The Effect of Parkinson Drug Timing on Cardiovascular Response during Treadmill Exercise in a Person with Parkinson Disease and Freezing of Gait

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ABSTRACT

Purpose: To examine the response of cerebral oxygenation during treadmill walking in a person with Parkinson disease (PD) who experiences freezing of gait (FOG) and to determine whether the oxygen response was related to the timing of his PD medication. **Client Description:** A 61-year-old man with PD performed two bouts of treadmill testing on the same day, during the on- and off-phases of his PD medication. **Measures and Outcome:** The client experienced two FOG episodes during the first testing session (on-phase with hypokinetic movement session). Cerebral oxygen response (measured by near-infrared spectroscopy) was stable until the FOG episodes occurred, at which point it decreased until the FOG episode was over. No electrocardiogram (ECG) changes or lightheadedness were noted; blood pressure (BP) remained stable. During the second exercise testing session (off-phase with dyskinetic movement session), the client did not experience any FOG episodes, and his cerebral oxygen response remained stable. Toward the end of the second testing session, he experienced lightheadedness and a drop in BP of approximately 30 mmHg, along with significant ST segment depression on his ECG. **Implications:** Haemodynamic and cerebral oxygen changes occurred that were specific to the timing of the client's PD medication and to his FOG episodes. This case study shows a person with PD demonstrating decreased cerebral oxygenation during FOG, which may be based on his variable response to levodopa medication or may be attributable to as yet unidentified physiologic mechanisms.

Key Words: blood pressure; exercise; levodopa; near-infrared spectroscopy; Parkinson disease.

RÉSUMÉ

Objectif : Analyser la réaction de l'oxygénation cérébrale au cours de la marche sur tapis roulant chez une personne souffrant de la maladie de Parkinson (MP) aux prises avec un blocage de la marche (*freezing of gait*, FOG), puis déterminer si la réaction de l'oxygène cérébral est liée à l'horaire selon lequel ses médicaments pour la MP sont administrés. **Description du client :** Un homme de 61 ans souffrant de la MP. Il a accompli deux tests sur tapis roulant la même journée, lorsque ses médicaments pour la MP étaient en phase et lorsqu'ils étaient hors-phase. **Mesures et résultat :** Le client a vécu deux épisodes de FOG au cours de la première séance de tests (en phase, avec séance de mouvements hypokinétiques). La réaction de l'oxygène cérébral (mesurée par spectroscopie proche infrarouge) était stable jusqu'à ce que le trouble de la démarche se manifeste; elle a alors décliné et est demeurée telle jusqu'à la fin de l'épisode de FOG. Aucun changement à l'électrocardiogramme (ECG) ni aucun étourdissement n'ont été observés et la tension artérielle (TA) est demeurée stable. Au cours de la deuxième séance de tests avec exercice (hors phase, avec séance de mouvements dyscinétiques), le client n'a pas subi d'épisodes de FOG et la réaction de l'oxygène cérébral est demeurée stable. À la fin de la deuxième séance, il a ressenti des étourdissements et sa tension artérielle a chuté d'environ 30 mmHg, et on a aussi constaté un fléchissement appréciable du segment ST de son ECG. **Conséquences :** Les changements survenus à l'oxygène hémodynamique et à l'oxygène cérébral étaient directement liés au moment de la prise des médicaments pour la MP par le patient et à ses épisodes de FOG. Cette étude de cas démontre que la baisse de l'oxygénation cérébrale au cours des épisodes de FOG chez une personne souffrant de MP peut s'expliquer par sa réaction variable à la lévodopa, ou peut être attribuable à des mécanismes physiologiques non encore identifiés.

Parkinson disease (PD) is a neurodegenerative disorder associated with dopaminergic and non-dopaminergic pathology. A common clinical manifestation of PD is freezing of gait (FOG),¹ which may be related to progression of the disease.² It has been suggested that the basic

mechanism of FOG is multifactorial, involving fundamental control of timing and step scaling, affective and cognitive states, and possible disturbances of higher-level motor control and visual perception.³ Levodopa is often used to improve motor function in people with

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PD. A phenomenon known as *wearing-off* may complicate levodopa therapy;¹ this phenomenon may be influenced by factors such as duration of therapy, age, levodopa dose, and ongoing nigrostriatal system degeneration.⁴

Pharmacologic strategies to manage wearing-off attempt to provide more continuous stimulation of post-synaptic striatal dopamine receptors by administering more frequent doses.⁴ In the medication off-phase (when dopamine levels are lowest),⁵ FOG responds well to levodopa, which suggests that dopamine deficiency may be the underlying pathophysiology.⁶ Unfortunately, side effects of levodopa may include dyskinesia and hypotension,^{1,7} and if these occur, levodopa use is often reduced, resulting in bradykinesia. This creates a dilemma for the person with PD between levodopa-induced dyskinesia and hypotension (both of which can increase the risk of falling) and using less levodopa (which means living with bradykinesia).

For people with PD, treadmill training can improve gait symmetry, speed, and rhythm, which may reduce FOG episodes by controlling timing and step scaling.^{8–10} Animal studies using a basal ganglia injury model have shown an exercise-induced neuroprotective mechanism,^{11,12} while human studies of PD have demonstrated improvements in motor performance with treadmill training using both visual and auditory external cueing.^{8,9,13} Treadmill exercise may improve the release and uptake of dopamine to maintain normal synaptic connections, possibly via greater cerebral oxygenation and the release of neurotrophic factors, which together promote cell survival and new cell growth.¹⁴ Specific mechanisms linking dopaminergic release, transmission, or receptor binding with exercise are not known.¹¹

Dysfunction of the autonomic nervous system can occur in people with PD, increasing their risk of developing blood pressure (BP) abnormalities,¹⁵ which may be further affected by levodopa therapy, the progression of PD, or both.⁷ During the off-phase of levodopa, BP has been reported to be higher than during the on-phase.¹⁶ Medication timing may also affect how BP and heart rate (HR) respond to exercise. However, DiFrancisco and colleagues (2009)¹⁷ have shown that the blunted BP and HR responses to exercise are more a manifestation of the disease than a function of the on- or off-phase of the medication.

In addition, abnormalities of autonomic regulation have been shown to alter the normal BP response to exercise, leading to reductions in tissue perfusion that potentially compromise cerebral oxygenation in people with PD.¹⁷ This phenomenon may be exacerbated by a wearing-off effect of levodopa.⁷ Although brain imaging and cerebral perfusion have been studied in people with FOG,¹⁸ we are not aware of any studies that have examined cerebral perfusion/oxygenation during the actual FOG episode during ambulation.

Our purpose in this case report is to explore cerebral oxygenation during treadmill walking and FOG in a client with PD. We also examined whether the cerebral oxygen response was related to the timing of his PD medication, an issue that, to our knowledge, has not been previously studied.

METHODS

Case description

A 61-year-old man with PD has been on levodopa/carbidopa medication for 13 years. His current dose is 1,000 mg/day. He was diagnosed with PD 16 years ago, but felt he had symptoms 5 years before the diagnosis. His additional medications are alprazolam (2 mg daily) for anxiety and herbal turkey rhubarb to improve gastrointestinal health. He has no documented history of cardiovascular disease. He lives with his wife and son and is not employed. He has a history of one fall per week related to his FOG episodes. The client was classified as Hoehn and Yahr (H&Y) stage 4. The H&Y scale is reliable and valid in people with mild to moderate PD (stages 2–4). One way the H&Y scale evaluates impairment and disability is through the assessment of postural instability as a primary index of disease severity.^{19,20}

The client was intermittently involved (1–2 × /wk when attending; 31 times over a 5-month period) with a group exercise programme offered at a community YMCA and run by a physical therapist, an occupational therapist, and volunteers.²¹ Exercise included treadmill walking (forward and backward) and both strengthening (hip and back extensors) and stretching exercises (trunk and lower-extremity muscle groups), along with a similar home exercise programme. He walked around his home up to 152.4 m (500 ft) daily and also participated in bowling once a week. At the time of testing, he was primarily a community ambulator and did not use an assistive device.

This client reports significant variability in the effectiveness of levodopa, which creates difficulty in determining dosage without inducing more frequent FOG episodes. Unlike many people with PD, he reports dyskinesia during the off-phase of his levodopa treatment and bradykinesia during the on-phase; the reason for this is unclear. During the off-phase of his dosing regimen, identified here as the period when he is becoming more dyskinetic, his dyskinesia makes walking exhausting.

The study was approved by Institutional Review Board of Concordia University Wisconsin, and the client signed an informed consent form.

Outcome measures

Cerebral oxygenation was measured using a four-channel continuous-wave near-infrared spectroscopy (NIRS) system (Artinis Medical Systems BV, Zetten, Netherlands). Light was transmitted through a fibre-optic cable with sensors consisting of a transmitter and

Figure 1 Near-infrared spectroscopy during client's on-phase exercise session showing a reduction in oxygenated (red/thickest tracing) and total hemoglobin (green/thinnest tracing) from baseline values (marked by arrows) during two FOG episodes. (Y = start of exercise; C = 3 on the rate of perceived exertion scale (RPE); D = 4 on RPE; E = 5 on RPE; F = 6 on RPE; G = 7 on RPE; K = FOG lasting approximately 1 min; L = walking; Z = end of exercise).

detector, using wavelengths of 775 nm and 845 nm to give relative changes in deoxygenated hemoglobin (HHb) and oxygenated hemoglobin (O_2Hb). To measure cerebral oxygenation, we placed the transmitter and receiver 5 cm apart in a small black plastic holder 2 cm above the left eyebrow, secured by double-sided adhesive tape, and shielded it from outside light by having the client wear a dark headband. NIRS can be used as a non-invasive means to assess oxygen-saturation changes in cerebral tissue.²² NIRS follows changes in cerebral oxygenation, which can equate to changes in cerebral blood volume. Assessing cerebral perfusion and oxygenation during ambulation is difficult, but the use of NIRS allows normal ambulation while the oxygenation response is assessed during the unpredictable episodes of FOG.

Blood oxygen saturation (SpO_2) was measured with a standard pulse oximeter (Ohmeda Biox 3740 Pulse Oximeter; Louisville, CO). Baseline BP, cerebral oxygen response, SpO_2 , and electrocardiogram (ECG; GE Case 12, GE Medical, Milwaukee, WI) recordings were obtained during a 10-minute seated rest before and continually throughout exercise. The treadmill protocol began at $2.68 \cdot \text{min}^{-1}$ and advanced in $2.68 \text{ m} \cdot \text{min}^{-1}$ increments every 30 seconds unless symptoms or FOG necessitated modification. Exercise was terminated when the participant was physically unable to continue or reached a rating of perceived exertion (RPE) corresponding to "hard" or "very hard," as measured on the numeric scale from the Cleveland Clinic Heart and Vascular Health and Prevention Web site.²³

RESULTS

Treadmill testing session 1 was conducted during the peak of the client's PD medication (on-phase), identified

as the approximate time of maximum action of levodopa. The client was dyskinetic before taking his medication but became noticeably hypokinetic during resting/pretest measurements, approximately 30 minutes after taking the dose. His resting HR and BP were 73 bpm and 106/64 mmHg respectively, with SpO_2 at 96% and a normal ECG. While on the treadmill (40 min after taking levodopa), he stated that his feet felt as if they were "glued to the floor." He experienced two separate FOG episodes during this session. The first occurred approximately 6 minutes into the test, at a pace of $10.7 \text{ m} \cdot \text{min}^{-1}$, and lasted about 1 minute. His HR and BP measured immediately after the FOG were 78 bpm and 104/76 mmHg respectively. Although SpO_2 remained stable, the NIRS measuring cerebral oxygenation showed a reduction in both O_2Hb and total hemoglobin (tHb). The decrease in O_2Hb and tHb returned to baseline by the end of the first FOG episode (see Figure 1, first arrow; Table 1).

After the first FOG episode, the client continued walking at the same pace for an additional 3 minutes and 50 seconds. At this point, a second FOG episode occurred, which also lasted about 1 minute. The client's HR was 90 bpm during the episode; his BP was 106/74 mmHg immediately before and after (see Table 1). The RPE obtained before this FOG episode was "hard" (5/10–6/10). The NIRS again showed a significant drop in O_2Hb and tHb; both responses returned to baseline after the second FOG episode (see Figure 1, second arrow). Exercise testing was terminated at this point, after 9 minutes and 50 seconds. No significant ECG or SpO_2 changes were noted, and the client did not report any lightheadedness. We did not obtain BP measurements during either FOG episode because the client was holding tightly to the treadmill handrails in an isometric fashion.

Table 1 Rest and Exercise Variables during Session 1 (On-Phase)

	Pace, m · min ⁻¹	HR, bpm	BP, mmHg	SpO ₂	RPE	Cerebral NIRS	
						O ₂ Hb	tHb
Prior to exercise	–	73	106/64	96	–	Baseline	Baseline
FOG (episode 1)	10.7	78	104/76*	No change	–	Decreased	Decreased
FOG (episode 2)	10.7	90	106/74*	96	Hard	Decreased	Decreased
Post exercise	–	75	102/70	–	–	Return to baseline	Return to baseline

*BP measured immediately following FOG episode.

m · min⁻¹ = metres per minute; HR = heart rate; bpm = beats per minute; BP = blood pressure; SpO₂ = blood oxygen saturation; RPE = Rating of Perceived Exertion scale; NIRS = near-infrared spectroscopy; O₂Hb = oxygenated hemoglobin; tHb = total hemoglobin; FOG = freezing of gait.

Figure 2 Near-infrared spectroscopy during client's off-phase exercise session, showing no change in oxygenated (red/thickest tracing) and total hemoglobin (green/thinnest tracing) from baseline values. (Y = start of exercise; A = 1 on the rate of perceived exertion scale (RPE); C = 3 on RPE; G = 7 on RPE; F = 6 on RPE; L = walking; Z = end of exercise).

The client's second exercise testing session was conducted on the same day, 2 hours after he took his prescribed levodopa; levodopa levels were presumed to be low at this time (off-phase). Immediately before this session, the client was beginning to exhibit dyskinetic movement. His pre-exercise HR and BP were 77 bpm and 108/70 mmHg respectively; SpO₂ was 96%, and his resting ECG was again normal. After 1 minute of exercise, the client reported a brief FOG episode causing minimal interruption of movement, which was noted by the researchers as less significant than the FOG that occurred during the on-phase exercise session. At the 3-minute mark, the client noted slight lightheadedness and identified his RPE as "moderate" (3/10). No ECG changes were noted. After 9 minutes of exercise, he reported RPE as "hard" to "very hard" (5/10–8/10), with more significant lightheadedness and the beginning of discomfort in his left shoulder, which he attributed to fatigue from his dyskinetic movements. His BP dropped to 74/40 mmHg, with a HR of 100 bpm. At this time, the ECG demon-

strated approximately 1.5 to 2 mm downsloping ST segment depression in lead V₅. Exercise was terminated at this point because of the significant drop in BP and the ECG changes. Total treadmill time for the second exercise session was 10 minutes and 1 second, ending at a peak speed of 13.4 m · min⁻¹. During recovery, the client was seated while his BP, ECG, and symptoms improved. BP at 4 minutes recovery was 96/58 mmHg, and the client's lightheadedness resolved completely. His ECG returned to pre-exercise baseline levels by 10 minutes post exercise, and BP remained stable. No significant NIRS-measured cerebral oxygen changes were noted during the second exercise testing session (see Figure 2 and Table 2).

DISCUSSION

This case study was conducted to explore the response of cerebral oxygenation during FOG while performing treadmill exercise. Physiologic characteristics of FOG can be difficult to evaluate because the episodes are brief

Table 2 Rest and Exercise Variables during Session 2 (Off-Phase)

	Pace, m · min ⁻¹	HR, bpm	BP, mmHg	SpO ₂	RPE	Cerebral NIRS	
						O ₂ Hb	tHb
Prior to exercise	–	77	108/70	96	–	Baseline	Baseline
Peak exercise	13.4	100	74/40	No change	Hard to very hard	No change	No change
Post exercise	–	–	96/58	–	–	–	–

m · min⁻¹ = metres per minute; HR = heart rate; bpm = beats per minute; BP = blood pressure; SpO₂ = blood oxygen saturation; RPE = rating of perceived exertion; NIRS = near infrared spectroscopy; O₂Hb = oxygenated hemoglobin; tHb = total hemoglobin.

and unpredictable. Although an abrupt reduction in the client's cerebral oxygenation during the FOG episodes was noted in the first exercise testing session (on-phase levodopa medication), there was no significant FOG during the second (off-phase) session, and no changes in cerebral oxygenation were observed. It is possible that the reduction in cerebral oxygenation during FOG is attributable to concurrent hypotension; however, because we were not able to measure BP during the episode (the client was holding tightly to the treadmill's handrails), it was not possible to determine whether a brief hypotensive response caused the reduced cerebral oxygenation seen during FOG or whether another physiologic mechanism was responsible.^{17,24}

Abnormal BP in the form of a blunted response to exercise has been identified in previous PD exercise research.¹⁷ Our results show a significant drop in BP during the off-phase exercise testing session, but no decrease during the on-phase session conducted at the same intensity, which cannot be considered a typical response to exercise in a person with PD. This response may be a result of the length of time the client has been on levodopa and the wearing-off effect, or it may be a combined effect of the medication and the progressive nature of PD.¹⁷ Interestingly, the cerebral oxygen response remained stable during the hypotensive episode. Abnormal cerebral oxygen responses have been identified in other clinical conditions, including cardiac patients whose cardiac output fails to increase normally with exercise,²⁵ and in people with traumatic brain injury during maximal handgrip contractions.²⁶ The specific mechanism underlying the client's drop in cerebral oxygenation is not known at this time; this question warrants further research.

During the off-phase exercise session, in addition to the BP abnormality, the client's ECG showed 1.5 mm ST segment depression, and he noted lightheadedness and discomfort in his left shoulder. Because there were no ST segment changes during the on-phase exercise session, during which BP remained stable, it seems reasonable to suggest that these ST segment changes during the off-phase session may have stemmed from a reduction in coronary perfusion pressure as a result of hypotension rather than overt coronary artery disease. Although auto-

regulation of coronary perfusion is usually maintained with systolic BP as low as 60–70 mmHg, the client's BP dropped to 74 mmHg, and this may have altered coronary perfusion, causing the ST segment changes.²⁷

One limitation of this case study was the use of continuous-wave NIRS, which measures O₂Hb, HHb, and tHb relative to a baseline measurement but cannot quantify the absolute oxygen saturation value, which would provide a more sensitive measure of cerebral oxygen response. Another limitation was our inability to obtain a BP measurement during the two actual FOG episodes. This problem likely could not have been solved using any non-invasive BP measurement device, due to the isometric contraction of this client's arms when he clenches the handrails during FOG episodes.

Implications

Our findings demonstrate both cardiovascular and cerebral oxygen responses that appear to be related to the timing of this individual's PD medication. Whether these findings are consistent in other people with PD who demonstrate FOG is unknown and requires further investigation. To our knowledge, this is the first time that reduced cerebral oxygenation has been observed in association with FOG during treadmill exercise in a person with PD. Our findings may be influenced by the fact that the client demonstrated a highly variable response to levodopa, possibly because of the duration of his levodopa therapy and the progression of his disease. Recognition of potential contributors to FOG may improve therapists' ability to treat this population and to identify factors that precipitate episodes of FOG. If these oxygen changes occur consistently with FOG, measures such as administering supplemental oxygen may improve exercise tolerance in people with PD. Further study of people with PD who experience FOG would be necessary to verify the consistency of these responses.

KEY MESSAGES

What is already known on this topic

To our knowledge, there are no studies in the literature describing the changes seen in cerebral oxygenation in a person with Parkinson disease (PD) during a freezing of gait (FOG) episode.

What this study adds

This case report contributes to the existing literature on the phenomenon of FOG in people with PD. Further study using NIRS or other measures of brain oxygenation may clarify findings from this study to improve exercise interventions for people with PD who have FOG episodes.

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