

Spatiotemporal Characteristics of Freezing of Gait in Patients After Hypoxic-Ischemic Brain Injury

A Pilot Study

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Abstract: The objective of this study was to investigate spatiotemporal characteristics with gait variability in patients with freezing of gait (FOG) after hypoxic-ischemic brain injury (HIBI).

Eleven patients showing FOG after HIBI and 15 normal controls were consecutively enrolled. We performed gait analysis using a computerized gait system (VICON MX-T10 Motion Analysis System) and compared spatiotemporal characteristics and gait variability in both groups. Additionally, we performed correlation analysis to identify the gait parameters associated with severity of freezing, which we measured based on unified Parkinson disease Rating Scale subscore.

Spatiotemporal characteristic of FOG patients showed increased stance time and double support phase and decreased swing time, single support phase, stride length, step length, and gait velocity compared with normal controls ($P < 0.05$). Besides baseline spatiotemporal characteristics, step time asymmetry and step length asymmetry were significantly increased in HIBI patients with FOG ($P < 0.05$). The coefficient of variation, which reflects the variability of each parameter, demonstrated increased cadence, stride time, swing time, single support phase, stride length, step length, and gait velocity variability in HIBI patients with FOG compared with normal controls ($P < 0.05$). Correlation analysis between FOG severity and spatiotemporal parameters revealed gait velocity, step length, and single support phase to be spatiotemporal parameters related to FOG severity ($P < 0.05$).

Our findings suggest that bilateral gait coordination deterioration plays a considerable role for pathophysiology of FOG in HIBI patients. Additional studies with a larger number of subjects are needed to further investigate the neural mechanism of FOG after HIBI.

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Abbreviations: BG = basal ganglia, CV = coefficient of variation, FOG = freezing of gait, HIBI = hypoxic ischemic brain injury, PD = Parkinson's disease.

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INTRODUCTION

Freezing of gait (FOG) is a unique gait disorder in which patients are unable to initiate or continue locomotion, and it is 1 of the most disabling and least understood symptoms in advanced Parkinson disease (PD).¹ In FOG, patients are unable to lift a foot to step forward, making the patients feel as if their foot is glued or magnetized to the ground. FOG is very troublesome because it increases the risk of falling, and it has a significant impact on quality of life in PD patients.²

Hypoxic-ischemic brain injury (HIBI) is a well-known consequence of cardiac arrest or respiratory failure, and there are 6 subtypes, which include ischemic, oligemic, anoxic, hypoxic, anemic, and histotoxic.³ The exact prevalence of HIBI remains unknown, but those who survive HIBI often experience several types of movement disorders such as Parkinsonism, myoclonus, dystonia, and chorea.⁴ However, FOG after HIBI has rarely been reported. Two previous studies on gait disturbance following HIBI suggested the causative pathological mechanism to be damage to the basal ganglia (BG) inducing a loss of functional integrity of the BG-thalamus-frontal cortex^{5,6}; however, the pathophysiology of FOG in PD and HIBI patients still remains poorly understood.

Previous research about gait characteristics of FOG in PD patients reported increased cadence and double support phase; decreased stride length, gait velocity, and single support phase; higher stride time variability; and greater gait asymmetry.⁷⁻¹⁰ However, no study has evaluated the gait characteristics of FOG after HIBI. Therefore, we performed this study to investigate the basic spatiotemporal characteristics and gait variability of FOG in patients after HIBI compared with those of normal controls. Additionally we sought to determine the relationships between various spatiotemporal parameters and severity of FOG in HIBI patients.

METHODS

Participants

From March 2009 to February 2015, 13 patients with FOG after HIBI were consecutively enrolled in this study. For normal controls, we recruited 15 age- and sex-matched healthy people in stable medical condition without any previous neurologic, orthopedic, or visual problems affecting locomotion. The etiologies of HIBI in the 13 FOG patients included 7 cases of cardiac arrest, 2 cases of respiratory failure, 2 cases of hypovolemia, and 2 cases of intoxication. All subjects underwent neurological and physical examination, which included Mini Mental Status Exam and Functional Independence Measure (FIM). Also we evaluated the Complex Figure test (copy) for visuospatial perception, the Block Design test for visuospatial processing of motor task, and muscle power using medical research council grading. Since an objective method for grading FOG severity in HIBI patients has not yet been established, we evaluated

severity using FOG subscore of unified Parkinson disease Rating Scale (UPDRS) ranging from 0, indicating no freezing, to 4, indicating frequent falls due to freezing. All participants provided written informed consent, and procedures were performed with the approval of the Institutional Review Board for Clinical Studies in our institution.

Protocol¹¹

All participants walked barefoot on an 8-m pathway at their preferred gait speed. Gait analysis data from 5 trials performed were collected for all participants who were asked to walk naturally at self-selected gait speed while looking forward ahead. Every data were gathered in the motion analysis laboratory. During the gait cycle, we measured the spatiotemporal parameters of gait cycle using computerized motion analysis system (VICON MX-T10 Motion Analysis System, Oxford Metrics Inc., Oxford, UK). All participants were equipped with reflective infrared makers of the VICON Plug-in-Gait model for motion analysis. An expert investigator who had clinical experience of motion analysis over 20 years placed a total of 16 infrared makers on the posterior superior iliac spine, anterior superior iliac spine, mid points of the lateral femur, lateral knee joint axis, mid points of the lateral tibia, lateral malleolus, heel, and dorsal foot between metatarsal heads 2 and 3. Also, we captured simultaneous gait motion with 6 digital videos from the front, rear, and side during gait cycle. Two force plates (AMTI OR 6-5, Advanced Mechanical Technology, Newton, MA) were embedded under the pathway but were not used for data analysis.

Data Analysis

Basic spatiotemporal parameters of gait were determined from the walking trial. Outcome variables included cadence, stride time, step time, stance time, swing time, single support phase, double support phase, stride length, step length, and gait velocity. Measures of asymmetry for step length and step time were calculated manually, as each variable can yield different information about gait asymmetry.^{9,12,13} Asymmetry measures were calculated using the following equation: asymmetry = $| \text{right measure} - \text{left measure} |$. The absolute asymmetry value was quantified using the average right-left difference for each trial of each patient.

Variability of each baseline spatiotemporal parameter during the gait cycle was calculated using coefficient of variation (CV = standard deviation/mean × 100%).^{8,14,15} The data from each trial for each participant were averaged to calculate an individual mean and standard deviation for each variable.

Statistical Analysis

Statistical analysis was performed using SPSS, 20.0 for windows. Chi-squared and Mann–Whiney tests were used to evaluate categorical (gender) and continuous (age, cognition, FIM) baseline characteristics between FOG patients and normal controls. The Mann–Whitney test was used to compare spatiotemporal gait parameters between the 2 groups. Multiple linear regression analysis was used to analyze relationships between spatiotemporal parameters and FOG severity. A *P* value of 0.05 or less was considered statistically significant.

RESULTS

We initially recruited 13 FOG patients, but 2 were excluded because they did not undergo gait analysis. The FOG patients group consisted of 9 men and 2 women with a mean age of 37.36 ± 15.78 years (range, 22–53 years), whereas the normal controls consisted of 11 men and 4 women with a mean age of 40.27 ± 15.48 years (range, 25–56 years). There was no significant difference between the 2 groups with respect to age or gender (*P* > 0.05). The mean duration of disease from onset was 14.27 ± 15.44 months, and the mean freezing UPDRS subscore, which reflects the severity of freezing, was 3.18 ± 1.17 at the time of evaluation. The mean Hoehn and Yahr scale score for the FOG patient group was 3.18 ± 0.72 . The Mini Mental Status Exam (FOG group: 20.45 ± 7.50 , control group: 29.27 ± 1.49 , *P* < 0.05) and FIM scores (FOG group: 58.45 ± 24.85 , control group: 125.60 ± 0.91 , *P* < 0.05) were significantly different between 2 groups, and they revealed severely impaired cognitive function and functional independence in the FOG group. Table 1 lists the individual baseline characteristics, the subtypes of FOG by phase of locomotion, the muscle power, the Rey Complex Figure test (copy) score, and the Block Design Test score. The brain magnetic resonance imaging (MRI) findings in FOG patients after HIBI showed heterogeneous cerebral injuries to the bilateral deep gray matter

TABLE 1. General Characteristics of Hypoxic-Ischemic Brain Injured Patients With FOG

Patient No.	Age, y	Gender	Duration, mo	H&Y Scale	FOG Grade	Subtype of FOG by Phase of Locomotion	Muscle Power	Rey Complex Figure Test (Copy)	Block Design Test
1	40	M	38	3	4	Start/turning/destination	4	34	47
2	41	M	3	4	4	Start/turning	3.5	5	13
3	26	M	4	4	3	Turning/destination	4	6	19
4	26	M	37	3	3	Start/turning	4	7	24
5	19	M	37	4	4	Turning/destination	4	5	17
6	28	M	18	3	4	Turning/destination	4	34	53
7	30	M	5	3	3	Start/turning	4	17	21
8	32	F	1	2	1	Tight quarter	4	35	51
9	68	F	4	2	1	Turning	4	NT	NT
10	36	M	4	3	4	Start/turning/destination	4	7	22
11	65	M	6	4	4	Start/turning/destination	3.5	13	45

FOG = freezing of gait, H&Y = Hoehn and Yahr, NT = not testable.

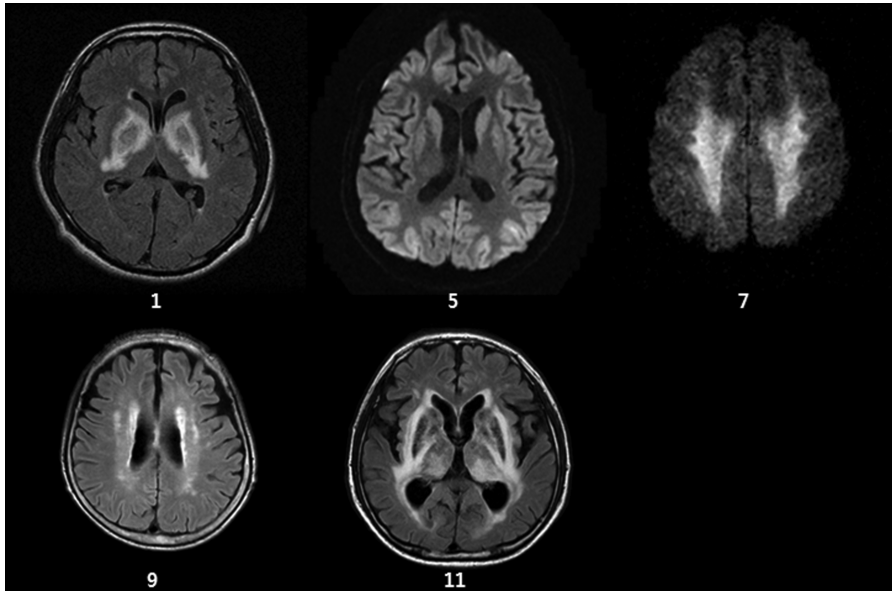


FIGURE 1. Brain magnetic resonance imaging findings of patients with freezing of gait after hypoxic-ischemic brain injury showed heterogeneous cerebral injuries to the bilateral deep gray matter (patients 1 and 11), diffuse cortices (patient 5), and diffuse deep white matter (patients 7 and 9).

(patients 1 and 11), diffuse cortices (patient 5), and diffuse deep white matter (patients 7 and 9) (Figure 1).

Spatiotemporal Characteristics of FOG After HIBI Compared With Those of Normal Controls

The FOG group showed significantly decreased swing time (28.14 vs 36.63, $P < 0.001$), single support phase (27.80 vs 37.00, $P < 0.001$), stride length (0.53 vs 1.19, $P < 0.001$), step length (0.27 vs 0.59, $P < 0.001$), and gait velocity (0.44 vs 1.09, $P < 0.001$) compared with normal controls. Additionally, the FOG group showed significantly increased stance time (71.86 vs 63.37, $P < 0.001$) and double support phase (44.06 vs 26.37, $P < 0.001$) compared with normal controls; however, there was no significant difference in cadence, stride time, or step time between the 2 groups ($P > 0.05$). On asymmetry

analysis, step length asymmetry (0.10 vs 0.02, $P = 0.001$) and step time asymmetry (0.09 vs 0.02, $P = 0.047$) were significantly increased in FOG patients compared with normal controls. Table 2 summarizes the spatiotemporal characteristics between the 2 groups. Based on CV, there was higher variability of cadence, stride time, swing time, single support phase, stride length, step length, and velocity in HIBI patients with FOG compared with normal controls (Table 3).

Correlation Analysis Between Spatiotemporal Parameters and FOG Severity

Multiple linear regression analysis revealed that gait velocity was significantly correlated with FOG severity ($r^2 = 0.408$, $P = 0.034$). Also, gait velocity + step length ($r^2 = 0.659$, $P = 0.014$) and gait velocity + step length + single

TABLE 2. Comparison of Spatiotemporal Characteristics Between HIBI Patients With FOG and Normal Controls

	HIBI Patients With FOG (N = 11)	Normal Controls (N = 15)	P Value
Cadence, steps/min	106.81 ± 43.21	109.51 ± 4.75	0.540
Stride time, s	1.67 ± 1.91	1.09 ± 0.04	0.474
Step time, s	0.90 ± 1.18	0.55 ± 0.03	0.760
Stance time, %	71.86 ± 7.73	63.37 ± 1.40	<0.001
Swing time, %	28.14 ± 7.73	36.63 ± 1.40	<0.001
Single support, %	27.80 ± 8.53	37.00 ± 1.92	<0.001
Double support, %	44.06 ± 15.52	26.37 ± 2.80	<0.001
Stride length, m	0.53 ± 0.26	1.19 ± 0.12	<0.001
Step length, m	0.27 ± 0.16	0.59 ± 0.06	<0.001
Gait velocity, m/s	0.44 ± 0.24	1.09 ± 0.13	<0.001
Step length asymmetry, m	0.10 ± 0.10	0.02 ± 0.02	0.001
Step time asymmetry, s	0.09 ± 0.15	0.02 ± 0.02	0.047

Values are mean ± standard deviation.
FOG = freezing of gait, HIBI = hypoxic-ischemic brain injury.

TABLE 3. Coefficients of Variation of Spatiotemporal Gait Patterns Between HIBI Patients With FOG and Normal Controls

	HIBI Patients With FOG (N = 11)	Normal Controls (N = 15)	P Value
Cadence, steps/min	6.38 ± 4.24	3.49 ± 1.77	0.020
Stride time, s	6.56 ± 3.90	3.47 ± 1.78	0.018
Step time, s	8.05 ± 4.01	5.07 ± 2.56	0.077
Stance time, %	4.20 ± 3.84	2.41 ± 1.52	0.413
Swing time, %	11.11 ± 11.93	4.02 ± 2.39	0.020
Single support, %	13.38 ± 10.50	4.29 ± 1.27	0.000
Double support, %	11.35 ± 7.67	10.45 ± 4.64	0.919
Stride length, m	13.64 ± 8.67	5.31 ± 3.04	0.003
Step length, m	27.69 ± 34.38	6.22 ± 3.30	0.002
Gait velocity, m/s	14.34 ± 10.34	7.19 ± 3.04	0.041

Values are mean ± standard deviation.
FOG = freezing of gait, HIBI = hypoxic-ischemic brain injury.

support phase ($r^2 = 938$, $P < 0.001$) showed significant correlation with FOG severity (Table 4). Other spatiotemporal parameters, including asymmetry factors, were not significantly associated with FOG severity.

DISCUSSION

To our knowledge, this is the first study to investigate spatiotemporal characteristics of FOG in patients after HIBI. Our results demonstrate that spatiotemporal parameters of swing time, single support phase, stride length, step length, and gait velocity were significantly decreased in the FOG group, while other parameters such as stance time and double support phase were significantly increased. Additionally, increased step time and step length asymmetries were found in the FOG group, and CV of the spatiotemporal parameters of cadence, stride time, swing time, single support phase, stride length, step length, and gait velocity were increased in the FOG group. These results suggest that deterioration of gait coordination is 1 of the pathophysiological mechanisms of FOG in patients after HIBI.

FOG is a common symptom in advanced PD, and several studies on gait analysis in PD patients with FOG have been reported. Compared with normal controls, PD patients with FOG in previous studies demonstrated decreased gait velocity, step length, and single support phase and increased cadence and double support phase.^{10,16} These results are similar to our findings in HIBI patients with FOG with the exception that cadence was not statistically different compared with normal controls. In addition to basic spatiotemporal characteristics, PD patients with FOG revealed increase in stride length asymmetry, stride time variability,^{8,15} step time, and step length asymmetry.⁹ Among the many hypotheses on the pathophysiology of FOG in PD, increased stride-to-stride variability and marked

gait asymmetry denote impairment of gait cycle coordination.^{17,18} From our CV results, which indicate single-subject gait parameter variability, HIBI patients with FOG showed an increase in step length asymmetry, step time asymmetry, cadence, stride time, swing time, single support phase, stride length, step length, and gait velocity. These findings suggest that the disturbance of bilateral gait coordination is an important factor in the pathophysiology of FOG in HIBI patients, similar to that of FOG in PD patients.

The pathophysiology of FOG is still unknown; however, we postulate that dysfunction of gait-related cerebral structures such as the BG circuit could provoke FOG. The BG is an important neural correlate for locomotion control and is susceptible to hypoxic-ischemic injury. Feve et al⁵ reported 4 cases of axial motor disturbance and FOG accompanied by bilateral BG lesions after HIBI. Severe HIBI primarily affects gray matter structures including the BG, thalami, and cerebral cortices (in particular, the sensorimotor and visual cortices).¹⁹ In PD patients, disturbance of the BG circuit connecting the thalamus and frontal lobe was shown to be a neural correlate in the pathophysiology of FOG.²⁰ However, in our study, MRI findings in patients with FOG after HIBI showed diffuse neural damage in the bilateral cerebral cortices, BG, thalami, and deep white matter. These finding suggest that the neural pathophysiology of FOG in HIBI patients is different from that of FOG in PD patients.

The association between FOG and cognitive dysfunction has long been recognized in PD patients. Such cognitive dysfunction includes frontal executive dysfunction, inattention, and anxiety.^{21,22} Also, Amboni et al²³ reported that the presence of FOG was considered to be a marker of early executive dysfunction in a 2-year follow-up study. In addition, it is well documented that PD subjects rely more on visual feedback to control balance and locomotion than healthy subjects.²⁴ PD freezers demonstrated impaired visual information processing,²⁵ and impairment of visuospatial processing is correlated with the severity of FOG in PD patients.²⁶ In our study, HIBI patients with FOG exhibited significant impairment of cognitive function, visuospatial perception and processing. The brain damage including parieto-occipital and frontal areas which is associated with cognitive and visuospatial dysfunction might affect the development of FOG in HIBI patients. In the future, functional neuroimaging studies about the relationship between FOG and cognitive, visuospatial dysfunction are recommended. Because we did not compare HIBI patients with FOG to those

TABLE 4. Correlations Between Spatiotemporal Parameters of Gait Analysis and Freezing of Gait Severity Score in Hypoxic-Ischemic Brain Injured Patients

	r ²	P Value
Gait velocity	0.408	0.034
Gait velocity + step length	0.659	0.014
Gait velocity + step length + single support	0.938	<0.001

without FOG, we could not conclusively determine the relationship between cognitive, visuospatial dysfunction and FOG in HIBI patients. However, it could be a potential pathophysiology of FOG, and further research comparing these 2 groups is warranted.

Falls are common and troublesome complications in elderly populations and advanced PD. There have been some reports that gait variability including the stride time and length variability was a predictor of falling.^{27,28} Nakamura et al²⁹ proposed that a CV of stride length of 7% puts the walker at a high risk of falling. In the present study, the CV of step length in normal control was 5.31%. On the other hand, subjects with FOG after HIBI was 13.64% which surpassed the suggested 7% threshold, and it implies that HIBI patients with FOG have high risk of falling. Considering the finding that subjects with FOG exceeded the proposed fall-related variability threshold, further validation is needed to determine the thresholds more sensitive for predicting future falls. In addition, the clinical application of preventive and compensatory rehabilitative program is needed to reduce the risk of future falling.

Our study has several limitations. The primary limitation is the small sample size. In a period of 6 years, we enrolled only 11 HIBI patients with FOG due to a low incidence of FOG after HIBI. In the future, studies with a larger sample size should be performed. The second limitation is that we used the mean values of spatiotemporal parameters after 5 gait trials. These mean values could represent general spatiotemporal characteristics of patients with FOG after HIBI, but they do not reflect spatiotemporal data just before gait block. Several previous studies focusing on FOG used gate analysis data just before gate block, and this method seemed to better reflect FOG.^{10,14} However, ours is the first study to investigate the gait characteristics of HIBI patients with FOG; hence, the general spatiotemporal characteristics of FOG in HIBI patients might have a significant meaning. Finally, we compared HIBI patients with FOG to normal controls. This makes it difficult to definitively conclude whether different characteristics between the 2 groups are attributable to FOG, HIBI, or both. Therefore, further studies performing a 3-group comparison between HIBI patients with FOG, without FOG, and normal control group are warranted.

In conclusion, patients with FOG after HIBI showed deterioration of bilateral gait coordination compared with normal controls. We assume that neural networks related to coordination contribute to the pathophysiology of FOG. Further research with a larger sample size and a more detailed group comparison are needed. Additionally, neuroimaging studies are recommended to determine the pathophysiology of FOG after HIBI.

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