Preliminary Exploration of the Efficacy and Mechanisms of Precision Exercise Prescription on Anxiety, Depressive State, and Cognitive Function in Stroke Patients: Postprint

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Abstract

Background: In the current rehabilitation environment, emotional problems and cognitive dysfunction in stroke patients are more concealed compared with motor, speech, and swallowing issues, and thus receive insufficient attention in clinical rehabilitation. However, these problems can cause adverse outcomes and affect rehabilitation outcomes.

Objective: To observe the therapeutic efficacy of precision exercise prescription on anxiety, depression, and cognitive function in stroke patients, and to preliminarily analyze its mechanism of action.

Methods: Eighty-four stroke patients hospitalized in the Rehabilitation Department of Changzhou Dean Hospital from January 2022 to March 2023 were selected and divided into a control group (42 cases) and an experimental group (42 cases) using the random number table method. The control group received conventional rehabilitation therapy, while the experimental group received precision exercise prescription in addition to conventional rehabilitation. The prescription was precisely formulated based on cardiopulmonary exercise testing (CPET) results and was implemented for 12 weeks. The Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Mini-Mental State Examination (MMSE) scores, and serum homocysteine (Hcy) levels were compared between the two groups before and after rehabilitation training. Pearson correlation analysis was performed between pre-training Hcy levels and SAS, SDS, and MMSE scores.

Results: All 42 patients in the experimental group successfully completed CPET and the 12-week precision exercise prescription rehabilitation without any adverse events. Before rehabilitation training, there were no statistically significant differences in SAS, SDS, MMSE scores, or Hcy levels between the two groups ($P>0.05$). After rehabilitation training, the experimental group showed decreased SAS and SDS scores and Hcy levels compared with pre-treatment ($P<0.05$), while the control group showed no statistically significant changes ($P>0.05$). Pearson correlation analysis revealed that pre-training Hcy levels were positively correlated with SAS and SDS scores ($r=0.420$ and 0.507, respectively, $P<0.05$), but not correlated with MMSE score ($r=0.079$, $P=0.473$).

Conclusion: Precision exercise prescription can significantly improve anxiety, depression, and cognitive function in stroke patients, and may serve as a novel therapeutic approach for clinical promotion and application. Hcy may be one of the mechanisms through which precision exercise prescription improves anxiety and depression in stroke patients; whether Hcy is associated with the improvement of cognitive function by this prescription requires further investigation.

Full Text

Efficacy and Preliminary Mechanism of Precise Exercise Prescribing for Anxiety, Depression, and Cognitive Function in Patients with Stroke

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Abstract

Background: In the current rehabilitation environment, emotional issues and cognitive dysfunctions in stroke patients are often overshadowed by physical, speech, and swallowing difficulties, leading to their underestimation in clinical rehabilitation. This oversight can result in adverse outcomes, impacting the overall success of rehabilitation. Currently, clinical treatments primarily rely on pharmacotherapy to alleviate symptoms, which has limited effectiveness and can cause a range of adverse reactions.

Objective: To observe the efficacy of precision exercise prescriptions on anxiety, depression, and cognitive functions in stroke patients and to preliminarily analyze the underlying mechanisms of action.

Methods: A total of 84 stroke patients hospitalized in the rehabilitation department of Changzhou Dean Hospital from January 2022 to March 2023 were selected and randomly divided into a control group (42 patients) and an experimental group (42 patients) using a random number table method. The control group received standard rehabilitation treatment, while the experimental group received precision exercise prescriptions based on cardiopulmonary exercise testing (CPET) results in addition to standard rehabilitation for 12 weeks. The Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Mini-Mental State Examination (MMSE) scores, and homocysteine (Hcy) levels were compared before and after rehabilitation training in both groups. Pearson correlation analysis was conducted between pre-rehabilitation Hcy levels and SAS, SDS, MMSE scores.

Results: All 42 patients in the experimental group completed the CPET and the 12-week precision exercise prescription rehabilitation without any adverse events. Before rehabilitation training, there were no statistically significant differences in SAS, SDS, MMSE scores, and Hcy levels between the two groups ($P>0.05$). After rehabilitation training, the experimental group showed significant reductions in SAS and SDS scores compared to pre-treatment ($P<0.05$), which were also lower than those in the control group ($P<0.05$). The MMSE scores increased compared to pre-treatment ($P<0.05$) and were higher than those in the control group ($P<0.05$). Hcy levels decreased compared to pre-treatment ($P<0.05$) and were lower than those in the control group ($P<0.05$). There were no significant differences in SAS, SDS, MMSE scores, and Hcy levels before and after rehabilitation training in the control group ($P>0.05$). Pearson correlation analysis revealed a positive correlation between Hcy levels and SAS, SDS scores ($r=0.420$ and $r=0.507$, respectively, $P<0.05$), but no correlation with MMSE scores ($r=0.079$, $P=0.473$).

Conclusion: Our findings suggest that precision exercise prescriptions significantly improve anxiety, depression, and cognitive functions in stroke patients, indicating their potential as a novel therapeutic approach in clinical applications. Hcy may be one of the mechanisms through which precision exercise prescriptions improve anxiety and depression in stroke patients. Further research is needed to determine whether Hcy is related to the improvement of cognitive functions through this prescription.

Keywords: Stroke; Cardiopulmonary exercise testing; Precise exercise prescription; Anxiety; Depression; Cognitive function; Homocysteine

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Introduction

As the number of stroke patients continues to increase, approximately 59% experience disability, leading to growing rehabilitation demands. Current stroke rehabilitation strategies primarily focus on restoring motor function in the affected limbs and postural control. However, stroke patients' ability to achieve self-care and reintegrate into society and family life depends not only on motor recovery but also on emotional status and cognitive function, which deserve greater attention. Research indicates that approximately one-third of stroke patients develop depression, and nearly one-quarter experience anxiety. These negative emotions correlate with increased disability, reduced quality of life, and higher mortality rates. Additionally, studies have found that the incidence of post-stroke cognitive impairment in China reaches as high as 53.1%, with affected patients more likely to experience social isolation and difficulty integrating into family life.

Current clinical treatments for emotional and cognitive disorders primarily rely on medication to improve symptoms, but with limited effectiveness and a range of adverse reactions. The purpose of this study is to explore whether a novel intervention, such as precise exercise prescription, can improve anxiety, depression, and cognitive function in stroke patients. Furthermore, many scholars have recently begun investigating the relationship between homocysteine (Hcy) and stroke, finding associations with anxiety, depression, and cognition. Leveraging our hospital's research capabilities, we examined whether exercise might influence emotional status and cognitive function by acting on Hcy levels.

Methods

Study Participants and General Information We selected 84 stroke patients hospitalized in the rehabilitation department of Changzhou Dean Hospital between January 2022 and March 2023, including 51 males and 33 females. There were 28 cases of cerebral hemorrhage and 56 cases of cerebral infarction; all had unilateral hemiplegia affecting upper and lower limbs, with 46 left-sided and 38 right-sided cases. Patients were randomly divided into control and experimental groups of 42 each using a random number table method. Comparisons of age, sex, BMI, stroke duration, stroke type, and hemiplegic side showed no statistically significant differences between groups (P>0.05) (Table 1).

Table 1 Comparison of general data between trial and control groups

<table>
<tr><th>Characteristic</th><th>Trial Group (n=42)</th><th>Control Group (n=42)</th><th>Test Statistic</th></tr>
<tr><td>Age (years)</td><td colspan="3">65.5$±7.3|66.0±7.9|–0.059
0.344^a||Sex(n)|||0.449^b||Male|25|26|||Female|17|16|||BMI(kg/m^{2})|24.1±2.5|24.2±$2.6</td></tr>
<tr><td>Stroke duration (months)</td><td>0.85 (0.4, 1.3)</td><td>0.95 (0.5, 1.3)</td><td>-0.305</td></tr>
<tr><td>Stroke type (n)</td><td></td><td></td><td>0.214</td></tr>
<tr><td>Cerebral hemorrhage</td><td>13</td><td>15</td><td></td></tr>
<tr><td>Cerebral infarction</td><td>29</td><td>27</td><td></td></tr>
<tr><td>Hemiplegic side (n)</td><td></td><td></td><td>0.769</td></tr>
<tr><td>Left</td><td>24</td><td>22</td><td></td></tr>
<tr><td>Right</td><td>18</td><td>20</td><td></td></tr>
</table>

Note: indicates t-value, indicates ^{2} value, indicates Z-value.

Inclusion and Exclusion Criteria **Inclusion criteria:** (1) New-onset stroke (cerebral infarction or hemorrhage) meeting the 2019 Chinese diagnostic criteria for major cerebrovascular diseases formulated by the Cerebrovascular Disease Group of the Neurology Branch of the Chinese Medical Association, with CT or MRI imaging evidence and stable condition; (2) Ability to walk independently for 10 m (with or without assistive devices); (3) MMSE score <27 points, indicating cognitive dysfunction, but able to understand simple instructions to ensure cooperation with testing and training; (4) SAS score $ $50 points and SDS score $ $53 points; (5) Age $ $18 years; (6) Voluntary signed informed consent.

Exclusion criteria: (1) Heart failure or history of cardiac surgery; (2) Severe aortic stenosis, arrhythmia, or pulmonary embolism; (3) Unstable blood glucose or blood pressure control; (4) Conditions affecting exercise performance such as joint pain, limb fractures, or intermittent claudication; (5) Severe cognitive or psychiatric disorders preventing effective communication; (6) Use of β-blockers.

This study was reviewed and approved by the Ethics Committee of Changzhou Dean Hospital (approval number: CZDALL-2021-013). All included patients signed informed consent before entering the study.

Intervention Protocol **1.2.1 Intervention methods for both groups:** All patients in both groups underwent SAS, SDS, and MMSE assessments before rehabilitation training, and venous blood was collected to detect Hcy levels. The experimental group additionally underwent cardiopulmonary exercise testing (CPET) to assess cardiopulmonary function. After completing all assessments, the control group received conventional rehabilitation training, while the experimental group received precise exercise prescriptions based on CPET-derived cardiopulmonary indicators for aerobic training in addition to conventional rehabilitation. Both groups trained for 12 weeks, and SAS, SDS, MMSE scores and Hcy levels were reassessed after the rehabilitation program. Comparisons were made between groups before and after training, and relationships between Hcy levels and SAS, SDS, MMSE scores were analyzed.

1.2.2 Cardiopulmonary exercise testing (CPET): A rehabilitation physician from our hospital who had received professional training and was proficient in CPET equipment conducted the testing. Before rehabilitation training, the experimental group underwent symptom-limited maximal incremental CPET using a German-made Carefusion cardiopulmonary exercise testing system (Model: Matster Screen) and a Chinese-made disc and limb-linked exercise device (Model: XPACE-5P). A ramp power increment protocol was selected, with power increments (10-15 W/min) chosen based on sex, age, and physical condition. Before each CPET, the equipment underwent environmental, volume, and gas automatic calibration. After wearing the instruments, patients rested seated on the limb-linked device for 3 minutes, then performed 3 minutes of no-load warm-up at 80 steps/min, followed by the power increment phase, aiming to reach symptom-limited maximal exercise load within

8-12 minutes, then recovered for 5-10 minutes before test completion. Throughout the test, 12-lead ECG, blood oxygen saturation, non-invasive blood pressure, and various pulmonary ventilation indicators were closely monitored, with testing terminated when absolute or relative exercise termination criteria specified by ACSM were met. Key indicators recorded included peak oxygen uptake (VO_2peak), percentage of predicted peak oxygen uptake (VO_2peak%pred), peak heart rate (HRpeak), resting heart rate (HRrest), peak metabolic equivalent (METpeak), peak load, anaerobic threshold (AT), peak respiratory exchange ratio (RERpeak), and Borg scales for dyspnea and leg fatigue. The anaerobic threshold was calculated using the V-slope method, and patients' respiratory and leg fatigue levels during testing were assessed using the Borg Scale Rating of Perceived Exertion (15-level scale, range 6-20).

1.2.3 Assessment of anxiety, depression, and cognitive function: The SAS and SDS were used to evaluate anxiety and depression symptoms. Both scales contain 20 items with 4-level scoring systems and have good reliability and validity for assessing subjective feelings in anxious and depressed patients. Anxiety rating criteria: SAS score <50 = no anxiety, 50-59 = mild anxiety, 60-69 = moderate anxiety, >69 = severe anxiety. Depression rating criteria: SDS score <53 = no depression, 53-62 = mild depression, 63-73 = moderate depression, >73 = severe depression. Cognitive function was assessed using the MMSE, a widely used cognitive screening tool covering five domains: orientation (0-10), memory (0-3), attention and calculation (0-5), recall (0-3), and language (0-9), with 30 total items and a maximum score of 30 points. Scores <27 indicate cognitive dysfunction.

1.2.4 Hcy detection method: Before and after rehabilitation training, 3 mL of fasting elbow venous blood was collected in the morning. Serum was separated, and plasma Hcy levels were measured using the cyclic enzymatic method with an automatic biochemical analyzer (Beckman AU5800) and reagent kit (Shanghai Kehua Bio-engineering Co., Ltd., calibration samples CAL1-CAL: 5$×$0.5 mL, registration number: Shanghai Medical Device Registration 20142400020). The reference range was 0-15.00 mol/L.

1.2.5 Rehabilitation protocol:

1.2.5.1 Conventional rehabilitation training: Both groups received conventional rehabilitation training including range of motion exercises, transfer training, trunk and hip-knee control training, gait training, balance training, cognitive training, and physical therapy, administered once daily, 5 times per week for 12 weeks.

1.2.5.2 Precision exercise prescription: The experimental group received additional precision exercise prescription training based on conventional rehabilitation. The prescription consisted of four components: exercise intensity, duration, frequency, and type. Specifically: exercise intensity was precisely determined based on the maximum heart rate measured by CPET, with target heart rate = (maximum heart rate - resting heart rate) × (50%-60%) + resting heart rate. Finger pulse oximetry monitored heart rate during exercise, which was maintained within this range for 30 minutes, plus 10-15 minutes warm-up before and 10-15 minutes cool-down after exercise. Training was performed once daily, 5 days per week for 12 weeks using the limb-linked device (Model: XPACE-5P), with Borg Scale ratings maintained at 11-13 during exercise.

Statistical Analysis Data were analyzed using SPSS 22.0 statistical software. Count data were expressed as absolute or relative numbers and compared between groups using ^{2} test. Normally distributed measurement data were expressed as ($\bar{x}$±s) and compared between groups using independent samples t-test, with paired t-test for within-group comparisons. Non-normally distributed measurement data were expressed as M(P_{25},P_{75}) and compared between groups using Mann-Whitney U test, with Wilcoxon signed-rank test for within-group comparisons. Pearson correlation analysis was used to examine relationships between Hcy levels and SAS, SDS, MMSE scores. P<0.05 was considered statistically significant.

Results

All 84 patients completed both SAS, SDS, MMSE assessments and Hcy blood tests. All 42 patients in the experimental group successfully completed CPET (Figure 1) without adverse events during the 12-week training period. Specific CPET indicators are shown in Table 2.

Table 2 Results of cardiopulmonary exercise testing before rehabilitation training in the trial group

<table>
<tr><th>Indicator</th><th>Value</th></tr>
<tr><td>VO_2peak (mL · kg^{-1} · min^{-1})</td><td>12.83$±2.96||VO{2}peak±10.02||METpeak|3.80±1.06||HRpe kg{-1}·min{-1}]|5.93(3.90, 9.19)||RERpeak|1.03±0.12||BorgScale(dyspnea level]</td></tr>
</table>

Note: VO_2peak = peak oxygen uptake, VO_2peak%pred = percentage of predicted peak oxygen uptake, HRrest = resting heart rate, HRpeak = peak heart rate, METpeak = peak metabolic equivalent, load peak = peak load, AT = anaerobic threshold, RERpeak = peak respiratory exchange ratio, Borg = Borg Scale Rating of Perceived Exertion (15-level scale, range 6-20).

Correlation Analysis Between Hcy Levels and SAS, SDS, MMSE Scores Pearson correlation analysis before rehabilitation training showed that blood Hcy levels were positively correlated with SAS and SDS scores (r=0.420, P<0.001; r=0.507, P<0.001), but not correlated with MMSE scores (r=0.079, P=0.473).

Comparison of SAS, SDS, MMSE Scores and Hcy Levels Between Groups Before and After Rehabilitation Training Before rehabilitation training, there were no statistically significant differences in SAS, SDS, MMSE scores, and Hcy levels between the two groups (P>0.05). After rehabilitation training, the experimental group showed significantly reduced SAS and SDS scores compared to pre-treatment, which were also lower than those in the control group; MMSE scores increased compared to pre-treatment and were higher than those in the control group; Hcy levels decreased compared to pre-treatment and were lower than those in the control group (all P<0.05). The control group showed no statistically significant differences in SAS, SDS, MMSE scores, and Hcy levels before and after rehabilitation training (P>0.05) (Table 3).

Table 3 Comparison of SAS, SDS, MMSE scores and Hcy levels between two groups before and after rehabilitation training

<table>
<tr><th>Measure</th><th>Before Training</th><th>After Training</th><th>t/Z paired</th><th>t/Z between groups</th></tr>
<tr><td></td><td>Trial</td><td>Control</td><td>Trial</td><td>Control</td></tr>
<tr><td>SAS (x̄±s, points)</td><td colspan="4">65.43$±8.99|64.52±7.33|48.62±7.66|66.29±7.89| < 7 (7,8) 7 (6,8) 9 (8,9) 0.001| < 0.001||$SDS(x±s, points)$|66.12±7.42|65.26±7.21|51.86±7.50|66.38±8.75| < 0.001| < 0.001||$Hcy(x±s, \mu mol/L)$|22.03±3.39|20.53±4.18|12.57±3.78|22.79±3.74| < 0.001| < 0.001||$MMSEtotal(x±s, points)$|20.83±2.32|21.74±2.14|26.02±1.69|21.12±2.01| < 0.001| < 0.001||$Orientation[M(P{25}, P{75}), points]$|7(6, 8)|7.5(7, 8)|9(8, 10)|7(7, 8)| < 0.001| < 0.001||$Memory[M(P{25}, P{75}), points]$|2(1, 2)|2(1, 2)|2(2, 3)|2(1, 2)| < 0.001| < 0.001||$Attention/calculation[M(P{25}, P{75}), points]$|3(3, 4)|3(3, 4)|4(4, 5)|3(3, 4)| < 0.001| < 0.001||$Recall[M(P{25}, P{75}), points]$|1(1, 2)|1(1, 2)|2(2, 3)|2(1, 2)| < 0.001| < 0.001||$Language[M(P{25}, P{75}$), points]</td></tr>
</table>

Note: SAS = Self-Rating Anxiety Scale, SDS = Self-Rating Depression Scale, MMSE = Mini-Mental State Examination; indicates Z-value.

Discussion

Expert consensus has highlighted that post-stroke anxiety and depression warrant attention because they can delay patient recovery and reduce quality of life.

The standard treatments for these conditions are medication and psychotherapy, but their efficacy is uncertain in the stroke population and they can cause adverse reactions such as sleep disorders, motor ataxia, and sensory abnormalities. Clinically, there is an urgent need to find safer and more effective measures to break through this therapeutic bottleneck. Although the link between exercise and mental health is well-established, few studies have examined this relationship in stroke patients. Additionally, more than one-third of patients are affected by cognitive impairment 3-12 months post-stroke, which persists for years in many individuals, hindering effective rehabilitation, affecting independence in daily activities, and even increasing mortality. Currently, there are no specific drugs for treating post-stroke cognitive impairment, and adverse reactions often limit their use. Consequently, non-pharmacological treatments have gained increasing attention. This study innovatively used precision exercise prescriptions for aerobic training to intervene in cognitive impairment in stroke patients, aiming to open new avenues for rehabilitation.

Our study found that after rehabilitation training, the experimental group showed significantly reduced SAS and SDS scores compared to pre-treatment ($P<0.05$) and lower than the control group ($P<0.05$), while the control group showed no significant differences in SAS and SDS scores before and after training ($P>0.05$). These results demonstrate that precision exercise prescriptions can improve anxiety and depression in stroke patients, consistent with research finding that aerobic exercise as a physical therapy with rehabilitation characteristics can effectively improve post-stroke depression. Exercise not only reduces the risk of depression but also alleviates its symptoms, though evidence is relatively insufficient in the stroke population. Graven et al. reported that only 2 out of 10 studies showed positive effects of exercise on alleviating post-stroke depressive symptoms. Other studies have shown that exercise has both antidepressant and anxiolytic effects. The underlying mechanisms by which exercise training improves mood in stroke patients remain unclear. Our Pearson correlation analysis showed a positive correlation between Hcy and anxiety/depression, similar to Li et al.'s findings that elevated blood Hcy exacerbates depression severity, indicating Hcy is a factor influencing anxiety and depression. After precision exercise prescription intervention, the experimental group showed significantly reduced Hcy levels compared to pre-treatment ($P<0.05$) and lower than the control group ($P<0.05$), suggesting that precision exercise prescriptions may participate in the pathogenesis of post-stroke depression and anxiety by influencing plasma Hcy levels. Additional mechanisms may include: aerobic exercise (Baduanjin) can regulate the synthesis and release of monoamine neurotransmitters such as serotonin to alleviate negative emotions; research has confirmed that exercise can alleviate post-stroke depression by regulating neurotransmitter levels, increasing brain-derived neurotrophic factor (BDNF), inhibiting neurotoxicity, and promoting nerve regeneration. Whether these mechanisms exist in the stroke population requires further investigation.

Our results also demonstrated that after three months of precision exercise prescription training, the experimental group showed significantly increased MMSE scores compared to pre-treatment ($P<0.05$) and higher than the control group ($P<0.05$), while the control group showed no significant difference in MMSE scores before and after conventional rehabilitation training ($P>0.05$). This suggests that precise individualized aerobic training programs help improve cognitive function in stroke patients. Vanderbeken et al.'s systematic review reported similar results, demonstrating positive effects of exercise on post-stroke cognitive activity. Marzolini et al. proved that combined aerobic and resistance training significantly improved MoCA scores in stroke patients from 22.5 to 24.0 points. However, a meta-analysis of 14 randomized controlled trials found that exercise training had clear positive effects on attention and processing speed in stroke patients, but no significant improvement in executive function and working memory. These inconsistent conclusions may result from different exercise modalities, intensities, and durations across studies. This study attempted to explore the mechanism by which precision exercise prescriptions improve cognition and found that the prescription significantly reduced Hcy levels, but no correlation existed between Hcy and MMSE scores. This differs from Zhang et al.'s conclusion that plasma Hcy significantly affects cognitive function in ischemic stroke patients, possibly due to sample size limitations preventing detection of a relationship between Hcy and cognitive improvement. Current mechanisms of exercise effects on cognition have been studied in animal experiments and other populations: Ploughman et al.'s animal experiments found that exercise can increase BDNF and insulin-like growth factor-1 levels, promoting synapse and dendrite formation; a study on older adults emphasized that physical exercise can cause hippocampal neuroplasticity changes; Austin et al.'s systematic review indicated that exercise can reduce lesion volume in stroke and protect surrounding tissue from inflammatory and oxidative damage. However, few studies have examined the mechanisms of aerobic exercise on cognitive impairment in stroke patients, and whether these mechanisms can be observed in this special population warrants further investigation.

Precision exercise prescriptions significantly improve anxiety, depression, and cognitive function in stroke patients. As a novel treatment approach, this exercise prescription will benefit patients' long-term comprehensive rehabilitation and deserves clinical promotion and application. The positive correlation between Hcy and SAS/SDS scores, combined with the prescription's significant Hcy-lowering effect, suggests Hcy may be one mechanism by which precision exercise prescriptions improve anxiety and depression in stroke patients. Whether Hcy is related to cognitive function improvement requires further verification through multi-center, large-sample studies. This study has limitations, including the lack of global consensus on exercise type, intensity, duration, and frequency effects on mood and cognition in stroke patients. The dose-response relationship between exercise intensity and mood/cognition should be a future research focus.

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Note: Figure translations are in progress. See original paper for figures.