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Short Communications

Levodopa responsive gait dynamics in OFF- and ONOFF-state freezing of gait in Parkinson's disease

Tuhin Virmani [a,b,*], Lakshmi Pillai [a], Aliyah Glover [a], Reid D. Landes [c,*]

[a] Department of Neurology, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA
[b] Department of Biomedical Informatics, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA
[c] Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

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ABSTRACT

Background: In people with Parkinson's disease (PwPD), Freezing of Gait (FOG) episodes can be levodopa responsive (OFF-FOG) or levodopa unresponsive (ONOFF-FOG). Steady-state gait abnormalities, outside of the freezing episodes themselves also exist and the response to levodopa in these different groups has not been previously documented.
Objectives: To define the levodopa responsiveness in steady-state gait in OFF-FOG and ONOFF-FOG individuals.
Methods: Steady-state gait was collected in both the effective levodopa OFF-state (doses withheld > 8 h) and ON-state (1 h after levodopa dosing) in 32 PwPD; 10 with OFF-FOG and 22 with ONOFF-FOG. Levodopa response was compared between the two groups in the mean and variability (CV) of 8 spatiotemporal gait parameters.
Results: Both OFF-FOG and ONOFF-FOG participants showed improvement in mean stride-length and stride-velocity with levodopa. Improvement was seen in the OFF-FOG but not the ONOFF-FOG groups in mean stride-width and CV Integrated pressure with levodopa.
Discussion: In this study we show that steady-state gait deficits improve with levodopa in PwPD with OFF-FOG and ONOFF-FOG, even though episodes of FOG did not resolve in the ONOFF-FOG group. Lowering levodopa in people with ONOFF-FOG, or levodopa-unresponsive freezing of gait, should be undertake with caution and objective gait titration at different levodopa doses may be beneficial. Further work is needed to elucidate the pathophysiologic mechanisms of these differences.

1. Introduction

Freezing of gait (FOG) is a debilitating feature of Parkinson's disease (PD) with limited treatment options. FOG is resolved by levodopa in some people with PD and is termed levodopa-responsive FOG or OFF-FOG. In others, levodopa may improve FOG to a degree but not completely resolve it, and this has been termed levodopa-unresponsive FOG, or levodopa ONOFF-FOG. Rarely FOG has been reported to occur in the levodopa medicated state but not the unmedicated state and this form has been termed ON-FOG [1–3]. People with ONOFF-FOG are older, have worse UPDRS scores, worse cognitive function, with lower quality of life, worse gait phenotype, but similar mood, apathy and sleep quality [4] than other people with PD. Both OFF-FOG and ONOFF-FOG groups show similar response to levodopa on the motor UPDRS, including in most domain scores [2]. However as per definition, the levodopa response in FOG episodes differs between groups. Whether the OFF-FOG and ONOFF-FOG phenotypes are on a continuum of disease severity or distinct pathophysiologic entities is still a matter of debate.

While FOG is an episodic phenomenon [5], steady-state gait abnormalities outside of freezing episodes differ between those with and without FOG [6]. Steady-state gait also objectively declines faster in those with FOG [7]. It has been suggested that ONOFF-FOG people may have different levodopa response curves [8], but whether or not levodopa helps steady-state gait abnormalities in the different FOG

Abbreviations: FOG, Freezing of Gait; OFF-FOG, OFF-levodopa Freezing of Gait; ONOFF-FOG, ON and OFF-levodopa Freezing of Gait; PD, Parkinson's Disease; UPDRS, Unified Parkinson's Disease Rating Scale; ON-FOG, ON-levodopa only Freezing of Gait; UAMS, University of Arkansas for Medical Sciences; PKMAS, Protokinetics Movement Analysis Software; FOG-Q, Freezing of Gait Questionnaire; MoCA, Montreal Cognitive Assessment; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; RBD, REM Sleep Behavior Disorder; RBD-Q, REM Sleep Behavior Disorder Questionnaire.

* Corresponding authors at: Department of Neurology, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA.
E-mail addresses: TVirmani@uams.edu (T. Virmani), RDLandes@uams.edu (R.D. Landes).

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phenotypes has not been studied. Increasing steady-state gait speed and stride-length could decrease fall risk thereby improving quality of life [9]. Our hypothesis was that steady-state gait in both OFF-state and ONOFF-state FOG would improve with levodopa in at least a set of common spatiotemporal gait parameters.

2. Methods

Thirty-two participants with PD based on UK brain bank criteria and with documented FOG on examination (termed definite FOG) were evaluated between December 2016 and January 2020. Written informed consent was obtained from all participants prior to conducting any study related procedures and the study was approved by the local Institutional Review Board (UAMS IRB# 203234) and conducted in accordance with the guidelines of the Declaration of Helsinki.

2.1. FOG classification:

Participants whose freezing resolved with levodopa were classified as OFF-FOG ($n = 10$) while those whose freezing continued 1 h after levodopa dosing were classified as ONOFF-FOG ($n = 22$); there were no participants who had FOG in only the ON-state (i.e., ON-FOG $n = 0$) All ONOFF-FOG participants had previously clinically titrated to higher levodopa doses (simulating a supra-ON-state) with continued FOG in the ON-state.

2.2. Gait assessments:

Steady-state gait was evaluated over 8 lengths of a 20-foot Zeno-walkway (Protokinetics, Havertown PA) in both the effective levodopa OFF-state (doses withheld > 8 h) and ON-state (1 h after dose). The mean and coefficient of variation (CV, the standard deviation divided by the mean) in 8 spatiotemporal gait parameters, integrated-pressure, foot-strike-length, stride-length, stride-width, stride-time, stride-velocity, swing-phase-percent and total-double-support-phase-percent were determined using Protokinetics Movement Analysis Software (PKMAS) for each participant. During foot step selection if a participant had a witnessed freeze on video and pressure trace, those footsteps were marked as other and not included in the steady state gait analysis [6,7]. For each participant, the change in these spatiotemporal parameters was determined subtracting their OFF levodopa from ON levodopa results; termed "levodopa response." Dyskinesias did not impact gait performance.

2.3. Other assessments

Participants also completed a Unified Parkinson's Disease Rating Scale (UPDRS) by a trained movement disorders neurologist (TV) and the freezing of gait questionnaire (FOG-Q) to quantify freezing severity. Non-motor features assessed included cognition on the Montreal Cognitive Assessment (MoCA), depression and anxiety on the Hamilton Depression (HAM-D) and Anxiety (HAM-A) scales, and REM sleep behavior disorder (RBD) on the RBD-questionnaire (RBD-Q).

2.4. Statistical analysis

Patient characteristics were compared between groups with Mann-Whitney *U*-tests and Pearson χ^2-tests. For UPDRS and spatiotemporal gait parameters, paired *t*-tests were used to evaluate levodopa response (the difference in scores between ON- and OFF-states) within group, and two-sample *t*-tests used for comparing levodopa response between groups. Results are presented with 95 % confidence intervals (CI95 %). The choice of using *t-tests* was made because for the 5 parameters that violated normal assumptions (mean stride-width and foot-strike-length, and CV stride-velocity, stride-width and stride-length) statistical results were more conservative with a *t*-test than with non-parametric bootstrap method. That is to say, nonparametric method found a significant difference whereas *t*-test did not (Supplementary Table 1). When comparing groups, we also evaluated whether the groups are equivalent with Two One-Sided Tests (two one-sided CI95 %). The two one-sided CI95 % may be used to test equivalence within a specified equivalence interval (e.g., ±1 SD).

3. Results

In our cohort, ONOFF-FOG participants were older (Table 1), but importantly were well matched for sex, disease duration and FOG duration (Table 1). Total daily levodopa dose and the dose of levodopa taken during the levodopa challenge while higher in the ONOFF-FOG group was not statistically significant (Table 1). Cognition on the MoCA, and anxiety were worse in the ONOFF-FOG groups while depression and RBD severity were trending higher (Table 1).

Fig. 1 presents levodopa response for each group in the left two panels and compares levodopa response between the groups in the right two panels. UPDRS and means of spatiotemporal gait parameters are in the top two panels of Fig. 1 and coefficients of variation (CV) of spatiotemporal gait parameters are in the bottom two panels. Results are presented in terms of Cohen's d effect size, which is the difference in means divided by the relevant SD; natural scale results are in Supplementary Table 2. Both OFF-FOG and ONOFF-FOG participants showed improvement in mean stride-length and stride-velocity with levodopa (Fig. 1A, left panel; Supplementary Table 2). OFF-FOG but not ONOFF-FOG participants, also had improved foot-strike-length, swing-phase-percent and total-double-support-phase-percent (Fig. 1A, left panel; Supplementary Table 2). Variability measures were not significantly

Table 1
Demographics and Assessments.

	OFF-FOG ($n = 10$)	ONOFF-FOG ($n = 22$)	Mann-Whitney *U*-Test (*Z*, *p*-value)
Age (years)	63.9 ± 9.3	73.5 ± 5.2	−2.887, 0.004
Sex (female/male)	3/7	7/15	#0.011, 0.918
Hoehn & Yahr score			
OFF-levodopa	2.1 ± 0.2	3.7 ± 0.7	−4.363, <0.001
ON-levodopa	2.0 ± 0.0	3.6 ± 0.7	−4.357, <0.001
Motor Unified Parkinson's Disease Rating score			
OFF-levodopa	24.5 ± 10.0	38.1 ± 7.8	−3.197, <0.001
ON-levodopa	17.0 ± 11.8	30.8 ± 10.0	−2.930, 0.003
Total Unified Parkinson's Disease Rating score			
OFF-levodopa	42.5 ± 13.6	66.2 ± 12.7	−3.722, <0.001
ON-levodopa	29.5 ± 17.0	56.0 ± 13.7	−3.437, <0.001
Duration with FOG (years)	4.3 ± 2.6	4.0 ± 2.1	−0.203, 0.839
FOG-Q score	8.9 ± 3.0	15.1 ± 2.0	−4.199, <0.001
Duration on ldopa (years)	6.6 ± 4.2	7.4 ± 4.4	−0.529, 0.597
Daily ldopa (mg/day)	888 ± 356	1069 ± 456	−0.979, 0.328
Ldopa challenge dose (mg)	214 ± 96	274 ± 101	−1.445, 0.148
On dopamine agonist	0 (0 %)	3 (14 %)	#1.505, 0.220
On MAO-Inhibitor	4 (40 %)	3 (14 %)	#2.796, 0.094
Dyskinesias reported at visit	3 (30 %)	11 (50 %)	#1.117, 0.290
MoCA score	26.2 ± 3.6	21.3 ± 4.4	−2.699, 0.007
HAM-D score	7.7 ± 3.7	11.7 ± 5.0	−1.839, 0.066
HAM-A score	5.0 ± 3.6	9.5 ± 5.3	−2.395, 0.017
RBD-Q score	7.2 ± 2.9	4.9 ± 3.1	−1.839, 0.066

#Pearson's $\chi^2_{(1)}$.

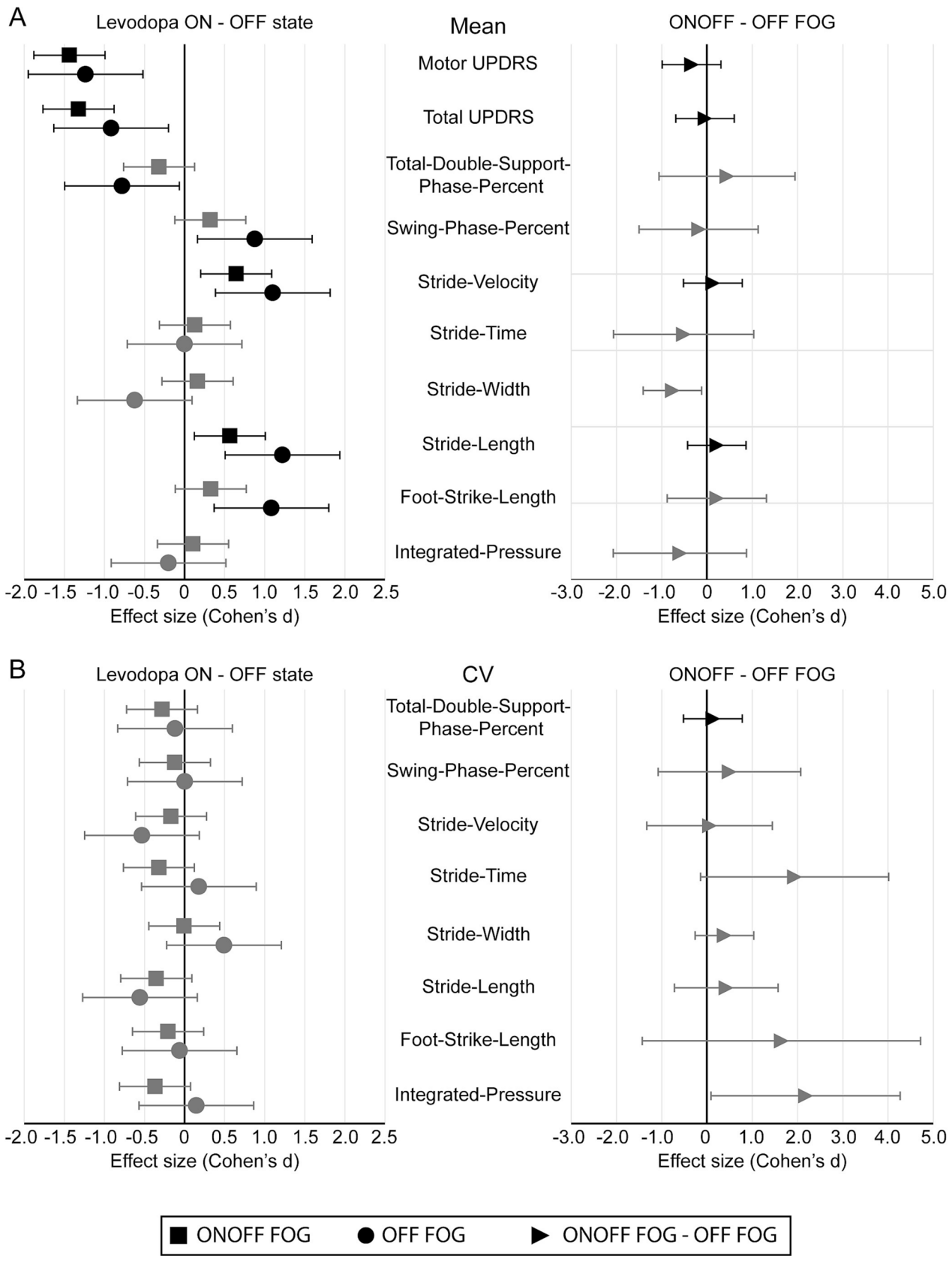

Fig. 1. Levodopa response in spatiotemporal gait parameters. The left panel (A,C) presents levodopa response (CI95 % for a difference) for OFF-FOG (circles) and ONOFF-FOG (squares) groups. The right panel (B,D) compares levodopa response (triangles) between OFF-FOG and ONOFF-FOG groups (CI95 % for equivalence within 1 SD). Black circles and squares indicate statistically significant differences (left panels) and black triangles indicate statistically significant equivalence within 1 SD (right panels). Gray symbols denote statistical non-significance. All significant results are in the direction of improvement with levodopa.

responsive to levodopa in either group (Fig. 1B, left panel). The difference between the ONOFF and OFF-FOG groups levodopa response for mean stride-velocity, stride-length (Fig. 1A, right panel) and CV total-double-support-phase-percent (Fig. 1B, right panel) were statistically within one standard deviation of one another, while the levodopa response in mean stride-width (Fig. 1A, right panel) and CV Integrated pressure (Fig. 1B, right panel) were statistically different (Fig. 1 right panel, two one-sided CI95 % not crossing 0 line). For both groups, levodopa reduced UPDRS scores by about 7.4 points (Supplementary Table 2).

4. Discussion

In this study we report for the first time a comparison of the response in steady-state gait parameters in participants with both ONOFF-FOG (or levodopa unresponsive FOG) and OFF-FOG (or levodopa responsive FOG). Those with OFF-FOG are expected to exhibit gait improvements when on levodopa; however, since freezing of gait does not improve this may not be a reasonable expectation for those with ONOFF-FOG. We found that both OFF-FOG and ONOFF-FOG participants showed improvements of similar magnitudes in mean stride-length and stride-velocity with levodopa suggesting that there may be a common circuit involved in dopaminergic gait response in these groups despite differential response in the response to freezing. On the other hand, improvement with levodopa was seen in the OFF-FOG but not the ONOFF-FOG groups in mean stride-width and CV Integrated pressure. This suggests that these features may mark changes in circuitry that may help differentiate the levodopa responsive and unresponsive freezing groups.

Prior studies in patients with PD that were not differentiated based on freezing status also reported walking speed and stride length improved [10], as in our study. It has previously been reported that levodopa increased step velocity and stride-length in patients with FOG [11]. In our study, we found that those who freeze while *ON* levodopa (ONOFF-FOG) experience longer stride-length and faster stride-velocity than when *OFF* levodopa; this underscores the need to still strive to optimize levodopa dose in those with ONOFF-FOG. We also corroborated the previous stride-length and stride-velocity findings in those with OFF-FOG. Titration of levodopa using objective measures to optimize gait may be beneficial in difficult to treat patients with levodopa unresponsive freezing of gait episodes as these patients are understandably fixated on the freezing response and may have difficulty noting other gait improvements [8].

Modulation of foot-strike-length and swing- and total-double-support improved significantly only in OFF-FOG, but the direction of improvement was in the same direction in both groups. This suggests that, at least for steady-state gait, dopamine responsive-pathways may be similarly affected in both OFF-FOG and ONOFF-FOG phenotypes. However, the fact that the freezing episodes show differential response to levodopa suggests that the pathophysiologic mechanisms underlying these episodes likely differ. Dysfunction in cholinergic pathways have been reported to be differentially affected in freezers [12], and warrants further exploration in the OFF-FOG and ON-OFF FOG groups.

One limitation of our study is that response to levodopa was evaluated at one time point, 1 h after dosing. It is possible that in people who take longer to reach their best ON-state we may have measured an incomplete response.

In summary, despite lack of improvement in freezing episodes with levodopa in ONOFF-FOG steady-state gait does improve, and titration of levodopa to optimize gait function using objective measures can be beneficial. Further work is needed to elucidate the pathophysiologic changes that subserve these different levodopa responses to different features of gait.

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CRediT authorship contribution statement

Tuhin Virmani: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Lakshmi Pillai:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Aliyah Glover:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Reid D. Landes:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Virmani received salary support from the University of Arkansas for Medical Sciences (UAMS), salary from the UAMS clinician scientist program (UAMS CSP), salary from a grant from the Parkinson's Foundation (PF-JFA-1935) and a pilot NIGMS award (GM110702). Ms. Glover and Ms. Pillai, received salary support from the UAMS CSP, PF and NIGMS pilot awards (to TV). Dr. Landes received salary support from NIH/NCATS and the PF grant. None of the authors have any financial disclosures or conflicts of interest related to the research covered in this manuscript.

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Appendix A. Supplementary data

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