The Association of Heart Rate Variability with Parkinsonian Motor Symptom Duration

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Purpose: Impaired cardiovascular autonomic regulation is a non-motor symptom of Parkinson’s disease (PD) and may increase long-term morbidity. This study applied frequency-domain analysis of heart rate variability (HRV) to understand the progression of sympathetic and parasympathetic cardiac regulation in patients with PD. Materials and Methods: In this cross-sectional study, 21 male and 11 female Taiwanese patients with advanced PD and 32 healthy gender- and age-matched subjects were enrolled. To minimize artifacts due to subject motion, daytime electrocardiograms for 5 minutes were recorded in awake patients during levodopa-on periods and controls. Using fast Fourier transformation, heart rate variables were quantified into a high-frequency power component [0.15-0.45 Hz, considered to reflect vagal (parasympathetic) regulation], low-frequency power component (0.04-0.15 Hz, reflecting mixed sympathetic and parasympathetic regulation), and low-frequency power in normalized units (reflecting sympathetic regulation). The significance of between-group differences was analyzed using the paired t-test. Pearson correlation analysis and stepwise regression analysis were applied to assess the correlation of patient age, PD duration, and disease severity (represented by the Unified Parkinson’s Disease Rating Scale) with each heart rate variables. Results: Impaired HRV is significantly correlated with the duration of PD, but not with disease severity and patient age. Meanwhile, parasympathetic heart rate variable is more likely than sympathetic heart rate variable to be affected by PD. Conclusion: PD is more likely to affect cardiac parasympathetic regulation than sympathetic regulation by time and the heart rate variables have the association with Parkinsonian motor symptom duration.

Key Words: Autonomic, heart rate variability, Parkinson’s disease

INTRODUCTION

Cardiovascular autonomic regulation has been reported to be impaired in Parkinson’s disease (PD) and may increase the long-term morbidity of patients with this disease.1-3 Moreover, the deterioration of functional performance in Parkinsonian patients with impaired autonomic function may be more rapid, and these patients prob-
ably require higher dosage of levodopa supplementation.

Heart rate change is primarily determined by cardiac autonomic regulation. Heart rate variability (HRV) is defined by irregularities in the interval between normal sinus beats. Frequency-domain analysis of HRV is a sophisticated and non-invasive tool for studying sympathetic and parasympathetic regulation of heart rate. The standard procedures and interpretation of HRV analysis were first reported in 1996. We have applied a modification of these procedures to investigate cardiac autonomic dysregulation in children with epilepsy. In this case-control study on a cohort of patients with advanced PD, we used the same technology to investigate the changes of HRV in adult Parkinsonian patients.

**MATERIALS AND METHODS**

**Study population**

We enrolled 32 Taiwanese patients with PD (21 male and 11 female; mean age: 62.2 years, range: 44-79 years), who planned to be treated by subthalamic deep brain stimulation at the Buddhist Hualien Tzu Chi General Hospital, Taiwan (Table 1). All patients met the clinical criteria for PD that at least two of the cardinal symptoms are present. The core assessment program including an acute levodopa test to measure the effects of levodopa on PD was used in all patients. The following was assessed: Unified Parkinson’s Disease Rating Scale (UPDRS) score, behavior from videotaped clips, Hoehn and Yahr (H-Y) stage, timing of rapid alternating movements, the time required to walk a distance of 7 meters, tremorography, cognitive performance (the Mini-Mental State Examination score), and brain magnetic resonance imaging images.

For ruling out the autonomic deterioration from other medical issues, none of the enrolled patients had evidence of arrhythmia, ischemic heart disease, heart failure, diabetes mellitus, multiple system atrophy, pure autonomic failure, PD with dementia as well as Parkinsonism with other brain diseases, such as traumatic brain injury or stroke. Patients who were taking propranolol or atenolol were also excluded because of the sympatholytic effects of such medications. Thirty-two age- and gender-matched healthy subjects were enrolled as the control group. The study protocol was approved by the Institutional Review Board of the Buddhist Tzu Chi General Hospital. All of the subjects gave their written informed consent at enrollment.

**Heart rate recording and frequency-domain analysis of HRV**

Since many muscle tremors would be recorded in a Parkinsonian patient during a long-term heart rate recording, especially in the levodopa-off period (without levodopa or dopamine agonist, etc. for at least 12 hours), daytime electrocardiograms (ECG) for 5 min were recorded in awake patients during levodopa-on periods (with levodopa use). Each subject lay quietly in a comfortable head-up 45-degree position during the heart rate recording. Lead I ECG signals were recorded using an analog-to-digital converter.

**Table 1. Clinical Features and Heart Rate Variables of Age- and Sex-Matched PD and Control Groups**

|                     | PD               | Control          | p value |
|---------------------|------------------|------------------|---------|
| RR (ms)             | 823.50±27.054    | 809.96±16.839    | 0.929   |
| LF [ln (ms²)]       | 4.22±0.266       | 4.89±0.128       | 0.029*  |
| LF decline rate      | -0.140           | -0.005           |         |
| HF [ln (ms²)]       | 3.46±0.309       | 4.32±0.125       | 0.014*  |
| HF decline rate      | -0.159           | -0.065           |         |
| LF% (nu)            | 51.96±3.557      | 50.38±3.196      | 0.736   |
| LF% decline rate     | +0.017           | +1.081           |         |
| PD duration (yr)    | 9.81±0.692       |                  |         |
| UPDRS-off (point)   | 75±4.279         |                  |         |
| UPDRS-on (point)    | 48.15±3.03       |                  |         |
| H-Y-off (grade)     | 3.20±0.136       |                  |         |
| H-Y-on (grade)      | 2.71±0.108       |                  |         |
| LEDD (point)        | 935.73±89.667    |                  |         |

RR, interval between two neighboring R waves; LF, low frequency power; HF, high frequency power; LF%, LF/(HF+LF) in normalized units; PD, Parkinson’s disease; UPDRS-off, Unified Parkinson’s Disease Rating Scale in levodopa-off period; UPDRS-on, Unified Parkinson’s Disease Rating Scale in levodopa-on period; H-Y-off, Hoehn and Yahr stage in levodopa-off period; H-Y-on, Hoehn and Yahr stage in levodopa-on period; LEDD, levodopa equivalent daily dose. *p<0.05.

The estimated change of value/year of duration.

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with a sampling rate of 512 Hz. Frequency-domain analysis was performed using a nonparametric method of fast Fourier transformation (FFT). The direct current component was deleted and a Hamming window was used to attenuate the leakage effect. For each time segment (288 s; 2048 data points), our algorithm estimated the power spectrum density on the basis of FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling process and the use of a Hamming window.\(^\text{10}\) The power spectrum was subsequently quantified into standard frequency-domain measurements as defined by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. The frequency-domain measurements included R-R intervals (the intervals between two neighboring R waves, RR) and heart rate variables: high-frequency power (0.15-0.45 Hz, HF), low-frequency power (0.04-0.15 Hz, LF), and LF% [LF/(HF+LF)] in normalized units. The HF and LF data were logarithmically transformed to correct for any skew in the distribution. The LF reflected contributions from mixed sympathetic and parasympathetic divisions. The HF was considered to reflect vagal (parasympathetic) regulation and the LF% was considered to mirror sympathetic regulation.\(^\text{6,7,10}\)

### Statistical analysis

All measures are presented as the mean and standard error (SE) of the mean. Differences in clinical features and heart rate variables between the matched PD and control groups were analyzed by the paired t-test. Pearson correlation coefficient (r) was used to measure correlations of patient age, PD duration, and disease severity (represented by UPDRS score in levodopa-off period, UPDRS-off) with heart rate variables including LF, HF, and LF%. Stepwise regression analysis was conducted to identify those factors associated with heart rate variables. All analyses were performed using SPSS (now called PASW) version 17.0 (SPSS Inc., Chicago, IL, USA) and statistical assessments were evaluated at the 0.05 level of significance.

### RESULTS

Table 1 demonstrated that the PD group had 9.813±0.692 years (mean±SE) in the duration of disease. The UPDRS scores and H-Y stages of the PD group were: 75±4.279 in UPDRS-off, 48.156±3.03 in UPDRS-on, 3.203±0.136 in H-Y-off, and 2.719±0.108 in H-Y-on. Differences in LF and HF values between PD and control groups were significant. The PD group had significantly lower LF [4.222±0.266 ln (ms\(^2\)) vs. 4.898±0.128 ln (ms\(^2\)), \(p=0.028\)] and lower HF [3.469±0.309 ln (ms\(^2\)) vs. 4.320±0.125 ln (ms\(^2\)), \(p=0.029\)] when compared to the age- and gender-matched control group. In the patient group, Pearson correlation analysis revealed that the rate of LF decline significantly correlated with PD duration (\(r=-0.364, p=0.041\)) but not with disease severity (UPDRS-off) and patient age (Fig. 1, Table 2). Similarly, the results indicated that lower HF was correlated with longer PD duration (\(r=-0.356, p=0.046\)). After adjustment for possible confounders, a stepwise regression using age, gender, PD duration, and UPDRS-off score still found significant correlation of heart rate variables such as LF and HF with long PD duration (Table 3). Furthermore, the results indicated that the duration of PD explained 13.3% and 12.7% of the variance in LF and HF measures, respectively. No variables were significantly correlated with the LF%. Meanwhile, increase in UPDRS-off was significantly correlated with PD duration with a slope of 2.578 points per year.

### DISCUSSION

Cardiovascular autonomic dysregulation in PD has been attributed to either central or peripheral autonomic regulatory impairment,\(^\text{11-14}\) involving the hypothalamus, insular cortex, locus coeruleus, dorsal motor nucleus of the vagus, intermediolateral nucleus of the thoracic cord, sympathetic ganglia, and sacral parasympathetic nuclei. Thus, PD affects both sympathetic and parasympathetic divisions, each of which can be evaluated by frequency-domain analysis of HRV.\(^\text{4-7}\) In this study, although the sympathetic indicator of autonomic cardiac regulation, LF%, was not significantly changed, the total and parasympathetic indicators (LF and HF) decreased significantly and correlated with disease duration. Some previous studies reported that levodopa replacement in Parkinsonian patients could decrease central sympathetic outflow, an unusual effect caused by the central D2 agonist action of levodopa.\(^\text{15,16}\) Based on it, some authors recommended monoamine oxidase B inhibitors to avoid the effect of levodopa on sympathetic regulation.\(^\text{17}\) We thought that the discordant changes in autonomic sympathetic and parasympathetic divisions in our results might stem from the effects of levodopa treatment and leave the cardiac parasympathetic dysregulation being more sensitive in the HRV study.
PD is not a rare degenerative disorder in aged population. However, aged people usually suffer from multiple degenerative diseases and many of those might affect the cardiovascular autonomic regulation. In this study with focus on pure PD itself, we excluded the patients with cardiac arrhythmia, ischemic heart disease, heart failure, diabetes mellitus, mul-

| Table 2. Correlations of LF, HF, and LF% with Patient Age, PD Duration and UPDRS-Off Score |
|---------------------------------|---------------------------------|---------------------------------|
|                                | Age (year)                      | PD duration (year)              | UPDRS-off (point)              |
|--------------------------------|---------------------------------|---------------------------------|---------------------------------|
| LF                             | Pearson correlation             | -0.059                          | -0.364                          | -0.279                          |
|                                | p value                         | 0.749                           | 0.041*                          | 0.122                           |
| HF                             | Pearson correlation             | 0.004                           | -0.356                          | -0.142                          |
|                                | p value                         | 0.981                           | 0.046*                          | 0.437                           |
| LF%                            | Pearson correlation             | -0.133                          | 0.003                           | -0.213                          |
|                                | p value                         | 0.468                           | 0.986                           | 0.241                           |

LF, low frequency power; HF, high frequency power; LF%, LF/(HF+LF) in normalized units; PD, Parkinson’s disease; UPDRS-off, Unified Parkinson’s Disease Rating Scale in levodopa-off period. *p<0.05.
In conclusion, PD is more likely to affect cardiac parasympathetic regulation than sympathetic regulation by time, and the heart rate variables have the association with Parkinsonian motor symptom duration.

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