Published in final edited form as:

Parkinsonism Relat Disord. 2009 November ; 15(9): 712–715. doi:10.1016/j.parkreldis.2009.03.001.

Is heart rate variability related to gait impairment in patients with Parkinson's disease? A pilot study

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Abstract

Background and Purpose—Impairments in gait and autonomic function are common in patients with Parkinson's disease (PD). These are likely independent symptoms, based on different etiologic mechanisms. However, a few recent reports have observed an association between motor function, in particular gait impairment, and autonomic function in PD. In those studies, the Unified Parkinson's Disease Rating Scale (UPDRS) was used to evaluate gait and motor function. The present study was performed to further examine this putative relationship using quantitative measures of autonomic function and gait in order to shed light on the underlying pathophysiology of these symptoms.

Methods—Nine healthy young, 15 healthy elderly and 18 PD patients were studied. Heart rate variability (HRV) measures were collected during rest. Gait speed, swing time and swing time variability were measured during a one-minute walk at comfortable speed. The motor portion of the UPDRS was also evaluated in all subjects.

Results—HRV values were highest in the young adults, intermediate in the healthy elderly controls, and lowest in the PD patients. Gait measures tended to deteriorate with age and were significantly worse in the PD patients, compared to the elderly controls. HRV was not correlated with any measure of gait performance ($p > 0.129$) nor with the UPDRS motor score ($p > 0.147$).

Discussion and Conclusions—The present findings support the idea that gait and autonomic function impairments co-exist in PD, but their etiology is based on distinct pathophysiological pathways, with minimal overlap.

Keywords

autonomic function; heart rate variability; Parkinson's disease; gait

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Authors report no conflict of interests

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INTRODUCTION

Parkinson's disease (PD) is associated with both motor symptoms and autonomic nervous system dysfunction [1]. A priori, one could suggest that while both symptoms are related to the pathology that underlies PD, the specific etiologies and pathological mechanisms that cause these symptoms are likely different and independent. Somewhat surprisingly, however, a few recent reports have found an association between autonomic function and motor function, in particular bradykinesia [2,3], hypokinesia [4] and midline motor symptoms, like gait impairment [2,5,6] in PD. In contrast, tremor [2–4,7], rigidity [2–4] and UPDRS-motor scores [5,8,9] have not been associated with autonomic function in PD, suggesting the involvement of separate pathophysiological pathways in the different motor symptoms [7]. The reported correlations between autonomic function and motor function are relatively weak (e.g., $r = 0.3$) [5], they may be related to a common source of disease severity, and these associations have not been observed consistently [2–9]. Thus, the relationship between decline in motor performance and autonomic changes remains somewhat controversial.

Autonomic function and motor function can be assessed in a variety of ways. To date, studies that have investigated the association between autonomic function and motor impairment in PD have relied on the commonly used Unified Parkinson's Disease Rating Scale (UPDRS) to assess motor function. (123)I-meta-iodobenzylguanidine (MIBG)-scanning and heart rate variability (HRV) were used to assess autonomic function. MIBG-uptake can be used to evaluate cardiac denervation as a marker of autonomic function at the level of the heart. HRV is a non-invasive, widely used measure of autonomic function which reflects the balance between the sympathetic and parasympathetic nervous systems. Typically, higher values of HRV reflect better health. Research using HRV has shown that the magnitude of the beat-to-beat fluctuations in heart rate, a measure of HRV, declines with ageing [10] and is further diminished in patients with PD, as compared to healthy elderly controls [2,4,9].

The aim of this investigation was to further examine the putative relationship between motor function, more specifically gait performance, and autonomic function changes in PD, using quantitative measures of gait and HRV as the measure of autonomic function, potentially contributing insight into the pathophysiology underlying this symptomatology and their possible relationships.

METHODS

Population

This report is based on the analysis of data collected under the DAPHNet study, a protocol investigating the dynamical analysis of physiological networks. Consecutive PD patients fulfilling the Parkinson's Disease Society Brain Bank Criteria and the following criteria were evaluated. Inclusion criteria for the PD patients also included: age between 50 and 80 years, Hoehn and Yahr stage II–IV, and use of anti-parkinsonian medications. The control group included age-matched healthy elderly subjects (50–80 years) and healthy young subjects (20–30 years).

Subjects with a history of cerebrovascular accidents, brain surgery, dementia, major depression, or traumatic head injury were excluded along with subjects suffering from diabetes mellitus or other diseases likely to influence gait. Subjects were also excluded if they used medications known to influence the autonomic system (e.g., anticholinergics, benzodiazepines, β blockers) or if they required a walking aid to ambulate.

Protocol and Analyses

The study was approved by the Helsinki committee of the Tel Aviv Sourasky Medical Center. All subjects were tested in the morning. Subjects with PD were tested in the “off” state, at least 12 hours after they took their anti-parkinsonian medications. All subjects were fitted with an ambulatory monitor that recorded the ECG and gait at a frequency of 256Hz (Mobi8-2b6a, Twente Medical Systems International). Gait was measured using insoles with four pressure-sensitive areas inserted in each shoe. The motor part of the UPDRS (part III) was used to quantify PD symptoms and the Mini Mental Status Examination (MMSE) was used as a screen for dementia and as a gross measure of cognitive function.

After providing informed written consent, data was collected during the following two periods: a supine quiet rest for 10 minutes (for HRV) and 1 minute of walking at a self-selected, comfortable pace along an 18 meter even surface. To determine HRV, a QRS-detection filter was used to remove artifacts and noise and the coefficient of variation (CV) of the heart rate was calculated using data derived from the entire 10 min resting period. The *standard deviation of the NN interval* (SDNN) was also calculated as it reflects the cyclic components responsible for variability in the period of recording and is another commonly used measure of HRV.

The high frequency (HF) component of the HRV power spectrum, reflecting the cardiac parasympathetic regulation (0.15—0.5Hz), and the low-frequency (LF) component reflecting the sympathetic modulation of the heart (0.04—0.15Hz) were computed to analyze the factors contributing to any differences in heart rate variability magnitude. LF/HF Ratio was calculated as a measure of the balance between the competing systems regulating HRV.

Temporal data from one minute of walking overground in a straight corridor was used. Gait speed was calculated based on the distance walked within one minute. Average swing time (%), a measure of dynamic balance, and swing time variability, a measure of the consistency and stability of the gait pattern previously associated with fall risk [11]. The CV was used to quantify swing time variability. For the control subjects, the average value of the right and left feet was used, since gait in healthy subjects is generally symmetrical. For the patients with PD, calculations were based on the predominantly affected side as reported by the patient and confirmed with the UPDRS, as PD typically causes an asymmetric gait. In 4 cases, footswitch data from the most affected side were not available and data from the other foot were used. The results did not change significantly when these subjects were excluded.

Statistics

Statistical analysis was performed using SPSS for Windows 15.0. Homogeneity was assessed using Levene’s test for equality of variance. In cases of skewness > 1.6, outliers were examined and if necessary removed. Between group comparisons were performed using one way-ANOVA-analysis. Pearson’s correlations analysis was used to examine the within group relationships between variables in the PD patients and elderly controls. Results were considered to be significant if $p < 0.05$. Summary measures are reported as mean $\pm$ SD.

RESULTS

Nine healthy young controls, 15 healthy elderly controls and 18 PD patients participated in the study. As mentioned above, all PD patients were taking anti-parkinsonian medications (e.g., levodopa, Amantadine, dopamine agonists, MAO-B inhibitors) at the time of the study. Subject characteristics are summarized in Table 1. As expected, UPDRS motor scores were highest in the patients with PD and lowest in the young controls.

Heart rate variability

As can be seen in Figure 1A and Table 1, HRV was lower in elderly controls, compared with young controls ($p=0.0001$). In addition, HRV was significantly lower in PD patients compared to the healthy elderly controls, as expected ($p=0.007$).

Gait

No significant differences in gait speed, swing time or swing time variability were seen between the young and elderly controls. As can be seen in Figure 1B, PD patients had a significantly lower gait speed, compared to the elderly controls (0.86 ± 0.03 vs. 1.01 ± 0.04 m/s, $p = 0.04$). Swing time variability was also significantly higher ($p=0.026$) in the PD patients (5.54 ± 4.52 %), compared to elderly controls (2.94 ± 1.45 %).

Correlations between gait and HRV

Among the elderly controls, HRV measures (i.e., CV, SDNN, and the LF/HF ratio) were not significantly correlated with swing time, swing time variability, gait speed, or UPDRS motor-scores ($p>0.250$, $r=-0.33$ – -0.35). Similarly, among the patients with PD, significant associations between HRV measures, on the one hand, and gait and UPDRS-motor scores, on the other, were not observed. The closest correlation was observed between HRV CV and swing time average ($r = -0.42$, $p>0.12$); note, the negative sign indicates an inverse relationship. Similar results were found when using Spearman correlations. Interestingly, at the same time, gait measures and UPDRS-motor scores were significantly correlated with each other among the PD patients (e.g., gait speed was correlated with UPDRS-motor score $r = -0.54$, $p=0.02$).

DISCUSSION

Our findings are consistent with previous research which demonstrated a decline in HRV due to ageing [10] and an even further decline in patients with PD [2,4,9]. The magnitude of the HRV estimated during ten minutes of supine rest was different in the three groups. In addition, the results are also consistent with previous research which found reduced gait speed and increased gait variability in patients with PD [12]. Although PD gait and HRV were both altered in PD, associations between HRV, on the one hand, and gait and UPDRS-motor performance, on the other, were not observed.

Our results support previous studies which found no association between autonomic function and the UPDRS-motor scores [4,8,9] and stand in contrast to other reports which demonstrated an association between autonomic nervous system function and motor symptoms in PD [2,5, 6]. In those studies, an association was shown between autonomic function, measured by MIBG-scanning and HRV, and midline motor symptoms, such as gait disturbances. Patients with more autonomic dysfunction tended to have more gait impairment. Motor function including gait performance was solely assessed by using UPDRS-subscales in these studies. In the present study, quantitative gait measures were used to assess gait performance and no significant correlations were observed. Perhaps, the quantitative measures of gait more accurately reflect the motor impairment, and thus, show different behavior.

In addition, in some of the previous studies, autonomic function was assessed by MIBG-uptake. MIBG-uptake is a measure of the function of the sympathetic nervous system, whereas HRV reflects the balance between the sympathetic and parasympathetic nervous systems. This could have contributed to the discrepancies seen when comparing the present study with earlier research. In addition, since PD patients included in our study were not taking beta-blockers or other cardiac medications, the group was relatively healthy and homogeneous from a cardiac perspective, possibly minimizing within group heterogeneity and the possibility of a significant

association between motor and autonomic measures. However, HRV was still different compared to controls, suggesting that this explanation is not likely.

Another possible explanation for the apparent discrepancy could be the limited sample size of the present study, however, given that any trends observed were in the direction opposite to that linking HRV to gait, this possibility is less likely. Supporting this is the fact that gait measures were significantly worse in the PD patients and were significantly associated with disease severity as measured by UPDRS-motor scores. These findings suggest that the sample size might not be the determining factor for the lack of any significant relationships between HRV and gait. Another explanation for the absence of any significant HRV-gait correlations may be related to the fact that the HRV-measures were based on 10 minutes of supine rest. In the future, tests of other aspects of HRV (e.g., valsalva, fixed respiration or long-term recordings) may identify other autonomic features not captured in the present study. Perhaps these may be more sensitive and may be related to gait. Still, the HRV measures used in the present study were sufficiently sensitive to identify group differences, supporting the idea that lack of any significant associations between HRV and gait was not a false negative finding related to the HRV method utilized in the present study.

Since degeneration is present in both the substantia nigra and the autonomic plexus in PD [1], our results might reflect the distinct pathophysiological pathways leading to degeneration in these separate anatomical locations. Furthermore, the observation in previous studies that some motor symptoms seem to be correlated with autonomic function, whereas others do not, suggests that even in the spectrum of motor symptoms multiple pathophysiological pathways might be involved.

In conclusion, the present findings do not support the idea that autonomic dysfunction and gait disorders in PD are based on a common, related mutual pathophysiology. Instead, they suggest that distinct mechanisms contribute to the deterioration of these two neurally controlled systems. Autonomic dysfunction (decrease in heart rate variability) and motor (gait) impairment apparently proceed along independent etiologic pathways or at least at different rates in PD. Nonetheless, additional work is needed to further unravel the underlying pathophysiology of autonomic dysfunction and gait alterations in PD.

Acknowledgments

The authors are grateful for the invaluable assistance of A. Weiss, N. Inbar, M. Plotnik, and I. Maiden. BB was supported by a Novo-Vidi grant. MA received a grant from the Huygens Scholarship Programme. NS was supported by the Hersenstichting Nederland. This work was supported in part by the European Commission in the context of the FP6 projects SENSATION-AAL, INFOS-IST-045622 and FET, 018474-2, DAPHNet.

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1.a

1.b

1.c

Figure 1.

A) HRV, specifically the coefficient of variation (%), in the patients with PD and the two control groups. B) Gait speed (m/s) in the patients with PD patients and the two control groups. C): Scatter plot showing the relationship between HRV and gait speed in PD patients and elderly controls. Among the elderly subjects, the Pearson correlation coefficient between HRV and gait speed was $r = 0.16$ ($p=0.40$). Among the patients with PD, the correlation coefficient was $r = -0.36$ ($p=0.20$). The negative sign suggests that if there is any association, higher values of HRV are associated with lower gait speeds in PD. In A) and B), the asterisk indicates significant differences from the elderly control group.

Table 1

Characteristics of the study population

Characteristics	PD patients (n=18)	Elderly controls (n=15)	Young controls (n=9)
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>
Age (years)	65.2 (5.9)	66.9 (9.7)	24.4 (2.5) *
Gender (% male)	66.7	40.0	77.8
Mini Mental State Exam (MMSE / 30)	28.2 (1.6) *	29.6 (0.51)	30.0 (0) *
Average heart rate (bpm)	69.7 (13.5)	70.7 (12.5)	75.5 (13.6)
Heart Rate Variability-CV (%)	2.07 (1.02) *	3.74 (1.97)	6.6 (1.6) *
Standard deviation of the N-N interval, SDNN (msec)	25 (18) *	38 (25)	54 (15)
Low / High Frequency Ratio	8.18 (6.21)	8.41 (6.77)	5.78 (4.16)
UPDRS motor score	28.6 (10.7) *	1.8 (0.8)	1.2 (1.2)
UPDRS total score	52.11 (18.3)		
Disease duration (years)	8.8 (7.0)		
Affected side	50.0% Lt. 33.3% Rt. 16.7% Sym.		

* significantly different from elderly controls