Exp Brain Res (2003) 149:187–194
DOI 10.1007/s00221-002-1354-8

RESEARCH ARTICLE

J. M. Hausdorff · J. D. Schaafsma · Y. Balash · A. L. Bartels · T. Gurevich · N. Giladi

Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait

Received: 31 October 2002 / Accepted: 15 November 2002 / Published online: 22 January 2003
© Springer-Verlag 2003

Abstract Patients with Parkinson's disease (PD) often experience freezing of gait, a debilitating phenomenon during which the subject suddenly becomes unable to start walking or to continue to move forward. Little is known about the gait of those subjects with PD who experience freezing of gait or the pathophysiology of freezing. One possibility is that freezing of gait is a truly paroxysmal phenomenon and that the usual walking pattern of subjects who experience freezing of gait is not different than that of other patients with PD who do not experience these transient episodes of freezing of gait. On the other hand, a recent study noted gait changes just prior to freezing and concluded that dyscontrol of the cadence of walking contributes to freezing. To address this question, we compared the gait of PD subjects with freezing of gait to PD subjects without freezing of gait. Given the potential importance of the dyscontrol of the cadence of walking in freezing, we focused on two aspects of gait dynamics: the average stride time (the inverse of cadence, a measure of the walking pace or rate) and the variability of the stride time (a measure of "dyscontrol," arrhythmicity and unsteadiness). We found that although the average stride time was similar in subjects with and without freezing, stride-to-stride variability was markedly increased among PD subjects with freezing of gait compared to those without freezing of gait, both while "on" ($P<0.020$) and "off" ($P<0.002$) anti-parkinsonian medications. Further, we found that increased gait variability was not related to other measures of motor control (while off medications) and levodopa apparently reduced gait variability, both in subjects with and without freezing. These results suggest that a paradigm shift should take place in our view of freezing of gait. PD subjects with freezing of gait have a continuous gait disturbance: the ability to regulate the stride-to-stride variations in gait timing and maintain a stable walking rhythm is markedly impaired in subjects with freezing of gait. In addition, these findings suggest that the inability to control cadence might play an important role in this debilitating phenomenon and highlight the key role of dopamine-mediated pathways in the stride-to-stride regulation of walking.

Keywords Gait variability · Parkinson's disease · Dopamine · Basal ganglia

J. M. Hausdorff (✉) · J. D. Schaafsma · Y. Balash · A. L. Bartels · T. Gurevich · N. Giladi
Movement Disorders Unit, Department of Neurology,
Tel-Aviv Sourasky Medical Center, Sackler School of Medicine,
Tel-Aviv University, 6 Weizmann Street, 64239 Tel Aviv, Israel
e-mail: jhausdor@caregroup.harvard.edu
Tel.: +972-3-6973081
Fax: +972-3-6974911

J. M. Hausdorff
Gerontology Division, Beth Israel Deaconess Medical Center and
Division on Aging, Harvard Medical School, Boston, MA, USA

Introduction

Freezing of gait (FOG) is a poorly understood, debilitating phenomenon that is common among subjects with parkinsonism (Fahn 1995; Giladi et al. 1997, 2001b; Giladi 2001; Yanagisawa et al. 2001; Lamberti et al. 1997). About 7% of subjects with mild Parkinson's disease (PD) and almost 50% of those with more advanced disease experience unpredictable, transient disturbances in their walking (Giladi et al. 1992, 2001b; Lamberti et al. 1997). For no apparent reason, subjects suddenly become unable to start walking or to continue to move forward. A feeling of being glued to the floor is typically noted. FOG can be quite disabling, impairing function, health-related quality of life, mobility, and independence (Gray and Hildebrand 2000; Fahn 1995; Giladi et al. 2001b). Subjects with FOG also have an increased risk for falls, nursing home admission, and mortality (Hely et al. 1999; Gray and Hildebrand 2000; Aita 1982).

Little is known about the gait of subjects who experience FOG and its pathophysiology (Giladi et al. 2001b; Nieuwboer et al. 2001). In contrast to the bradykinetic changes that are common in PD and occur

continuously (e.g., slowed gait) (Morris et al. 1994, 1996), from the phenomenological point of view, FOG is characterized as a paroxysmal gait disturbance (Fahn 1995; Giladi et al. 2001b; Halliday et al. 1998). Fahn (1995) described freezing as a transient event, interrupting the normal, voluntary activity, and Lamberti et al. (1997) also emphasized the "sudden and transient" nature of freezing. In other words, FOG typically occurs without apparent warning, suddenly preventing (e.g., start hesitation) or interrupting usual walking. In between freezing episodes, gait appears to be similar to that of other subjects with PD. Thus, one possibility is that FOG is a truly paroxysmal phenomenon and that the walking pattern of subjects who experience FOG is not different than that of other patients with PD whose locomotion is not interrupted by FOG. On the other hand, a recent study noted gait changes just prior to freezing and suggested that freezing is caused by a combination of an increasing inability to generate stride length superimposed on a dyscontrol of the cadence of walking (Nieuwboer et al. 2001). In that case, it is possible that the motor abnormalities of persons with PD and FOG are not confined to freezing, but rather persons with FOG have gait disturbances even between the FOG episodes.

To address this question and gain insight into the pathophysiology of FOG, we compared the usual gait of PD subjects with FOG to PD subjects without FOG. Given the potential importance of the dyscontrol of the cadence of walking to freezing, we focused on two aspects of gait dynamics: the average stride time (the inverse of cadence, a measure of the walking pace or rate) and the variability of the stride time (a measure of "dyscontrol," arrhythmicity and unsteadiness). Previous investigations observed increased arrhythmicity, i.e., increased stride-to-stride variability, in the gait of subjects with PD compared to healthy controls (Blin et al. 1991; Hausdorff et al. 1998); however, these studies did not examine the question of freezing. Here we tested the hypothesis that PD subjects who experience FOG might exhibit increased arrhythmicity and hence increased stride-to-stride variability during usual locomotion compared to PD subjects who did not experience FOG.

Materials and methods

Subjects and protocol

Subjects with idiopathic PD, as defined by the UK Brain Bank criteria (Gelb et al. 1999), were recruited from the outpatient clinic of the Movement Disorders Unit of the Tel Aviv Sourasky Medical Center. Subjects were invited to participate if they were between the ages of 50 and 80 years, were on levodopa treatment, experienced motor response fluctuations, and had a Hoehn and Yahr (1967) score less than 4 while in an "off" state (i.e., at least 12 h off anti-parkinsonian medications). Subjects were excluded if their disease was recently diagnosed (disease duration less than 2 years), if they had brain surgery in the past, or if they had clinically significant co-morbidities likely to affect gait including diabetes, rheumatic or orthopedic disease, dementia, depression, or history of stroke, as determined by clinical or radiological evaluation.

To compare and contrast subjects with and without freezing, the study population was characterized with respect to age, gender, duration of symptoms, Mini-Mental State Exam (MMSE) scores (Folstein et al. 1975), and the Unified Parkinson's disease Rating Scale (UPDRS) scores (Fahn et al. 1987). As previously suggested, subscore indices of motor function were also determined from the UPDRS (Giladi et al. 2001b). The FOG questionnaire was used to quantify self-report history of mobility, gait disturbances, and freezing (Giladi et al. 2000). Subjects were classified as "freezers" if they reported FOG or if FOG was observed during the walking protocol (see below). (There was excellent agreement between self-report and observation.) Subjects were also asked to use a visual analog scale (VAS) to rank their motor state on a scale of 0 (worst, most difficult state over the past week) to 10 (best) to compare "on" and "off" states and insure that subjects were tested in a true "on" state.

All subjects were first assessed in the morning, at least 12 h after they took their last anti-parkinsonian medication, while in a self-assessed "off" state. The assessment during the "off" state included the evaluation of motor function (part III of the UPDRS), as well as the assessment of gait (see below). After the assessments in the "off" condition, subjects took their regular morning dose of levodopa. We then waited until the subjects reported that they reached their regular "on" state (i.e., they reported that the dopamine had taken its full effect). At that time, we repeated the evaluation of the full UPDRS and the walking task and assessed mental status using the MMSE.

Walking protocol

Subjects were instructed to stand up from a chair, walk at their normal pace on level ground for 20 m, turn and walk the same route back, ending with a half turn and return to a seated position. This walk was repeated so that the subjects were studied while walking a total of 80 m (both in "on" and "off" states). Study subjects were not aware of the specific questions or hypothesis of this investigation.

The study was approved by the Human Studies Committee of the Tel-Aviv Sourasky Medical Center. All subjects provided informed written consent according to the Declaration of Helsinki prior to entering the study.

Observation-based determination of freezing

Subjects were videotaped during the 80-m walking task (see above) and as they walked from the examination room to the testing area (an additional 50 m). Videotapes were analyzed (Giladi et al. 2002) to determine the presence or absence of FOG and the severity of freezing (the number of freezing episodes) and to identify walking times that were free of freezing. To determine the severity of freezing, the videotapes of the walking tasks were analyzed independently by three experienced neurologists who determined the number of episodes of FOG for each subject (Giladi et al. 2002). Specifically, the observers counted all episodes where patients had a freezing episode including transient difficulty with gait initiation, turning, passing through a narrow space, or while walking, events that often elicit freezing (Fahn 1995; Giladi et al. 2001b). The average scores of the three observers were used as the measure of the severity of FOG (i.e., no. of freezing episodes).

Assessment of gait dynamics

Previously described methods were used to evaluate gait dynamics (Hausdorff et al. 1998, 2001) during the 80-m walking task. Briefly, to measure the gait rhythm and the timing of the gait cycle (i.e., the stride time), force sensitive insoles were placed in the subject's shoe. Two sensors are used, one under the heel and the other under the balls of the feet and the toes, and the data from both sensors are combined before the recording. These inserts produce a measure of

the force applied to the ground during ambulation. A small, lightweight (5.5×2x9 cm; 0.1 kg) recorder was worn on the ankle and held in place using an ankle wallet. An on board A/D converter (12 bit) sampled the output of the footswitches at 300 Hz and stored the digitized force record. Subsequently, the digitized data were transferred to a computer workstation for analysis using software that extracts the initial contact time of each stride (Hausdorff et al. 1995). From the force signal, the stride time or duration of the gait cycle (time from initial contact of one foot to subsequent contact of the same foot) was determined for each stride during the 80-m walk by applying a previously validated algorithm that locates initial contact times (and hence the stride time) by finding large increases in the force and changes in the slope of the force (Hausdorff et al. 1995). We note that when subjects "shuffle," it may be challenging to determine a true toe-off. Because we focused on heel-strike to heel-strike, or initial contact time to initial contact time, a distinct and large increase in force is readily observed even during shuffling and the determination of the stride times was not an issue in the present study.

To focus on the assessment of the dynamics of continuous, "normal" walking, the video was reviewed and, for each lap, the walking segment with the longest contiguous walk that did not include FOG was determined. The insoles and videos were synchronized. The first two strides of each "normal" gait segment were excluded and a maximum of the next 15 strides from each segment were included for analysis. To insure that the analysis was not influenced by "outliers" and to focus on "intrinsic" normal dynamics, a median filter was then applied to remove data points that were three standard deviations (SDs) greater than or less than the median value (Hausdorff et al. 1998, 2001). There was strong agreement (r >0.9) between the values obtained before and after application of the median filter. Subsequently, the average stride time was determined for each segment. Stride time variability, the magnitude of the stride-to-stride fluctuations in the gait cycle duration, was calculated by determining the standard deviation and the coefficient of variation (CV) of each subject's stride time (Hausdorff et al. 1998, 2001; Maki 1997). These measures of stride-to-stride variability reflect gait instability and have been shown to prospectively predict falls (Hausdorff et al. 1998, 2001; Maki 1997).

Statistics

Results are reported as mean ± SD. Subjects with and without freezing were compared using Fisher's exact test for categorical data. For continuous data, the Wilcoxon Rank Sum test (a non-parametric equivalent of the two-sample t-test, also known as the Mann-Whitney U test), was used to compare subjects with and without freezing. The Wilcoxon Signed Rank test, a non-parametric analog of the paired t-test, was used to evaluate within group changes (e.g., response to levodopa). Spearman's correlation coefficient was used to evaluate the association among measures. Multiple regression analysis (both before and after log transformation) was used to study the relationship between FOG and gait measures after adjustment for co-variates. A P value less than 0.05 (two-tailed) was considered statistically significant. Statistical analysis was performed using SPSS for Windows (version 10.1).

Results

Thirty-two subjects participated in this study. The study group consisted of 9 (28%) women and 23 men with an average age of 62.0±7.5 years and a mean duration of PD symptoms of 9.6±3.9 years. The mean score on the MMSE was 28.0±2.0. The mean scores on the UPDRS (total) while in "off" and "on" were 44.3±16.0 and 25.6±11.5, respectively.

"Off" freezers vs. non-freezers

In "off," 21 of the 32 subjects were freezers. On average, "off" freezers experienced 9.7 freezing episodes during the 80-m walk. As summarized in Table 1, "off" freezers and "off" non-freezers were similar with respect to age,

Table 1 Characteristics (in "off") of subjects with and without "off" freezing[a]

	Subjects with no "off" FOG (n=11)	Subjects with "off" FOG (n=21)	P value
Age (years)	62.2±6.4	61.9±8.2	0.845
Gender (% men)	82	67	0.630
MMSE	28.5±2.0	27.9±2.0	0.298
Disease duration (years)	7.7±2.5	10.7±4.2	0.064
Self-report of condition (0–10)	4.2±1.7	4.0±2.2	0.603
FOG questionnaire score	2.9±2.6	14.2±4.1	0.0005*
No. of freezing episodes	0±0	9.7±8.2	0.0001*
UPDRS measures while in "off" state			
Total UPDRS score	35.2±11.8	49.0±16.1	0.012*
Mental (part I)	0.9±0.9	1.9±1.4	0.046*
ADL (part II)	9.7±5.0	17.6±7.1	0.002*
Motor score (part III)	18.8±6.5	22.8±8.3	0.271
Bradykinesia index	15.0±5.9	16.1±8.1	0.907
Speech index	1.7±1.3	2.5±1.7	0.223
Tremor index	4.9±7.1	3.6±5.3	0.389
Rigidity index	7.6±4.2	7.0±3.6	0.845
Falls question (ADL Q13)	0.2±0.4	0.9±1.1	0.045*
Gait index	1.8±1.1	4.2±1.7	0.0001*
Balance index	1.3±1.2	2.7±1.7	0.024*
FOG question (ADL Q14)	0±0	2.6±0.8	0.0001*

[a] Subject characteristics were evaluated while "off" levodopa medication for at least 12 h (see Materials and methods), except for the MMSE, which was assessed while on medication. For all UPDRS measures, the higher the number the greater the impairment. For the MMSE, 30 is the best possible score. Questions 13 and 14 on the UPDRS evaluate the frequency of falling and freezing (e.g., 0 = no falls or no FOG), respectively. Previously established indices (Giladi et al. 2001b) were used to summarize specific subsets of the UPDRS motor score. *P<0.05

Table 2 Gait dynamics (in "off") of subjects with and without off" freezing (CV coefficient of variation)

	Subjects with no "off" FOG (n=11)	Subjects with "off" FOG (n=21)	P value
Average stride time (ms)	1,007±77	972±182	0.785
Stride time standard deviation (ms)	33±8	55±38	0.014*
Stride time CV (%)	3.3±0.7	6.1±5.5	0.002*

*P<0.05

Table 3 Characteristics (in "on") of subjects with and without freezing in the "on" state

	Subjects with no FOG while "on" (n=21)	Subjects with FOG while "on" (n=11)	P value
Age (years)	60.9±7.5	64.1±7.4	0.289
Gender (% men)	76	64	0.681
MMSE	28.5±1.7	27.1±2.2	0.059
Disease duration (years)	8.9±3.1	11.1±5.0	0.328
Condition (0–10)	7.8±1.7	7.5±0.8	0.287
FOG questionnaire score	0.3±0.7	6.2±4.4	0.0001*
No. of freezing episodes	0±0	6.2±4.4	0.0001*
UPDRS measures while in an "on" state			
Total UPDRS score	22.4±10.8	31.8±10.8	0.03*
Mental (part I)	1.4±1.4	1.8±1.1	0.367
ADL (part II)	4.8±4.1	8.9±4.7	0.014*
Motor (part III)	8.7±5.5	14.5±5.9	0.012*
Bradykinesia index	5.9±5.0	10.5±5.9	0.034*
Speech index	1.0±1.1	2.2±1.4	0.017*
Tremor index	1.0±1.7	0.4±0.9	0.271
Rigidity index	4.1±3.3	4.3±2.1	0.584
Falls question (ADL Q13)	0.1±0.4	0.5±0.7	0.048*
Gait index	0.4±0.7	2.0±1.9	0.039*
Balance index	1.0±0.9	2.5±1.5	0.004*
FOG question (ADL Q14)	0±0	1.8±1.1	0.0001*

*P<0.05

gender, self-evaluation of condition, and motor score. Bradykinesia, rigidity, speech and tremor indices were also similar in "off" freezers and "off" non-freezers.

While in "off," the average stride time was similar in subjects with and without "of" freezing (Table 2). In contrast, gait variability measures, both the stride time SD and CV, were much larger among subjects with "off" freezing compared to those without. The UPDRS indices of gait and balance (Table 1) were also different in subjects with and without freezing, consistent with the measured changes in gait in the "off" freezers.

Effect of levodopa on gait dynamics in freezers and non-freezers

For "off" freezers and non-freezers, the average stride time did not change in response to levodopa. In contrast, stride time variability was lower when subjects were re-tested on levodopa, for both "off" freezers and "off" non-freezers. For example, comparing "off" to "on," the stride time SD was reduced by 7±13 ms in "off" non-freezers (P<0.04) and by 18±25 ms in "off" freezers (P<0.001). The magnitude of this reduction did not significantly depend on the group (P=0.11); rather, stride-to-stride variability of both freezers and non-freezers was reduced in response to levodopa. The decrease in stride-to-stride variability (from "off" to "on" state) was highly correlated with the decrease in the number of freezing episodes (r=0.50; P=0.004). When tested in an "on" state, there was no longer any difference in the gait variability (or mean stride time) of the 21 subjects who experienced "off" FOG and those that did not (P>0.73).

From among the 21 "off" freezers, 11 subjects also experienced FOG while in an "on" state. On average, these 11 subjects experienced 6.2 freezing episodes during the walking protocol during the "on" state. As summarized in Table 3, subjects with and without FOG during "on" were similar with respect to age, gender, self-evaluation of condition, and disease duration. The average stride time was similar in subjects with and without freezing in the "on" state. In contrast, gait variability measures, both the stride time SD and CV, were much larger among subjects who still experienced FOG during the "on" state compared to those without FOG in the "on" state (Table 4). As was the case for "off" freezing, gait variability during "on" was significantly related to the number of freezing episodes during "on," although the relationship was not as strong as it was in the "off" state.

Table 4 Gait dynamics (in "on") of subjects with and without freezing in the "on" state

	Subjects with no FOG while "on" (n=21)	Subjects with FOG while "on" (n=11)	P value
Average stride time (ms)	1,012±90	1,044±160	0.639
Stride time standard deviation (ms)	26±10	47±28	0.016*
Stride time CV (%)	2.6±1.0	4.5±2.4	0.020*

Table 5 Association between gait variability, freezing severity, and motor impairment in "on" and "off" states. Shown are the Spearman's correlation coefficients (P values). No. of freezing episodes and UPDRS measures are the values as determined in "on" and "off" states

	No. of freezing episodes	UPDRS FOG Q14	UPDRS Motor Score
"Off" stride time CV	0.63 (0.0001)*	0.51 (0.003)*	0.33 (0.065)
"On" stride time CV	0.37 (0.039)*	0.46 (0.009)*	0.60 (0.0001)*

*denotes a statistically significant relationship

Gait variability and motor function

As noted in Table 5, gait variability was significantly related to the number of freezing episodes, but was not significantly associated with UPDRS motor scores while subjects were in the "off" state. Consistent with this, in stepwise multiple regression analysis that included age, disease duration and the UPDRS motor score (part III) as potential covariates, stride time CV in "off" was significantly related to freezing (present/absent or no. of episodes), but not to global motor function (UPDRS part III) or any of the other potential covariates.

These relationships were different when subjects were re-tested in an "on" state. At this time, there was a significant association between UPDRS motor score and gait variability. In stepwise multiple regression analysis that included age, disease duration, and UPDRS motor score (part III) and freezing (present/absent or no. of episodes) as potential covariates, stride time CV was only related to UPDRS motor score (part III), but not to freezing. In other words, after adjusting for UPDRS motor score, gait variability was similar in subjects with or without FOG in an "on" state. This result is consistent with the fact that while in an "off" state, "off" freezers and non-freezers had similar motor function but in the "on" state, motor function, bradykinesia, and speech were all significantly worse in the subjects with freezing. In other words, those subjects who still experienced FOG during "on" did not improve as much in response to levodopa as subjects without FOG during "on."

Is the increased variability in freezing related only to the freezing episode?

Above, we noted increased stride-to-stride variability in subjects with "off" freezing, compared to those without (Table 2). Here we examine whether this increased variability is simply a by-product or "artifact" of the freezing episode itself. Although all freezing episodes were excluded from the analysis, perhaps the change in rhythm just prior to or immediately after a freezing episode caused increased variability during this time, but otherwise gait variability is unchanged in freezers compared to non-freezers. In the analysis described above, the first two strides of each lap were excluded. If, instead, we exclude the first and last three strides from each lap (or the three strides before and after the longest freezing-free walking episode), moving further away from any freezing episode, we still find increased variability in "off" freezers compared to "off" non-freezers. For example, stride time CV while in "off" was 5.2±2.4% and 3.1±1.2% in "off" freezers and non-freezers, respectively (P=0.011). Moving further away from any freezing episodes, we find virtually identical results when the first and last four strides were excluded from the analysis. Stride time CV was 5.1±2.4% and 3.3±1.4%, in "off" freezers and non-freezers, respectively (P=0.019). When the first and last five strides were excluded, similar results were obtained as well. Stride time CV was 5.1±2.6% in "off" freezers and 3.5±1.5 in non-freezers (P=0.078). Note that the difference in stride time CV calculated after excluding the first and last three strides or the first and last five strides was very small, inconsistent, and similar (P=0.71) in "off" freezers (ΔCV=0.12) and non-freezers (ΔCV=0.04). Similar results were obtained if the first and last six strides were excluded from the analysis (or using the SD instead of the CV). Note too that the relationships shown in Table 5 were similar when stride time CV was determined after excluding additional strides and moving away from any freezing episodes. The differences between subjects who still had FOG during "on" and those that did not were also not dependent on how many strides were removed from the analysis.

Discussion

In this first study of the gait dynamics of PD subjects with freezing of gait, we find several key results: (1) between FOG episodes, the mean stride time (cadence or step rate) is similar in PD subjects with and without FOG, both "on" and "off" medications. (2) Casual visual observation may suggest that the usual, non-freezing gait of subjects with

freezing is not different from subjects who do not have freezing. Surprisingly, however, we find markedly increased stride-to-stride variability in subjects with freezing compared to those without, both in "on" and "off" states. (3) Levodopa apparently reduces gait variability, both in subjects with and without freezing. (4) In "on," the increased gait variability among subjects with FOG was associated and could be explained by differences in global motor function. In contrast, in "off," global motor function was not different in subjects with and without FOG and could not account for the increased stride-to-stride variability observed among the subjects with FOG.

Classically, the cardinal motor features of PD include bradykinesia, rigidity, and tremor (Leenders and Oertel 2001). More recently, it has been argued that FOG should be added to this list, in part because of its important independent effects on function and quality of life in PD and in part because the pathophysiologic mechanisms that contribute to FOG may be different from those of other features of PD (Fahn 1995; Giladi et al. 2001b). Here we find that subjects with "off" FOG apparently have altered locomotion, specifically increased stride-to-stride variability, that is not related to the other classic parkinsonian motor features. During "off," bradykinesia, rigidity, and tremor are similar in subjects with and without freezing, as is the average walking cadence; yet the stride time variability is markedly increased in subjects with freezing (recall Tables 1, 2). The ability to regulate walking on a stride-by-stride basis is impaired in these subjects. This increased gait variability is closely related to the severity (or frequency) of freezing (recall Table 5).

The relationship between FOG and stride-to-stride variability is apparently different when subjects are "on" or "off" levodopa. In an "off" state, as mentioned above, the relationship is largely independent of other aspects of motor function (or, in other words, different factors influence FOG and other aspects of motor function). In contrast, on medication, motor function is different in subjects with and without FOG and this difference may also account for the increased stride-to-stride variability. It is possible, however, that this "dependence" of stride-to-stride variability in "on" merely reflects patient-to-patient variations in the response to levodopa; motor function and stride-to-stride variability may have parallel responses. Although "on" freezing may sometimes be a side effect of levodopa (Biglan and Holloway 2001; Ambani and Van Woert 1973; Imai et al. 1993), in the present study, all of the subjects who experienced FOG during "on" also experienced FOG during "off." This suggests that those subjects who had FOG in "on" may have been undertreated and may not have received the maximal benefit from levodopa, both with respect to FOG and motor function. In the future, it might be helpful to further assess the effect of different doses of levodopa to evaluate this question. Either way, we suggest that when thinking about the mechanisms that contribute to FOG, one should focus on our findings in "off," i.e., in the state that reflects the underlying pathophysiology, where UPDRS-measured aspects of motor control clearly do not sufficiently explain the presence of FOG.

It is interesting to speculate about this relationship between FOG and increased stride variability in the untreated state. A priori, one might have hypothesized that there is no relationship between the two; these are two distinct, unrelated pathologic consequences of PD. Our findings clearly refute this idea. A second possibility is that parallel, but different pathologic mechanisms are responsible for FOG and the increased stride-to-stride variability observed in subjects with FOG. A third possibility is that one pathologic mechanism is the source of FOG and increased stride-to-stride variability. Severity of freezing, as measured by the number of FOG episodes observed, was closely related to the stride-to-stride variability and the effect of levodopa on freezing paralleled the effect on stride-to-stride variability. From one viewpoint, therefore, both FOG and increased stride-to-stride variability may be manifestations of arrhythmicity and poor stride-to-stride control. According to this possibility, disturbances in the same dopamine-mediated locomotor network contribute to dyscontrol, increased stride-to-stride variability and FOG in PD. Perhaps increased stride-to-stride variability and FOG are variations of the same theme, two ends of the spectrum. FOG may be viewed as the result of severe dys-synchronization of leg muscle activation and simultaneous activation of agonist and antagonist muscles (Fahn 1995; Andrews 1973; Giladi et al. 2001a). Freezing episodes may be an extreme expression of dyscontrol while the increased stride-to-stride variability may reflect more mild dys-synchronization of muscle activation and fluctuations in force generation (Hausdorff et al. 1998; Sheridan et al. 1987). Perhaps increased variability might be a marker of primary arrhythmicity or instability in the locomotor network that leads to FOG in the extreme cases.

Alternatively, one could also further suggest that there is some actual cause and effect relationship. It is possible that the increased stride-to-stride variability increases the susceptibility to freezing. When arrhythmicity or stride variability passes above a certain threshold, it sets the stage for FOG. This possibility is consistent with the explanation of Nieuwboer et al. that dyscontrol in the cadence of walking brings about FOG (Nieuwboer et al. 2001). SPECT studies by Fabre et al. indicate that there are no differences between PD subjects with and without freezing in the rest state, at least in terms of frontal lobe perfusion, suggesting that the pathophysiology that is responsible for freezing is truly transient and paroxysmal (Fabre et al. 1998). Nonetheless, although FOG is a paroxysmal event and increased stride-to-stride variability in PD is apparently a continuous abnormality, this "threshold" relationship could explain how a continuous gait abnormality is a risk factor for a transient gait abnormality, i.e., FOG.

Of course, FOG and increased stride-to-stride variability may not share a cause and effect relationship at all. Increased stride-to-stride variability has been observed in other populations who do not display FOG (Maki 1997;

Nakamura et al. 1996; Hausdorff et al. 2000, 2001) and in PD subjects (without FOG) compared to healthy controls (Blin et al. 1991; Hausdorff et al. 1998). One could argue, therefore, that increased variability and FOG are independent and variability is not specific to PD subjects with freezing. Clearly, increased variability is by itself insufficient to cause FOG. Nonetheless, compared to PD subjects who do not have freezing, a markedly exaggerated inability to regulate stride-to-stride variability appears to be a critical feature of the gait of patients with FOG. Perhaps these two phenomena are markers of certain features that are common in advanced PD and both respond to therapy similarly. Study of other populations (e.g., primary freezing of gait; Achiron et al. 1993) where FOG is present without additional motor impairment might shed light on the relationship between FOG and gait variability. Either way, it is important to note that the marked improvement in stride-to-stride variability seen in response to levodopa, both in subjects with and without FOG, suggests that a central, dopamine-dependent mechanism plays a key role in the stride-to-stride regulation of walking. It remains to be seen if the basal ganglia actually generate the motor program or merely influence its output. Either way, it is important to keep in mind the distinction between the mean stride time (which is similar in subjects with and without FOG) and the stride time variability.

Reduced stride length and hence gait speed are common in Parkinson's disease. A number of theories have been proposed to explain this change in walking. Gait hypokinesia may be related to a disturbance of the motor set for whole movement sequences or to the disruption of internal cues that enable the stringing together of submovements within a given motor plan (Morris et al. 1994, 1996, 1998). Like FOG and the ability to regulate stride-to-stride variability, stride length is also modulated by the basal ganglia and also apparently improves in response to levodopa. A recent PET study suggests that reduced dopamine availability in the nigrostriatal projection might be responsible for some of the gait changes observed in Parkinson's disease (Ouchi et al. 2001).

In the present study, we, unfortunately, did not measure stride length or stride length variability. Morris and colleagues have shown that (mean) cadence can be modified and is relatively intact in PD and, if the walking rate changes, (mean) cadence will vary with (mean) stride length (Morris et al. 1994, 1998). Thus, one could argue that stride length and stride length variability are the keys to the gait disturbance in PD (and stride time variability is not relevant). Here, we describe stride-to-stride variations (fluctuations) in the stride time at a given mean cadence/stride length. Since the studies by Morris et al. indicate that cadence and stride length are closely linked, we suggest that the stride-to-stride variability in stride time will likely reflect an important aspect of the stride-to-stride control of gait, generally, and stride length, in particular. The few studies that have measured both stride length variability and stride time variability (albeit using less than ideal methods) have shown that both measures generally behave similarly (e.g., both appear to be optimized at "usual" walking speed). While there is some advantage of directly measuring stride-to-stride variations in stride length, stride-to-stride variability of timing was the only long-term stride-to-stride measure available when this study was performed. In the future, however, it might be helpful to evaluate the relationship between FOG, stride time variability, and stride length and stride length variability and to determine, perhaps using imaging techniques, if common mechanisms are responsible for these alterations in movement control or if they are mediated by independent dopamine-mediated locomotor networks.

Freezing of gait is a perplexing phenomenon that is common among patients with advanced PD and advanced parkinsonism. The results of the present study should cause a "paradigm shift" in our view of freezing of gait. Previously it was generally believed that freezing of gait is a completely transient, paroxysmal phenomenon and that when the patient overcomes the motor blockade, all traces of the freezing apparently vanish and gait performance appears to become normal (for PD). Here we demonstrate, for the first time, that gait disturbances in subjects with freezing of gait are not transient. Instead, the ability to regulate the stride-to-stride fluctuations in walking is severely impaired in subjects with freezing of gait (compared to other subjects with Parkinson's disease) and there are alterations in the gait of subjects with PD and FOG even between freezing episodes. Subjects with PD and FOG have diminished gait stability and increased arrhythmicity. Perhaps investigations that assess other aspects of gait, balance and motor control (e.g., EMG and kinematic studies) and their relationship to freezing could help to further explain this debilitating gait disturbance.

Acknowledgements This work was supported in part by NIH grants AG-14100, RR-13622, HD-39838 and AG-08812. We thank E. Shabtai and D. Comanshter for assistance with statistical analysis and the subjects for their time and effort.

References

Achiron A, Ziv I, Goren M, Goldberg H, Zoldan Y, Sroka H, Melamed E (1993) Primary progressive freezing gait. Mov Disord 8:293–297

Aita JF (1982) Why patients with Parkinson's disease fall. JAMA 247:515–516

Ambani LM, Van Woert MH (1973) Start hesitation – a side effect of long-term levodopa therapy. N Engl J Med 288:1113–1115

Andrews CJ (1973) Influence of dystonia on the response to long-term l-dopa therapy in Parkinson's disease. J Neurol Neurosurg Psychiatry 36:630–636

Biglan K, Holloway RG (2001) Initial treatment of early Parkinson's disease: a review of recent, randomized controlled trials. Curr Neurol Neurosci Rep 1:329–336

Blin O, Ferrandez AM, Pailhous J, Serratrice G (1991) Dopa-sensitive and dopa-resistant gait parameters in Parkinson's disease. J Neurol Sci 103:51–54

Fabre N, Brefel C, Sabatini U, Celsis P, Montastruc JL, Chollet F, Rascol O (1998) Normal frontal perfusion in patients with frozen gait. Mov Disord 13:677–683

Fahn S (1995) The freezing phenomenon in parkinsonism. Adv Neurol 67:53–63

Fahn S, Elton R, members of the UPDRS Developmental Committee (1987) Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M (eds) Recent developments in Parkinson's disease. Florham Park, NJ, pp 153–163

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198

Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. Arch Neurol 56:33–39

Giladi N (2001) Freezing of gait. Clinical overview. Adv Neurol 87:191–197

Giladi N, McMahon D, Przedborski S, Flaster E, Guillory S, Kostic V, Fahn S (1992) Motor blocks in Parkinson's disease. Neurology 42:333–339

Giladi N, Kao R, Fahn S (1997) Freezing phenomenon in patients with parkinsonian syndromes. Mov Disord 12:302–305

Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD (2000) Construction of freezing of gait questionnaire for patients with Parkinsonism. 6:165–170

Giladi N, Gurevich T, Shabtai H, Paleacu D, Simon ES (2001a) The effect of botulinum toxin injections to the calf muscles on freezing of gait in parkinsonism: a pilot study. J Neurol 248:572–576

Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, Tanner C (2001b) Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology 56:1712–1721

Giladi N, Bartlels A, Balash Y, Schaafsma J, Gurevitch T, Comanester D, Hausdorff JM (2002) How is freezing of gait in patients with PD related to akinesia/bradykinesia? Neurology 58 (Suppl 3):P04.060

Gray P, Hildebrand K (2000) Fall risk factors in Parkinson's disease. J Neurosci Nurs 32:222–228

Halliday SE, Winter DA, Frank JS, Patla AE, Prince F (1998) The initiation of gait in young, elderly, and Parkinson's disease subjects. Gait Posture 8:8–14

Hausdorff JM, Ladin Z, Wei JY (1995) Footswitch system for measurement of the temporal parameters of gait. J Biomech 28:347–351

Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL (1998) Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. Mov Disord 13:428–437

Hausdorff JM, Lertratanakul A, Cudkowicz ME, Peterson AL, Kaliton D, Goldberger AL (2000) Dynamic markers of altered gait rhythm in amyotrophic lateral sclerosis. J Appl Physiol 88:2045–2053

Hausdorff JM, Rios DA, Edelberg HK (2001) Gait variability and fall risk in community-living older adults: a 1-year prospective study. Arch Phys Med Rehabil 82:1050–1056

Hely MA, Morris JG, Traficante R, Reid WG, O'Sullivan DJ, Williamson PM (1999) The Sydney multicentre study of Parkinson's disease: progression and mortality at 10 years. J Neurol Neurosurg Psychiatry 67:300–307

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427–442

Imai H, Nakamura T, Kondo T, Narabayashi H (1993) Dopa-unresponsive pure akinesia or freezing. A condition within a wide spectrum of PSP? Adv Neurol 60:622–625

Lamberti P, Armenise S, Castaldo V, de Mari M, Iliceto G, Tronci P, Serlenga L (1997) Freezing gait in Parkinson's disease. Eur Neurol 38:297–301

Leenders KL, Oertel WH (2001) Parkinson's disease: clinical signs and symptoms, neural mechanisms, positron emission tomography, and therapeutic interventions. Neural Plast 8:99–110

Maki BE (1997) Gait changes in older adults: predictors of falls or indicators of fear. J Am Geriatr Soc 45:313–320

Morris ME, Iansek R, Matyas TA, Summers JJ (1994) The pathogenesis of gait hypokinesia in Parkinson's disease. Brain 117:1169–1181

Morris ME, Iansek R, Matyas TA, Summers JJ (1996) Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. Brain 119:551–568

Morris M, Iansek R, Matyas T, Summers J (1998) Abnormalities in the stride length-cadence relation in parkinsonian gait. Mov Disord 13:61–69

Nakamura T, Meguro K, Sasaki H (1996) Relationship between falls and stride length variability in senile dementia of the Alzheimer type. Gerontology 42:108–113

Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E (2001) Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Mov Disord 16:1066–1075

Ouchi Y, Kanno T, Okada H, Yoshikawa E, Futatsubashi M, Nobezawa S, Torizuka T, Tanaka K (2001) Changes in dopamine availability in the nigrostriatal and mesocortical dopaminergic systems by gait in Parkinson's disease. Brain 124:784–792

Sheridan MR, Flowers KA, Hurrell J (1987) Programming and execution of movement in Parkinson's disease. Brain 110:1247–1271

Yanagisawa N, Hayashi R, Mitoma H (2001) Pathophysiology of frozen gait in Parkinsonism. Adv Neurol 87:199–207