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*Original Article*

# Heart rate variability in patients with Parkinson's disease complicated with orthostatic hypotension

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**Abstract:** Orthostatic hypotension (OH) is a major presentation of autonomic dysfunction in Parkinson's disease (PD). Heart rate variability (HRV) can be used to detect abnormal changes in autonomic function at an early stage. The current study aimed to identify PD patients with OH at an early stage, analyzing HRV indexes. A total of 170 PD patients were continuously recruited and divided into PD with OH (PD-OH, n = 55) or PD with no OH (PD-NOH, n = 115) groups, based on blood pressure values measured in both supine and upright positions. General demographic and clinical data were recorded. The PD-OH group showed significantly older age, longer disease duration, more diabetes cases, more coronary heart disease cases, higher levels of fasting blood glucose, higher levels of glycated hemoglobin A1c, higher levodopa-equivalent daily doses, higher Hoehn-Yahr stage, higher Unified PD Rating Scale III scores, and higher Scale for Outcomes in PD for Autonomic Symptoms than the PD-NOH group ($P < 0.05$). HRV indices were acquired by analyzing 24-hour ambulatory electrocardiograms. Compared with the PD-NOH group, HRV indices, including the standard deviation of all normal-normal intervals (SDNN), SDNN index, standard deviation of the average normal-normal intervals (SDANN), and HRV triangular index, were clearly lower in the PD-OH group ($P < 0.05$). Using variables, $p$ values < 0.10 between the PD-OH and PD-NOH groups as independent variables, as well as the presence or absence of OH as dependent variables, multivariate logistic regression was performed. Results showed that age (B, 0.085; OR value, 1.088; 95% CI, 1.033~1.146; $P < 0.05$) and SDNN (B, -0.047; OR value, 0.954; 95% CI, 0.912~0.998; $P < 0.05$) were independent related factors for patients in the PD-OH group. In summary, age was an independent risk factor for development of OH in PD patients. Reduced SDNN was independently related to PD with OH.

**Keywords:** Parkinson's disease, orthostatic hypotension, 24-hour ambulatory electrocardiogram, heart rate variability

## Introduction

Parkinson's disease (PD) is a common neurodegenerative disease in the elderly. PD patients not only have motor symptoms (MSs), including resting tremors, rigidity, bradykinesia, and abnormal posture and gait, but also present non-motor symptoms (NMSs). These include autonomic dysfunction, abnormal sensation, sleeping disorders, and neuropsychiatric symptoms [1]. Concerning symptoms of autonomic dysfunction in PD patients, cardiovascular symptoms have gained increasing attention. Orthostatic hypotension (OH) is a major presentation of autonomic dysfunction in the cardiovascular system. Frequently, PD with OH (PD-OH) patients fall and sustain injuries, leading to increased risks of disability and mortality [2].

Heart rate variability (HRV) represents beat-to-beat alterations in normal sinus rhythm. It results from the interaction between sympathetic and parasympathetic activity of the autonomic nervous system. HRV can be used to detect abnormal changes in autonomic function at an early stage. Therefore, HRV is valu-

able for prediction and early diagnosis of autonomic nervous system dysfunction [3]. HRV is a common parameter used to assess extrapyramidal diseases, especially autonomic function in PD patients [4]. With the development of computer technology, 24-hour ambulatory electrocardiograms (ECG) can provide more HRV indices. ECG has become an effective method for HRV analysis [5]. Research concerning the relationship between HRV indices, derived from 24-hour ambulatory ECGs, and OH in PD patients is lacking. Therefore, the current study acquired HRV indices in PD patients, analyzing 24-hour ambulatory ECGs. The aim of this study was to explore HRV, detecting OH occurrence in PD patients as early as possible.

## Materials and methods

### *Ethics statement*

This project was approved by the Institutional Review Board of Beijing Tiantan Hospital. All participants provided written informed consent. This study met the guidelines of Capital Medical University, abiding by the Helsinki Declaration concerning ethical principles for medical research involving human subjects.

### *Participants*

Clinically established PD patients and clinically probable PD patients were consecutively recruited according to the latest diagnostic criteria for PD published by the Movement Disorder Society 2015 [6]. PD patients were excluded from the study if they met any of the following criteria: (1) Unable to cope with BP measurements while in supine and upright positions; (2) Chronic psychiatric diseases, neuromuscular diseases, and infectious diseases of the central nervous system; (3) With malignant tumors; (4) Frequent ventricular premature beats, atrial fibrillation, atrial flutter, or pre-excitation syndrome; (5) Acute myocardial infarction, myocarditis, or severe heart valve disease; (6) Severe lung, liver, kidney, blood diseases, or other wasting diseases; and (7) Acute/chronic general infectious diseases. A total of 170 PD patients were recruited for the study from May 2016 to May 2018.

### *Diagnostic criteria for OH*

OH is defined as a reduction in systolic BP of more than 20 mmHg and/or diastolic BP of more than 10 mmHg from baseline within 3 minutes of moving into an upright position. This is based on American Autonomic Society and American Academy of Neurology diagnostic criteria of 1996 [7]. A total of 170 PD patients were divided into the PD-OH group or PD with no OH (PD-NOH) group.

### *Assessment of clinical features*

General demographic and clinical data, including gender, age, duration, body mass index (BMI), fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c) were recorded, in addition to the number of PD patients taking antihypertensive drugs and nitrates. History of hypertension, diabetes, and coronary heart disease was also recorded. Information concerning anti-PD medications was collected and levodopa-equivalent daily doses (LEDD) were calculated [8]. Severity of PD was assessed by Hoehn-Yahr (H-Y) stage. Motor symptoms were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) III [9]. Autonomic symptoms were assessed by the Scale for Outcomes in PD for Autonomic Symptoms (SCOPA-AUT) [10].

### *BP measurements in supine and upright positions*

Brachial artery BP levels of the upper right arm were measured at 9:00-10:00 AM on the day after admission using an OMRON electronic sphygmomanometer (model HEM-7071). After resting for 10 minutes, the supine BP was measured twice at 5-minute intervals after lying down. Average supine BP levels were then calculated. Next, PD patients were instructed to stay in the upright position. BP levels were measured within 3 minutes. The upper arm measurement position was at the same level as the heart.

### *Twenty-four-hour ambulatory ECG monitoring (Holter monitoring)*

A Shenzhen Boying Holter monitor (BI9800) was used for 24-hour ambulatory ECG monitoring. Patients maintained normal daily activities during 24-hour Holter testing. For HRV analysis, Holter recordings of all patients were evaluated, manually, removing the artifacts. HRV variables were then automatically calculated. The current study analyzed time-domain indices of HRV, recording the standard deviation (SD) of

**Table 1.** Demographic variables and clinical features between PD-OH and PD-NOH groups

| | PD-OH group (n = 55) | PD-NOH group (n = 115) | *P* value |
|---|---|---|---|
| Male [x/n (%)] | 33/55 (60.00%) | 55/115 (47.82%) | 0.137 |
| Age (year, $\bar{X} \pm S$) | 71.13 ± 8.16 | 62.40 ± 10.74 | < 0.001 |
| Duration [year, M (Q1-Q3)] | 5.00 (3.00~8.00) | 3.00 (2.00~6.00) | < 0.001 |
| BMI ($kg/m^2$, $\bar{X} \pm S$) | 23.85 ± 3.92 | 23.98 ± 3.48 | 0.827 |
| FBG [mmol, M (Q1-Q3)] | 4.93 (4.58~5.87) | 4.72 (4.44~5.31) | 0.030 |
| HbA1c [%, M (Q1-Q3)] | 5.90 (5.50~6.50) | 5.50 (5.30~5.90) | < 0.001 |
| Hypertension [x/n (%)] | 23/55 (41.82%) | 46/115 (40.00%) | 0.821 |
| The number of patients taking antihypertensive drugs [x/n (%)] | 20/55 (36.36%) | 44/115 (38.26%) | 0.473 |
| Diabetes [x/n (%)] | 18/55 (32.73%) | 20/115 (17.39%) | 0.025 |
| Coronary heart disease [x/n (%)] | 12/55 (21.82%) | 10/115 (8.70%) | 0.017 |
| The number of patients taking nitrates [x/n (%)] | 8/55 (14.55%) | 8/115 (6.96%) | 0.113 |
| H-Y stage [M (Q1-Q3)] | 2.50 (2.00~3.00) | 2.00 (1.00~2.50) | < 0.001 |
| UPDRS III score [M (Q1-Q3)] | 34.00 (24.00~45.00) | 23.00 (14.00~32.00) | < 0.001 |
| LEDD [mg, M (Q1-Q3)] | 441.67 (275.00~700.00) | 291.67 (50.00~496.88) | < 0.001 |
| SCOPA-AUT score [M (Q1-Q3)] | 43.00 (34.00~48.00) | 38.00 (33.00~44.00) | 0.017 |

PD-OH, Parkinson's disease with orthostatic hypotension; PD-NOH, Parkinson's disease with no orthostatic hypotension; BMI, Body Mass Index, FBG; Fasting blood glucose; HbA1c, glycated hemoglobin A1c; H-Y stage, Hoehn-Yahr stage; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, Levodopa-equivalent daily dose; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic.

all normal-normal (NN) intervals (SDNN), averages of NN intervals during all 5-minute periods that constitute the 24-hour day (SDANN), SDNN indexes, and successive normal-normal differences (SDSD). Percentages of NN intervals differing more than 50 msec from each other (pNN50), the square root of the mean squared differences of successive NN intervals (RMSSD), and the HRV triangular index (integral of the density distribution (number of all NN intervals) divided by the maximum of the density distribution) were also analyzed. Reference values included normal time-domain reference values published in the Guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology in 1996 [5].

*Statistical analysis*

Statistical analyses were carried out using SPSS Statistics 20.0 (Chicago, IL, USA). Demographic variables, clinical features, and heart rate variability levels were compared between PD-OH and PD-NOH groups. Continuous variables, if normally distributed, are presented as mean ± standard deviation. The two groups were compared using two-tailed t-tests. If variables were not normally distributed, they are presented as medians (quartile). The two groups were compared using rank-sum tests. For enumeration data, percentages are used and $\chi^2$ tests were carried, comparing differences between the two groups. Multivariate logistic regression analysis was performed, aiming to identify independent influencing factors for development of OH in PD patients. $P < 0.05$ indicates statistical significance.

## Results

*Demographic and clinical characteristics of PD-OH patients*

Of the 170 PD patients recruited, 55 patients had concurrent OH, with a frequency of 32.35%. The remaining 115 patients without OH accounted for 67.65%. They were placed in the PD-NOH group. Results showed that patients in the PD-OH group had significantly older age, longer disease duration, more diabetes cases, more coronary heart disease cases, higher levels of FBG, higher levels of HbA1c, and higher LEDD, compared with patients in the PD-NOH group ($p < 0.05$). UPDRS III scores and H-Y stages of the PD-OH group were also clearly higher than those in the PD-NOH group ($p < 0.05$), indicating that the PD-OH group was in a more advanced disease stage with more serious motor symptoms, respectively. The PD-OH group showed higher SCOPA-AUT scores than the PD-NOH group ($p < 0.05$) (**Table 1**), indicating notably compromised autonomic dysfunction in the PD-OH group. No statistically significant differences in sex, BMI, past hypertension history, the number of PD patients taking antihypertensive drugs and nitrates were identified between the PD-OH and PD-NOH group ($p > 0.05$) (**Table 1**).

**Table 2.** Heart rate variability between PD-OH and PD-NOH groups

| | PD-OH group (n = 52) | PD-NOH group (n = 95) | *P* value |
|---|---|---|---|
| SDNN [msec, M (Q1-Q3)] | 89.99 (64.28~107.37) | 107.95 (89.61~121.86) | < 0.001 |
| SDSD [msec, M (Q1-Q3)] | 17.75 (14.08~32.27) | 17.80 (13.49~27.64) | 0.735 |
| RMSSD [msec, M (Q1-Q3)] | 22.16 (18.52~40.35) | 23.06 (18.48~31.36) | 0.998 |
| pNN50 [%, M (Q1-Q3)] | 1.96 (0.80~5.05) | 2.15 (0.91~5.48) | 0.466 |
| SDANN [msec, M (Q1-Q3)] | 83.30 (61.56~98.04) | 98.69 (81.32~113.12) | 0.001 |
| SDNN index [msec, M (Q1-Q3)] | 28.78 (22.68~38.69) | 37.19 (28.82~45.02) | < 0.001 |
| HRV triangular index [M (Q1-Q3)] | 23.40 (15.98~27.40) | 28.64 (21.86~33.09) | 0.001 |

PD-OH, Parkinson's disease with orthostatic hypotension; PD-NOH, Parkinson's disease with no orthostatic hypotension; SDNN, Standard deviation of normal-normal intervals; SDSD, standard deviation of successive normal-normal differences; RMSSD, Square root of the mean squared differences of successive normal-normal intervals; pNN50, proportion of normal-normal intervals differing more than 50 ms to the total number of normal-normal intervals; SDANN, Standard deviation of the average normal-normal intervals; HRV, Heart rate variability.

**Table 3.** Multivariate logistic regression analysis of influencing factors of PD-OH

| | B | SE | Wals | OR value | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Age | 0.085 | 0.026 | 10.262 | 1.088 | 1.033~1.146 | 0.001** |
| Duration | 0.056 | 0.078 | 0.509 | 1.057 | 0.907~1.233 | 0.476 |
| Fasting blood sugar | -0.370 | 0.338 | 1.199 | 0.691 | 0.356~1.339 | 0.273 |
| Glycated hemoglobin A1c | 0.529 | 0.462 | 1.308 | 1.697 | 0.686~4.200 | 0.253 |
| Diabetes | 0.536 | 0.712 | 0.567 | 1.709 | 0.424~6.893 | 0.452 |
| Coronary heart disease | -0.013 | 0.652 | 0.000 | 0.987 | 0.275~3.542 | 0.984 |
| H-Y stage | 0.383 | 0.381 | 1.011 | 1.466 | 0.695~3.091 | 0.315 |
| UPDRS III score | 0.011 | 0.020 | 0.295 | 1.011 | 0.972~1.051 | 0.587 |
| Levodopa equivalent daily dose | 0.001 | 0.001 | 0.657 | 1.001 | 0.999~1.002 | 0.418 |
| SCOPA-AUT score | -0.033 | 0.030 | 1.234 | 0.967 | 0.912~1.026 | 0.267 |
| SDNN | -0.047 | 0.023 | 4.259 | 0.954 | 0.912~0.998 | 0.039* |
| SDNN index | -0.027 | 0.023 | 1.337 | 0.974 | 0.931~1.019 | 0.248 |
| SDANN | 0.030 | 0.019 | 2.549 | 1.031 | 0.993~1.070 | 0.110 |
| HRV triangular index | -0.001 | 0.003 | 0.063 | 0.999 | 0.993~1.006 | 0.803 |

PD-OH, Parkinson's disease with orthostatic hypotension; B, unstandardized beta reported from regression analysis; SE, Standard error; OR, odds ratio; 95% CI, 95% Confidence interval; H-Y stage, Hoehn-Yahr stage; UPDRS, Unified Parkinson's Disease Rating Scale; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic; SDNN, Standard deviation of normal-normal intervals; SDANN, Standard deviation of the average normal-normal intervals; HRV, Heart rate variability. *, $p < 0.05$; **, $P < 0.01$.

*HRV between PD-OH and PD-NOH groups*

HRV was compared between the two groups. Results indicated that SDNN, SDNN index, SDANN, and HRV triangular indexes were clearly lower in the PD-OH group than those in the PD-NOH group ($p < 0.05$) (**Table 2**). No significant differences were found in the HRV indices, including SDSD, RMSSD, and PNN50 ($p > 0.05$) (**Table 2**).

*Multivariate logistic regression analysis of factors affecting PD-OH*

Variables with a *p* value < 0.10 between PD-OH and PD-NOH groups included age, disease duration, past DM and CAD history, FBG, HbA1c, LEDD, H-Y stage, UPDRS III score, SCOPA-AUT scores, SDNN, SDNN index, SDANN, and HRV triangular index. Using the above factors as independent variables and the presence or absence of OH as dependent variables, multivariate logistic regression was performed with the enter method. Results showed that age (B, 0.085; OR value, 1.088; 95% CI, 1.033~1.146; $P < 0.05$) and SDNN (B, -0.047; OR value, 0.954; 95% CI, 0.912~0.998; $P < 0.05$) were independent related factors for patients in the PD-OH group (**Table 3**), suggesting that older age is an independent risk factor for PD-OH. In addition, reduced SDNN was independently related to PD-OH. In summary, older age and reduced SDNN were shown to be independent

risk factors for development of OH in PD patients.

## Discussion

OH is a common NMS in PD patients. Of the 170 PD patients in the current study, 55 developed OH, with a frequency of 32.25%. Velseboer et al. [11] reported an incidence rate of PD-OH was 30.1%, based on a meta-analysis of 25 studies, in accord with present findings.

Multiple studies have revealed that incidence of OH increases with age [12, 13]. The current study observed that PD-OH patients were older than PD-NOH patients (**Table 1**). Logistic regression analysis showed age as a risk factor for development of OH in PD patients (**Table 3**). With increasing age, sensitivity levels of baroreceptors in the carotid sinus and the aortic arch gradually decrease. Arterial elasticity also decreases. Therefore, the function of the sympathetic nervous system undergoes degenerative changes, leading to development of OH [14].

In the current study, patients in the PD-OH group had longer disease duration, higher UPDRS III scores, and more advanced H-Y stage, as well as increased levodopa-equivalent doses, compared to patients in the PD-NOH group (**Table 1**). Occurrence of OH in PD patients may be closely related to the effects of decreased noradrenergic innervation in both the heart region and extracardiac region [3]. Oka et al. [15] found that plasma levels of norepinephrine showed a decreasing trend in PD patients, with a prolonged disease duration and PD progression. PD patients with advanced H-Y stage showed clearly reduced plasma levels of norepinephrine, suggesting that development of OH may be related to the severity of PD. As the disease duration of PD progresses, PD patients will take more types of anti-PD medications and/or increase dosages. Development of OH is related to the use of anti-PD medications. Multiple anti-PD medications, such as levodopa and benserazide hydrochloride, can disturb autonomic function, inducing or exacerbating OH [16].

Due to autonomic nervous system damage caused by insulin resistance and high blood glucose, DM patients are vulnerable to autonomic nerve damage [17]. DM patients are prone to plaque formation in the carotid arteries and peripheral arteries. This can lead to decreased arterial elasticity, affecting the distribution of blood flow upon postural changes and impacting blood pressure regulation. For these reasons, DM patients are susceptible to OH development [18].

In the current study, an increased percentage of patients in the PD-OH group had previous CAD history, compared to patients in the PD-NOH group (**Table 1**). CAD has been reported to be a risk factor for development of OH [19]. CAD patients often take nitrate drugs. Nitrate drugs can increase the risk of OH development in CAD patients by altering vasodilation functions [20]. Although there were no statistically significant differences in the number of patients taking nitrate drugs between the PD-OH group and PD-NOH group ($P > 0.05$) (**Table 1**), the proportion of patients taking nitrate drugs in the PD-OH group was higher than that in the PD-NOH group (14.55% for the PD-OH group and 6.96% for the PD-NOH group).

Autonomic dysfunction is a common NMS in PD. Autonomic dysfunction in PD patients is directly related to quality of life levels [21]. OH is a major presentation of autonomic dysfunction in PD patients. HRV detection is a non-invasive, practical, and simple measure, assessing autonomic function [22]. HRV has been used as an evaluation index in multiple studies of autonomic function in PD patients [23, 24]. Only a few studies have been reported concerning HRV in PD-OH patients. However, HRV indices were extracted from 10-second ECGs. The authors commented that a 10-second regular ECG may not be able to evaluate HRV in PD patients [24]. Since longer recording epochs better represent the cardiovascular system's response to a wider range of environment stimuli and workloads, HRV indices derived from 24-hour ambulatory ECGs achieve greater predictive power than short-term measurements [5, 25, 26], thus serving as the "gold standard" for clinical HRV assessment [27, 28].

In this study, HRV-related indices were obtained from 24-hour Holter monitoring of PD patients. HRV indices, including SDNN, SDNN index, SDANN, and HRV triangular indexes, were all obviously reduced in the PD-OH group, compared to those in the PD-NOH group (**Table 2**). The nature of the association between reduced HRV and PD patients with OH and its mecha-

nisms remains unknown. Deposition of Lewy bodies and Lewy neurites in the dorsal motor nucleus of the vagus and in cardiac sympathetic innervation could be one of the causes for changes in HRV observed in PD patients [29]. Many studies have reported that sympathetic nerve-mediated cardiovascular stimulation failed in PD patients after they lost cardiac sympathetic innervation. This impaired sympathetic function, leading to decreased venous return and occurrence of OH [30-32]. PD patients have a lower sympathetic response, even without OH, compared to healthy people. However, the decreased sympathetic response was more obvious in PD patients with OH [33]. Shibata et al. [34] observed that cardiac parasympathetic dysfunction occurred with sympathetic denervation, as revealed by (123) I-MIBG myocardial scintigraphy in PD. They reported that it contributed to the development of orthostatic hypotension.

All indicators concerning HRV are defined by special reports published in the European Heart Journal in 1996 [5]. According to time domain analysis, SDNN, SDNN index, and HRV triangular indexes reflect overall variability. SDANN reflects sympathetic tension, while RMSSD, SDSD, and pNN50 reflect vagal tone. In the current study, the reduction of SDNN, SDNN index, SDANN, and HRV triangulation indexes in the PD-OH group may be related to decreases of sympathetic nervous tension or impaired sympathovagal balance in PD patients with OH. Parasympathetic function was less compromised in PD patients with OH. RMSSD, SDSD, and pNN50 reflect parasympathetic activity. They were not significantly different between the PD-OH and PD-NOH group.

After adjusting for disease duration, past DM or CAD history, FBG, HbA1c, LEDD, H-Y stage, UPDRS III scores, SCOPA-AUT scores, SDNN index, SDANN, and HRV triangular indexes, multivariate logistic regression showed reduced SDNN as an independent related factor for development of OH in PD patients (B, -0.047; 95% CI, 0.912~0.998; $P < 0.05$) (**Table 3**). These findings suggest an important role for HRV in the screening of PD patients with OH. Regarding PD patients, doctors should pay more attention to SDNN values, aiming to identify OH and intervene as early as possible.

In recent years, several studies have indicated that an increasing number of PD patients have died suddenly due to unknown reasons. This is called "Sudden Unexpected Death in Parkinson's Disease (SUDPAR) [35]. Some researchers believe that SUDPAR is related to cardiovascular autonomic dysfunction in PD [36, 37]. SDNN is the "gold standard" for medical stratification of cardiac risk [5]. SDNN, extracted from 24-hours recordings, is a robust predictor of adverse cardiovascular events and mortality. Whether SUDPAR is related to reduced HRV warrants further investigation. Overall, reduced HRV levels should be closely monitored in PD patients, especially for PD patients with OH. This could potentially improve prognosis and minimize the risk of development of cardiac and cerebrovascular complications.

There were several limitations to the current study, however: 1) PD patients participating in this study needed to be able to cooperate during multiple tests, including blood pressure measurement, a series of scale assessments, and ambulatory ECG monitoring. Therefore, several PD patients with severe medical conditions could not complete all examinations. They were not included in the study, possibly impacting final results; and 2) Because collection of ambulatory ECG monitoring data from normal populations with matched ages is difficult, the current study did not have a normal control group. Additionally, because HRV index data from a large sample size extracted from the normal population was lacking, there were no unified standard HRV indexes. This complicated the application of HRV in clinical screening. In future studies, a more accurate range of normal HRV values is necessary.

## Conclusion

In summary, PD patients showed a high prevalence of OH. Age was shown to be a risk factor for development of OH in PD patients. In addition, reduced SDNN was apparently related to PD with OH. The most common method of examining activity levels and regulatory functions of the autonomic nervous system, quantitatively and non-invasively, HRV plays an important role in the early diagnosis of PD patients that develop OH.

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## Disclosure of conflict of interest

None.

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