

Skeletal Muscle Pump Impairment in Parkinson's Disease: Preliminary Results

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Abstract

The purpose of this study is to investigate if impairments in leg muscle contractions affect blood pressure (BP) regulation in patients with Parkinson's disease (PD). Simultaneous BP, electrocardiogram, and bilateral electromyogram (EMG) of the tibialis anterior, lateral and medial gastrocnemius, and soleus muscles were recorded from 16 patients with PD and 12 healthy controls in supine (5 minutes), head-up tilt test (15 minutes), and standing positions (5 minutes). Convergent Cross Mapping was used to examine the causal relationship of the muscle pump baroreflex ($SBP \rightarrow EMG_{imp}$) and the effect of muscle activity on systolic blood pressure ($EMG_{imp} \rightarrow SBP$). Preliminary results showed that PD participants have less effective lower leg skeletal muscle pump compared to the control group while no difference was found in the muscle pump baroreflex. Muscle pump causality was lower for all muscles in PD patients compared to the control group. Our data suggest that PD patients show a reduced causal effect of skeletal muscle pump on blood pressure. The obtained results also highlight the impairment of the ability of muscle pump to effectively control blood pressure in PD patients. The findings of this study can assist in the development of an effective system for monitoring orthostatic tolerance via muscle pump to prevent syncope and falls in PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by its motor symptoms: tremor, rigidity, bradykinesia, and postural instability. PD also presents with numerous non-motor symptoms, including autonomic dysfunction. Dysautonomia in PD contributes to impaired functioning across multiple domains, such as the cardiovascular system. In PD, decreased heart rate

variability and baroreflex sensitivity reflect two features of poor cardiac control that can result in the clinical manifestation of orthostatic hypotension [1,2].

Orthostatic hypotension (OH) is clinically diagnosed as a drop in systolic blood pressure (BP) by 20 mmHg or diastolic BP by 10 mmHg within 3 minutes of standing from a supine or seated position. Previous research has primarily focused on autonomic cardiac control mechanisms resulting in OH in PD [3,4]. However, cardiac baroreflex mechanisms tend to be rapid in response and less effective in restoring significant declines in blood pressure. Rather, the contraction of leg muscles plays an important role in compressing blood vessels and returning pooled venous blood to the heart during standing (skeletal muscle pump [5]). Reliance on the skeletal muscles for blood pressure regulation is greater for healthy older adults compared to young adults [6], despite increased muscle atrophy with age and PD [7], making it a mechanism of interest in the study of PD. Age-related changes and muscle weakness, in combination with PD-related bradykinesia and rigidity, can potentially affect the effectiveness of the skeletal muscle pump in PD. Bradykinesia is characterized by the slowing of voluntary movement that affects the entire body (i.e., reduced facial expressions, the diminished amplitude of arm swing during walking, slower gait speed). Rigidity is characterized by stiffness of muscle tone and resistance to stretching and relaxation of muscles. Together, these motor symptoms may diminish the reactivity of the skeletal muscle pump to rapidly respond to a decline in blood pressure [8].

A cardio-postural model has been used to investigate the control loops involved in maintaining blood pressure in PD and age-matched healthy controls. A skeletal muscle pump ($EMG_{imp} \rightarrow SBP$) examines the effect skeletal muscles have on blood pressure through muscle activation. The muscle pump baroreflex ($SBP \rightarrow EMG_{imp}$) reflects skeletal muscle activation acting on blood pressure as a result of the baroreflex mechanism. We predicted that due

to age-related changes in skeletal muscles, compounded by motor and non-motor symptoms related to the disease, PD patients would show poorer muscle pump and muscle pump baroreflex activation compared to healthy controls.

2. Materials and Methods

2.1. Dataset

Data were analyzed from 16 PD patients (9 males, 7 females) and 12 healthy controls (2 males, 10 females). All data were recorded at the Sanford Health Movement Disorder Center in Fargo, ND, USA. Participants were excluded for serious neurological, cardiac, or medical conditions. Informed consent for participation was obtained from all participants, in accordance with the Declaration of Helsinki.

All participants completed the Montreal Cognitive Assessment (MOCA), Scales for Outcomes in Parkinson's disease – Autonomic Dysfunction (SCOPA-AUT), Orthostatic Hypotension Questionnaire (OHQ), and Multidimensional Fatigue Inventory (MFI). Motor symptoms were assessed in PD patients using the MDS-Unified Parkinson's disease Rating Scale, Motor Symptoms (MDS-UPDRS, III). The levodopa equivalency daily dosage (LEDD, [9]) was also obtained for all PD patients. We used a head-up tilt table to induce orthostatic challenge. Baseline readings were recorded for five minutes in supine. Participants were then tilted to 70° for 15 minutes. Following the tilt test, participants passively stood on a force platform without manipulation for at least five minutes (the first minute was removed to eliminate motion artifact during tilt-to-stand transition).

2.2. Data Acquisition

Simultaneous electrocardiogram (ECG), blood pressure (BP) using finger photoplethysmography (Finapres Nova), and electromyogram (EMG; BIOPAC) were recorded from 16 patients (age: 65 ± 5 years) with PD and 12 (age: 69 ± 6 years) healthy controls. The EMG data were obtained from the bilateral tibialis anterior (TA), lateral and medial gastrocnemius (LG, MG), and soleus (SOL) muscles. A sampling rate of 2,000 Hz was used to acquire data.

2.3. Data Processing

The last five minutes of standing data were analyzed. The R-R interval time series was defined by the time difference between two adjacent QRS complexes and then used to calculate heart rate (HR). The beat-by-beat systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated by obtaining the blood pressure maximum and minimum values between successive heartbeats. Mean

arterial pressure (MAP) was calculated using DBP and MAP as $MAP = (SBP + 2*DBP)/3$.

Beat-to-beat EMG (EMG impulse, EMG_{imp}) for individual muscles were obtained as the mean area under the rectified EMG envelope between successive heartbeats. Convergent cross-mapping (CCM) was used to provide a quantification of the level of causality between signal pairs for skeletal muscle pump ($EMG_{imp} \rightarrow SBP$) and the muscle pump baroreflex ($SBP \rightarrow EMG_{imp}$). CCM values vary between 0 and 1 with 1 indicating a stronger causality of signal X on signal Y ($X \rightarrow Y$), for methodology, see [5]).

2.4. Statistical Analysis

Test for normality of the data was conducted using the Shapiro-Wilk test at $\alpha = 0.05$. An unpaired t-test (normally distributed data) or Wilcoxon rank-sum test (data failed the normality test) was conducted to test the significance of the differences between Parkinson's disease patients and healthy controls. The test results were considered significant at $\alpha = 0.05$. Data are reported as mean (standard deviation) unless otherwise noted. All statistical tests were performed using R.

3. Results

Table 1 shows the characteristics for 16 PD patients and 12 healthy controls.

Table 1. Characteristics of the subjects considered in this study. Table lists mean (SD) and †represents significant differences between Parkinson's patients and healthy controls.

	Parkinson's Patients	Healthy Controls
Age (years)	65 (5.0)	69 (6.0)
Height (cm)	174.3 (8.6) †	163 (8.2)
Weight (kg)	89 (18.4) †	70 (8.1)
MOCA	27 (1.7)	27.7 (1.6)
SCOPA-AUT	12.7 (8.2) †	6.7 (3.7)
OHQ	6.9 (7.2)	4.4 (6.1)
MFI Total	44.5 (15.7)	37.5 (11.5)
MDS-UPDRS	23 (9.6)	--
LEDD	612.7 (353.7)	--

Averaged values of cardiovascular and musculoskeletal variables are shown in Table 2. No difference in HR ($p = 0.87$), SBP ($p = 0.45$), DBP ($p = 0.94$), MAP ($p = 0.67$), EMG_{imp} ($p = 0.65$), EMG_{imp} for MG ($p = 0.81$), and EMG_{imp} for SOL ($p = 0.23$) was observed in Parkinson's patients compared to healthy controls. However, EMG_{imp}

for LG and TA were higher in PD patients compared to healthy controls ($p = 0.04$, $p = 0.05$).

Table 2. Cardiovascular and musculoskeletal parameters for Parkinson's patients and healthy controls. Table lists mean (SD) and † represents significant differences between the two groups.

	Parkinson's Patients	Healthy Controls
HR (bpm)	85 (10.8)	85 (12.2)
SBP (mmHg)	125 (14.5)	129 (14.9)
DBP (mmHg)	84 (8.2)	84 (9.8)
MAP (mmHg)	98 (9.3)	99 (10.1)
EMG _{imp} ($\mu V \cdot s$)	82.5 (27.7)	77.5 (29.6)
EMG _{imp} (MG) ($\mu V \cdot s$)	19.3 (10.6)	20.2 (9.9)
EMG _{imp} (LG) ($\mu V \cdot s$)	16.9 (6.3) †	12.6 (4.5)
EMG _{imp} (TA) ($\mu V \cdot s$)	16 (14.8) †	9.4 (6.6)
EMG _{imp} (SOL) ($\mu V \cdot s$)	28.7 (11.9)	35.3 (15.4)

Parkinson's patients have lower skeletal muscle pump effect on blood pressure ($EMG_{imp} \rightarrow SBP$) compared to healthy controls (0.93 ± 0.04 vs 0.96 ± 0.02 , $p = 0.03$). The effectiveness of muscle contractions on pumping blood to the venous circulation and increasing blood pressure ($EMG_{imp} \rightarrow SBP$) was lower for all muscles in PD patients compared to healthy controls (MG: 0.92 ± 0.05 vs 0.96 ± 0.02 , $p = 0.04$; LG: 0.92 ± 0.05 vs 0.96 ± 0.02 , $p = 0.05$; TA: 0.93 ± 0.04 vs 0.96 ± 0.03 , $p = 0.04$; SOL: 0.93 ± 0.04 vs 0.96 ± 0.02 , $p = 0.02$) as shown in Figure 1.

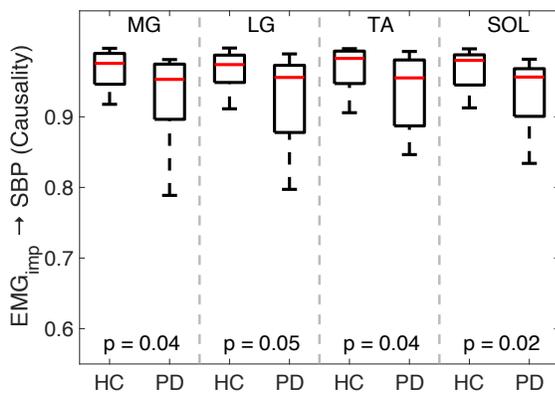


Figure 1. Effect of Parkinson's disease on muscle pump ($EMG_{imp} \rightarrow SBP$) causality for individual muscles.

No difference was found in the muscle pump baroreflex ($SBP \rightarrow EMG_{imp}$), between Parkinson's patients and healthy controls ($p=0.73$, Figure 2).

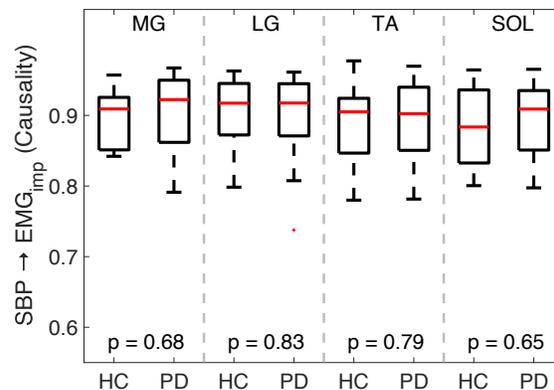


Figure 2. Effect of Parkinson's disease on muscle pump baroreflex ($SBP \rightarrow EMG_{imp}$) causality for individual muscles.

4. Discussion

Dysautonomia is a non-motor symptom prevalent in PD and contributes to poor blood pressure regulation. Previous research has focused on the role of cardiovascular control of blood pressure in PD [2-4]; however, the skeletal leg muscles also play a significant role in maintaining blood pressure during standing [5, 6]. We predicted that PD patients would show poorer skeletal muscle pump and muscle pump baroreflex activation compared to healthy controls. Poorer autonomic functioning, increased muscle weakness, and adverse motor symptoms (rigidity, bradykinesia) in PD patients would be expected to contribute to poorer effectiveness of both muscle-pump mechanisms compared to healthy controls [1-4,6,7].

Our findings supported significant differences between PD patients and healthy controls in skeletal muscle pump but not muscle pump baroreflex activation. A lack of group differences in the muscle pump baroreflex activation would suggest that this mechanism plays a limited role in the observed differences in poorer blood pressure regulation in PD patients. Rather, we found a significant difference between the groups in the mechanical skeletal-muscle pump by lower skeletal muscles (individually and together) to control blood pressure. PD patients showed less causality of the of skeletal muscle pump on BP regulation compared to healthy controls, suggesting that this difference is driven by an impaired ability of leg muscles to pump venous blood back to the heart following orthostatic challenge. This would be supported by previous research suggesting that PD patients experience increased muscle weakness compared to healthy controls [7]. Additionally, PD-related bradykinesia and rigidity may contribute to poor skeletal muscle activation in regulating blood pressure. Slower activation of the skeletal muscles (bradykinesia) and resistance of the skeletal muscles to react to the pooling of venous blood (rigidity) may drive

poorer PD-related causality of the skeletal muscle pump in regulating blood pressure following orthostatic challenge. Although no differences were observed in the contribution of individual skeletal leg muscles, rigidity has been found to be more pronounced in flexor muscles compared to extensor muscles [8].

The data presented in this paper is part of a larger project including center-of-pressure data from a force platform following an orthostatic challenge. It will be important to investigate the aforementioned blood pressure mechanisms in the context of postural stability. A cardio-postural control loop may provide an increased understanding of the multiple mechanisms contributing to poor blood pressure regulation in PD and early symptoms of orthostatic hypotension.

5. Conclusion

In this study, we investigated the causal effect of skeletal muscle pump on blood pressure regulation between PD patients and healthy controls following orthostatic challenge. Our goal was to evaluate if blood pressure regulation was being driven by the skeletal muscle pump ($EMG_{imp} \rightarrow SBP$) or by baroreflex mediated muscle pump activation ($SBP \rightarrow EMG_{imp}$). Contrary to previous research focusing solely on cardiovascular involvement and impairments in PD-related regulation of blood pressure, our findings suggest that an impaired skeletal muscle pump is a mechanism that requires additional research and attention in the PD population. Future research will focus on investigating the effect of skeletal muscle pump on postural control, in addition to blood pressure regulation.

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