ΔHR/ΔWR derived from CPET; A novel predictor of 'off' symptom in Parkinson's disease

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(Citation)
Parkinsonism & Related Disorders,92:101-104

(Issue Date)
2021-11-02

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/0100485977

Title page

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Word count: 1894 words not including abstract and references.

Running head: ΔHR/ΔWR; a predictor of 'off' symptom in PD

Conflict of Interests: The authors declare that there is no conflict of interests regarding the publication of this article.

Key words: Parkinson's disease, Wearing-off and on-off symptom, Chronotropic incompetence, Cardiopulmonary Exercise Testing (CPET), The Unified Parkinson's Disease Rating Scale (UPDRS).

Abstract

Introduction; Chronotropic incompetence (CI) is broadly defined as the inability of the heart to increase its rate commensurate with increased activity. In this study, we tried to clarify the link between CI and UPDRS part II (off-on), which was calculated by subtracting part II (on) from part II (off), in patients with Parkinson's disease (PD).

Methods; Thirty-six hospitalized patients were examined by using cardiopulmonary exercise testing (CPET) for exercise tolerance (ΔVO2/ΔWR and peak VO2/W) and the presence of CI (ΔHR/ΔWR), and using electrocardiogram for heart rate variability.

Results; We originally divided the patients into three groups; Group I (ΔHR/ΔWR x100 <15) (N=3), Group II (15≥, <60) (N=28), Group III (>60) (N=5). Since Group I and III were significantly smaller and older than Group II, we focused and divided into two groups; Group II CI (+), the PD patients with CI (15≤ ΔHR/ΔWR x100 <35), and Group II CI (-), those patients without that (35≤ ΔHR/ΔWR x100 <60). ΔVO2/ΔWR and peak VO2/W in CI (+) patients was lower than CI (-) (P=0.022 and P=0.096, respectively). HF power (parasympathetic activity) tends to be decreased, whereas LF/HF ratio (sympathetic activity) was increased in CI (+) patients as compared with CI (-). The UPDRS part II (off-on) of CI (+) patients was significantly higher than CI (-) (P=0.023).

Conclusions; In PD patients, the difference between 'on' and 'off' in activities of daily living might be predicted by using ΔHR/ΔWR x100 obtained by CPET as an index.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which impairs motor function including rest tremor, bradykinesia, rigidity and loss of postural reflexes, and non-motor function including autonomic dysfunction, cognitive abnormalities and sleep disorders [1].

The central pathological feature of PD has been reported to be the loss of neurons in the substantia nigra pars compacta, which leads to striatal dopamine deficiency in the patients. Levodopa, a prodrug to dopamine, is recognized as the most effective therapy for PD, while chronic use of oral formulations can ultimately lead to treatment complication such as motor and non-motor fluctuations [2]. In particular, the majority of patients experience shorter duration of response to individual doses (wearing-off symptoms), alternative phases with good and poor response to medication (on-off symptoms) and involuntary movements of the head, trunk or limbs (dyskinesias) [1]. A clinical state of the disease including these symptoms can evaluate by using the Unified Parkinson's Disease Rating Scale (UPDRS), which is the most commonly accepted instrument and is composed of four parts; (I) Mentation, Behavior and Mood; (II) Activities of Daily Living (ADL) (for both "on" and "off" symptoms); (III) Motor Examination; and (IV) Complications of Therapy [3].

Chronotropic incompetence (CI) is broadly defined as the inability of the heart to increase its rate commensurate with increased activity or demand [4]. The presence of CI is associated with pathogenesis of PD; the maximum heart rate (HR) was lower during cardiac stress testing as compared with controls [5]. However, the link between CI and UPDRS score in patients with PD is unclear. The aim of this study was to clarify the association between $\Delta HR/\Delta WR$, which is the ratio of change in heart rate (HR) to that in

work rate (WR), derived from Cardiopulmonary Exercise Testing (CPET) and UPDRS score in patients with PD.

Materials and Methods

Subjects

Thirty-six hospitalized patients with Parkinson's disease [20 male and 16 female subjects; 68.5 years old, 6.6 standard deviation (SD)] receiving medical care at Hyogo Prefectural Rehabilitation Center at Nishi-harima in Japan were included. Disease severity was assessed with the Hoehn and Yahr scale [6] and UPDRS. This study was approved by the ethics committee of the institution. Written informed consent was obtained from each patient before study enrolment.

Cardiopulmonary Exercise Testing (CPET)

The exercise test was performed with a cycle ergometer [StrengthErgo.240, Mitsubishi electric, Tokyo, Japan] according to a 10W/min ramp protocol. The exercise test started with a rest zone for 3 min, followed by a warm-up zone for 3 min at 10 Watt. Then, the workload increased 10 Watt/min through the exercise test. Peak VO2/W, ΔVO2/ΔWR and ΔHR/ΔWR x100 were analyzed by the breath-by-breath method (Aero monitor, AE-310S, Minato medical science, Osaka, Japan).

Heart Rate Variability (HRV)

HRV was also evaluated in the supine position during spontaneous breathing as previously reported [7]. Briefly, Lead II ECG signals were collected for 150 sec with one electrode on the right wrist (negative) and two on the left leg (positive and ground) for

ECG. The frequency domains of HRV derived from ECG were analyzed by the maximum entropy method (MEM) (Reflex Meijin, CROSSWELL, Yokohama, Japan). The sampling frequency for all recordings was 1,000 Hz. The low-frequency (LF) power (0.04–0.15 Hz), high-frequency (HF) power (0.15–0.4 Hz), and the ratio of LF to HF (L/H ratio) were calculated in accordance with standards for the spectral analysis of HRV. HF power and L/H ratio were used as a marker of parasympathetic and sympathetic activity, respectively.

Statistical analysis

We assessed statistical significance using Student t-test for Table 1, Figure 1B, 1C and 1D, Fisher's exact test for Table 1, or Tukey test for Supplementary Table 1, as appropriate, and considered a probability of <5% ($P < 0.05$) to be statistically significant. To evaluate the diagnostic values, area under the receiver operating characteristic (ROC) curve was adapted. The cutoff values were determined by the points on the ROC with minimum distance from the upper-left corner of the graph. The statistical analysis was performed by EZR software version 1.36, based on R and R commander [8].

Results

Distribution of ΔHR/ΔWR x100 in patients with Parkinson's disease

Based on the slope of ΔHR/ΔWR x100 obtained from CPET, we have come to the conclusion that it can be divided the patients with PD into three main categories as follows; (Group I) ΔHR/ΔWR x100 <15, N=3, (Group II) 15≤ ΔHR/ΔWR x100 <60, N=28, (Group III) ΔHR/ΔWR x100 ≥60, N=5 (Figure 1A). As a result, Group I and III

were smaller and older than Group II, indicating that this difference was associated with physical size (Supplementary Table 1).

PD patients with chronotropic incompetence (CI) are impaired an exercise tolerance

Therefore, we next focused on Group II, and further divided into two groups; Group II CI (+), the PD patients with CI (15≤ ΔHR/ΔWR x100 <35), and Group II CI (-), those patients without one (35≤ ΔHR/ΔWR x100 <60). These groups were similar in height, weight, BMI, disease duration, L-dopa equivalent capacity, Hoehn and Yahr stage and incidence of wearing-off (Table 1). In addition, ΔVO2/ΔWR and peak VO2/W in Group II CI (+) was lower than Group II CI (-), respectively (P=0.022 and P=0.096) (Figure 1B). These results suggest that PD patients with CI could impair an exercise tolerance.

Relation between PD patients with CI and autonomic nerve system (ANS)

It has been reported that CI was associated with dysfunction of ANS [9]. We next examined HRV components to evaluate ANS function in patients with PD, and found that HF power tends to be decreased, whereas L/H ratio was increased in Group II CI (+) as compared with Group II CI (-) (Figure 1C). These features could indicate that ANS function of PD patients who have a CI was predominantly controlled by sympathetic activity.

ΔHR/ΔWR x100 derived from CPET can predict whether the difference between the 'on' and 'off' states in ADL is large in patients with PD.

We further examined the relation between CI and UPDRS score in patients with PD. The UPDRS was commonly used to evaluate the disease activity of patients with PD, which is composed of four parts about non-motor and motor experiences of daily living and motor complications [3]. As results, each score of all parts did not different between Group II CI (+) and Group II CI (-). We next focused on part II about ADL, and found that when part II (off-on) score was calculated by subtracting part II (on) from part II (off), the score of Group II CI (+) was significantly higher than Group II CI (-) (P=0.023) (Figure 1D). Interestingly, the Hoehn and Yahr scale did not differ between Group II CI (+) and CI (-). In addition, this significance also did not recognize in the case of dividing into two groups, with or without CI, based on previous reports about definition of that (data not shown) [9]. To evaluate the diagnostic values of ΔHR/ΔWR x100, we further defined a score of 2 or more on part II (off-on) as a large difference between 'on' and 'off' states in ADL. The diagnostic power of ΔHR/ΔWR x100 with a cutoff of 34.1 showed 71.4% sensitivity and 78.6% specificity, and AUC was 0.668 based on ROC analysis (Figure 1E).

Discussion

We found that there were three major distributions in patients with PD, according to the result of ΔHR/ΔWR x100 derived from CPET. One of the main reasons was the difference in body size. However, both groups I and III in this study had small sample size (N=3-5), and we have not yet been able to analyze why there are differences in ΔHR/ΔWR x100 due to differences in body size. On the other hand, it has been reported that ΔHR under exercise using an ergometer is higher in patients with PD [10]. Group III

in our group also has an abnormally higher ΔHR/ΔWR x100, and there may be disease-specific factors other than differences in body size.

Part II of the UPDRS assesses ADL in patients with PD, separately for ‘on’ (when their medications work effectively) and ‘off’ (when medications wear off). In this study, we found that the CI (+) patients in Group II showed a large difference between ‘on’ state and ‘off’ state in ADL based on the UPDRS part II score. ‘off’ symptoms of PD patients seem to occur with long-term administration of therapeutic drugs [2], but in our case, there was no difference in disease duration, L-dopa equivalent capacity, the incidence of wearing-off and the Hoehn and Yahr scale. In other words, despite the same severity of the disease, there seems to be a group of people who strongly experience the difference between ‘on’ and ‘off’ in ADL and those who do not. In this sense, it may be meaningful to evaluate ΔHR/ΔWR derived from CPET. In fact, ROC analysis in our case showed that the diagnostic power of ΔHR/ΔWR x100 with a cutoff of 34.1 showed 71.4% sensitivity and 78.6% specificity. Although sensitivity and specificity are not high, we believe that large-scale studies are needed in the future in this regard. Therefore, we expect that ΔHR/ΔWR x100 obtained by the CPET can be used as an index to predict whether the difference between the ‘on’ and ‘off’ states in ADL is large.

Why did PD patients with CI strongly experience the difference between the ‘on’ and ‘off’ states in ADL? It is thought that CI is related to ANS function [9], and we examined HRV components in the patients with and without CI. Although our study was small sample size, parasympathetic activity tended to be suppressed, and sympathetic activity tended to be predominant in the patients with CI compared to those without CI at rest.

Interestingly, this imbalance of autonomic activity is also observed in heart failure patients [11], however, NT-proBNP, a diagnostic biomarker for heart failure and cardiac dysfunction, of all PD patients in this study remain within the normal range. In addition, it has been reported that patients with heart failure have a higher heart rate at rest due to the predominance of sympathetic nervous activity [11], but in this study, there was no difference in heart rate at rest between the groups with and without CI. Furthermore, the cardiac sympathetic nervous system is impaired in PD patients as their symptoms progress [12], in contrast, the PD patients with CI is not necessarily more severely affected, and the sympathetic nervous system activity was also dominant in this study. We think further analysis is required in this point.

In conclusion, we found, for the first time, that whether PD patients with CI strongly experience the difference between "on" and "off" status in ADL, might be detected by using ΔHR/ΔWR x100 obtained by CPET as an index. These findings may be a predictor of ADL and quality of life in PD patients.

Author contribution

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. KY had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: KY. Acquisition of data: KY, HT, SN, KT, YM and KM. Analysis and interpretation of data: KY and KM.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Figure legend

Figure 1. Association with ΔHR/ΔWR x 100 derived from cardiopulmonary exercise testing **(CPET) in patients with Parkinson's disease (PD).**

(A) Distribution of ΔHR/ΔWR x 100 derived from CPET in patients with PD.

Results were divided into Group I (<15), II (≥15, <60) and III (≥60). Among Group II, we defined the patients with chronotropic incompetence (CI) if ΔHR/ΔWR x 100 was between 15 and 35, and those without CI if it was between 35 and 60.

(B, C, D) Difference in exercise tolerance, autonomic nerve system and UPDRS score between PD patients with CI (solid) and without that (slash). PD patients with CI were impaired an exercise tolerance, tended to be decreased in parasympathetic (HF power), and increased in sympathetic activity (LF/HF ratio) as compared to those patients without CI. In addition, when UPDRS part II (off-on) score was calculated by subtracting part II

(on) from part II (off), PD patients with CI strongly experienced the difference between ‘on’ and ‘off’ in ADL. Statistical analysis was performed by Student t-test.

(E) Receiver operating characteristic (ROC) curve for discriminating UPDRS part II off-on (≤2) from off-on (>2) in patients with PD.

The diagnostic power of ΔHR/ΔWR x 100 (cutoff, 34.1) showed 71.4% sensitivity and 78.6% specificity, respectively.

Title: ΔHR/ΔWR derived from CPET; a novel predictor of ‘off’ symptom in patients with Parkinson's disease

Highlight

· The parameter of ΔHR/ΔWR can be obtained from CPET (Cardiopulmonary Exercise Testing).
· ΔHR/ΔWR was suitable for assessing the presence of CI (Chronotropic incompetence).
· The patients with Parkinson’s disease (PD) who have CI, impaired an exercise tolerance.
· PD patients with CI had a difference in the UPDRS part II score when they were on and off.
· PD patients who have CI felt the difference between ‘on’ and ‘off’ in activities of daily living.

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Table 1. Patient profile in PD patients with CI (+) and CI (-).

	Group II CI (+) (N=16)	Group II CI (-) (N=12)	*P* value
Age (years old)	67.9 ± 7.1	68.3 ± 5.5	0.855
Height (cm)	162.8 ± 8.5	162.2 ± 10.8	0.860
Weight (kg)	64.0 ± 8.3	62.1 ± 9.2	0.565
BMI (kg/m^2)	24.2 ± 3.4	23.6 ± 2.4	0.575
Disease duration (years)	5.2 ± 3.8	6.1 ± 5.3	0.604
L-dopa equivalent capacity (mg/day)	630 ± 293	581 ± 251	0.645
Hoehn and Yahr stage	3.1 ± 0.3	3.0 ± 0.4	0.630
Incidence of wearing-off (%)	11/16 (81.3)	10/12 (83.3)	1.000*

Based on result of ΔHR/ΔWR x 100 derived from CPET, we defined ΔHR/ΔWR x 100 (≥15, <35) as PD patients with chronotropic incompetence (CI), and ΔHR/ΔWR x 100 (≥35, <60) as the patients without CI. Mean ± standard deviation (SD). *P* values were determined by Student t-test, except as indicated otherwise. *Determined by Fisher's exact test.

Figure 1

A

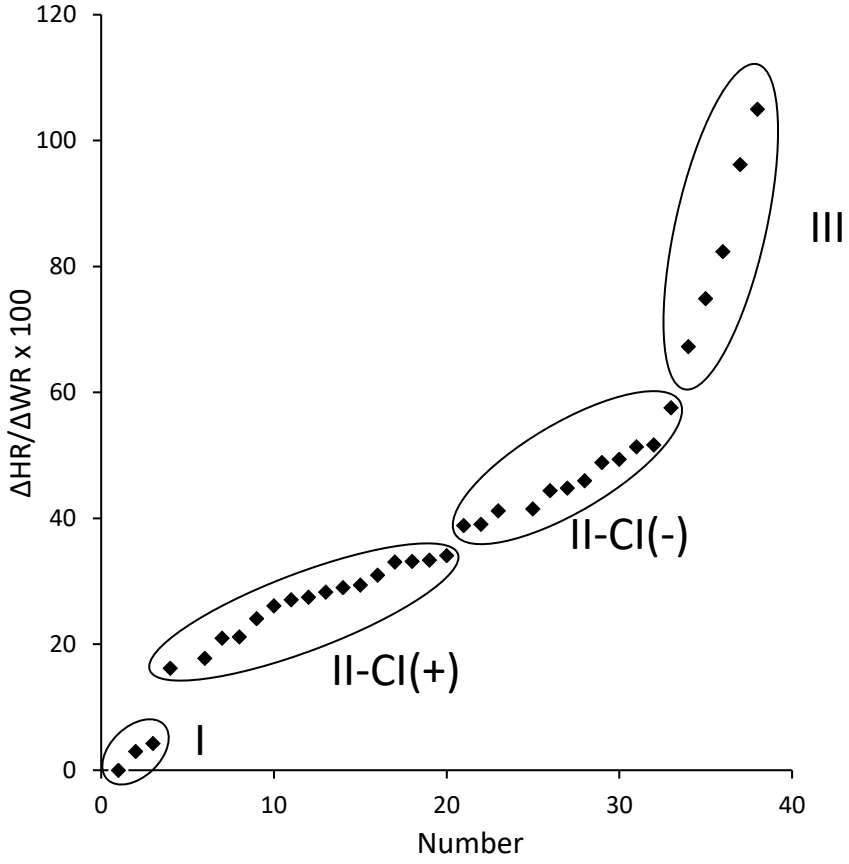

120
100
80
60
40
20
0
ΔHR/ΔWR x 100
0
10
20
30
40
Number
I
II-CI(+)
II-CI(-)
III

Figure 1

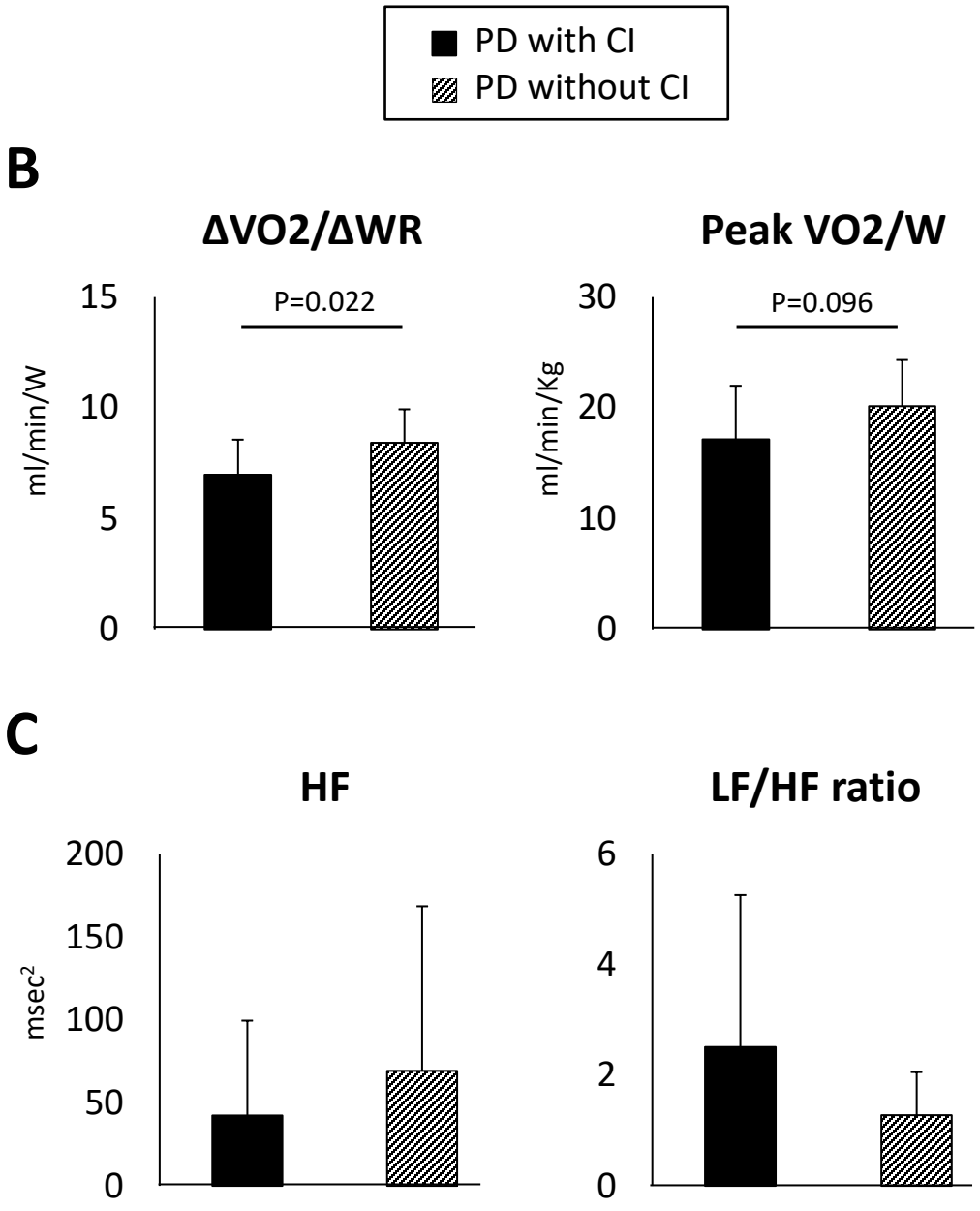

PD with CI
PD without CI
B
ΔVO2/ΔWR
P=0.022
ml/min/W
15
10
5
0
Peak VO2/W
P=0.096
ml/min/Kg
30
20
10
0
C
HF
msec²
200
150
100
50
0
LF/HF ratio
6
4
2
0

Figure 1

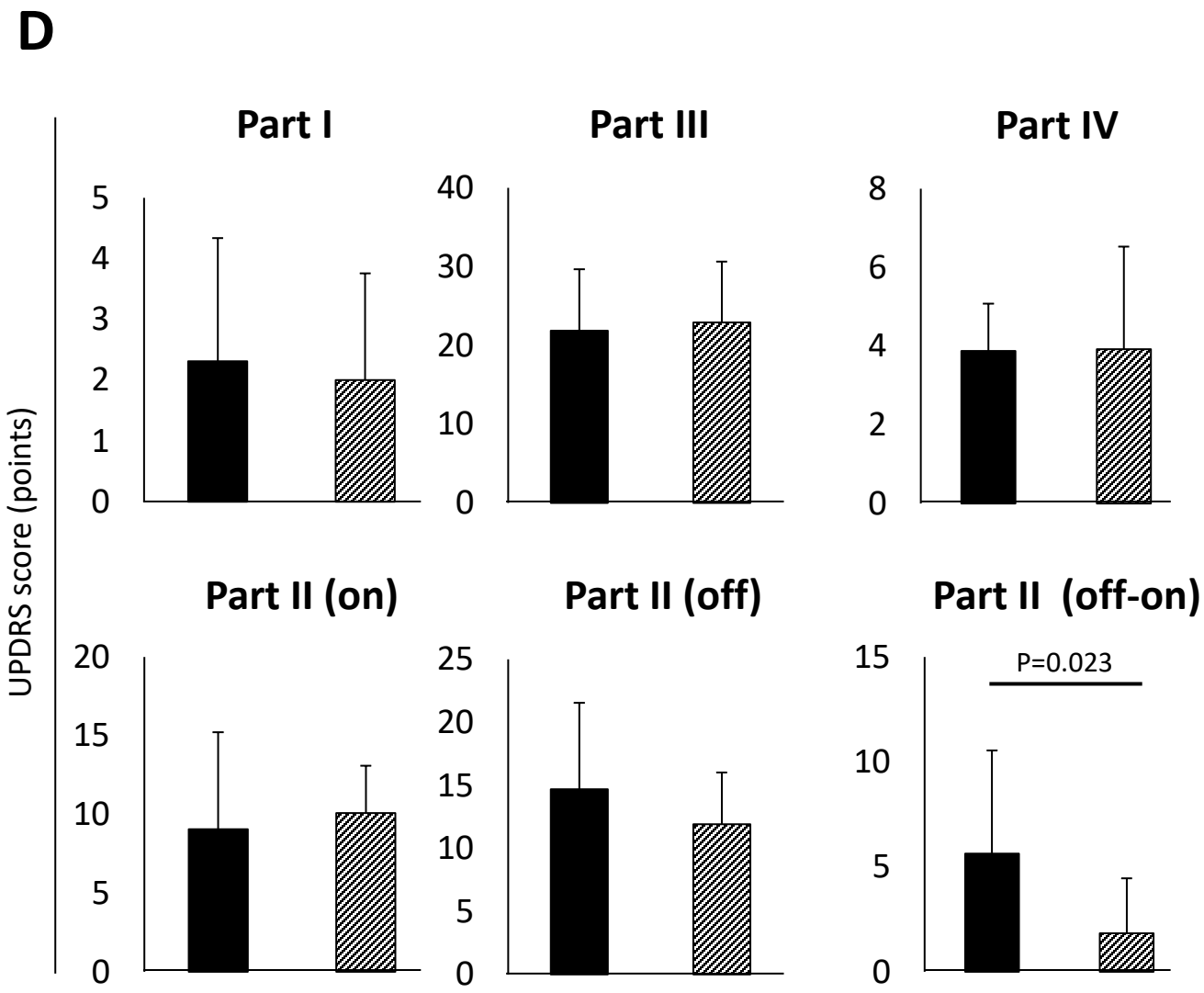
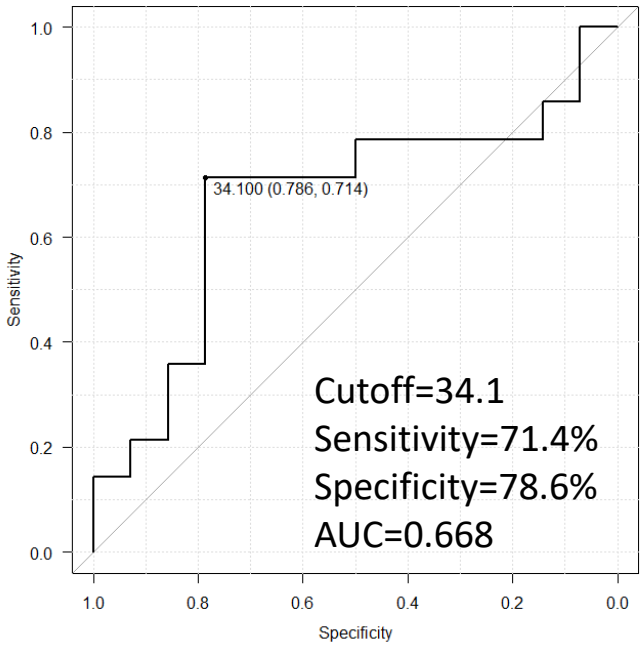

D
Part I
Part III
Part IV
Part II (on)
Part II (off)
Part II (off-on)
UPDRS score (points)
P=0.023

Figure 1

E


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
34.100 (0.786, 0.714)
Cutoff=34.1
Sensitivity=71.4%
Specificity=78.6%
AUC=0.668
1.0
0.8
0.6
0.4
0.2
0.0
Specificity