.0075)	0.012 (0.0029)	.052	.856	.893
Symmetry	1.03 (0.332)	1.01 (0.308)	1.01 (0.148)	.852	---	---	---	1.00 (0.224)	1.05 (0.165)	.584	.179	.308
Strike Angle (deg)												
Mean	8.0 (11.01)	15.0 (11.46)	23.6 (3.09)	< .001 [a, b, c]	.018	< .001	.006	10.6 (9.95)	17.5 (9.25)	.002	.003 [f]	.197
CV*	15.9 (29.91)	12.0 (6.07)	5.1 (1.82)	< .001 [a, b, c]	.045	< .001	< .001	16.8 (18.78)	8.5 (7.52)	.047	.003 [f]	.485
SD1*	1.4 (0.95)	1.4 (0.35)	1.0 (0.35)	.062	---	---	---	1.5 (1.14)	1.4 (0.53)	.292	.752	.133
SD2*	1.9 (1.33)	2.4 (0.72)	1.8 (0.98)	.086	---	---	---	2.2 (1.86)	2.0 (0.52)	.319	.449	.069
Symmetry	0.96 (0.243)	1.03 (0.255)	0.97 (0.123)	.374	---	---	---	0.96 (0.245)	1.07 (0.266)	.540	.053	.286

Data are presented as median (Interquartile range (IQR)). Cells that are shaded in light ($p<.05$) and dark ($p< .01$) grey highlight significant correlations to aid visual interpretation. Additionally, for each gait variable, the symmetry value was calculated by taking the ratio of the mean value of the right side to the mean value of the left side. No statistically significant difference between groups was observed for the symmetry. The results for the left foot are reported in Supplementary material 2.

*Log transformation was done to obtain a normal distribution.

[a] Statistical significance ($p < .05$) for group effect in GLM analysis using sex as a covariate (sex effect and interaction between group and sex not significant).

[b] Statistical significance ($p < .05$) for group effect in GLM analysis using age as a covariate (age effect and interaction between group and age not significant).

[c] Statistical significance ($p < .05$) for group effect in GLM analysis using MoCA as a covariate (MoCA effect and interaction between group and MoCA not significant).
[e] Significant difference ($p < .05$) between Off and On state was found for VaP group by Paired t-test.
[f] Significant difference ($p < .05$) between Off and On state was found for IPD group by Paired t-test.