Association of heart rate variability with clinical outcome in Parkinsonian patients after subthalamic deep brain stimulation: A retrospective cohort study

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Background/Purpose: Lower sympathetic and parasympathetic function increases the morbidity in Parkinsonian patients. We conducted this retrospective study to elucidate the effect of subthalamic deep brain stimulation (STN-DBS) on autonomic cardiovascular regulation of patients with Parkinson's disease.

Methods: Twelve men and four women with advanced Parkinson's disease (mean age: 63 years) who underwent bilateral STN-DBS were followed up for 9–32 months. Daytime electrocardiography for 5 minutes and rating scores were recorded before and after surgery. Good response was defined as improvement >50% in the Unified Parkinson's Disease Rating Scale (UPDRS), and a fair response as improvement between 10% and 50% after surgery. Digitalized electrocardiography signals such as high-frequency power [HF; 0.15–0.45 Hz, to reflect vagal (parasympathetic) regulation], low-frequency power (LF; 0.04–0.15 Hz, contributed from mixed sympathetic and parasympathetic divisions), and the fraction of LF/(HF + LF) in normalized units (LF%, to reflect sympathetic regulation) were transformed with fast Fourier transformation to power spectrum and heart rate variables.

Results: Six male and two female patients were good responders and the others were fair responders. There were no significant differences in height, weight, duration of disease, levodopa equivalent daily dose, preoperative and postoperative UPDRS, and DBS-off and levodopa-off UPDRS between the good and fair response groups. There were no significant differences between the good and fair response groups for preoperative heart rate interval, LF values, LF% values, and HF values. Compared with preoperative values, the good response
group showed a significant increase in LF but not in heart rate, LF%, and HF after surgery. In contrast, the fair response group showed no significant change in all heart rate variables postoperatively.

Conclusion: Our study showed an improvement in autonomic cardiovascular regulation in Parkinsonian patients with >50% improvement in rating scale after STN-DBS, which implied morbidity reduction in nonmotor symptoms among such patients.

Introduction

Impaired autonomic cardiovascular regulation, with lower sympathetic and parasympathetic function, has been reported in patients with Parkinson’s disease (PD), which is a nonmotor symptom of PD and increases a long-term morbidity in patients.1–3 Parkinsonian patients with impaired autonomic function experience a more rapid deterioration in functional performance; therefore, treatment of these patients may require earlier levodopa supplementation or increased dosage.3 In addition to pharmacological treatment, subthalamic nucleus deep brain stimulation (STN-DBS) is an effective modality for treating advanced PD.4 We have previously shown that patients can achieve significant improvement in the Unified PD Rating Scale (UPDRS) and reduction in levodopa equivalent daily dose (LEDD) scores after STN-DBS.5

Kaufmann et al have reported increasing heart rate in Parkinsonian patients after STN-DBS, although sympathetic or parasympathetic indicators were not examined in a long-term follow-up study.6 Frequency-domain analysis of heart rate variability (HRV) is a sophisticated and noninvasive tool for studying neural regulation of the heart rate. The standard procedures and interpretation of HRV analysis were first reported in 1996.7 We have applied a modification of these procedures to investigate autonomic cardiovascular regulation in aging and epilepsy patients.8,9 In this retrospective study of a cohort of Parkinsonian patients with bilateral STN-DBS, we used the same technology to investigate the long-term effect of STN-DBS on autonomic cardiovascular regulation.

Patients and methods

Patients and controls

We consecutively enrolled 12 male and 4 female patients with advanced PD (mean age: 63 years, range: 47–79 years), who underwent bilateral STN-DBS and were followed up for 9–32 months (mean: 18.88 months) postoperatively. All patients met the clinical criteria for PD before surgery, in that at least two of the cardinal symptoms were present. The core assessment program was used for all patients, including an acute levodopa test to measure the effect of levodopa on the UPDRS.10 The following assessments were made: behavior was videotaped, Hoehn and Yahr stage was assessed, rapid alternating movements were time tested, walking was assessed as the time required to walk a distance of 7 m, a tremorography test was performed, the Mini-Mental State Examination was administered, and morphological imaging was acquired with magnetic resonance imaging (MRI).

None of these patients had evidence of arrhythmia, diabetes mellitus, multiple system atrophy, or pure autonomic failure. Patients who were taking propranolol or atenolol were excluded from this study because of the sympatholytic effects of such medications. The Ethical Committee of the Tzu Chi University and Hospital approved this study. All of the patients gave their informed consent at enrollment.

Surgical procedures

We used MRI and microelectrode recording to target the STN.5 The standard MRI (General Electric, 1.5 T; Milwaukee, WI, USA) settings were 0.75-mm thickness for T1W axial images, 2-mm thickness for T2W axial images, and 3-mm thickness for T2W coronal images. All images were taken on contiguous slices. The images were transferred into the Digital Imaging and Communications in Medicine database and to the BrainLab Vector-Vision (Westchester, IL, USA) neuronavigation workstation for three-dimensional reconstruction. The tentative surgical target coordinates for the tip of the permanent implantable electrode were set at the lowest central border of the STN by direct visualization on MR images. On the axial slice, this location was about 1–2 mm lateral of the red nucleus at the level of the superior colliculus of the midbrain. A Leksell G-frame (Elekta Instruments, Atlanta, GA, USA) was used for the stereotactic procedure. The electrodes were implanted under fluoroscopic guidance after the microelectrode recording procedures. Stereotactic intraoperative fluoroscopy was used for the guidance to achieve final electrode position. The final electrode coordinates were confirmed by MRI within 3 months postoperatively. The details of the surgical procedures have been published previously.5

Two weeks after surgery, we started STN-DBS with a frequency of 130 Hz, pulse width of 60 microseconds and amplitude of 0.5 V. The amplitude of DBS in each patient was gradually increased upon the response of the patient’s motor symptoms, and with maximal amplitude of 4 V.

Outcome assessment of STN-DBS

After surgery, we conducted follow-up visits with the patients at regular intervals and compared the follow-up rating scores and LEDD with the preoperative baseline drug-off measures (without levodopa for at least 12 hours). On follow-up examinations, UPDRS scores were recorded during the periods of DBS-on and DBS-off, both under the condition of drug-off. The effect of STN-DBS was defined as
the UPDRS improvement rate in normalized units, which was determined by comparing the score of DBS-on, drug-off to the preoperative drug-off score. Patient outcome was defined as good response if the improvement rate was >50% and fair if the improvement rate was between 10% and 50% after STN-DBS.

Heart rate recording and frequency-domain analysis of HRV

Many muscle tremors are recorded in a patient during drug-off periods; daytime electrocardiograms (ECGs) for 5 minutes were recorded in drug-on periods before surgery and in DBS-on and drug-on periods at follow-up for comparison. Each awake patient lay in a quiet and comfortable head-up 45-degree posture during heart rate recording. Lead I ECG signals were recorded using an analog-to-digital converter with a sampling rate of 512 Hz. Frequency-domain analysis was performed using a nonparametric method of fast Fourier transformation. The direct current component was deleted and a Hamming window was used to attenuate the leakage effect. For each time segment (288 seconds; 2048 data points), our algorithm estimated the power spectrum density on the basis of fast Fourier transformation. The resultant power spectrum was corrected for attenuation that resulted from the sampling and the Hamming window.9 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. These included the R-R intervals (the intervals between two neighboring R waves, RR), high-frequency power (HF; 0.15–0.45 Hz), low-frequency power (LF; 0.04–0.15 Hz), 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 was contributed from mixed sympathetic and parasympathetic divisions. The HF was considered to reflect vagal (parasympathetic) regulation, and the LF% was considered to mirror sympathetic regulation.7–9

Statistical analysis

Data are presented as mean ± standard error. The significance of differences between good and fair response groups was analyzed using Student t test. Paired t tests were performed for comparisons between preoperative and postoperative values in the same group of patients. All statistical assessments were evaluated at the 0.05 level of significant difference.

Results

Clinical outcome of STN-DBS

At the end of our follow-up study, six male and two female patients were categorized as good responders (63.13 ± 2.28% improvement of UPDRS), whereas the other six male and two female patients were categorized as fair responders (30.59 ± 3.53% improvement of UPDRS, p < 0.001) (Table 1). There were no significant difference in height, weight, duration of PD, LDED, preoperative and postoperative UPDRS, and DBS-off and drug-off UPDRS between good and fair response groups (Table 1). Compared with the fair response group, the good response group had significantly lower UPDRS scores during the postoperative DBS-on and drug-off period (33.63 ± 3.55 vs. 47.75 ± 3.01, p = 0.009).

One female patient in the fair response group who could not tolerate the discomfort of DBS-off symptoms at the end of 25 months follow-up refused to undergo assessment of postoperative LDED and DBS-off, drug-off UPDRS values.

Heart rate and heart rate variables after STN-DBS

There was no significant difference between fair and good response groups for preoperative RR, LF, LF%, and HF values. Figure 1 demonstrates changes in heart rate variables before and after STN-DBS. Compared with preoperative values, the good response group showed a significant increase in LF (5.04 ± 0.36 ln[ms²] vs. 3.95 ± 0.39 ln[ms²], p = 0.026), but not in RR, LF%, and HF values, after surgery. In contrast, the fair response group showed no significant change in heart rate variables postoperatively compared with preoperative values.

When we analyzed the changes (values after STN-DBS – values before STN-DBS) in heart rate and variables, there was no significant difference between fair and good response groups (RR, p = 0.17; LF, p = 0.18; LF%, p = 0.88; HF, p = 0.089).

Discussion

Although STN-DBS has been a promising treatment option for advanced PD for more than a decade, it has remained unclear what long-term neurophysiological changes in the autonomic nervous system occur. The typical stimulation paradigm for STN-DBS includes sustained high-frequency (usually > 100 Hz) and high-voltage (usually > 1 V) stimulation. Some studies have found that the tetanic stimulation silences subthalamic neurons during this treatment.12,13 An anatomical study has revealed the connections between the subthalamic nucleus and hypothalamus,14 which is known as an autonomic regulatory region. Although the STN—hypothalamus connection has been documented, the detailed communication and interaction between these two deep brain structures are not yet clear. Combining these with our results, long-term stimulation might silences the subthalamus and interacts with central autonomic regulatory regions to cause a significant increase in HRV among patients with prominent or good response to STN-DBS. It implies that STN-DBS has a morbidity reduction effect on autonomic cardiovascular regulation, which is a nonmotor symptom in these patients.

In this study, we observed 16 Parkinsonian patients with STN-DBS for a mean duration of 18.88 months. There was no long-term change in heart rate or RR interval at the end of follow-up study for either fair or good response patients when compared with a previous short-term report of increasing heart rate with STN-DBS.6 This reveals that cardiovascular regulation may be more prominently influenced by STN-DBS in the short-term, whereas the long-term
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Data are presented as mean ± SE. Improvement by STN-DBS = (UPRDS (Pre-op, Drug-off) – UPRDS (Post-op, DBS-on, Drug-off))/UPRDS (Pre-op, Drug-off) in normalized units.

*A p value < 0.05, Student t test, good response group versus fair response group.

F = female; LEDD = levodopa equivalent daily dose; M = male; PD = Parkinson’s disease; Post-op = postoperative; Pre-op = preoperative; SE = standard error; STN-DBS = subthalamic deep brain stimulation; UPDRS = Unified Parkinson’s Disease Rating Scale.
changes may be less significant, and need careful investi-
gation to identify.

STN-DBS has been well documented to improve patients’
daily performance in many studies, as measured by the
rating scores of PD.4,5,11 From these studies, the average
improvement rates of UPDRS were usually 40–50% after
STN-DBS. Based on previous reports, we defined the good
response rate to be >50% in the present study. However, to
date, there is no universal standard to define good, fair, or
poor improvement after STN-DBS in Parkinsonian patients.

A previous study revealed no change in heart rate
variables in 14 Parkinsonian patients with STN-DBS during
a 12-month follow-up.15 Gentil et al have reported signifi-
cant improvement in respiratory function after STN-DBS.16
Their results have suggested that autonomic function of
visceral organs is increased by STN-DBS, which inspired us
to analyze our data from a different viewpoint than in
previous studies. In our preliminary analysis of follow-up
data, we also found no significant difference in heart rate
variables when we analyzed pooled data of all patients.
However, if we separated the patients into good and fair
responders to STN-DBS, we found a significant increase in
LF among the good responders. Although we did not find
significant changes in the sympathetic indicator, LF%, and

Figure 1. Changes of RR, LF, LF% \([LF/(HF+LF)]\) in normalized units], and HF after subthalamic deep brain stimulation relative to
preoperative values. Data are presented as mean ± standard error. *A p value <0.05, paired t test. The good response group
showed significant increase in LF \([p = 0.026]\) but not in RR, LF%, and HF. The fair response group showed no significant change in
heart rate variables. HF = high-frequency power; LF = low-frequency power; Post-op = postoperative; Pre-op = preoperative.
the parasympathetic indicator, HF, probably because of a limited number of follow-up patients. We believe that the analysis in a larger group of patients in the future could help to elucidate the details of the effects of STN-DBS on autonomic function.

Autonomic cardiovascular dysregulation in PD has been documented in central and peripheral autonomic regulatory regions. In addition to the hypothalamus, the insular cortex, the dorsal motor nucleus of the vagus, the intermediolateral nucleus of the thoracic cord, sympathetic ganglia, and the sacral parasympathetic nuclei have been found to be affected by PD. Either sympathetic or parasympathetic division could be affected by PD, and these two divisions can be individually studied by frequency-domain analysis of HRV. However, the change in autonomic cardiovascular regulation may come from the effects of different dosages of anti-Parkinsonian medications. In previous studies, levodopa could induce negative effects on autonomic function by decreasing central sympathetic outflow, which was caused by the central D2 agonist action. The selective inhibitor of monoamine oxidase, selegiline, can diminish sympathetic activity. In contrast, the catechol-O-methyltransferase inhibitor tolcapone does not influence autonomic cardiovascular regulation after 6 months of treatment. In patients with advanced PD, treatment with a combination of anti-Parkinsonian medications is usually given, and it would be a confounding factor for studying autonomic function of patients. In this study, we observed that the good response group had a reduction of LEDD from 911.89 ± 145.66 to 386.41 ± 57.79 and the fair response group had a reduction from 910.55 ± 136.71 to 410.36 ± 100.49 postoperatively. Because there was no significant difference in LEDD between the two groups pre- and postoperatively, the observed change in heart rate variables was considered to be caused by STN-DBS alone.

HRV could physiologically vary widely, even in healthy individuals, possibly due to the effects of circadian rhythms, sex, age, weight, or body mass index. In the present study, all heart rate variables were recorded and analyzed during daytime to avoid major circadian effects. Obtaining recordings and heart rate variables before and after STN-DBS in the same patients with the same posture can minimize interindividual anthropometric and posture-confounding effects. We planned to study the effects of STN-DBS on HRV over time; therefore, changes in body weight or body mass index in any patient could not be avoided. However, we believe that our study may be accurate with regard to showing the long-term effects of STN-DBS on HRV.

HRV can be studied using 5-minute, 10-minute, or 24-hour ECG recording with heart rate measured by frequency-domain analysis of HRV in a single patient. A 24-hour ECG recording can provide circadian changes in HRV and is considered to be the standard procedure. However, a 5- or 10-minute ECG recording is highly assessable and correlated with a 24-hour recording, and a positive result suggests a 24-hour recording of ECG with analysis of circadian changes of HRV in patients.

In STN-DBS treated Parkinsonian patients, we found significantly increased LF of HRV in patients with >50% improvement in UPDRS scores. These findings suggest an association of improvement in autonomic cardiovascular regulation and good response to STN-DBS, which imply probable morbidity reduction in nonmotor symptoms among such patients with STN-DBS.

Acknowledgment

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References


