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ORIGINAL ARTICLE

The effects of low-intensity resistance training with or without blood flow restriction on serum BDNF, VEGF and perception in patients with post-stroke depression

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Abstract

BACKGROUND: Post-stroke depression (PSD) has a significant effect on patients' quality of life and is often accompanied by a decrease in serum brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) levels. Although exercise is an effective way to improve the body's endocrine environment, traditional high-intensity resistance exercise is not yet readily accepted.
PURPOSE: To compare the acute effects of high and low resistance training with or without blood flow restriction on perception, BDNF, and VEGF levels in patients with PSD.
METHOD: A total of 24 patients with PSD participated in 2 40% 1- Repetition Maximum (RM) low-intensity resistance training sessions (the low-intensity resistance training group (LOW group) had no blood flow restriction belt; the low-intensity blood flow restriction group (L-BFR group) was required to wear a 120-160 mmHg pressure cuff at the proximal end of the limb) and 1 80% 1-RM high-intensity resistance training session (HIGH group). Elbow venous blood was collected before and after exercise to test for ratings of perceived exertion (RPE), serum blood lactic acid (BLA), BDNF, and VEGF levels.
RESULT AND CONCLUSION: There were no statistical differences between the RPE, BLA, BDNF, and VEGF levels of each group before exercise. After exercise, the RPE, BLA, and BDNF levels of the LOW group increased significantly ($P < 0.05$); the change in VEGF level of the LOW group was not significantly different from that before exercise ($P > 0.05$), and the indexes of the L-BFR group and the HIGH group were significant after the increase in exercise ($P < 0.05$). Analysis between groups showed that the changes in BLA, BDNF, and VEGF levels in the L-BFR group and HIGH group were higher than those in the LOW group, and the statistical difference was significant ($P < 0.05$); there was no change between the statistical difference of the L-BFR group and HIGH group ($P > 0.05$).

The difference in RPE before and after exercise in the HIGH group was significantly higher than that in the L-BFR group ($P < 0.05$) and the difference in RPE before and after exercise in the L-BFR group was significantly higher than that in the LOW group ($P < 0.05$). Blood flow restriction resistance exercise may increase the serum BNDF and VEGF levels of PSD patients by increasing the body's BLA concentration. Although its effect is similar to that of traditional high-intensity resistance exercise, subjective physical strength is lower during blood flow restriction resistance exercise.

Introduction

Stroke often occurs in middle-aged and old people and significantly affects the patients' quality of life. After a stroke, different degrees of depression are often followed, called Post-stroke depression (PSD)(Eng & Reime 2014), which is a type of post-stroke depression that includes a variety of neurological and physical symptoms. Symptomatic complex affective disorders are often accompanied by a decrease in serum brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) levels (Hadidi *et al.* 2017). Exercise therapy is a safe and effective rehabilitation programme that can not only prevent the occurrence of ischaemic stroke, but also improve learning, memory, spatial recognition ability, and emotional state after stroke by increasing neuroprotective factors such as BDNF and VEGF (Radak *et al.* 2001). However, the traditional high-intensity resistance programme, which includes high exercise intensity and exercise risk, is not suitable for PSD patients in the long-term, so it is necessary to find a safer and more feasible training programme to replace it. Recent studies have shown that resistance exercise combined with blood flow restriction can increase the body's metabolic stress and produce more blood lactic acid (BLA) at a lower load. The effect is similar to that of high-intensity resistance exercise (Rolnick N 2020), and the production of BDNF and VEGF is closely related to the BLA content(Pedersen 2019). The question was whether low-intensity resistance exercise, combined with blood flow restriction, is able to enhance the levels of BDNF and VEGF in PSD patients by increasing blood lactate. At present, there are only a few studies on the application of blood flow restriction in exercise rehabilitation of PSD patients, therefore it is unclear what potential advantages it holds over traditional high-intensity resistance exercise. This study aimed to address this issue by examining the effects of blood flow restriction resistance exercise on patients' PSD acute reaction during exercise.

METHOD

Subjects

A total of 24 patients with ischaemic stroke hospitalised in Qingdao Hiser hospital between September 2015 and September 2020 were selected. The inclusion criteria of subjects included: 1. Ischaemic stroke was diagnosed by cranial computed tomography (CT) or magnetic resonance imaging (MRI). 2. A Hamilton Depression scale (Hamilton depression rating scale, HAMD) score of ≥ 8. 3. The course of the disease was within 3 months. 4. Barthel index > 30. 5. The Brunnstrom stages were IV and V. 6. The muscle strength of the affected limb was higher than grade III, and the muscle tension of the modified Ashworth scale was lower than grade I.

Exclusion criteria: 1. People with a history of mental illness. 2. People with obvious cognitive impairments. 3. Combination with peripheral neuropathy. 4. People who have experienced exercise-related discomforts, such as angina, coronary heart disease, and myasthenia gravis. 5. Those have been diagnosed as a haemorrhagic stroke. 6. People who have taken antipyretics, analgesics, dopamine, and other drugs that affect autonomic nerve function within 2 weeks. The hospital ethics committee approved this study, and all selected subjects signed an informed consent form. The basic conditions of the subjects are shown in Table 1.

Research design

Before the formal test, all subjects continued to undergo routine early rehabilitation and stroke medications. First, each subject underwent a maximum muscle strength test, followed by 3 randomised resistance exercise tests (1. Low-intensity resistance exercise (LOW group); 2. Blood flow restriction low-intensity resistance exercise (L-BFR group); 3. High-intensity resistance exercise (HIGH)). There were 3 days between each test, and the test duration was between 14:00 and 17:00. Cubital venous blood was collected before and immediately after exercise, to test for blood biochemical indicators. The subjects were asked about RPE before and after exercise (using the Borg 6-20 scale to assess the subject's subjective physical sensation before and after exercise) and were required to wear a blood oxygen saturation finger clip (AM-807-C, Maxim, Shenzhen) throughout the process for safety purposes.

Maximum muscle strength test

First, the subjects were familiarised with the use of the 4 test instruments (see 1.4 for the form of exercise) and performed tests using the 4 instruments after the preparation activities were completed. Subjects chose an initial weight (50%-70% 1-RM) according to the range of self-predictability. After each test was completed, the load was increased by 10-20% until the subject was unable to complete the predetermined number of repetitions. The speed and joint range of motion were kept constant during exercise, with a rest period of 120 seconds between the 2 tests, and the maximum weight completed was recorded as 1-RM.

Exercise plan

The implementation of the resistance exercise programme for stroke patients was based on the

Tab. 1. Basic conditions of subjects (n = 24)

Age	Gender		Course of disease (day)	Side of hemiplegia		HAMD score (24 items)
	Male	Female		left	right	
47.83 ± 4.83	14	10	44.42 ± 3.96	13	11	8.83 ± 1.09

Tab. 2. Test result table of the subject's muscle strength (n = 24)

	1-RM (kg)	80% 1-RM (kg)	40% 1-RM (kg)
Sitting shoulder lifting	28.88 ± 5.64	23.10 ± 4.52	11.55 ± 2.26
Sitting arm pull-down	34.75 ± 7.72	27.80 ± 6.18	13.90 ± 3.09
Sitting Chest Press	36.83 ± 10.12	29.47 ± 8.10	14.73 ± 4.05
Sitting leg Press	56.79 ± 11.82	45.43 ± 9.46	22.72 ± 4.73

previous study (Hogg *et al.* 2020). The LOW group and the HIGH group were required to complete 3 groups of 40% 1-RM and 80% 1-RM resistance exercises, respectively. This was repeated 10 times for each group, with a 120 second resting period between groups. Exercises targeted the large muscles of the whole body, mainly 4 actions, including sitting pull-down (FCM 5120, HUR, Finland), sitting shoulder press (FCM 5120, HUR, Finland), sitting chest push (FCM 5140, HUR, Finland), sitting leg kick (FCM 5545), HUR, Finland).

The source of resistance in the HUR exercise equipment was air resistance, which was safer for the subjects. An experimenter instructed the exercise throughout the programme and actively encouraged the subjects to complete the exercise. In the L-BFR group, a blood flow restriction band (SC12L, Hokanson, USA) had to be worn at the proximal end of the moving limbs based on the LOW group test procedure, and the upper and lower limb pressures were set to 120 mmHg and 160 mmHg respectively.

blood test

Cubital venous blood was collected before and immediately after exercise. After standing for 30 minutes, serum samples were separated from blood cells by centrifugation (3000 rpm, 15 minutes), and stored at -80 °C for further analysis. The instructions of the kit were strictly followed, and the Enzyme-linked immunosorbent assay (ELISA) was used to test the serum for the presence of BDNF and VEGF. An automatic biochemical analyser and supporting reagents (Boao Biological Company, Nanjing) were used to detect serum BLA levels.

Statistical methods

The Shapiro-Wilk normality test was used to determine the normal distribution of various index data. In addition, two-factor repeated measurement analysis of variance was used to evaluate the landlord effects and interaction effects of BDNF and VEGF changes in three groups at 2 time points (i.e., pre-exercise: pre, post-exercise: post); a paired-sample t-test was used to analyse the RPE and BLA exercises in each group.

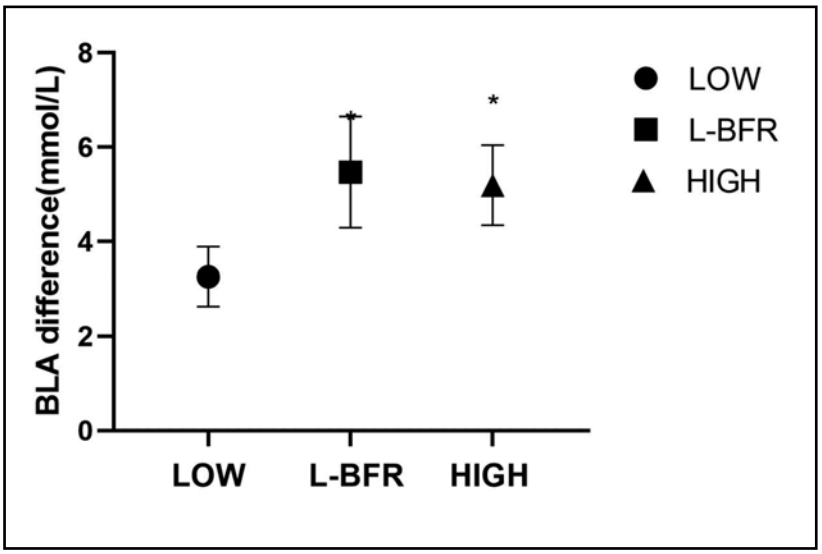

Fig. 1. Comparison chart of BLA change difference before and after exercise of each group. Note: * represents a statistically significant difference compared with the LOW group ($P < 0.05$).

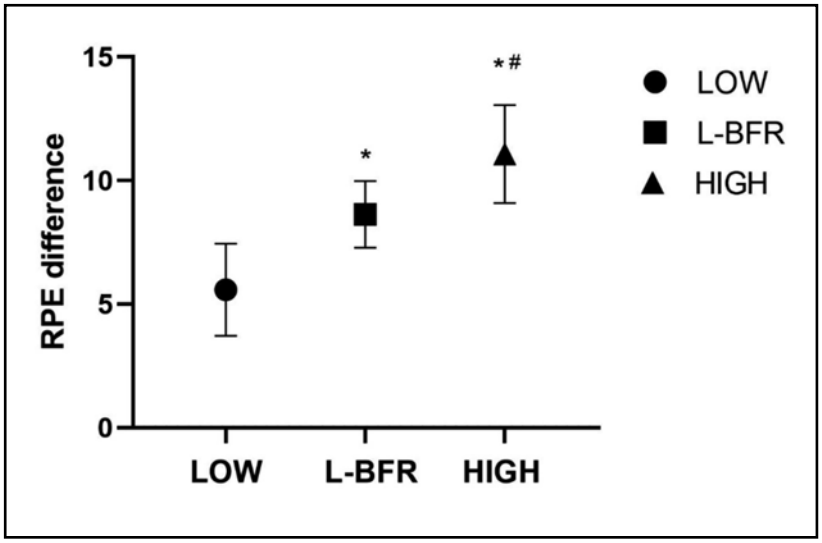

Fig. 2. Comparison chart of the changes in RPE difference before and after exercise of each group
Note: * represents a statistically significant difference compared with the LOW group ($P < 0.05$); # represents a statistically significant difference compared with the L-BFR group ($P < 0.05$).

The Newman-Keuls method was used for multiple comparisons of the difference between before and after exercises, when the main effect or the interaction effect was significant. Statistical analysis was performed using the SPSS 24.0 software (IBM, USA). All data were expressed as mean±standard deviation (Mean ± SD). $P < 0.05$ was considered statistically significant.

RESULTS

After the subject's maximum muscle strength was tested, the 40% or 80% 1-RM required for exercise was calculated according to the maximum muscle strength of each movement (see Table 2).

After exercise, BLA levels in the LOW (1.72 ± 0.36 vs 4.98 ± 0.61), L-BFR (1.55 ± 0.31 vs 7.01 ± 1.07), and HIGH (1.75 ± 0.35 vs 6.94 ± 0.94) groups increased significantly, $P < 0.05$. As shown in Figure 1, the changes in BLA levels of the L-BFR and HIGH groups were higher than those of the LOW group, and the difference was statistically significant ($P < 0.05$); there was no statistical difference between the L-BFR and HIGH groups ($P > 0.05$).

After exercise, the BLA levels in the LOW (6.46 ± 0.51 vs 12.04 ± 1.88), L-BFR (6.42 ±0.50 vs 15.04 ± 1.27), and HIGH (6.50 ± 0.51 vs 17.58 ± 1.95) groups displayed significant increments, $P < 0.05$. As shown in Figure 2, the changes in BLA levels of the L-BFR and HIGH groups were higher than those of the LOW group, and the difference was statistically significant ($P < 0.05$); the change in the HIGH group was significantly higher than the L-BFR group ($P < 0.05$).

As shown in Figure 3, there was no statistical difference in serum BDNF concentration of each group before exercise ($P > 0.05$). BDNF concentrations of each group significantly increased after exercise ($P < 0.05$)

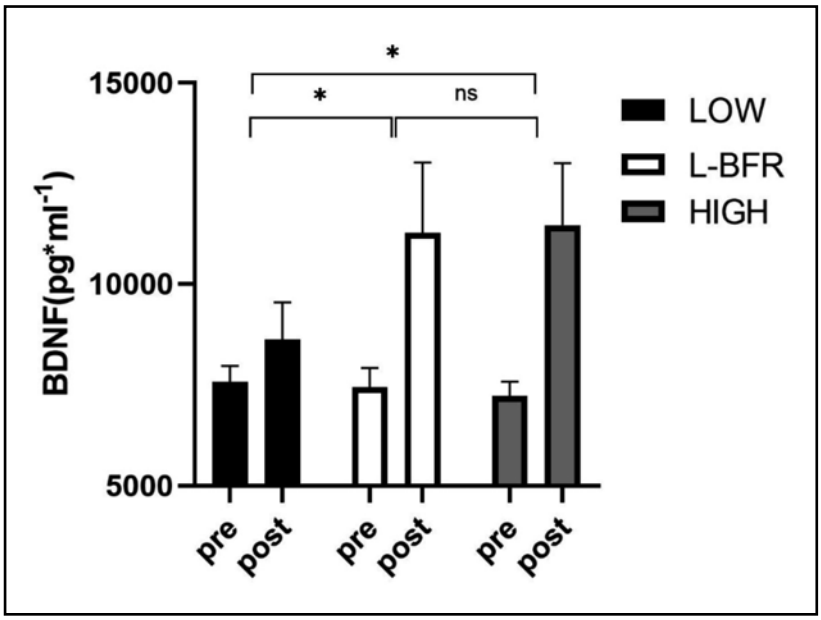

Fig. 3. BDNF concentration changes before and after two groups of exercises
Note: ns represents no statistical difference between the two groups of changes ($P > 0.05$); * represents a statistically significant difference between the two groups of changes ($P < 0.05$).

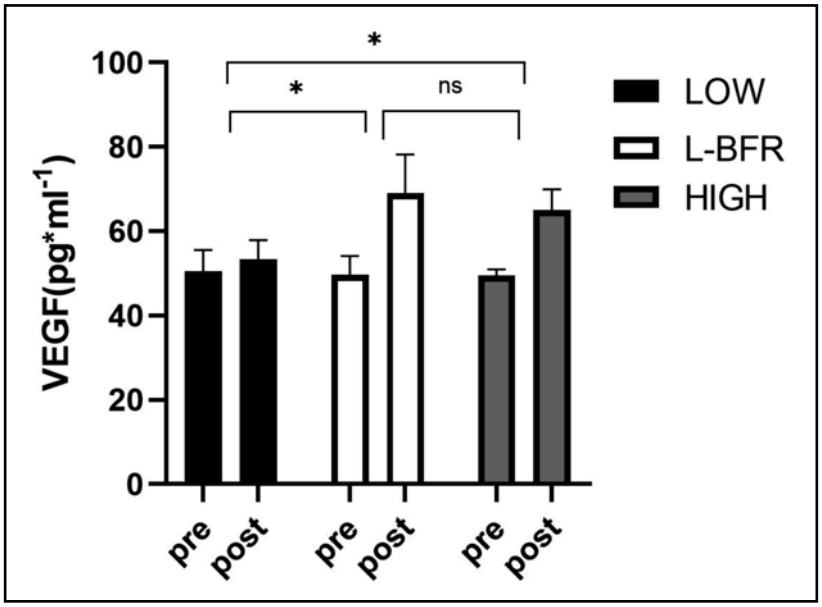

Fig. 4. Diagram of VEGF changes in the two groups before and after exercise
Note: ns represents no statistical difference between the two groups of changes ($P > 0.05$); * represents a statistically significant difference between the two groups of changes ($P < 0.05$).

and repeated measurement analysis of variance showed that the changes in each group had an interactive effect ($P < 0.05$). The changes in BDNF concentration before and after exercise in the L-BFR group and HIGH group were significantly higher than those of the LOW group, $P < 0.05$; there was no statistical significant difference ($P > 0.05$) between the L-BFR and HIGH groups.

As shown in Figure 4, there was no statistical difference in the serum VEGF concentration of each group before exercise ($P > 0.05$). While the VEGF concentrations of the L-BFR and HIGH groups increased significantly after exercise ($P < 0.05$), the VEGF concentration of the LOW group after exercise was not significantly different from before exercise ($P > 0.05$). Repeated measurement analysis of variance showed that the changes in each group had an interactive effect ($P < 0.05$). The changes in VEGF concentrations before and after exercise in the L-BFR and HIGH groups were significantly higher than those of the LOW group, $P < 0.05$; there was no statistical difference ($P > 0.05$) between the L-BFR and HIGH groups.

DISCUSSION

This study was a cross-sectional experiment to examine the effects of low-intensity resistance exercise combined with blood flow restriction on serum BLA, BDNF, VEGF, and RPE in PSD patients. Previously, resistance exercises were mainly used for the rehabilitation of stroke patients, while traditional high-intensity resistance exercises were not only more intense but also less safe and not suitable for long-term exercise. A recent study has shown that high-intensity resistance exercises require 3 weeks and after resistance training, there was a 26% joint pain rate among stroke patients (Hogg *et al.* 2020). This study was based on the previous exercise programme (Hogg *et al.* 2020), with no adverse events occurring in each group. Since the current range of cuff pressure suitable for stroke patients was not yet clear, the lowest pressure value used by subjects of the same age in resistance exercises was based on (Segal *et al.* 2015). The findings of the study showed that the L-BFR group was more conducive to the increase of serum BLA, BDNF, and VEGF levels after exercise in PSD patients than the LOW group, and the effect of the L-BFR group was similar to that of the HIGH group. However, the PRE level after exercise in the L-BFR group was lower compared to the HIGH group.

As a common complication of stroke, PSD not only reduces the quality of life and neurological function during the rehabilitation process but also increases the risk of recurrence (Almhdawi *et al.* 2021). At present, the mechanism of PSD is still not clear but it is believed that abnormal secretion of neurotransmitters, damage to the neurotrophic state, and excessive apoptosis of nerve cells may contribute to the onset of PSD (Xu *et al.* 2018).

BDNF is a neurotrophic factor closely linked to PSD that has previously been established (Lee & Kim 2010). Low levels of BDNF reduce the expression of tyrosin-related kinase receptor B (TrkB) and p75 neurotrophin receptor ($p75^{NTR}$), leading to a decrease in the recruitment of cyclic adenosine monophosphate (cAMP) response element-binding proteins to targeted sites on genes that mediate learning and memory, thereby reducing the neurological function of PSD patients (Lu *et al.* 2014; Yang *et al.* 2009; Matsumoto *et al.* 2008). In addition, studies have shown that BDNF can pass through the blood-brain barrier (Pan *et al.* 1998), and about 75% of peripheral BDNF comes from the brain (Rasmussen *et al.* 2009; Krabbe *et al.* 2007). Therefore, changes in serum BDNF may reflect changes in central BDNF to a certain extent. Exercise is an effective

way to increase BDNF and enhance cognitive ability to improve the structural and functional plasticity of the brain. Higher exercise intensity may trigger a greater BDNF response (Saucedo Marquez *et al.* 2015), but also poses higher exercise risks, especially for PSD patients; therefore, high-intensity resistance exercises may not be suitable. The results of this study show that the use of blood flow restriction at the same exercise intensity can increase the peripheral BDNF levels of PSD patients and is similar to the effect of high-intensity training (LOW: 13.8% vs L-BFR: 51.2% vs HIGH: 58.3%).

This effect could be linked to the higher BLA levels after blood flow restriction (Ferris *et al.* 2007) which can reduce the transport of BLA by inhibiting the blood flow of the moving limbs and reduce the recovery rate. For a long time, BLA has simply been regarded as a by-product of anaerobic energy supply. However, it is now believed that lactic acid is an essential signalling molecule that is involved in several metabolic processes (Magistretti & Allaman 2018). In addition, lactic acid can cross the blood-brain barrier through the Monocarboxylate Transporter (MCT)(Proia *et al.* 2016) to reach neurons (Camandola & Mattson 2017), which provides the basis for its involvement in the regulation of the central system. However, the mechanism of the interaction between lactic acid and BDNF is yet to be determined, though it is speculated that it is possible that:

1. Lactic acid promotes the expression of neuroplasticity-related genes and the production of BDNF by enhancing the activity of N-methyl-D-aspartic acid (NMDA) receptors in neurons (Yang *et al.* 2014).

2. Lactate induces peroxisome proliferator-activated receptor γcoactivator-1 (PGC-1)-fibronectin type III via sirtuin-1 (SIRT1) activation of the Fibronectin Type III Domain-Containing protein 5 (FNDC5)-BDNF pathway which promotes the production of BDNF (El Hayek *et al.* 2019) . In addition, VEGF is also closely related to the occurrence and development of PSD. At present, like BDNF, it is also regarded as a potential therapeutic target for anti-depression (Warner-Schmidt & Duman 2008) as it can primarily cross the blood-brain barrier to improve brain deficiency and promote the growth of nerves and blood vessels, with blood protecting the nerves (Maass *et al.* 2016).

Findings have shown that VEGF levels in the L-BFR and HIGH groups increased significantly before and after exercise, but there was no significant change in the LOW group. It is possible that BFR restricted the blood flow of the limbs, which placed the body in a relatively hypoxic environment and promoted the secretion of peripheral VEGF by increasing hypoxia inducible factor-1 (HIF-1) (Ohno H 2012). In addition, a recent study discovered that blood lactic acid could also regulate the expression of central VEGF under the mediation of hydroxycarboxylic acid receptor 1 (HCAR1) in the blood-brain barrier. The study showed that after 7 weeks of treadmill exercise, mice lacking HCAR1 did not display VEGF expression and capillary density increase in the dentate gyrus or sensorimotor cortex (Morland *et al.* 2017). This suggested that HCAR1 is essential for exercise-derived BLA-mediated VEGF expression and angiogenesis in specific brain regions.

RPE is an effective indicator of subjective feelings during exercise, and exercise compliance can be improved by increasing positive subjective feelings in the exercise program (Salmon *et al.* 2003). Although low-intensity BFR exercise had similar effects on the BLA, BDNF, and VEGF levels of PSD patients to traditional high-intensity resistance exercise, the results of this study show that the difference in RPE before and after exercise in the L-BFR group was significantly lower than the HIGH group. L-BFR group exercise intensity is related to lower cuff pressure, and similar results have been described in previous studies (Freitas *et al.* 2021; Miller *et al.* 2020). While there have been no studies on stroke patients, it was previously mentioned that healthy people perform 30% 1-RM + 50% LOP BFR exercises. The RPE was significantly lower than 80% 1-RM high-intensity resistance exercise (5.9±0.8 VS 9.5±1.0). These results suggested that low-intensity BFR exercises may be more compliant than traditional high-intensity resistance exercises. The reasons for subjective physical strength during exercise may vary, such as exercise intensity, rest interval, cuff type, and cuff pressure, and do not exclusively depend on the level of BLA (Lixandrao *et al.* 2019).

There are also several limitations to this study. Firstly, although peripheral VEGF and BDNF are closely related to the central nervous system, their precise values in the brain could not be accurately measured due to technical limitations, and only reflect changes in central VEGF and BDNF to a certain extent. Secondly, due to the experimental procedure's limitations, it was not possible to conduct a comprehensive assessment of the subjects' physical function and mood immediately after exercise. Finally, it was not clear whether there were differences in the effects of blood flow restriction under different pressures, and it is important to improve on this in subsequent studies.

In summary, blood flow restriction resistance exercise may be able to increase the serum BNDF and VEGF levels of PSD patients by increasing the body's BLA concentration. While it is similar to the traditional high-intensity resistance exercise, the subjective physical strength is lower during the blood flow restriction resistance exercise, and there is higher exercise compliance.

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