# **Application of blood flow restriction training in lower limb rehabilitation**

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Abstract. With the popularity of national fitness campaigns, sports injuries, especially lower limb injuries such as anterior cruciate ligament tears and ankle sprains, are increasing year by year. There are limitations in traditional treatment such as muscle atrophy. In recent years, the blood flow restriction training method (BFRT) which simulates high-intensity exercise with low intensity and limits arterial and venous blood flow to promote muscle growth and strength enhancement, has drawn attention as a novel approach to rehabilitation. This article reviews the application of BFRT in the rehabilitation of lower limb injuries, discusses its effects on muscle function, pain management and quality of life, and evaluates its safety and prospects for clinical application. BFRT reduces mechanical stress, relieves pain, improves endurance and aerobic capacity, and improves cardiovascular function. However, there are discomfort and potential risks, such as muscle injury and thrombosis, which require individualised adjustments and standardised training. BFRT has shown positive result(reducing pain &oedema and improving function)s in rehabilitation of ACL reconstruction (ACLR) and chronic ankle instability (CAI). In addition, BFRT has been shown to aid in the functional recovery of the lower extremity in patients with Achilles tendon injuries and strokes. Despite the positive effects of BFRT, relevant studies have problems such as small sample sizes and non-uniform parameters. BFRT is considered a safe training modality, but contraindications should be examined before clinical application. Future research endeavours should investigate the impact of BFRT in many rehabilitation contexts and enhance tailored rehabilitation strategies. In order to maximize the therapeutic benefit, a rehabilitation training program should be developed and refined with a minimum effective dose based on the quantification of the in vivo physiological response to BFRT. The identification of the optimal prognostic approach will help to advance the standardisation of BFR treatment methods.

**Keywords:** Blood flow restriction training, Rehabilitation, Lower limb injuries, Anterior cruciate ligament reconstruction, Chronic ankle instability

#### 1. Introduction

The rise of the national fitness movement has coincided with an increase in the number of people suffering from sports injuries. Data from the State General Administration of Sports indicates that the incidence of sports injuries in China is between 10 and 20 per cent. It is estimated that in the future there will be more than 100 million people in need of sports injury prevention and treatment every year. Lower limb injuries are a common occurrence and include ACL tears, ankle sprains, knee osteoarthritis, Achilles tendon tears, and so forth. Patients' quality of life and physiological function are significantly

impacted by these injuries. The risk of secondary injuries can also rise if protection and training are not implemented on time. In the current management of lower limb sports injuries, long-term fixation and reduction of joint muscle activity are the most commonly employed treatment methods. These techniques do have some drawbacks, though, such as the possibility of reduced muscle mass and atrophy. According to statistics from the American College of Sports Medicine, high-load resistance training at a level of  $\geq$ 70%1RM is advised in order to promote muscle hypertrophy and strength. Nevertheless, it is challenging to achieve the desired muscle strength levels in patients with lower limb joint injuries and those who have undergone surgery through traditional high-load resistance training. Consequently, in order to identify an alternative training method to replace the traditional high-load training, BFRT has been progressively implemented in the field of rehabilitation, while ensuring patient safety. In the current management of lower limb sports injuries, two treatment methods are most commonly employed: long-term fixation and reduction of joint muscle activity. However, these methods have certain limitations, including muscle atrophy and a reduction in muscle mass. The data from the American College of Sports Medicine indicates that in order to increase muscle hypertrophy and muscle strength, it is recommended to use high-load resistance training at a level of  $\ge 70\%$  1RM. However, it is challenging to achieve the desired muscle strength levels in patients with lower limb joint muscle injuries and those who have undergone surgery through traditional high-load resistance training. Consequently, an alternative training method, BFRT, has been progressively implemented in the field of rehabilitation in order to identify a replacement for traditional high-load training, while ensuring patient safety [1].

Initially, BFRT—also referred to as pressure training, or KAATSU—was employed to enhance sports performance. This approach simulates the effects of high-load exercise at a lower exercise intensity (20-40% 1RM) by applying pressure to one part of the body during exercise, partially limiting arterial flow and completely restricting venous flow [2].BFR training is valued for its ability to promote muscle growth and strength gain, especially in situations where traditional high-load training is not feasible or appropriate. Studies in recent years have shown that BFR training can reduce mechanical stress, relieve muscle joint pain and increase muscle strength, while improving patients' muscle endurance and aerobic capacity, improving cardiovascular physiological levels, and increasing quality of life [3].

BFR is a way of restricting arterial blood flow to muscles and preventing venous blood from returning through the use of pneumatic cuffs and elastic bands during exercise, so it is prone to discomfort. A "personalized" adjustment method that is tailored to the patient's cuff type, width, and material can help minimize discomfort in part and facilitate the execution of the exercise and rehabilitation regimen. However, studies have also shown that while long-term BFR training might improve physical fitness, improper application of the technique can raise the risk of thrombosis and muscle injury[4].It can be observed that if BFR is to be implemented as a new form of rehabilitation treatment, it is essential to develop standardised BFR training guidelines and to conduct rigorous evaluations of its efficacy in diverse patient populations. This is crucial to ensure patient safety and the desired outcomes of rehabilitation.

This article will review the application status of BFR training in lower limb injury rehabilitation, discuss its impact on muscle function, pain management and quality of life, and evaluate its safety and potential clinical application prospects, with a view to providing clinicians and rehabilitation professionals with scientific basis and practical guidance on the effective use of BFR training in lower limb injury rehabilitation.

## 2. Overview of BFR

## 2.1. History of BFR

BFR was first developed in the 1970s by Dr. Yoshiaki Soto, who introduced the concept of occlusive moderate therapy, also known as KAATSU. This involved the use of ropes and bags that act as tourniquets to restrict blood flow. Although KAATSU training was not yet fully developed at the outset,

it played a pioneering role in the field of electrodynamic pressure blood band training and modern BFR training. The first study on BFRT appeared in 1998, with the application of an electrodynamic pressure blood band. In 2000, further studies of blood restriction training methods were conducted safely with the help of the third generation of pressurised blood bands. The initial applications of blood restriction training (BFRT) were primarily utilised in the context of sports, with the objective of enhancing the muscle strength of athletes and those whose muscles were weak and unable to withstand the typical training loads encountered in such activities. This included individuals belonging to the older age groups [5]. With its considerable potential, BRFT has been used extensively in the field of clinical medical rehabilitation in recent years, particularly in the area of musculoskeletal damage.

## 2.2. Mechanism

The precise mechanism by which BFR training increases muscle strength, endurance and hypertrophy remain unclear. Potential mechanisms include metabolic stress, increased secretion of muscle-growthrelated hormones, changes in nerve recruitment patterns, alterations in biomolecular pathways promoting protein synthesis and muscle swelling. Among these factors, metabolic stress is a key contributor to muscle hypertrophy. This mostly happens in the anaerobic glycolysis phase, which leads to the build-up of lactic acid, hydrogen ions, and inorganic phosphate, among other metabolic byproducts. The rise in growth hormone (GH), insulin-like growth factor-1 (IGF-1), testosterone, and other hormone levels that follows BFR exercise is directly linked to the buildup of metabolic byproducts [6]. The Henneman order of size principle posits that the body initially recruits Class I neurons under low load, and that the metabolic reaction generated during BFR low-load resistance training is analogous to that of traditional high-load resistance exercise. In advance of fatigue, Class I muscle fibres are recruited, forcing the activation of Class II muscle fibres under low load. This is because the accumulation of metabolites can also stimulate Group III and Group IV afferent nerve fibres, which innervate alpha motor neurons that inhibit the contraction of class I muscle fibres. This causes the body to activate class II muscle fibres in advance, which are more sensitive to muscle growth and promote muscle nerve adaptation [4]. Moreover, BFR has been shown to increase white matter synthesis and promote muscle hypertrophy by phosphorylating the mammalian target of rapamycin (mTOR) and ribosome S6 kinase (S6K1). The increase of muscle endurance may be due to the hypoxic environment of BFR training, which improves the secretion levels of endothelial nitric oxide synthase and vascular endothelial cell growth factor (VEGF), promotes the generation of muscle capillaries and intracellular mitochondria, and improves the activity of aerobic metabolic enzymes to enhance muscle endurance [7].In addition to the aforementioned factors, the increase in intramuscular fluid resulting from extracellular fluid transfer following BFR training can also contribute to muscle hypertrophy. This process is primarily mediated by the inhibition of protein decomposition, promotion of protein synthesis and fat consumption [8].

## 2.3. Training patterns

At present, the main BRF training methods are active BFR training and passive BFR training. In passive BFR training, no load is applied to the muscles, only by obstructing venous blood return and restricting arterial blood, creating a hypoxic environment and increasing metabolic stress response. The active BFR training is divided into resistance and aerobic training two modes, aerobic training is the help of inflatable cuff and tourniquet cycling, walking and other aerobic training. BRF active resistance training is the mainstream of clinical rehabilitation at present. Taking knee injury as an example, according to the current research [9]: Usually selected is 40%-80% arterial /Limb occlusion pressure (A/LOP), 20%-40% training load of 1RM, fixed pressure of 80-200mmHg, The training routine was divided into four sets of 75 repetitions (30-15-15-15), with 30-60s rest between the groups, and 2-5 training sessions per week for 4-12 weeks.

### 3. Application of BFRT in lower limb rehabilitation

#### 3.1. ACLR rehabilitation

With more than two million ACL injuries occurring worldwide each year, ligament reconstruction surgery is a necessary treatment option for those who want to return to sports and return to a near-normal life. In order to reduce the effect of postoperative muscle atrophy and improve knee function, it is important to increase quadriceps strength as soon as possible after surgery [10]. Therefore, BFR training, which is easy for patients to bear and carry out, is applied to early rehabilitation training after ACL reconstruction.

In clinical studies, quadriceps volume, muscle strength, knee function and joint pain are generally assessed using hamstring cross-section area (CSA), peak knee flexion and extension torque (isokinetic muscle strength test), knee function scale (IKDC, YBT, etc.) and pain assessment scale (NPRS, etc.). At present, the main research direction is the difference of blood flow limiting pressure, training load and training frequency.

Hughes et al. conducted several studies on BFR by controlling 80%LOP and performing a 30%1RM single-leg press twice a week for 8 weeks [11,12]. A preliminary investigation revealed that low-load BFR training evoked a more pronounced perceptual response and muscle pain perception than traditional high-load training (p < 0.05). However, the blood pressure response was comparable to that observed in the high-load training group. The hypothesis that low-load BFR training may result in a reduction in knee pain was put forth.2019 saw the completion of another research that demonstrated BFRT can effectively lower knee discomfort and edema in ACLR patients, which is advantageous for the condition's early rehabilitation [13].Moreover, there is no discernible difference in fatigue levels between low-load BFR training and standard high-load training in terms of its impact on muscle growth and strength. It was discovered that in every course, the BFRT group experienced considerably less mean knee discomfort than the standard rehabilitation intervention group (p < 0.05, d = 2.5 (95% CI: 2.2-2.8). The potential for improving knee joint function suggests that low-load BFR training is a suitable early intervention after ACL surgery.

Additionally, Li Xuefeng et al. showed that, in comparison to general low-load training, controlling different blood flow limiting pressures [control group&experimental group(40%&80%AOP)] and administering regular low-load resistance exercises to both the control group and the experimental group produced significantly greater increases in knee extension muscle strength and volume [10]. In the 40%AOP and 80%AOP groups, the average relative peak torque of the knee extensor muscle at 60°/s rose from 94.05 N·m/kg to 123.94 N·m/kg and 152.04 N·m/kg, respectively. Additionally, at 180°/s, there was statistical significance (P < 0.05) for the control group (73.28 N·m/kg), 40% AOP group (102.06 N·m/kg), and 80% AOP group (137.65 N·m/kg). Blood flow restriction training also significantly improved bilateral difference and stability of the knee joint, as indicated by the IKDC and YBT scores [40%AOP group IKDC: mean difference of 7.67(95% CI: -11.93, -3.40); YBT: 0.04 (0.03,0.06)]. It is advised to apply BFR training with a higher degree of blood flow restriction in order to maximize advantages, since studies have demonstrated that the functional levels of blood flow restriction in the 80%AOP group are much higher than those of the 40%AOP group.Curran et al. conducted a study investigating high-load (70%1RM) BFR training [14]. They trained twice a week for eight weeks, using a mean limit of 138mmHg. The results showed that there was no statistically significant increase in quadriceps muscular strength, activity, or volume when BFR was combined with high-load training. Additionally, no appreciable distinction was found between BFR and traditional high-load training (P > 0.1). It can be concluded that BFR training enhances muscle function through a mechanism that goes beyond simple additive effects. As such, it may not be required to combine BFRT with high-intensity resistance training. Similar to the research direction of Curren et al., another clinical study was also divided into two groups with BFRT and without BFRT and conducted 50min of selfweight low-intensity BFR training per day through 130mmHg-180mmHg restricted pressure. The crosssectional area of the quadriceps did not significantly differ between the BFR training group and the regular intervention group after 14 days. The study suggests that the load used in the study was too small

(less than 10%1RM) and did not reach the minimum intensity at which BFR training can cause muscle hypertrophy [15]. Combining the above studies, BFRT control at 60% to 80%LOP limiting pressure, 20% to 30%1RM 2-5 times per week for 4-12 weeks can effectively prevent and better reduce the disused quadriceps atrophy, increase muscle strength and volume, and knee edema and pain. Restoring the function and motion of knee joint as soon as possible is conducive to promoting the rehabilitation process of knee joint. Details are shown in Table 1.

## 3.2. CAI rehabilitation

With an incidence of 1.37/1000, lateral ankle sprains are among the most frequent musculoskeletal injuries, making up 25%–30% of sports-related injuries, particularly among athletes (such as those involved in football, basketball, volleyball, rugby, dancesport, etc.) [16].Additionally, chronic ankle instability, which is defined by recurring episodes and ankle displacement along with persistent ankle discomfort, edema, and recurrent sprains, is estimated to develop in 40% of individuals who have lateral ankle sprains. Its mechanism is not clear but may be related to impaired strength and posture control, decreased proprioception, and neuromuscular control disorders [17]. Therefore, rehabilitation focuses on proprioception, muscle strength, balance and postural control. Muscle activation around the ankle, ankle function, muscle volume and muscle strength were determined by electromyography, star shift balance test (SEBT), Y balance test (YBT), isokinetic muscle strength test and muscle cross-section area, respectively. At present, there are few studies on the application of BFRT to CAI, and CAI involves multiple systems such as muscle, bone and nerve, and the specific intervention effect is still in the stage of exploration.

The latest study found that BFR intervention combined with traditional rehabilitation training and low-load training showed beneficial therapeutic effects. Werasirirat et al. and Shen Liu et al. trained 3 times/week at a limiting pressure of 80%LOP for 4 weeks [17,18]. Those 2 authors did this by combining self-weight and low load with conventional rehabilitation exercises like proprioception, balance training on both feet, and resistance training of the muscles surrounding the ankle.

The findings of Shen Liu's experimental investigation showed that there was a significant improvement (P < 0.05) in the CAIT score of BFR combined with traditional training, a significant increase (P < 0.05) in the activation of the evertor muscle, and a significant reduction (P < 0.01) in pain. Werasirirat et al. showed that BFR combined with traditional training significantly improved ankle plantar flexor muscle strength and ankle joint muscle strength, as well as peroneus longus CSA and ankle joint stability (P < 0.05). Ziliang et al. conducted trials twice a week for up to six weeks and applied ankle resistance training has been shown to have an impact on CAI patients' ankle muscular strength, muscle volume, and balance that is comparable to that of conventional high-load training. Nevertheless, low-load BFRT has been demonstrated to enhance valgus muscle strength and dynamic balance of the ankle joint to a greater extent during the early intervention period (p < 0.05). Therefore, BFR training combined with traditional rehabilitation intervention or low-load resistance training can achieve more beneficial effects, which has a good control effect on pain of CAI patients and can provide new ideas for CAI rehabilitation.

In addition, in Burkhardt et al. 's study, researcher applied BFR intervention to patients with dynamic balance exercise, performed four sets (30-15-15-15) of anterior, posteromedial-medial, and posterolateral stretches, and recorded the activation of muscle groups around the ankle and perceived fatigue and postural status after the trial with EMG [20]. The outcomes demonstrated that BFR intervention was linked to higher levels of exhaustion and postural instability than conventional intervention; the only notable changes were observed in the activation of the soleus muscle (P=0.03) and the lateral femoris muscle (P <0.001). Mahmound et al. treated CAI female patients with a specific temporal blood flow restriction with BFR independently, and the results revealed no appreciable improvement in the patients' dynamic balance or muscular strength (P>0.06) [21].Combined with these two studies, BFR as an independent treatment or combined with self-weight, There is no significant effect on the improvement of dynamic balance and muscle strength in CAI patients, but patients have

fatigue and other discomfort at the subjective level, which may be related to the increase of metabolism and insufficient applied load. Details are shown in Table 1.

Table 1. A summary of studies on the application of BFRT to ACLR rehabilitation and CAI rehabilitation

Author (Year)	Injury Type	Sample (n)	Training variables			BFR Parameter (mmHg/AOP/LOP)			
			Training load (1RM)	Training sets	Rest	Training Frequency	Cuff Width	BFR pressure	Therapeutic effect
Hughes (2018) [11]	ACLR	30	30%/70%	Unilateral leg press (4sets 30,15,15,15 reps)	30s	2x/wk 8wk	11.5cm	80%LOP	Low-load BFRT had a stronger perceptual response, less knee pain than controls, and no differences in blood pressure parameters were observed
Hughes (2019) [12]	ACLR	24	30%	Unilateral leg press (4sets 30,15,15,15 reps)	30s	2x/wk 8wk	11.5cm	80%LOP	Low load Compared to standard high-load resistance training, BFRT has equivalent levels of fatigue and lower musculoskeletal
Hughes (2019) [13]	ACLR	28	30%	Unilateral leg press (4sets 30,15,15,15 reps)	30s	2x/wk 8wk	11.5cm	80%LOP	Low-load BFRT and conventional high-load resistance training have similar effects on muscle strength and volume, with BFRT providing a better reduction in knee pain and swelling
Xuefeng Li(2023) [10]	ACLR	23	Low Load Training	Body Weight Training, Bicycle, reps Barbell training (2sets 30,15,15,15)	30s	2x/wk 8wk	Unspecified	40%&80% AOP	Low-load BFRT effectively improves the strength and volume of the knee extensor muscles, reduces the difference between the affected side and the healthy side, and helps to recover the function of the knee joint
Curran (2020) [14]	ACLR	28	70%	Body Weight Training (4sets 10,10,10,10 reps)	120s	2x/wk 8wk	Unspecified	80%LOP	blec combined with high load results were similar to the effects of traditional high load training, with no significant improvement in quadriceps strength or volume Apkle dorsidexion
Shen Liu(2023) [17]	CAI	23	Low Load Training	Ankle proprioception, lower extremity strength,balance training	30s	3x/wk 4 wk	5em	Wilson Standard Level7	strength increased significantly, CAIT scores improved significantly, and joint discomfort significantly decreased when BFRT and traditional rehabilitation were combined.

Ziliang Wen(2023)	CAI	46	20%- 40%+ 70%- 85%	4sets 30,15,15,15 reps Ankle training	30s	2x/wk 6 wk	Unspecified	Unspecified	While low load BFRT is just as effective as typical high-load training, it performs better in terms of improving the strength of the ankle valgus muscle and the early phases of dynamic balance early on.
Werasirirat (2022)	CAI	16	Body Weight Training	Unilateral leg press (4sets 30,15,15,15 reps) 、Unilateral leg deep squat (3sets 10reps) 、 YBT Reaching	30s	3x/wk 4 wk	10cm	80%LOP	BRFT combined with traditional rehabilitation is more effective in improving muscle strength, size and functional performance.
Mahmoud (2023)	CAI	39	Low Load Training	plantar flexion, dorsiflexion, varus and valgus training with Elastic Band (3sets 10reps)	25s	3x/wk 4 wk	10cm	80%LOP(180mmHg- 230mmHg)	BFR is ineffective as a stand-alone treatment for female CAI patients in terms of strength, dynamic balance and physical functioning
Burkhardt (2020)	CAI	25	Body Weight Training	Extension of the ankle in anterior, posterior medial and posterior lateral directions4sets (30,15,15,15reps)	Unspecified	2 times	Unspecified	80%LOP	Only the lateral femoral muscles were significantly increased, the flounder muscles were slightly enhanced, and greater postural instability and strain were perceived during BFR training.

## Table 1. (continued).

## *3.3. Other injuries*

BFRT was used on eighteen patients who had ruptured Achilles tendon by Bentzen, A. et al. [22]. The findings showed that BFRT could improve muscle strength and endurance in patients with ruptured Achilles tendon faster and with less load, as well as lessen pain and make up for the inadequate recovery of Achilles tendon function that comes from traditional rehabilitation's inability to improve muscle strength quickly and effectively in the early stage of the condition.Patient adherence to the intervention was 88%, and the questionnaire showed that 92% of patients were likely or very likely to recommend BFRT to others.

A randomized study, randomly assigned 34 stroke patients to the BFR combined exercise training group (BRE-ET)(experimental group) or exercise training group (ET)(control group) [23]. On the basis of daily routine rehabilitation, the experimental group underwent exercise training and BFR combined exercise training, while the control group engaged in exercise training twice a day. Patients were evaluated using Brunnstrom stage, muscle strength (MMT), muscle tone (MAS), active joint motion (AROM), Fugl-Meyer Rating Scale - Lower extremity Portion (FMA-LE), standing and Walking time test (TUGT), and modified Barthel Index (MBI). The findings indicated that both groups' AROM and hip abduction muscle strength of the hemiplegic side ankle plantar flexion were considerably improved after 20 days of treatment (P < 0.001), with the experimental group outperforming the control group. P=0.014; P=0.048 showed that the experimental group outperformed the control group. Before and after therapy, there was a statistically significant improvement in both groups' FMA-LE, TUGT, and MBI scores (P < 0.001).Following the intervention, the TUGT of the experimental group exhibited a statistically significant difference from that observed during the treatment period (P = 0.002). The findings indicate that BFR, when combined with exercise training, can enhance lower limb function to

a greater extent than conventional exercise training. Moreover, it has been demonstrated to have a more pronounced clinical therapeutic effect on walking function and activities of daily living in stroke patients.

## 4. Discussion

The potential mechanisms of action of BFRT, including metabolic stress, increased hormone secretion, and altered forms of neural recruitment, provide a scientific basis for understanding how BFRT promotes muscle adaptation, however, these potential mechanisms are often speculative. In addition, the sample size of many quoted tests is small, which is easy to cause the accident of the test. Moreover, there is no uniform standard for the parameters of blood flow restriction using BFR in each experiment. For example, some experiments use the limiting pressure, some use the absolute pressure of mmHg, and the personalized arterial occlusion pressure (AOP). The width of the cuff also has an impact on the effect of blood flow restriction, and the greater the width, the smaller the limiting pressure. Therefore, how to accurately describe the degree of blood flow restriction and impose personalized restrictions on patients is the focus of future regulation. As an emerging rehabilitation method, its safety is also the focus of attention, and few studies involve safety issues. At present, the main adverse reactions recorded were acute muscle pain and fatigue, rhabdomyolysis (0.008%), lower limb ecchymosis, swelling, etc. But most studies have reported no adverse effects. At present, the available evidence indicates that BFRT remains a relatively safe training method, with a low frequency of adverse reactions. However, it is recommended that all patients should be examined for contraindications of BFR before applying this training method to clinical treatment. The positive effects of BFR training have been proven, but in clinical practice, how to precisely control the pressure of blood flow restriction, how to personalize the training regimen according to the specific situation of the patient, and how to combine other rehabilitation means to maximize the effect of BFR training are still questions that need further research.

## 5. Conclusion

BFRT, as a new type of rehabilitation training in combination with low-load training or traditional interventions, has shown positive effects on muscle growth, strength improvement, and pain control. For individuals who cannot do traditional high-load training, BFRT provides a safe, low-load alternative. In ACLR rehabilitation, BFRT can effectively reduce knee pain and edema, improve function, and provide a new way for patients to recover early. In addition, BFRT combined with traditional rehabilitation can reduce pain and better restore muscle strength and joint stability in patients with chronic ankle instability (CAI), but more rehabilitation effects need to be further studied. It also plays a certain role in other Achilles tendon injuries and lower limb function in stroke patients. Further studies are required to investigate the effects of BFRT in a range of rehabilitation scenarios and to optimise its application in personalised rehabilitation plans. Secondly, in the future, clinicians should extend the follow-up period, register a larger and more diverse sample size, and use randomized techniques to identify appropriate prescription indications for rehabilitating patients to ensure the effectiveness and safety of clinical application. Finally, a series of chain symptoms caused by physiological reactions in BFRT should be studied in combination with different methods, and a quantitative analysis should be made to develop and improve rehabilitation training programs with minimum effective dose and maximum effect for different clinical populations.

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