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Original Article

Enhanced Parkinson's gait, reduced fall risk, and improved cognitive function through multimodal rehabilitation combined with rivastigmine treatment

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Abstract: Objective: This study aimed to examine the effects of combined rehabilitation and rivastigmine treatment on patients with Parkinson's disease (PD). Methods: Gait parameters were assessed using the Gibbon Gait Analyzer in fifteen patients. Baseline gait data and cognitive assessments were collected. Each patient underwent external counterpulsation therapy, transcranial magnetic stimulation therapy, and exercise therapy for one hour per day, five days a week for three weeks. Post-intervention, gait and cognitive data were re-evaluated. Alongside their standard PD medications, all participants were administered rivastigmine throughout the study period. Results: The intervention significantly enhanced motor function in the single-task test, evidenced by marked improvements in gait metrics such as stride width and walking speed, and a substantial reduction in fall risk. Cognitive function, assessed by mini-mental state examination and Montreal cognitive assessment, showed an improvement trend after the three-week intervention. Improvements in dual-task walking function were observed, although these changes did not reach statistical significance. Conclusion: Multimodal exercise training combined with rivastigmine treatment significantly improves certain gait parameters in the single-task test, enhances balance, and reduces the risk of falling in patients with PD. Cognitive function also demonstrated improvement.

Keywords: Parkinson's disease, multimodal exercise, external counterpulsation therapy, transcranial magnetic stimulation, rivastigmine

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide [1, 2]. It manifests with symptoms such as rigidity, bradykinesia, and resting tremors [3]. Antiparkinsonian medications are primarily used for treatment; however, their efficacy often diminishes about five years post-initiation, leading to worsened motor fluctuations, dyskinesia, dystonia, coordination deficits, and arthralgia [4, 5]. As PD progresses, patients experience decreased postural stability, difficulties in gait and balance, frequent falls, and impaired daily activities [6, 7].

Exercise and physical therapy are vital in complementing medical treatments, enhancing balance, gait, and motor coordination through induced neuronal plasticity [8]. These therapies increase cerebral blood flow, support neural circuits, and strengthen synaptic connectivity [9]. Specific therapies like Tai chi, dance, and music have been tailored for PD management [10]. Enhanced external counterpulsation, a non-invasive therapy, boosts aortic blood flow and pressure by cyclically inflating and deflating air sacs around the buttocks, thighs, and calves, thereby improving blood supply to the brain and other vital organs [11]. Transcranial magnetic stimulation, which employs magnetic fields to stimulate brain tissue, is extensively utilized for treating brain lesion-induced disorders such as treatment-resistant depression and post-stroke cognitive impairments [12]. The impact of transcranial magnetic stimulation on gait disturbances in PD patients remains underexplored. An inherent decline in choliner-

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gic function is known to exacerbate gait issues, postural instability, and cognitive deficits [13, 14]. Clinical methods for correlating gait with fall risk in PD primarily utilize clinical rating scales and quantitative biomechanical assessments. The chair rising test and three-step fall prediction test are reliable tools for predicting fall risk in PD. However, clinical scale assessments in PD are often based on brief observations during patient visits, potentially introducing subjectivity influenced by the examiner's experience.

This study employed the Gibbon gait analyzer, a device developed in China, for precise gait analysis [15]. It measures stride length, pace, toe landing, and swing phase ankle dorsiflexion angle during the 10-meter walk test (10MWT), providing comprehensive assessments of fall risk and other factors. This system allows for an objective evaluation of gait modifications pre- and post-rehabilitation treatment.

Currently, various rehabilitation techniques are applied in clinical PD treatment, but due to the intricate mechanisms of rehabilitation, pinpointing effective evaluation indices for these treatments is challenging. We hypothesized that a combination of acetylcholinesterase inhibitor treatment and rehabilitation would enhance gait stability, thereby preventing falls and improving cognitive function in PD patients. The objective of this study was to verify this hypothesis using the Gibbon gait detection system, which also offers a quantitative basis for assessing clinical rehabilitation outcomes.

Materials and methods

Participants

This cross-sectional study was approved by the Ethics Committee of Jiangbin Hospital of Guangxi Zhuang Autonomous Region (Approval No. 2020-01). Written informed consent was obtained from all participants. We enrolled 15 patients who met the Movement Disorder Society's clinically established criteria for PD [16] and who visited the outpatient clinic of Jiangbin Hospital between December 2021 and April 2022. Inclusion criteria: we included patients with clinically established PD, at Hoehn and Yahr stages 1 to 4, indicating mild to moderate disease severity. Participants were required to have the ability to walk independently, as determined by Tinetti Mobility Test scores, be on stable anti-Parkinsonian medication for at least four weeks prior to enrollment with no expected changes during the study period, and have no prior use of anti-dementia drugs. Exclusion criteria: other neurological or psychiatric conditions that could affect cognitive function or gait, severe visual or hearing impairments, significant comorbidities that could restrict participation in the rehabilitation program, cognitive impairment affecting daily functioning as indicated by Mini-Mental State Examination (MMSE) scores below a threshold, and inability to comply with study procedures or follow-up assessments.

Baseline data were collected on factors that could influence patients' gait, including cognitive function, hypertension, diabetes, smoking, alcohol consumption, and cerebrovascular load. The scoring of white matter hyperintensity (WMH) included: (1) ≥1 lacunar infarction; (2) Fazekas score of mid-deep WMH ≥2 and/or periventricular WMH score of 3; (3) ≥1 deep or subtentorial microbleed; (4) Moderate to severe (grade 2-4) perivascular space in the basal ganglia.

Gibbon gait analyzer

The Gibbon gait analyzer employs high-precision, low-power sensors combined with intelligent analysis software for real-time, multidimensional gait analysis (**Figure 1**). It records detailed walking data through advanced sensor calibration, filtering, denoising technologies, and a fusion algorithm, ensuring the accuracy of measured parameters such as distance, angle, time, and stress during the walking test. Subjects were equipped with smart shoes and lower limb data acquisition modules to collect gait data both before and after a three-week period of multimodal rehabilitation treatment. Assessments included free walking (walking in a straight line without distractions) and dual-task walking (where subjects performed verbal arithmetic and named animals while walking), each over a distance of 10 meters. Data from each session were uploaded to the cloud in packet form for further analysis.

This precise gait analysis tool, comprising smart shoes and lower limb data acquisition

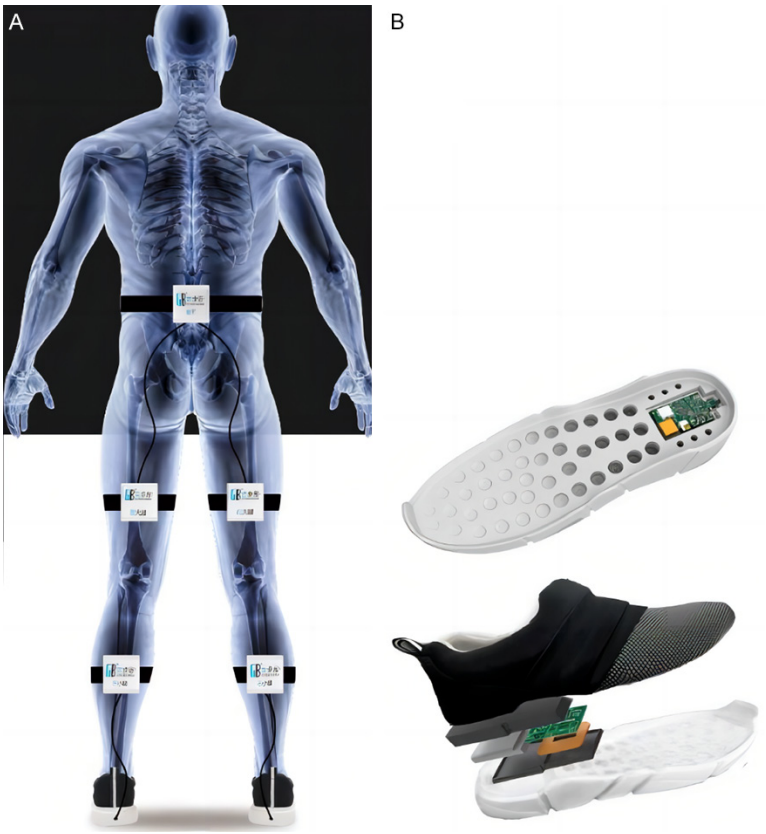

Figure 1. The Gibbon gait analyzer. A: Schematic diagram illustrating the process of gait data collection. B: The device's smart shoe, which is utilized for collecting gait data.

modules, was provided by Dalian Qianhan Technology Co., Ltd., located at Room 2402-1, 24/F, Block A, 32A Torch Road, Dalian High-tech Industrial Park, Liaoning Province, China. The system uses advanced sensors and software to capture detailed gait data during walking tests.

Cloud storage services

Data uploading and storage were managed by Dalian Qianhan Technology Co., Ltd., at the same address. The cloud service facilitated secure and accessible data management, ensuring that gait parameters collected during the study were preserved and available for subsequent analysis.

Multimodal rehabilitation treatment

Participants engaged in three specific rehabilitation exercises: (1) Enhanced external counterpulsation therapy: Participants lay flat on a treatment bed for each one-hour session. This innovative therapy, originating from China, utilizes a special airbag sleeve wrapped around the patient's calves, thighs, and buttocks. An electronic control system synchronizes with the patient's R wave from an electrocardiogram, and a computer calculates the timing of inflation and deflation of each airbag. During the diastolic phase of the heart cycle, the airbags inflate sequentially from distal to proximal segments with a delay of approximately 50 milliseconds to augment diastolic blood pressure. Conversely, during systole, the airbags deflate rapidly and synchronously, reducing the volume of blood in the aorta and subsequently decreasing cardiac afterload (**Figure 2**). (2) Repetitive transcranial magnetic stimulation (rTMS): This neuromodulation technique employs a magnetic field to stimulate the cerebral cortex non-invasively and painlessly. The system charges a high-voltage, large-capacity capacitor, which discharges through a thyristor to generate a current of several thousand amperes through the stimulation coil. According to Faraday's law of electromagnetic induction, a 1-5T pulsed magnetic field is produced, which penetrates the skull and scalp to depolarize brain neurons, triggering physiological changes. In this study, the primary motor cortical areas of subjects were stimulated at a high frequency (10 Hz) for one hour (**Figure 3**). (3) Sports training: Participants underwent muscle massage and joint relaxation treatments to stretch tight muscles and enhance joint mobility. Additionally, they received assistance with neck and waist extensions, as well as lateral flexions and rotations, for one hour daily (**Figure 4**).

These three rehabilitation modalities were conducted once daily, five days a week, with gait assessments repeated after three weeks of rehabilitation. Consistency in therapy was maintained by employing the same rehabilita-

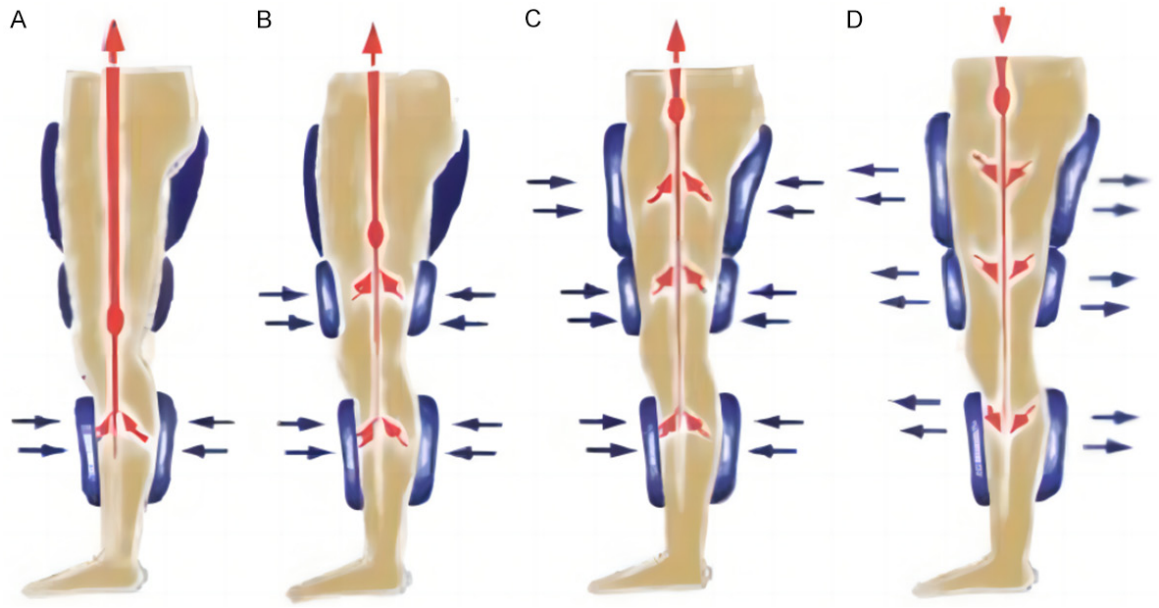

Figure 2. Schematic diagram of one cycle of external counterpulsation inflation and deflation. A: Inflation of the lower thighs. B: Inflation of the upper thighs. C: Inflation of the buttocks. D: Deflation of all airbags. The schematic diagram illustrates the cycle of external counterpulsation, where specially designed airbags are wrapped around the patient's calves, thighs, and buttocks. An electronic control system detects the patient's ECG R-wave and calculates the heart's systolic and diastolic phases in real-time using a computer. Based on these calculations, the airbag system inflates and deflates in sequence. During diastole, the airbags inflate sequentially from the lower thighs to the buttocks with a time delay of approximately 50 milliseconds, increasing diastolic pressure. As the heart enters systole, the computer instructs the airbags to deflate rapidly and synchronously, reducing the pressure on the lower limbs. This allows the arteries to dilate, receiving blood from the aorta, thereby reducing the heart's afterload.

Figure 3. The patient is undergoing transcranial magnetic stimulation.

tion therapists and techniques for all participants. The specific steps of this study are illustrated in **Figure 5**.

Drug intervention

All patients continued their standard antiparkinsonian medications throughout the study. The initial daily dose of rivastigmine was set at 3 mg, administered as two 1.5 mg tablets taken twice daily. After two weeks, the dosage was increased to 6 mg per day, administered as two 3 mg tablets taken twice daily, and maintained at this level for the duration of the study.

Statistical analysis

Descriptive statistics were reported as mean ± standard deviation (SD) for continuous variables. The distribution of these variables was verified for normality using the Shapiro-Wilk test. Comparative analyses before and after the intervention were conducted using either the paired Student's t-test or the Wilcoxon matched-pairs signed-ranks test, as appropriate. Data analysis was performed using STATA version 21 statistical software (Stata Corp., College Station, TX, USA). A *p*-value of less than 0.05 was considered statistically significant.

Figure 4. Several representative methods of sports training. A: Wrist and interphalang eal joint extension. B: Torso rotation. C: Upper extremity joint extension. D: Upper extremity joint extension. E: Correct forward bend.

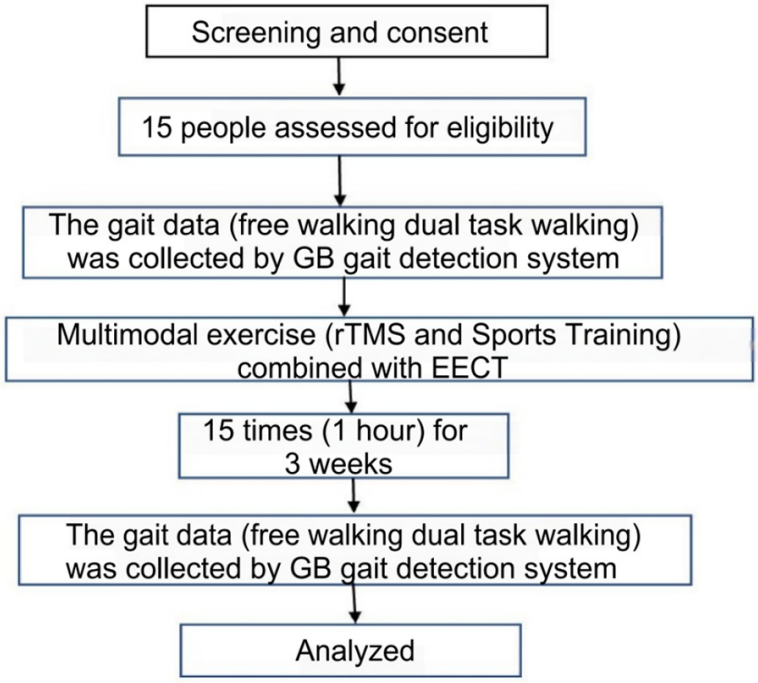

Figure 5. Flowchart of the operation of the study.

Results

Patient's general condition

This study enrolled 15 patients diagnosed with PD, averaging 64.8 years of age (**Table 1**). The cohort included six men and nine women, predominantly at Hoehn and Yahr stages indicating unilateral and axial involvement. Cognitive assessment revealed mild impairment in most participants, as indicated by average scores on the MMSE and Barthel scale, with the latter suggesting that the majority were capable of self-care. Only one patient exhibited significant cognitive decline. Prevalence of hypertension, diabetes, and other cardiovascular and cerebrovascular risk factors was low among the participants, with minimal or no white matter hyperintensity (WMH) detected in the brain parenchyma.

Adverse reactions and motor functions

All participants completed the three-week comprehensive rehabilitation program without adverse reactions. Post-intervention observations showed improvements in self-perceived motor functions. Gait test results indicated that short-term multimodal rehabilitation significantly enhanced motor functions. Specifically, there was a reduced risk of falling (P=0.009),

Table 1. Baseline demographic and clinical profile

Variables	Total (n=15)	Male (n=6)	Female (n=9)	P
Age, mean ± SD (years)	64.80±11.83	62.5±15.57	66.3±9.33	0.562
Educational background (years)	8.07±3.41	9.00±3.63	7.44±3.32	0.405
High blood pressure, n (%)				0.580
Yes	5 (33.3%)	1 (16.7%)	4 (44.4%)	
No	10 (66.7%)	5 (83.3%)	5 (55.6%)	
Diabetes, n (%)				1.000
Yes	1 (6.7%)	0 (0%)	1 (11.1%)	
No	14 (93.3%)	6 (100%)	8 (88.9%)	
Smoking status, n (%)				0.044
Yes	3 (20%)	3 (50%)	0 (0%)	
No	12 (80%)	3 (50%)	9 (100%)	
Drinking status, n (%)				0.143
Yes	2 (13.3%)	2 (33.3%)	0 (0%)	
No	13 (86.7%)	4 (66.7%)	9 (100%)	
The score of WMH, n (%)				0.049
4	0 (0%)	0 (0%)	0 (0%)	
3	2 (13.3%)	1 (16.7%)	1 (11.1%)	
2	1 (6.7%)	1 (16.7%)	0 (0%)	
1	5 (33.3%)	0 (0%)	5 (55.6%)	
0	7 (46.7%)	4 (66.7%)	3 (33.3%)	
Hoehn and Yahr score, mean ± SD	2.21±1.03	2.17±0.98	2.33±1.12	0.781
Rankin scale score, mean ± SD	1.67±0.82	1.67±0.82	1.67±0.87	1.000
Barthle scale score, mean ± SD	88.00±13.33	91.67±9.83	85.56±15.30	0.405
MMSE, mean ± SD	23.73±4.46	25.17±3.37	22.78±5.04	0.329
MOCA, mean ± SD	17.67±5.77	19.50±5.09	16.44±6.15	0.332

Note: WMH, white matter hyperintensity; MMSE, mini-mental state examination; MOCA, Montreal cognitive assessment. Due to rounding, the total sum of percentages may slightly exceed 100%.

increased stride width (with statistically significant changes in the right stride length, P=0.006), faster walking speed (P=0.010), higher stride frequency (P=0.024), shorter support phase (P=0.010), and improved toe and heel angles off the ground (with statistically significant changes in the right toe and heel angles, as well as the left toe angle, P=0.033, P=0.039, and P=0.046, respectively. **Table 2**).

Walking function

The dual-task gait assessment showed improvements, although they were not statistically significant. The data indicated a trend towards reduced fall risk (P=0.063), wider stride (P=0.081), and faster walking speed (P=0.114), with a more stable stride frequency. Additionally, there were minor, non-significant improvements in the support phase (P=0.297) and toe and heel angles (**Table 3**).

General cognitive function

After three weeks of combined rehabilitation and rivastigmine treatment, there was a significant improvement in general cognitive function as measured by the MMSE (P=0.016) and Montreal cognitive assessment (MOCA, P= 0.000, **Table 4**). All patients were well-monitored during treatment, and no serious adverse events were reported.

Discussion

This study is the first to demonstrate that external counterpulsation combined with multimodal motor training significantly improves gait parameters and balance function. Three weeks of rehabilitation, including lisdexamfetamine treatment, had a positive impact on motor function in patients with PD. This included a reduction in fall risk, decreased duration of the

Table 2. Comparison of gait data before and after rehabilitation combined with rivastigmine treatment (the part of free walking)

Variables	Pre	Post	P
The risk of falls (%)	8.207±5.017	6.573±4.906	0.009
Stride length (left) (m)	0.874±0.219	0.949±0.220	0.057
Stride length (right) (m)	0.858±0.341	0.959±0.359	0.006
Walking speed (m/s)	0.729±0.263	0.837±0.250	0.010
Stride frequency (steps/min)	99.566±11.370	104.580±6.601	0.024
Support phase (%)	67.267±2.968	65.520±2.378	0.010
Swing phase (%)	32.733±2.968	34.480±2.378	0.010
Average left toe angle off the ground	37.340±7.457	40.127±6.508	0.046
Average right toe angle off the ground	38.333±7.189	41.407±6.031	0.033
Average left heel angle	22.653±7.901	25.213±7.585	0.048
Average right heel angle	21.140±7.372	23.393±7.082	0.039

Table 3. Comparison of gait data before and after rehabilitation combined with rivastigmine treatment (the part of dual task walking)

Variables	Pre	Post	P
The risk of falls (%)	10.140±6.772	8.173±5.501	0.063
Stride length (left) (m)	0.798±0.248	0.841±0.231	0.275
Stride length (right) (m)	0.793±0.361	0.869±0.347	0.081
Walking speed (m/s)	0.662±0.238	0.723±0.259	0.114
Stride frequency (steps/min)	100.374±14.614	100.791±14.198	0.873
Support phase (%)	67.773±3.415	67.180±3.294	0.297
Swing phase (%)	32.227±3.415	32.820±3.293	0.297
Average left toe angle off the ground	34.127±9.802	36.600±7.689	0.121
Average right toe angle off the ground	34.813±9.219	37.787±6.724	0.109
Average left heel angle	20.240±8.521	21.693±7.917	0.208
Average right heel angle	18.620±7.807	20.627±7.035	0.096

Table 4. Comparison of cognition in patients before and after rehabilitation combined with rivastigmine treatment

Variables	Pre	Post	P
MMSE, mean ± SD	23.73±4.46	24.47±3.62	0.016
MOCA, mean ± SD	17.67±5.77	18.47±5.51	<0.001

Note: MMSE, mini-mental state examination; MOCA, Montreal cognitive assessment.

bracing period, increased walking speed, enhanced cognitive level, and improvements in walking frequency, ground clearance angle, and heel clearance angle.

Multimodal motor rehabilitation may influence gait parameters through several mechanisms, including the induction of neuroplasticity, modulation of neuronal cell function, and alteration of intracranial neurotransmitter levels [17]. These processes collectively enhance brain function, evident from the reduced fall risk and improvements in walking speed, cadence, ground release angle, and heel strike angle. Previous studies have indicated that high-frequency repetitive transcranial magnetic stimulation activates excitatory trans-synaptic transmission, modulates subcortical and telecortical function, affects serotonin levels, and influences the expression of neurotransmitters such as brain-derived neurotrophic factor, dopamine, glutamate, and other neurotransmitters, thereby increasing neuronal activity and regional excitability [18, 19]. These mechanisms may explain the beneficial effects of multimodal rehabilitation training combined with rivastigmine therapy on motor function in PD patients observed in our study.

Extracorporeal counterpulsation therapy, a non-invasive physical intervention, has recently become a promising option in the rehabilitation of PD. This therapy utilizes a series of airbags that sequentially inflate and deflate, applying external pressure to the limbs and buttocks. This action modulates systemic blood flow and enhances vascular endothelial function, thereby improving vascular elasticity. By significantly increasing venous return from the lower limbs, extracorporeal counterpulsation boosts cardiac output and coronary perfusion pressure, which enhances cardiac function and overall circulation [20]. For individuals with PD, who frequently suffer from limb impairments due to motor disabilities and muscle rigidity, this therapy can relieve muscle stiffness and pain, and improve muscle strength and flexibility, thus enhancing limb functionality [21].

Simultaneously, the value of aerobic exercise in exercise rehabilitation for patients with PD has been increasingly recognized. Aerobic activities, such as walking, running, and swimming, are characterized by their continuous and rhythmic nature, improving cardiorespiratory fitness and endurance. Studies suggest that aerobic exercise can stimulate the release of dopamine in the brain, an essential neurotransmitter involved in regulating movement, mood, and cognition [22, 23]. In PD patients, the loss of dopaminergic neurons in the substantia nigra and degeneration of the nigrostriatal dopaminergic pathway lead to motor impairments due to decreased dopamine levels. Therefore, enhancing dopamine levels through aerobic exercise may alleviate motor symptoms and improve the quality of life in PD patients [22, 23].

In this study, the combined use of rehabilitation therapy and rivastigmine was observed to significantly improve both cognitive function and walking abilities in individuals with PD, supporting findings from previous studies. A prior randomized, double-blind, placebo-controlled study indicated a trend towards enhanced cognition in PD patients with mild cognitive impairment treated with rivastigmine [24]. An open-label trial also reported a reduction in neuropsychiatric inventory scores among patients with PD dementia during rivastigmine treatment, with scores reverting after the medication was discontinued [25]. Furthermore, rivastigmine has been shown to improve gait stability, potentially leading to a decreased incidence of falling [26].

Our rehabilitation protocol included flexibility exercises designed to actively stretch muscles, ligaments, and joints. Such exercises, focusing on stretching and balance, have been proven to effectively improve muscle tone, which positively impacts balance and walking pace. Additionally, exercise training as an adjunctive therapy has been shown to promote corticostriatal plasticity and enhance dopamine release, crucial for improving motor function in PD patients [27]. The reduction in falls associated with rivastigmine treatment likely occurs through the enhancement of cognitive function, particularly attention, which helps compensate for gait deficits caused by striatal dopaminergic loss, or it may directly influence gait mechanics [28].

It is important to note that the 3-week multimodal rehabilitation intervention in this study did not significantly impact gait under dual-task conditions, correlating with cognitive assessments that revealed varying degrees of cognitive impairment in most patients. These findings align with previous research indicating that cognitive decline can affect gait performance, especially under conditions requiring heightened attentional demands [29]. The observed cognitive deficits, particularly in attention and executive functions, may be linked to defective cholinergic projections in the basal forebrain cortex [30, 31]. This cognitive dysfunction is associated with the pathophysiology of PD. Moreover, underlying diseases such as hypertension, diabetes, smoking, and drinking were not common among the study participants, suggesting that these factors may not relate directly to PD. Prolonged rehabilitation could potentially yield more pronounced changes in gait parameters during dual-task testing if cognitive improvements are sustained, warranting further long-term investigation.

Traditional gait and postural balance analysis techniques, such as force platforms and motion cameras, are complex and costly, requiring professional operation, which poses significant challenges for medical assessments. This study utilized a Gibbon wearable device to objectively assess patients' fall risk, pace, joint angle, plantar pressure, stride, and other

parameters, proving to be an effective clinical and home-based neurological assessment tool.

This study's limitations include having a small sample size, necessitating further research with more cases to confirm these findings. Additionally, the quasi-experimental design employed does not establish a causal relationship between multimodal rehabilitation exercise combined with external counterpulsation therapy and motor function improvements. Moreover, as all participants were from the same region, the generalizability of the results to other populations may be limited. Future research should involve controlled trials and cohort studies that account for various confounding factors to validate these results.

The combination of multimodal exercise training with rivastigmine treatment showed improvements in certain gait parameters during single-task tests, enhanced balance function, and reduced fall risk. Cognitive levels also improved. The Gibbon gait analyzer proved to be a simple and effective tool for assessing motor function in PD patients, suitable for clinical use. Extended duration of exercise and cognitive rehabilitation may be necessary to further enhance motor and cognitive function.

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Disclosure of conflict of interest

None.

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