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Hemodynamic and Hormonal Responses to an Exercise Test in Parkinson's Disease Patients without Orthostatic Hypotension

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HEMODYNAMIC AND HORMONAL RESPONSES TO AN EXERCISE TEST IN PARKINSON’S DISEASE PATIENTS WITHOUT ORTHOSTATIC HYPOTENSION

By
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A DISSERTATION

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HEMODYNAMIC AND HORMONAL RESPONSES TO AN EXERCISE TEST IN PARKINSON’S DISEASE PATIENTS WITHOUT ORTHOSTATIC HYPOTENSION

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The aim of this investigation was to examine how heart rate, hemodynamics, and norepinephrine are affected by an exercise stress test in Parkinson’s disease (PD) patients. Fourteen individuals with PD (mean age, 68±12 yrs; Hoehn and Yahr stage 1-3) and sixteen healthy individuals (mean age, 66±7 yrs) performed a sub-maximal exercise test on a cycle ergometer. Heart rate (HR), norepinephrine (NE), blood pressure (BP), and other hemodynamic variables including cardiac output (Q), stroke volume (SV), systemic vascular resistance (SVR), and end-diastolic volume (EDV) were measured in a fasted state during supine rest, active standing, exercise, and supine recovery in all participants. Index values were used for all hemodynamic measures to account for differences in body size. Peak HR and percent of age-predicted maximum HR achieved were significantly blunted in PD patients compared to controls. HR remained significantly elevated in the PD group throughout recovery when compared to controls. Measures of BP, including systolic, diastolic, and mean arterial pressure were all significantly lower during active standing in PD compared to controls. Although differences in peak BP during exercise did not reach significance, average values for PD patients were lower than those seen in healthy controls. There were no significant
differences in SV or Q at any time-points. SVR decreased to a significantly greater
degree following the onset of exercise in PD and differences remained significant through
two stages of the exercise test. Differences were also observed during the first minute of
supine recovery. EDV was significantly lower in PD at nearly all time-points. As exercise
intensity increased, this difference lost significance, but returned following a steep
decrease during recovery. NE changed significantly from rest to exercise and recovery,
but there were no significant differences between groups at any time-point. This was the
first study to assess the effects of exercise stress testing on cardiac and vascular function
in PD patients. Despite significant between-group differences in EDV at rest and during
recovery, and SVR during exercise, cardiac index was not affected. Compensatory
adjustments in HR and SV in PD patients may have accounted for the maintenance of
blood circulation. The inability of our PD patients to reach their age-predicted target HR
values is something that practitioners must take into account when prescribing high-
intensity exercise, as using predicted values may overestimate true exercise capacity.
Future studies are needed to determine how this affects participation, adherence, and
physiological and performance adaptations to exercise training at different intensities.
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CHAPTER 1: INTRODUCTION

Parkinson’s disease (PD) has long been characterized by the presence of motor symptoms, first described by James Parkinson in the 19th century. The symptoms include bradykinesia, muscular rigidity, resting tremor, and postural and gait impairment. They are associated with loss of dopaminergic neurons and intracytoplasmic inclusions (Lewy bodies) in surviving substantia nigra pars compacta neurons. Although movement abnormalities remain central to the diagnosis of PD, non-motor features are increasingly more accepted. New diagnostic criteria put forth by the Movement Disorders Society now include the presence of either olfactory loss or cardiac sympathetic denervation on metaiodobenzylguanidine (MIBG) scintigraphy as supporting criteria to clinically establish PD.

Despite advances in imaging technology, diagnostic criteria, and insight into the potential underlying causes of PD, many healthcare practitioners initiate therapy only when symptoms have sufficiently interfered with a person’s daily life and sense of wellbeing. This strategy may be complicated by the belief held by some individuals that tremor, difficulty walking, or generalized slowness is a normal part of aging, and thus, may not seek medical attention in a timely manner. In addition to PD, there are other similar neurodegenerative diseases including corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy that fall under the umbrella of the degenerative parkinsonisms; their responses to medication is less satisfactory and their prognoses poorer than PD. Due to the complex nature of parkinsonian disorders and the subsequent clinical challenge of making a definitive diagnosis, identifying additional
diagnostic criteria and creating new diagnostic testing protocols are of considerable importance.

Autonomic dysfunction has been extensively reported in PD patients, with the major clinical manifestations being disruption of normal hemodynamics at rest, and during standing and exercise.\textsuperscript{6-9} Furthermore, cardiovascular autonomic dysfunction or dysautonomia, has been identified as a premotor feature in multiple types of PD and appears to worsen with disease progression.\textsuperscript{8} One retrospective cohort study reported that multiple cardiovascular measures including peak heart rate (HR), percentage of predicted maximum HR achieved, and peak mean blood pressure were significantly lower during a cardiac stress test in individuals that were later diagnosed with PD, than in those that remained unaffected by the disease.\textsuperscript{10} This finding is consistent with the Braak hypothesis suggesting that PD patients have Lewy body pathology in the autonomic centers and postganglionic sympathetic nervous system, which is present in the pre-motor phase prior to the onset of nigral degeneration.\textsuperscript{11,12} Significantly, the patterns of autonomic features in idiopathic PD differ from those of other parkinsonian disorders like multiple system atrophy or progressive supranuclear palsy.\textsuperscript{11} Therefore, early detection may prove helpful not only for diagnosing PD in the premotor phase, but also in differentiating between PD and other closely related disorders.

Researchers have begun to detail the mechanisms and physiological consequences of cardiovascular dysautonomia in PD patients.\textsuperscript{8,13,14} However, very few have attempted to identify the presence or effects of cardiovascular abnormalities before, during, and after an exercise stress test. Despite a limited amount of research, the majority of findings regarding blood pressure (BP) and HR during exercise indicate that peak BP and HR
appear to be blunted in PD patients compared to healthy, age-matched individuals.\textsuperscript{15-17} Nakamura et al. reported that velocity index, an indicator of cardiac contractility, was impaired during exercise testing in PD compared to controls.\textsuperscript{18} Additionally, hyperdynamic cardiac contractility, as assessed by peak aortic flow velocity following Dobutamine stress testing, was also present in PD patients, further demonstrating denervation within the heart and an impaired noradrenergic response.\textsuperscript{19} Plasma norepinephrine (NE) levels, indicative of sympathetic nervous system activity, were also reported to be significantly lower at baseline and at peak exercise in PD patients when compared to controls.\textsuperscript{15}

Numerous studies have revealed that PD patients on average, are only able to achieve 75-85\% of their age-predicted maximum heart rate.\textsuperscript{15,16,20,21} Despite the volume of recent findings demonstrating this reduced capacity and comparable peak blood pressure in PD patients, guidelines provided by the American College of Sports Medicine and several other organizations, including the World Health Organization and the National Institute of Health, predominantly rely on exercise intensity recommendations designated for healthy adults. Thus, by providing more evidence and a greater understanding of the limitations of PD patients and the mechanisms involved, guidelines for exercise can be better tailored to fit the specific needs of this population.

Although recent research has demonstrated cardiovascular dysregulation during exercise stress testing in PD patients, no studies to date have attempted to quantify the degree to which other hemodynamic variables indicative of cardiac function and systemic vascular regulation may contribute to impaired BP and HR responses. Determining the mechanisms by which BP and HR are affected during exercise by examining the
hemodynamic and humoral factors that regulate each, may provide a critical missing link for researchers seeking targets for the diagnosis and treatment of the disease. Therefore, the purpose of the current study was to assess cardiovascular and NE responses to a sub-maximal exercise stress test in PD patients and healthy, age-matched adults. This is the first study to assess other hemodynamic variables that underlie the regulation of BP and HR including systemic vascular resistance, cardiac output (Q) and stroke volume (SV), and end-diastolic volume (EDV). Additionally, we examined the relationships between NE and multiple hemodynamic variables at rest, during exercise, and in recovery.

We hypothesized that hemodynamic responses would be blunted in PD patients at peak exercise, NE concentrations would be significantly lower in PD at rest and peak exercise, and these values would be significantly and positively correlated to BP and measures of cardiac contractility. Additionally, we hypothesized that systolic blood pressure (SBP), HR, and NE would remain significantly elevated during recovery in PD patients compared to controls.
CHAPTER 2: METHODS

Participants

Participants were recruited from local South Florida communities using flyers, phone calls to individuals from our internal database and by Neurologists at the School of Medicine’s Division of Parkinson’s Disease and Movement Disorders. The criteria for inclusion were that volunteers should be between 45 and 85 years of age, be diagnosed with Stage 1, 2, or 3 on the Hoehn and Yahr scale for PD, or be a healthy individual with no unresolved cardiovascular, neuromuscular, metabolic, and/or musculoskeletal disease. Participants were excluded if they (1) had been advised by their physician not to perform exercise; (2) had participated within the past three months in a strenuous structured exercise program defined as conducting vigorous exercise three or more days per week; (3) were prescribed any medications that can affect cardiovascular measures; (4) were diagnosed with orthostatic hypotension; (5) had any additional neurological disorder in which symptoms might mask or confound those typically present in PD; or, (6) were unable to provide informed consent. A CONSORT flow diagram of the study is provided in Figure 1. All forms, questionnaires, and protocols were approved by the University's Institutional Review Board and all participants signed an informed consent prior to participation.

Experimental Protocol

The study compared hemodynamic and NE responses to a sub-maximal exercise stress test in PD patients and healthy, age-matched adults. A power analysis was performed to determine the required sample size using mean values with standard deviations for submaximal SBP values from a similar study16 during which participants
completed an exercise test on a cycle ergometer. To yield a minimum power of 0.80 with an alpha level set at 0.05, a total of 16 participants in each group were required. Participants visited the laboratory on two separate days for evaluation: (1) Pre-exercise test evaluation, (2) Exercise testing. The study timeline is presented in Figure 2.

**Pre-Exercise Test Evaluation**

On day one, participants received detailed information regarding the study including testing equipment, test protocols, and the potential risks and benefits associated with the testing. Participants completed all forms and questionnaires including a health history questionnaire, the Global Physical Activity Questionnaire (GPAQ), and the informed consent. PD patients were also evaluated using part III of the Movement Disorders Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS). Evaluations were completed by a member of the research team who was trained and certified to administer the assessment by the Movement Disorders Society. A Hoehn and Yahr stage was also determined during this assessment.

**Cycle Ergometer Exercise Test**

All participants underwent a symptom-limited, sub-maximal exercise stress test. Participants arrived at the laboratory between 6-10 am following a 12-hour fast. PD patients were instructed to arrive in the “on” state, meaning that all parkinsonian medications were taken as prescribed by their physician prior to arriving. They were asked to take their usual medications no later than 45-60 minutes before testing to ensure adequate response time. The testing session lasted approximately one hour and was comprised of four stages: resting, active standing, exercise testing, and recovery. A timeline for exercise testing procedures is depicted in Figure 3.
Participants were first placed in a supine position on a padded table. An intravenous catheter was inserted in an antecubital vein for blood collection. Electrocardiography (ECG) electrodes were applied to monitor heart electrical activity using a 12-lead monitoring system and an automated blood pressure cuff was placed on the participants arm (opposite to the arm with the indwelling catheter). Hemodynamic measures included SBP, diastolic blood pressure (DBP), systemic vascular resistance (SVR), SV, EDV, and Q. These were measured throughout rest, exercise, and recovery. Following the 20-minute resting phase, participants were asked to stand quietly for five minutes to assess orthostatic tolerance (active standing phase).

For the exercise test, participants were fitted (10-15° knee flexion at bottom of the pedal cycle) on a Monarch electronically-braked cycle ergometer (Model 839E, Vansbro, Sweden). Testing began with a three-minute warm-up set at a workload of 15 W. Participants were asked to maintain a pedaling speed of 50-70 rpm. Following the warm-up, workload was increased by 20 W for each subsequent three-minute stage. If HR failed to increase more than 15 bpm from stage one-to-two, workload was increased by 25 W for each stage and if the increase was less than 10 bpm, then workload was increased by 30 W for each subsequent stage. Participants exercised until they reached 85% of their age-predicted maximum heart rate (HR_{max}), became symptomatic, or requested to stop. BP, HR, and rating of perceived exertion (RPE) were recorded at the two-minute mark of each stage using the automatic electronic BP cuff (Tango M2, Suntech Medical), electronic ECG software (Cardiosoft, GE Healthcare), and the 15-point Borg rating scale, respectively. All other hemodynamic measures were monitored on a beat-by-beat basis using an impedance cardiography device (PhysioFlow Enduro, Paris, France). Briefly, the
PhysioFlow provides information on cardiac function by performing an analysis of transthoracic bio-impedance recording in association with an ECG signal. It measures changes in impedance by injecting a high frequency alternating electrical current of low magnitude towards the thorax between two electrodes positioned on the neck and another two on the xiphoid process. Two additional electrodes are used to record an ECG signal. A more detailed description, as well as measures of device validity are presented elsewhere. At the completion of the exercise test, participants were asked to sit quietly on the cycle ergometer for two minutes to allow assessment of heart rate recovery (HRR). Following passive rest, participants returned to the supine position for ten more minutes of recovery.

**Blood Collection and Analysis**

To measure NE, 3 cc of venous blood were collected at minute 15 of supine rest, and identical draws were taken at minute three during the warm-up period of the exercise test, immediately post-exercise, and at minute five of supine recovery. Immediately following collection, blood samples were spun at 2500 rpm for 15 minutes at 4°C. Plasma was then separated and stored at -20°C until analysis. NE concentrations were determined using high-performance liquid chromatography with electrochemical detection. Blood specimens were tested and analyzed at the University’s Laboratory for Clinical and Biological Studies.

**Statistical Analysis**

A power analysis was performed to determine the required sample size. Mean values with standard deviations for submaximal SBP values were used from a similar study (16) in which participants completed an exercise test on a cycle ergometer. To yield a
minimum power of 0.80 with an alpha level set at 0.05, a total of 14 participants was required in each group. Descriptive statistics were calculated to provide participants’ characteristics. Additionally, all data collected from the GPAQ were cleaned and analyzed using coding provided by EpiInfo, based on guidelines established by the World Health Organization. A 2 (group) x 14 (time) repeated-measures ANOVA was used to examine significant within- and between-group differences for all hemodynamic measures. Missing values were replaced using the series mean for the respective group. When there were greater than three missing values for any group, data were assessed for that time point compared to resting values only. A 2 (group) x 4 (time) repeated-measures ANOVA was used to examine significant within- and between group differences for NE. Bonferroni post hoc analyses were used to assess pairwise differences. A Pearson product-moment correlation coefficient was computed to assess the relationships between NE and SBP, and NE and SVR. The strength of each association is interpreted as follows: weak = .1 < |r| < .3, moderate = .3 < |r| < .5, strong = |r| > .5. All significance tests were two-tailed and a significance level of p < .05 was set a priori. Effects sizes for Hedge’s g are interpreted as: 0.80 is considered large, 0.50 is considered medium, and 0.20 is considered small. All statistical analyses were performed using SPSS, version 24 statistical package (IBM SPSS Statistics, Armonk, NY).
CHAPTER 3: RESULTS

As shown in Figure 1, a total of 30 participants were tested and included in the analysis: 16 healthy controls (CON) and 14 PD patients. Baseline characteristics are shown in Table 1. PD patients weighed significantly less at baseline compared to their age-matched counterparts (MD=-13.6, \( p = .01 \)). Due to this significant difference, index values (relative to body weight) were calculated for all hemodynamic measures. For the GPAQ (Table 2), the CON group achieved a greater level of total metabolic equivalents (MET) per week when compared to the PD group (MD=2482.0, \( p < .01 \)). However, there were no significant differences for the “Recreation”, “Travel”, or “Sedentary” categories. Table 3 provides the percentage of participants from each group who completed each corresponding stage of the exercise stress test. Only 43% of PD patients reached stage 4, while 75% of healthy controls reached this stage. Additionally, six healthy controls reached stage 5 (38%), while no PD patients passed stage 4. There was no significant between-group difference in RPE at peak exercise (CON=15.0 ± 2.0; PD=16.1 ± 2.4).

Heart Rate

Results for HR and percentage of age-predicted maximum heart rate (APMHR) are displayed in Table 4. HR significantly increased from baseline for all time-points in the PD group, while significant increases were first noted at five minutes during active standing for CON. There was a significant between-group difference for HR at one-minute of active standing with a higher HR for PD than CON (MD=6.5, CI [.6, 12.5], \( p = .03 \), \( g = .80 \)). Peak HR was significantly higher in the CON group (MD=9.7, CI [.8, 18.5], \( p = .03 \), \( g = .80 \)). HRR at two minutes post-exercise was significantly lower in PD compared to CON (MD=-14.4, CI [-24.0, -4.8], \( p < .01 \), \( g = .110 \)), whereas HR at five-
minutes into recovery was significantly higher in PD compared to CON (MD=8.1, CI [.2, 16.0], \( p=.045, g=0.75 \)). Results for percentage of APMHR achieved were similar to those for HR, revealing a significantly higher value at one-minute of active standing for PD (MD=5.3, CI [.3, 10.3], \( p=.04, g=0.77 \)), higher for CON at peak (MD=4.7, CI [1.4, 8.0], \( p<.01, g=1.03 \)), and higher for PD at minute five of recovery (MD=6.2, CI [.5, 11.9], \( p=.03, g=0.80 \)). Additionally, PD patients remained at a higher percentage of their APMHR at minute ten of recovery (MD=6.0, CI [.1, 11.8], \( p=.046, g=0.74 \)).

**Hemodynamics**

**Blood Pressure**

Results for systolic, diastolic, and mean arterial pressure are displayed in Table 5. For PD, SBP values did not significantly increase above rest until stage 3, and the difference returned to a non-significant level by minute one of recovery. However, for CON, SBP significantly increased at one-minute of active standing. SBP was significantly higher than resting for CON at stages 3-5, but not at later time-points. Data for MAP are similar to those of SBP for both groups, with the exception that MAP was not significantly higher than rest for PD post-exercise. At rest, only DBP was significantly lower in PD than CON (MD=-7.8, CI [-13.9, -1.6], \( p=.015, g=-0.92 \)). DBP and MAP at one-minute of active standing were significantly lower in PD (MD=-6.5, CI [-11.6, -1.4], \( p=.014, g=-0.93 \), (MD=-7.1, CI [-13.4, -.8], \( p=.03, g=-0.82 \), respectively. Values for SBP at one-minute of active standing approached significance with a trend toward a lower SBP in the PD group (MD=-11.2, CI [-23.3, .9], \( p=.06, g=-0.68 \)). All measures of BP were significantly lower for PD compared to CON at minute three of active standing (SBP: MD=-11.8, CI [-23.4, -.2], \( p=.046, g=-0.74 \); DBP: MD=-6.3, CI [-11.5, -1.1], \( p=.019, g=-
0.88; MAP: MD=-7.1, CI [-13.5, -.6], \( p = .03 \), \( g = -0.79 \). Although peak values for SBP and MAP were not significantly different between-groups, the effect size for each was moderately strong (SBP: MD=-14.7, CI [-33.3, 3.8], \( p = .11 \), \( g = -0.58 \); MAP: MD=-12.5, CI [-23.4, -1.6], \( p = .12 \), \( g = -0.58 \)).

**Systemic Vascular Resistance**

All other hemodynamic values including SVR, EDV, SV, and Q were standardized to each participant’s weight and presented as indices to adjust for any differences that existed due to significant differences in baseline weight. Results for all other hemodynamic values are displayed in Figure 4. For CON, there was a significant decrease in SVR during the warm-up for the exercise test (MD=−735.6, \( p < .001 \)). SVR values remained significantly lower than rest for all remaining time-points. A similar trend was observed for the PD group; however, SVR values increased by minute five of recovery, the difference failed to reach significance (MD=−425.0, \( p = .12 \)). Although not significant, mean values for SVR at rest were lower in PD compared to CON (MD=−270.2, CI [−550.9, 10.5], \( p = .059 \), \( g = -0.70 \)). In the PD group, SVR decreased more steeply during exercise, revealing a significant between-group difference by stage 1 (MD=−335.9, CI [−637.0, -34.9], \( p = .03 \), \( g = -0.81 \)). Values remained significantly lower at stage 2 (MD=−338.6, CI [−591.7, -85.4], \( p = .01 \), \( g = -0.98 \)), but were not significant for stages 3 and 4. SVR was again significantly lower in PD at minute-one of recovery (MD=−328.6, CI [−593.7, -63.6], \( p = .017 \), \( g = -0.90 \)), but not at minutes five or ten. Despite significantly lower values during exercise and minute one of recovery, SVR reached a higher percentage relative to baseline for PD compared to CON at minutes five (81% vs. 74%) and ten (83% vs. 79%) of recovery.
**End-Diastolic Volume**

For the CON group, EDV was significantly increased above rest at stage 1 (MD=6.4, \(p=0.03\)). This was not true for stage 2, however, there was a significant difference during stages 3 through 4 (S3: MD=6.2, \(p=0.03\); S4: MD=6.2, \(p=0.02\)). The PD group did not see a significant increase relative to resting values until stage 2 (MD=12.6, \(p=0.02\)). Similar to CON, this significant difference persisted through the remaining stages of the exercise test (S3: MD=10.7, \(p=0.001\); S4: MD=13.9, \(p=0.001\)). EDV was significantly lower in PD compared to CON during minute three (MD=-10.2, CI [-19.5, -1.76], \(p=0.004\), \(g=-0.79\)) and minute five (MD=-12.2, CI [-22.7, -1.7], \(p=0.002\), \(g=-0.84\)) of active standing. Additionally, EDV was significantly lower in PD compared to CON during recovery (1 min: MD=-9.7, CI [-17.2, -2.2], \(p=0.01\), \(g=-0.95\); 5 min: MD=-7.1, CI [-13.9, -3.43], \(p=0.04\), \(g=-0.78\)).

**Stroke Volume**

When compared to resting values, significantly greater SV was observed for both groups at stage 2 (CON: MD=11.7, \(p<0.01\); PD: MD=14.4, \(p<0.001\)). SV remained significantly increased throughout the remaining stages for CON (S3: MD=12.7, \(p<0.001\); S4: MD=14.4, \(p<0.001\); S5: MD=15.6, \(p=0.01\)) and PD (S3: MD=11.6, \(p<0.001\); S4: MD=13.3, \(p<0.01\)); however, no significant between-group differences were observed. For both groups, SV was significantly elevated at minute one of recovery (CON: MD=7.1, \(p<0.01\’\); PD: MD=6.4, \(p=0.04\)), but not for minutes five or ten.

**Cardiac Index**

For both groups, Q significantly increased during the warm-up (CON: MD=1.4, \(p<0.01\); PD: MD=1.9, \(p<0.001\)) and remained significantly elevated for all remaining time-points. There were no significant between-group differences for any time-points.
Norepinephrine

Changes in norepinephrine during testing are displayed in Figure 5. There were no significant between-group differences for any time-points. During exercise, there was a significant increase from resting measures for PD (MD=695.1, \( p = .001 \)) and CON (MD=624.4, \( p = .001 \)). Values at peak exercise were also significantly greater than at rest for both PD (MD=1097.1, \( p < .001 \)) and CON (MD=1409.5, \( p < .001 \)).

Correlation Analyses

Results for all correlation analyses are presented in Table 6. For the CON group, there was a strong positive correlation between NE and HR at rest (\( r = .64, p = .01 \)), and during exercise (\( r = .68, p = .01 \)). There were no significant correlations between NE and HR for the PD group. For CON, there was a strong negative correlation between NE and SVR at peak exercise (\( r = -.73, p < .01 \)). There were no other significant correlations for either group.
CHAPTER 4: DISCUSSION

The novel attribute of the present study was the evaluation of hemodynamic variables, along with heart rate and norepinephrine, at rest, during an exercise stress test, and throughout recovery in PD patients without orthostatic hypotension. The main findings were that, compared to healthy controls, participants with PD had lower HR at peak exercise, diminished BP response to active standing, and altered hemodynamic responses at rest, during exercise, and in recovery.

As expected, values for peak HR and percent APMHR were blunted for PD compared to healthy controls. This findings are in agreement with several previous studies and appears to occur independent of testing modality.15,16,20-22 Numerous studies in PD patients have reported autonomic imbalances 23-26 that may directly underlie abnormalities in HR, though a definitive relationship has yet to be established. The predominant theory suggests that impaired ability to increase HR in PD patients, to a similar extent as healthy individuals at peak exercise, is due primarily to cardiac sympathetic denervation,18,26,27 and that sympathetic denervation can begin early in the disease process.25,28

A novel finding from the present study was that HR significantly increased by one minute of active standing in PD, but not until minute five for CON. This is a unique finding, as other studies have shown no significant increases in HR during tilt in PD patients.13,29 SBP significantly increased by minute one of active standing in the CON group, but not PD, and significant between-group differences were observable by minute three. However, changes in SVR were not significantly different at these time-points. To compensate for an immediate reduction in central blood volume, as occurs during an
active standing test, either HR, SBP, or both must be increased. Because the presence of cardiac sympathetic denervation would theoretically limit PD patients’ ability to increase HR, another mechanism must be responsible for the observed changes in the PD group. We theorize that due to an observed inability to increase BP to compensate for gravitational effects on blood distribution, activation of cardiopulmonary baroreceptors may have produced the near-immediate increase in HR. The unloading of cardiopulmonary receptors during active standing may have resulted in not only sympathetic stimulation, but also parasympathetic withdrawal. It is the latter, that we suggest may have produced a significant increase in HR at the observed time-points.

Although HRR has been studied following sub-maximal and maximal stress testing, to our knowledge, no study to date has reported findings from a PD population following a sub-maximal test. Our results demonstrate that PD patients have a significantly reduced ability to regulated HR following peak exercise. Cole and colleagues reported that a normal HRR could be defined as a difference in HR of ≤ 42 bpm two minutes following a sub-maximal exercise test. On average, HRR in PD patients was ~24 bpm, while the average for CON was ~39 bpm. Studies have indicated that parasympathetic return is the primary factor in regulating HR following exercise, and parasympathetic dysfunction has been reported to occur concurrent with sympathetic dysfunction in PD patients, which may explain this finding. Another novel finding was that HR and percentage of APMHR remained significantly elevated in PD compared to CON during supine recovery. Only one other study, by Reuter et al., has measured HR into recovery following an exercise stress test. Although their data did not yield significant responses at these time points, mean values were higher in the PD group compared to CON. It is
unclear, based on our outcome measures, why this was observed since NE values were not significantly higher for PD in recovery. Again, as was the case for HRR, parasympathetic dysfunction may be a possible explanation.

Findings regarding blood pressure responses during orthostatic stress and exercise are equivocal, particularly in studies involving PD patients without orthostatic hypotension. Nonetheless, there is consensus among researchers that blood pressure responses of PD patients are blunted at peak exercise intensities. Our results revealed that DBP was significantly lower at rest in PD. This is not a unique observation as results from a study by Palma and colleagues reported similar findings.10 As mentioned previously, SBP increased significantly by minute one of active standing in CON but not PD. This finding, in conjunction with non-significant increases in HR in the CON group, suggests that healthy adults were able to compensate for alterations in blood redistribution during standing by modulating blood pressure, whereas PD patients appeared to rely on greater increases in HR. Similar results with regard to SBP have been reported in studies using tilt-table testing.29 In contrast to our hypothesis, there were no significant between-group differences in SBP or MAP at peak exercise between groups, although large mean differences were apparent. This finding, while not significant, is in agreement with results reported by Kanegusuku et al., which revealed lower SBP values in PD patients at sub-maximal and peak intensities.16 While an insignificant finding was not expected, one other study has reported similar results.18

This study was the first to our knowledge to assess measures of cardiac response, systemic blood flow, and systemic vascular resistance during exercise in PD patients. Although there are no normative data for these measures in individuals with PD, a study
by Cain et al. provides age-specific norms for healthy individuals. Their data show that, although not significant, SV and EDV decrease with age, particularly after age 60. Based on normative values, resting SV in both groups was slightly higher than mean values presented for a similar age group. Notably, resting EDV values in PD patients were about 20 mL lower than age-specific norms, and were significantly lower than the CON group. One study by Perez and colleagues, which used ICG to assess hemodynamics in a similar PD population reported resting values for SVR and SV. Mean values for our PD group, although slightly lower, fell within the standard deviations presented in their study.

Patterns of change for SV and SVR in PD patients during a tilt table test reported by Perez and colleagues reflect those seen in the current study, in that mean SV values decreased while mean SVR values increased. Although the populations were similar, final position (60 degrees of tilt vs. fully erect for active standing) and time of recording (minute 20 of tilt vs. minutes 1, 3, and 5 of active standing) differed between studies, making comparisons less reliable.

During exercise, changes in SV and Q were comparable to those reported in other studies using treadmill exercise and cycling. It should be noted, however, that these studies included predominately younger subjects. Mean values for SVR at rest were higher for both groups than those reported in a younger population, but were comparable to reported values for an age-matched healthy population at rest and peak exercise. This finding is not unexpected as SVR generally increases with age. An important and previously unreported finding is that PD patients had a significantly steeper drop in SVR at the onset of exercise compared to CON. This is evidenced by
significant between-group differences observed during stages 1 and 2 of the exercise test. Interestingly, NE levels increased comparably in both groups, and mean values for PD patients were higher during stage 1. Thus, another mechanism must be responsible for a decreased ability to compensate for exercise-induced vasodilation. It is possible that a decreased ability to regulate vascular tone as a result of Lewy body aggregation and sympathetic denervation in the superior mesenteric artery,\textsuperscript{40} renal cortex,\textsuperscript{41} and other peripheral sites\textsuperscript{42} that constrict as exercise intensity increases, may have contributed to such a sharp decline. There were no significant correlations for SVR and NE at any time-points for PD. A significant negative correlation was noted for the CON group at peak exercise, indicating that lower SVR values were associated with higher NE values. This finding implies that circulating NE alone is not sufficient to explain changes in SVR and subsequently MAP. It is more likely that the myriad of local factors that induce vasodilation such as increased shear stress, oxygen tension, and build-up of metabolic by-products\textsuperscript{30} are predominately responsible for exercise-induced responses. Future research measuring changes in local vascular resistance during exercise in this population is needed. Perhaps the most statistically significant findings were for EDV. At multiple time-points during testing, EDV was lower in PD compared to CON. This is likely a result of significantly lower BP during each corresponding time-point and lower average SVR during time points where EDV was significantly different between-groups. Interestingly, despite significantly lower EDV values in PD patients, SV was not significantly affected. This in turn, allowed the maintenance of cardiac output during all time-points. SV is affected by preload, myocardial contractility, and afterload. Preload, as reflected by EDV, was lower in PD, and based on the assumption of decreased
contractility as demonstrated in previous research, decreased afterload may have allowed for compensation of SV. This in-turn, led to the maintenance of cardiac index. As differences in SVR became significant between groups, differences in SV became less apparent, with the PD group seeing sharper increases from baseline levels. Significantly lower BP at these time-points may have also contributed to the lower afterload, and thus maintenance of SV.

Norepinephrine deficiency in PD has recently drawn more attention and numerous studies have demonstrated differences in the release and uptake in PD patients, particularly those with more advanced disease.\textsuperscript{13,43,44} The prominent loss of noradrenergic cardiac innervation is among the earliest pathophysiological features of PD\textsuperscript{13} and has been demonstrated in numerous studies by cardiac scintigraphy using MIBG.\textsuperscript{24,41,45} Sympathetic denervation in PD patients has been suggested to be more pronounced in the left ventricle\textsuperscript{46}, which would theoretically limit sympathetic-induced increases in contractility and SV. However, based on our results, there is no evidence of effects on SV. In contrast to other studies that reported significant differences in NE at rest in PD patients, our study revealed no statistical difference. One possible explanation is that our participants may have been more trained than those in other studies that only assessed sedentary PD patients, and that this resulted in resting concentrations that were closer to those of their healthy counterparts. Our study was the first to further assess potential differences in NE by taking measures at the onset of exercise and in recovery. Results revealed that patterns of increase in NE were similar between-groups at all time-points and that NE significantly increased from baseline by stage 1 of exercise and at peak for both groups. At peak exercise, there was not a significant difference in NE between
groups. However, average NE concentrations in PD patients were lower than in CON.
DiFransciso-Donoghue and colleagues conducted the only other study to date to assess
teaches changes in NE from rest to peak exercise. They reported significantly lower values at
peak exercise in PD patients. However, participants were asked to complete a maximal
effort that may have led to greater differences than those seen in our study. It is plausible
that a reduced capacity to synthesize, release, and bind NE at myocardial sites of
innervation may have contributed to the blunted cardiovascular responses observed,
particularly with regard to peak HR. Despite lower mean values for NE at peak exercise
in the PD group, average values in recovery were slightly higher than CON. Research
suggests that there is an age-related decrease in ability to clear excess NE from
circulation, especially following exercise. However, more research is needed to
determine if clearance is affected to a greater degree as a result of PD pathology.

**Study Limitations**

This study has a number of limitations. Because this study included patients with a
range of disease severity (stage 1-3), it is possible that more blunted responses by those
with greater disease severity were balanced by those with mild PD. A larger study
consisting of distinct groups separated by disease severity is warranted to address this
concern. In an effort to study a more general population of PD patients, this study
included patients with a variety of parkinsonian medications and doses. Because of this, it
is possible that responses may have been altered due to medication. However, a previous
study reported no effect of parkinsonian medication on cardiovascular responses. Due
to the nature of our measurements, it was appropriate to exclude individuals prescribed
any cardiovascular medication. This reduces the generalizability of our findings and does
not adequately address expected responses for the large number of healthy individuals or PD patients with hypertension or other cardiovascular disease. Norepinephrine was assessed locally by measuring plasma concentrations. Plasma concentration is the net result of secretion, neuronal uptake, intra- and extra-neuronal metabolism, and clearance, and represents only a small percentage of overall NE in circulation. Therefore, it is difficult to attribute any significant differences in NE to the other physiological variables measured. Results are limited to sub-maximal tests performed on a cycle ergometer and may be different than those performed at a maximum intensity or when using a different exercise modality. Finally, total calculated physical activity was greater in the control group compared to PD patients. While some participants were excluded on the basis of their reported exercise routine, we could not entirely account for this difference between groups. Thus, training status may have affected some outcome measures.

Conclusions

Participants with PD demonstrated blunted heart rate and hemodynamic responses at rest, during a sub-maximal exercise test, and in recovery. Our finding that PD patients were largely unable to reach their age-predicted target heart rate implies that their capacity to conduct high-intensity exercise using predicted values may be limited. Future research is needed using stress echocardiography or more invasive techniques to determine how cardiac function and peripheral blood flow are affected in PD. Cardiovascular dysautonomia is present in many PD patients, even in the pre-motor stage, and identification of significant differences in hemodynamics may offer an additional biomarker for the early diagnosis of PD and may aid in assessing the progression of disease severity.
REFERENCES


FIGURES

Figure 1. Consort participant flow
Figure 2. Study timeline

ACSM=American College of Sports Medicine; MDS-UPDRS=Movement Disorders Society-Unified Parkinson’s Disease Rating Scale; HR=heart rate; SVR=systemic vascular resistance; Q=cardiac output; SV=stroke volume; EDV=end-diastolic volume; BP=blood pressure; AMPHR=age-predicted maximum heart rate
Figure 3. Exercise test timeline

- Blood Draw
- Blood Pressure

* All Other Hemodynamic Variable Will Be Monitored Continuously
Figure 4. Time-course changes and between-group differences in measured hemodynamic variables

All values are displayed as means ± SE; black dots=PD; white dots=CON; † indicates a significant between-group difference at the observed time-point, $p<.05$. 
Figure 5. Changes in norepinephrine across multiple time-points

Black bar=PD; gray bar=CON; *indicates a significant difference from rest.
Table 1. Baseline characteristics for all participants

<table>
<thead>
<tr>
<th>PD (n=14) (3 F, 11 M)</th>
<th>CON (n=16) (7 F, 9 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>68.9 ± 12.1</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>166.7 ± 9.9</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>68.6 ± 12.5</td>
</tr>
<tr>
<td><strong>Hoehn and Yahr Stage</strong></td>
<td>1 (n=4), 2 (n=5), 3 (n=5)</td>
</tr>
<tr>
<td><strong>UPDRS Part III</strong></td>
<td>31.5 ± 14.3</td>
</tr>
</tbody>
</table>

PD=Parkinson’s disease; CON=healthy control; UPDRS=Unified Parkinson’s Disease Rating Scale; † indicates significant between-group difference, $p < .05$. 
Table 2. Measures from the Global Physical Activity Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Total (METs/wk)</td>
<td>1392.5 (925.6)</td>
<td>3874.6 (2183.7)†</td>
</tr>
<tr>
<td>Work (METs/wk)</td>
<td>480.0 (1370.3)</td>
<td>1070.0 (2135.3)</td>
</tr>
<tr>
<td>Travel (METs/wk)</td>
<td>478.0 (647.5)</td>
<td>383.6 (613.8)</td>
</tr>
<tr>
<td>Recreation (METs/wk)</td>
<td>945.0 (880.5)</td>
<td>2130.0 (1855.6)</td>
</tr>
<tr>
<td>Sedentary (hr/day)</td>
<td>6.1 (3.6)</td>
<td>3.9 (2.9)</td>
</tr>
</tbody>
</table>

PD=Parkinson’s disease; CON=healthy control; SD=standard deviation; MET=metabolic equivalent; † indicates significant between-group difference, *p* < .05.
Table 3. Percentage of participants who completed each stage of the exercise test

<table>
<thead>
<tr>
<th>Stage</th>
<th>PD (n=14) (%)</th>
<th>CON (n=16) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>14 (100)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>13 (93)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>10 (71)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>6 (43)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>0 (0)</td>
<td>6 (38)</td>
</tr>
</tbody>
</table>

PD=Parkinson’s disease; CON=healthy control.
Table 4. Changes from baseline and between-group differences in measures of heart rate at all time points

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Heart Rate (bpm)</th>
<th>Percent Age-Predicted Maximum Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td></td>
<td>Between-Group Difference (p-value)</td>
<td>Between-Group Difference (p-value)</td>
</tr>
<tr>
<td>PD</td>
<td>CON</td>
<td>PD</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Rest</td>
<td>65 (2)</td>
<td>61 (2)</td>
</tr>
<tr>
<td>Standing 1 min</td>
<td>73 (2)*</td>
<td>67 (2)</td>
</tr>
<tr>
<td>Standing 3 min</td>
<td>72 (2)*</td>
<td>67 (2)</td>
</tr>
<tr>
<td>Standing 5 min</td>
<td>71 (2)*</td>
<td>67 (2)*</td>
</tr>
<tr>
<td>Warm-up</td>
<td>89 (3)*</td>
<td>80 (3)*</td>
</tr>
<tr>
<td>Stage 1</td>
<td>98 (4)*</td>
<td>88 (3)*</td>
</tr>
<tr>
<td>Stage 2</td>
<td>105 (4)*</td>
<td>99 (4)*</td>
</tr>
<tr>
<td>Stage 3</td>
<td>113 (3)*</td>
<td>104 (3)*</td>
</tr>
<tr>
<td>Stage 4</td>
<td>119 (5)*</td>
<td>119 (4)*</td>
</tr>
<tr>
<td>Stage 5</td>
<td>-</td>
<td>131 (3)*</td>
</tr>
<tr>
<td>Peak Value</td>
<td>117 (3)*</td>
<td>126 (3)*</td>
</tr>
<tr>
<td>Post-Exercise (2 min)</td>
<td>94 (3)*</td>
<td>88 (3)*</td>
</tr>
<tr>
<td>Recovery 1 min</td>
<td>82 (3)*</td>
<td>76 (3)*</td>
</tr>
<tr>
<td>Recovery 5 min</td>
<td>81 (3)*</td>
<td>73 (3)*</td>
</tr>
<tr>
<td>Recovery 10 min</td>
<td>78 (3)*</td>
<td>71 (3)*</td>
</tr>
<tr>
<td>Heart Rate Recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 (3) 39 (3) &lt;.01†</td>
<td></td>
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</tr>
</tbody>
</table>

PD=Parkinson’s disease; CON=healthy control; SE=standard error of the mean; APMHR=age predicted maximum heart rate; * indicates significantly different from rest, $p < .05$; † indicates significant between-group difference, $p < .05$. 
Table 5. Changes from baseline and between-group differences in measures of blood pressure at all time points

<table>
<thead>
<tr>
<th>Time Point</th>
<th>SBP (mmHg) Mean (SE)</th>
<th>Between-Group Difference (p-value)</th>
<th>DBP (mmHg) Mean (SE)</th>
<th>Between-Group Difference (p-value)</th>
<th>MAP (mmHg) Mean (SE)</th>
<th>Between-Group Difference (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>PD 128 (4)</td>
<td>CON 136 (4)</td>
<td>PD 77 (2)</td>
<td>CON 85 (2)</td>
<td>PD 95 (3)</td>
<td>CON 102 (2)</td>
</tr>
<tr>
<td>Standing</td>
<td>PD 130 (4)</td>
<td>CON 141 (4)*</td>
<td>PD 82 (2)</td>
<td>CON 89 (2)</td>
<td>PD 99 (2)</td>
<td>CON 106 (2)</td>
</tr>
<tr>
<td>1 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>PD 136 (4)</td>
<td>CON 148 (4)*</td>
<td>PD .046</td>
<td>CON 83 (2)</td>
<td>PD 102 (2)</td>
<td>CON 109 (2)</td>
</tr>
<tr>
<td>3 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>PD 137 (4)</td>
<td>CON 147 (4)*</td>
<td>PD .11</td>
<td>CON 85 (2)</td>
<td>PD 103 (2)</td>
<td>CON 108 (2)</td>
</tr>
<tr>
<td>5 min</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Warm-up</td>
<td>PD 143 (5)</td>
<td>CON 142 (5)</td>
<td>PD .95</td>
<td>CON 76 (4)</td>
<td>PD 99 (4)</td>
<td>CON 102 (3)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>PD 142 (5)</td>
<td>CON 146 (5)</td>
<td>PD .62</td>
<td>CON 75 (3)</td>
<td>PD 99 (3)</td>
<td>CON 104 (3)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>PD 158 (6)*</td>
<td>CON 157 (6)</td>
<td>PD .87</td>
<td>CON 81 (4)</td>
<td>PD 108 (4)</td>
<td>CON 108 (4)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>PD 159 (7)*</td>
<td>CON 167 (6)*</td>
<td>PD .41</td>
<td>CON 81 (4)</td>
<td>PD 108 (4)</td>
<td>CON 111 (4)*</td>
</tr>
<tr>
<td>Stage 4</td>
<td>PD 18 (12)*</td>
<td>CON 179 (8)*</td>
<td>PD .96</td>
<td>CON 76 (6)</td>
<td>PD 100 (9)</td>
<td>CON 118 (6)*</td>
</tr>
<tr>
<td>Stage 5</td>
<td>- 196 (2)*</td>
<td>- - 88 (13)</td>
<td>- - 124 (9)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Peak Value</td>
<td>PD 166 (7)*</td>
<td>CON 181 (6)*</td>
<td>PD .11</td>
<td>CON 81 (4)</td>
<td>PD 107 (5)</td>
<td>CON 119 (5)</td>
</tr>
<tr>
<td>Post-Exercise</td>
<td>PD 150 (5)*</td>
<td>CON 151 (5)</td>
<td>PD .91</td>
<td>CON 80 (3)</td>
<td>PD 106 (3)</td>
<td>CON 109 (3)</td>
</tr>
<tr>
<td>(2 min)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>1 min</td>
<td>5 min</td>
<td>10 min</td>
<td></td>
<td></td>
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<tr>
<td>SBP</td>
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<tr>
<td>DBP</td>
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<tr>
<td>MAP</td>
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<tr>
<td>PD</td>
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<td>CON</td>
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<tr>
<td>SE</td>
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</tr>
</tbody>
</table>

SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; PD=Parkinson’s disease; CON=healthy control; SE=standard error of the mean; * indicates significantly different from rest, $p < .05$; † indicates significant between-group difference, $p < .05$. 
Table 6. Correlation analyses

<table>
<thead>
<tr>
<th>NE</th>
<th>CON</th>
<th></th>
<th>PD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>MAP</td>
<td>SVR</td>
<td>HR</td>
</tr>
<tr>
<td>Rest</td>
<td>.64*</td>
<td>.24</td>
<td>.16</td>
<td>.13</td>
</tr>
<tr>
<td>Exercise</td>
<td>.68*</td>
<td>-.31</td>
<td>-.30</td>
<td>.05</td>
</tr>
<tr>
<td>Peak Exercise</td>
<td>.41</td>
<td>-.41</td>
<td>-.73*</td>
<td>.34</td>
</tr>
<tr>
<td>Recovery</td>
<td>.45</td>
<td>.21</td>
<td>.15</td>
<td>.07</td>
</tr>
</tbody>
</table>

*Correlation significant at $p < .05$; data are Pearson’s correlation coefficients; NE=norepinephrine; CON=healthy controls; PD=Parkinson’s disease; HR=heart rate; MAP=mean arterial pressure; SVR=systemic vascular resistance index.