Effect of levodopa on cardiovascular autonomic function in Parkinson's disease with and without orthostatic hypotension: a cross-over study

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Protocol Summary

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Sponsor:	UNIVERSITY OF UTAH RESEARCH FOUNDATION
Principal Investigator:	Guillaume Lamotte
Internal Staff and Sub-Investigators:	**Site Name** / **Staff Names** University of Utah / Guillaume Lamotte Principal Investigator

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Background and Introduction

Parkinson's disease (PD) is characterized by the gradual onset of motor symptoms such as bradykinesia, rigidity, tremor, gait difficulties and postural instability, as well as non-motor symptoms such as cognitive impairment and autonomic dysfunction among others [1]. Neurogenic orthostatic hypotension (nOH) is the main clinical manifestation of cardiovascular autonomic dysfunction [2]. The arterial baroreflex allows for beat-to- beat regulation of the blood pressure and heart rate via differential modulation of its cardiovagal (parasympathetic) and noradrenergic (sympathetic) efferent limbs [3]. Several mechanisms may contribute to nOH in PD including baroreflex-cardiovagal and baroreflex-sympathetic noradrenergic failure [2]. The prevalence of nOH in PD increases with age and disease duration; however, several studies have documented that nOH may appear early in the course of PD and reported prevalence of nOH in PD ranges from 30% to 65% [4, 5]. The presence of nOH in PD is associated with poor outcomes related to cardiovascular events, increased morbidity and mortality, more rapid disease progression, cognitive impairment, and falls [6].

Levodopa is a precursor of dopamine and is the treatment of choice to treat the motor symptoms of PD; however, the effect of levodopa on cardiovascular autonomic function in PD is poorly understood. Orthostatic hypotension has been documented as a potential side effect of levodopa in different studies [7, 8]. As a result, clinicians may be reluctant to prescribe levodopa in patients with PD with nOH (PD+OH), which leads to suboptimal management of motor symptoms. On the other hand, several studies failed to show any clear relationship between levodopa and orthostatic hypotension in patients with PD [9-12]. Important limitations of prior studies include the lack of detailed investigation of baroreflex cardiovagal and sympathetic noradrenergic functions and the fact that the same patients were not tested on and off levodopa.

We propose to investigate the effects of levodopa on cardiovascular autonomic function in patients with PD+OH and PD without nOH (PD-OH) by performing standardized autonomic testing in the same patients on and off levodopa.

References:

1. Kalia LV, Lang AE. Parkinson's disease. Lancet (London, England) 2015;386:896-912.
2. Pfeiffer RF. Autonomic Dysfunction in Parkinson's Disease. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics 2020;17:1464-1479.
3. Kaufmann H, Norcliffe-Kaufmann L, Palma JA. Baroreflex Dysfunction. The New England journal of medicine 2020;382:163-178.
4. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RM. Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. Parkinsonism Relat Disord 2011;17:724-729.

5. Hiorth YH, Pedersen KF, Dalen I, Tysnes OB, Alves G. Orthostatic hypotension in Parkinson disease: A 7-year prospective population-based study. Neurology 2019;93:e1526-e1534.
6. De Pablo-Fernandez E, Tur C, Revesz T, Lees AJ, Holton JL, Warner TT. Association of Autonomic Dysfunction With Disease Progression and Survival in Parkinson Disease. JAMA neurology 2017;74:970-976.
7. Bouhaddi M, Vuillier F, Fortrat JO et al. Impaired cardiovascular autonomic control in newly and long-term-treated patients with Parkinson's disease: involvement of L-dopa therapy. Auton Neurosci 2004;116:30-8.
8. Senard JM, Rai S, Lapeyre-Mestre M et al. Prevalence of orthostatic hypotension in Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;63:584-589.
9. Goldstein DS, Eldadah BA, Holmes C et al. Neurocirculatory abnormalities in Parkinson disease with orthostatic hypotension: independence from levodopa treatment. Hypertension 2005;46:1333-9.
10. Jost WH, Altmann C, Fiesel T, Becht B, Ringwald S, Hoppe T. Influence of levodopa on orthostatic hypotension in Parkinson's Disease. Neurol Neurochir Pol 2020;54:200-203.
11. Perez-Lloret S, Rey MV, Fabre N et al. Factors related to orthostatic hypotension in Parkinson's disease. Parkinsonism & related disorders 2012;18:501-5.

Purpose and Objectives

We propose to investigate the effects of levodopa on cardiovascular autonomic function in patients with Parkinson's Disease with orthostatic hypotension (PD+OH) and Parkinson's Disease without neurogenic orthostatic hypotension (PD-OH) by performing standardized autonomic testing in the same patients on and off levodopa.

Objectives

AIM #1. The primary objective of the study is to investigate the effect of levodopa on cardiovascular autonomic function in participants with PD (with and without OH) Participants with PD+OH and PD-OH will undergo autonomic testing of baroreflex cardiovagal and sympathetic noradrenergic functions on and off of levodopa on two separate days. The primary endpoint will be the change in systolic blood pressure from supine to tilt at 3 minutes. Results of autonomic testing on levodopa will be compared to testing off levodopa in all participants. Each patient will be his or her own control. Secondary endpoints will include validated indices of baroreflex cardiovagal and baroreflex sympathetic noradrenergic functions. Although levodopa may have a mild hypotensive effect, we hypothesize that levodopa will not induce or worsen the drop in blood pressure from supine to tilt at 3 minutes and will not worsen neurogenic orthostatic hypotension. Planned secondary endpoints will also investigate the differences in orthostatic vital signs with active standing and tilt table testing in patients with PD and the relationship between autonomic testing and the orthostatic symptom severity questionnaire.

AIM #2. Determine if levodopa has a different effect on cardiovascular autonomic function in participants with PD+OH compared to participants with PD-OH
The data from autonomic testing performed for AIM#1 will be used to assess AIM#2. The primary endpoint for AIM#2 will be indices of baroreflex cardiovagal and noradrenergic function. We hypothesize that levodopa will not alter baroreflex cardiovagal and sympathetic noradrenergic functions in either PD+OH or PD-OH.

Study Population

Age of Participants: 18+

Sample Size:
At Utah:
All Centers: 40

Inclusion Criteria:
All participants:

- Age 18 or older
- Diagnosis of PD based on consensus criteria (Movement Disorder Society Criteria for Parkinson's disease) [13].

For PD+OH group:

- Orthostatic hypotension defined by sustained drop in systolic blood pressure > 20 mmHg and/or a drop in diastolic blood pressure > 10 mmHg within 3 minutes from supine to standing during active standing or tilt [14].
- Autonomic testing and a ratio orthostatic heart rate change / systolic blood pressure change < 0.5 bpm/mmHg will confirm a neurogenic etiology [15].

References

13. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2015;30(12):1591-601.

14. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72.

15. Norcliffe-Kaufmann L, Kaufmann H, Palma JA, Shibao CA, Biaggioni I, Peltier AC, et al. Orthostatic heart rate changes in patients with autonomic failure caused by neurodegenerative synucleinopathies. Ann Neurol. 2018;83(3):522-31.

Exclusion Criteria:

Participant exclusion criteria

- Current usage of medications with potential to affect autonomic or sensory testing, in which the medication can't be held 48 hours prior to testing (e.g. antihypertensives, muscle relaxants, stimulants, and some antidepressants that alter sympathetic function). Participants will be instructed to obtain approval from prescribing providers in cases a medication must be held
- Cognitive impairment according to the principal investigator that would limit the ability to follow instructions during testing
- Usage of dopamine agonists -- this class of medication is associated with orthostatic hypotension and residual medication effects may confound the results of the study due to the long half-life
- Contraindication to the Valsalva maneuver (known middle ear damage or disease, Moya-Moya disease, myocardial infarction within 6 months, and retinal detachment within 6 months)

Design

Prospective Biomedical Intervention or Experiment

Study Procedures

Recruitment/Participant Identification Process:

- Potential participants with PD will be identified from the movement disorders clinic. The principal investigator (Dr. Guillaume Lamotte) will be responsible to review charts and medical records to ensure eligibility. Co-investigators listed on the IRB as well as other U of Utah Healthcare providers who have been made aware of the study, may offer enrollment to potential participants in person in a clinic setting. In the event that a patient expresses interest in participating in research, our principal investigator (or approved study personnel) will contact the patient to provide additional information regarding the study.

- Information about the study will also be displayed in the movement disorder bi-annual newsletter. Research study flyers will be available for all patients seen in the movement disorders clinic. The flyers will be available in the waiting room. Participants can also be recruited from the community through local PD Support Groups and word of mouth, and can contact the primary investigator (or approved study personnel) to inquire about screening for the study. Advertisement on the University of Utah study locator website may also be used as a recruitment method.

Informed Consent:

Description of location(s) where consent will be obtained:
Consent will be obtained in a dedicated space for clinical assessments of research subjects at University of Utah Headache Clinic (INC), University of Utah Neurology/Neurosurgery Clinic (INC and CNC), or Headache Physiology Laboratory (383 Colorow Drive).

Description of the consent process(es), including the timing of consent:
The principal investigator (or approved personnel) will obtain consent prior to performing any of the study procedures, and will explain the necessary information to allow the subject to make an informed decision about participation in the study. During the consent process, the background and purpose of the study, the study procedures, review the risks and benefits of the study, and review the process involved in the protection of personal identifiable information will be explained. Inclusion and exclusion criteria for the study will also be reviewed. Participants will have time to discuss any questions or concerns with the principal investigator. Throughout the study, study personnel will also give participants opportunities to ask questions and get more information about the study protocol for ongoing informed consent.

Procedures:
Screening: When the PI (or approved study personnel) makes contact with potential participant, basic information will be obtained to determine eligibility, including: medical history, PD diagnosis date and symptoms, current medications, among others.

Consent Process: Informed consent will be completed. Participants will complete the informed consent form on paper, or via REDCap. Participants will receive a paper copy per their request. Prior to signing the consent form, study personnel will thoroughly explain all study procedures and provide participants with ample time to ask any questions. The study team will continue to provide participants with opportunities to ask questions to ensure ongoing informed consent throughout the progress of the study.

Clinical assessment: The primary investigator will perform a medical history and physical examination before the testing procedures (baseline visit). The baseline visit will be performed on levodopa. The scales and assessments will include the Composite Autonomic Symptoms Score 31 (COMPASS 31), the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I, II, III, and Hoehn and Yahr stage. The clinical assessment and scales are part of the standard of care in PD. Orthostatic vital signs (standing and supine measures of heart rate and blood pressure) will be performed during the baseline visit with active standing and the day of off-levodopa autonomic testing.

Autonomic testing: All participants will undergo autonomic testing on two separate days. The first autonomic testing will occur within 4 weeks of the baseline visit. The two autonomic tests will occur within a 2-week timeframe. To avoid any confounding of treatment effects and period effects, the order of testing (on versus off levodopa) will be randomized so testing on the first day will be on-levodopa for half of the participants and off-levodopa for the other participants. The procedures performed in this study are part of standardized clinical autonomic function testing. Autonomic testing will be performed by a research assistant with expertise in autonomic testing.

Each participant will undergo testing in the on-levodopa state (45min to 1h after taking their regular dose of levodopa in the morning) and off-levodopa state. For testing in the off-state, the last dose of levodopa will be taken at least 12 hours before testing. Off-state in PD is expected to cause some degree of discomfort related to re-emergence / exacerbation of the motor and non-motor symptoms of PD. To limit the duration of the off-state, autonomic testing will be performed early in the morning between 7am and 8am. As soon as the autonomic testing is completed, the participant will be allowed to take levodopa. A participant may not be eligible for the study if the investigator believes that holding levodopa for testing is not safe. Briefly withholding levodopa, and/or medications that can interfere with heart rate or blood pressure measures, on the morning of the test is part of standard clinical autonomic function testing and is known to be well tolerated based on extensive clinical experience of the PI.

Participants will be instructed to have a standardized low-carbohydrate meal in the morning to avoid the confounding effects of postprandial hypotension and instructed to maintain a stable fluid intake to avoid volume shifts.

Autonomic testing will include non-invasive monitoring of blood pressure and heart rate during the Valsalva maneuver and during a 10-minutes head-up tilt.

Electrocardiogram (ECG): For monitoring the ECG, electrocardiographic leads are applied to the chest, abdomen, neck, or arms. All participants have ECG monitoring during the Valsalva maneuver and tilt table testing described below. Measurement of beat-to-beat heart rate part of standard clinical autonomic function testing.

Finger blood pressure measurement: A finger cuff is applied for non-invasive measurement of continuous blood pressure. All participants have finger blood pressure monitoring during the Valsalva maneuver and tilt table testing described below. Tracking blood pressure continuously via a finger cuff device is part of standard clinical autonomic function testing.

Brachial blood pressure: A clinical automated brachial cuff is applied for measurement of brachial blood pressure. All participants have brachial blood pressure monitoring before and during head-up tilt table testing. Measuring brachial blood pressure is part of standard clinical autonomic function testing.

Respiration: A device for continuous monitoring of respiration is applied to the chest. All participants have respiratory monitoring during the experimental manipulations described below, unless technical limitations obviate such monitoring. Monitoring respiration is part of standard clinical autonomic function testing.

Valsalva maneuver: Assessment of beat-to-beat blood pressure and heart rate during and after performance of the Valsalva maneuver is a well-accepted standard autonomic function test. The participant lies supine on a tilt table with head on pillow. The participant blows or strains against a resistance for 12 seconds at 40 mmHg and then relaxes. If a “square wave” phenomenon is observed, the subject may be tilted at 20 degrees head up and the procedure repeated. At least 3 Valsalva maneuvers are done. The maneuvers are repeated (at least 1 minute between repetitions), until a technically adequate recording is obtained. Indices of

baroreflex-cardiovagal and cardiovascular noradrenergic functions are derived from the heart rate and blood pressure responses to the Valsalva maneuver. Indices of baroreflex cardiovagal function include the Valsalva ratio derived from the maximum heart rate generated by the Valsalva maneuver divided by the lowest heart rate occurring within 30 s of the peak heart rate and the slope of the relationship between cardiac R-R interval vs. systolic blood pressure in Phase II of the Valsalva maneuver is taken as a measure of baroreflex-cardiovagal gain (BRS-V). Indices of baroreflex cardiovascular noradrenergic function include the difference in BP between baseline and the end of Phase II, the pressure recovery time (PRT) which is the time from the nadir of the systolic blood pressure in Phase III of the Valsalva maneuver to complete return of systolic blood pressure to baseline, the adrenergic baroreflex sensitivity which is calculated from the slope of the line reflecting the difference of the baseline systolic blood pressure and the lowest systolic blood pressure in Phase III and the areas below the baseline systolic blood pressure calculated in Phase II (BRA-II) and IV (BRA-IV) of the Valsalva maneuver.

Head-up tilt table testing: The participant lies supine for at least 10 minutes after placement of monitoring leads. Baseline hemodynamic measures are taken. Then the participant is tilted head-up to 70 degrees from horizontal using a motorized tilt table. The duration is up to 10 minutes but may be less for safety reasons if the blood pressure decreases rapidly and progressively. Hemodynamic measures are taken at regular interval during and after tilt. Head-up tilt is part of standard clinical autonomic function testing.

Statistical Methods, Data Analysis and Interpretation

Summary statistics will be used to describe demographic and clinical variables. A sample size of 40 will achieve a power of 80% and a level of significance of 5%, for detecting a mean of 8 mmHg in ΔSBP-3' between the ON and OFF states with a within subject standard deviation of 20 mmHg based on published data on the effect of levodopa on supine and standing blood pressure in people with PD. The main statistical analysis will be conducted using mixed-effects regression models (linear mixed models), which will allow for the correlation of repeated measures within subjects. The response variable in our models will be ΔSBP-3', and the primary predictors will be the ON vs. OFF levodopa state and the period (visit 2 versus visit 3). A random intercept will be included for each subject to account for the within-subject correlation. For analyses of secondary outcomes, we will fit a mixed effect model and adjust the p value for multiple comparisons using the Hochberg multiple comparison procedure. Changes in blood pressure and heart rate with active standing and indices of baroreflex cardiovagal and sympathetic noradrenergic function OFF levodopa will be compared between PD+OH and PD−OH with Student t tests.