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# Can blood flow restriction induce cross-education of muscle strength and volume? A systematic review and meta-analysis

Liang Sun<sup>1</sup>, Yi Yang<sup>1</sup>Jiong Luo<sup>1</sup>\*

<sup>1</sup>Research Centre for Exercise Detoxification, College of Physical Education, Southwest University, Chongqing,

#### China, 400715

Liang Sun, male, a graduate student; Research direction: Physical fitness and health promotion. email: 1263088363@qq.com, Tel:19115584918

Affiliation: Research Centre for Exercise Detoxification, College of Physical Education, Southwest University, Chongqing, China

Yi Yang, male, a graduate student; Research direction: Physical fitness and health promotion. email: 1390330627@qq.com, Tel: 18383570623

Affiliation: Research Centre for Exercise Detoxification, College of Physical Education, Southwest University, Chongqing, China

#### \*Corresponding author:

Jiong Luo (1966-), male, Professor, doctor, doctoral supervisor, research direction: physical fitness and health promotion, email: 784682301@qq.com, Tel: 13108991439

Affiliation: Research Centre for Exercise Detoxification, College of Physical Education, Southwest University, Chongqing, China

#### **Author Contributions**

Liang Sun conceived the study, took part on the screening process and data extraction, drafted the manuscript; Jiong Luo formulated the review criteria and helped to revise the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

#### **Conflict of Interest:**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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1	Can blood flow restriction induce cross-education of muscle strength and
2	volume? A systematic review and meta-analysis
3	
4	Objective: This research systematically assesses the effects of low-load blood flow restriction on
5	the cross-education of muscle strength and volume, providing evidence-based guidance for
6	clinicians and rehabilitation therapists.
7	Method: The literature search utilized databases such as PubMed, Web of Science, and Embase.
8	Quality assessment employed the Cochrane Collaboration's RCT bias evaluation tool. Data
9	synthesis, forest plot creation, and publication bias assessment were performed with Reman 5.4
10	software. This study is registered with the International Platform of Registered Systematic Review
11	and Meta-analysis Protocols (INPLASY), 202440038.
12	Result: Six meta-analyses, encompassing 259 undergraduate students, were performed. Results
13	indicated a markedly enhanced cross-education effect in muscle strength induction via blood flow
14	restriction, surpassing that of traditional unilateral training and control groups. Nonetheless, the
15	cross-education impact on muscle volume induction showed no notable variance among the
16	groups.
17	Conclusion: Blood flow restriction has been shown to effectively induce cross-education in
18	muscle strength. Nevertheless, additional research is required to determine its impact on muscle
19	volume cross-education. Reduced exercise intensity with blood flow restriction may augment
20	neural activation, implying possible advantages in rehabilitative training for individuals with
21	neurological conditions—meriting additional investigation.

22 **Keywords:** Blood flow restriction; Cross-education; Muscle strength; Muscle volume

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# 24 **1. Introduction**

25 Blood flow restriction training (BFR), also known as KAATSU, was developed by Dr. Yoshiaki Sato in Japan as a novel method to enhance muscle strength and exercise performance<sup>1</sup>. BFR 26 27 involves partially restricting arterial blood flow and fully restricting venous return from the muscles to the heart during exercise, without completely obstructing blood circulation<sup>2, 3</sup>.Utilizing 28 29 pressure cuffs on limbs, BFR can be integrated with diverse exercises, yielding substantial benefits 30 in rehabilitation, muscle strengthening, and hypertrophy. BFR is applied across a spectrum of 31 individuals, including athletes, the generally healthy, and the middle-aged to elderly population<sup>4</sup>. In controlled settings, BFR is considered a safe practice for the overall healthy population. This 32 method is fully viable, although individuals with cardiovascular conditions, such as heart disease 33 and hypertension, should proceed under the guidance of healthcare professionals to carefully 34 assess the possibility of engaging in BFR training or formulating a training regimen<sup>4-6</sup>.Research 35 36 categorizes BFR into resistance exercise (RE), aerobic exercise (AE), or a blend of both. Recent studies have innovatively merged electromyographic (ES) with neuromuscular stimulation and 37 incorporated Whole Body Vibration (WBV).<sup>2</sup>. When compared to isolated low-intensity load 38 training, the integration of BFR has been shown to enhance muscle strength and hypertrophy more 39 40 effectively<sup>7</sup>.

41 Cross-education (CE) is characterized by a marked enhancement in strength and adaptability of the contralateral, untrained limb following unilateral limb training8. The underlying mechanism of 42 43 cross-education remains a focal point of research, with competing hypotheses including neural and 44 myogenic mechanisms, yet a consensus has not been reached. While initial theories posited 45 myogenic mechanisms as the cause of cross-education9, subsequent research indicates an absence 46 of significant size changes in contralateral homologous muscles, suggesting a neurogenic mechanism. Bilateral-access and cross-activation represent two theoretical models explaining the 47 neural mechanisms, wherein both the brain and spinal cord are implicated <sup>10</sup>. The bilateral-access 48 model posits that the movement patterns of unilateral activities are mirrored by attempting to 49 perform identical tasks on the opposite side of the body<sup>11</sup>. The cross-activation model 50 demonstrates that adaptations from unilateral movements can transfer to the contralateral side of 51the body<sup>12</sup>. Despite the lack of consensus regarding the mechanism of cross-education, its 52

53 characteristics and potential applications have been extensively investigated. Cross-education can 54 manifest in various muscle groups, including those of the upper limb—such as the rotator cuff, select elbow flexors, and wrist flexors<sup>13-15</sup>—and the lower limb, like certain ankle dorsiflexors and 55 knee extensors<sup>16</sup>. Several techniques have been identified to effectively facilitate CE, such as 56 neuromuscular electrical stimulation, targeted electroacupuncture, and independent muscle 57 58 contraction exercises. The prevalent approach involves employing conventional resistance training as a catalyst by modulating load intensities, training volumes, and contraction techniques. 59 60 Nonetheless, investigations into blood flow restriction techniques as a means of induction remain comparatively limited<sup>17-22</sup>. In recent years, the application of cross-education in clinical settings has 61 expanded, particularly in the early rehabilitation of unilateral neurological conditions like stroke. 62 Cross-education not only aids in preventing complications but also enhances muscle strength and 63 function in the affected limb; Initiating contralateral training early post-anterior cruciate ligament 64 reconstruction (ACLR) may enhance the recuperation of quadriceps muscle strength following the 65 procedure<sup>16</sup>. The clinical application of cross-education is progressively broadening, encompassing 66 67 both neurological and orthopedic conditions.

Despite uncertainties about the mechanisms of CE effects, their indispensable role in certain 68 clinical rehabilitation populations is evident. BFR is simpler and more patient-friendly than 69 traditional methods used to induce CE effects. The nervous system serves as the conduit for CE 70 effects, with substantial evidence pointing to the untrained hemisphere as the primary mediator<sup>23</sup>, 71 despite incomplete knowledge of the specific cortical and neurophysiological adaptations. 72 However, these cortical adaptations ultimately occur at the motor unit level<sup>24</sup>. In general, the initial 73 74 increase in muscle strength is greatly influenced by the activation patterns of motor units, whereas later stages correlate more with maximal muscle strength<sup>25-27</sup>. BFR can notably improve 75 neuromuscular adaptability<sup>28-33</sup>. Yet, experimental studies are lacking on whether this enhanced 76 77 adaptation can be transferred to the untrained side and the extent to which it can be preserved. 78Considering the test population, individuals without prior training experience, who have greater 79 potential for neuromuscular improvement, may benefit more from BFR in enhancing motor unit 80 recruitment than from traditional resistance training. However, for elite professional athletes, the 81 marginal gains offered by this method may appear insignificant. From a neural mechanism 82 standpoint, the general population aligns well with the training principles of BFR and CE,

presenting ample opportunity for enhancement. Injured athletes may find this training more
suitable for preserving their skill level and decelerating the decline in muscle strength.

85 CE effects are typically more pronounced following high-load exercise, with evidence 86 indicating that, in comparison to low-load exercise at 30% of one-repetition maximum (1RM), high-load exercise at 70% 1RM yields greater benefits<sup>34-36</sup>. However, for certain populations, such 87 as patients undergoing clinical rehabilitation or the middle-aged and elderly, high-load lifting may 88 89 be impractical. Therefore, identifying effective strategies to enhance the efficacy of low-load 90 exercises is crucial for these individuals. Integrating blood flow restriction training with low-load 91 exercise could amplify the cross-education benefits to match those achieved with high-load exercise<sup>37, 38</sup>. BFR has demonstrated a more substantial increase in muscle size and strength 92 compared to conventional equal-load exercise<sup>39</sup>. In conclusion, CE could potentially yield superior 93 94 outcomes when coupled with BFR.

The investigation into whether BFR can augment CE benefits is still nascent. Current research on this topic typically involves small sample sizes, with approximately 10 participants per group<sup>37,</sup> a<sup>38</sup>, and lacks a systematic analysis both domestically and internationally. Given the aforementioned context, this study employs a meta-analytic approach to systematically assess whether low-load BFR can facilitate CE of muscle strength and volume, offering empirical support for clinicians and rehabilitation specialists.

101 **2. Methods** 

## 102 **2.1 Guidelines and ethical review**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>40</sup> in this systematic review. As this study was a review, no ethical approval was necessary. The methods and protocol registration were preregistered prior to conducting the review: INPLASY, no.202090098, DOI:10.37766/inplasy2024.4.0038.

## 107 **2.2 Search strategy**

Retrieved literature published as of March 1, 2024, through databases such as PubMed, Web of
Science, and Embase. Used ("blood flow restriction" OR "vascular occlusion" OR "katsu" OR
"Occlusion training") and ("cross-education" OR "cross education" OR "cross transfer" OR "cross
training" OR "interlimb transfer" OR "strength transfer" OR "unilateral strength training" OR

"unilateral resistance training" OR "contralateral strength training" OR "resistance training" OR "strength training") to perform a Boolean logic search for English search terms. Two researchers independently screened the titles and abstracts of the retrieved articles, and when there was disagreement, a third researcher intervened.

#### 116 **2.3 Inclusion and Exclusion Criteria**

In adherence to the PICOS framework for systematic reviews, this study's inclusion criteria were: ①participants are adults aged 18 or older; ②interventions consist of synchronous training for a minimum of 4 weeks; ③comparisons include at least one unilateral training group or a non-intervention control; ④outcomes report on at least one measure of maximal force, voluntary contraction, isometric strength, torque, or muscle cross-sectional area pre- and post-intervention; 5 the research design is experimental.

Exclusion criteria were: (1)absence of a strength training group; (2)outcome measures excluding muscle-related indicators; (3)animal studies; (4)unpublished works; (5)duplicate publications; (6) concurrent interventions like diet control or cognitive training during the study period.

#### 126 **2.4 Screening of literature**

After the literature search was completed, two researchers independently double-blind screened the literature according to the inclusion and exclusion criteria mentioned above. Firstly, they imported the literature into Endnote X9 software for deduplication, conducted preliminary screening of reading titles and abstracts, and downloaded and screened the remaining literature in full. Then the two researchers compared the extracted literature, and if there were any differences, they discussed with the third researcher to decide whether to include it in this article

#### 133 **2.5 Data extraction**

Two researchers read the full text of the included literature and extracted the required information according to a standardized process. The extracted information included: first author information, publication years, grouping situation, age, sample size, training characteristics (content, period, frequency, intensity), and outcome indicators after exercise intervention (maximum strength, maximum voluntary contraction, maximum voluntary isometric contraction, rate of torque development, and cross-sectional area). When the outcome indicates were repeatedly measured, the first measurement result after intervention was extracted. Two researchers resolved their differences through discussion, and when there was disagreement, a third researcher intervened. If there was missing data in the literature, they contacted the author via email to provide the missing data, and used Web Plot Digitizer software (Version 4.1; E, USA) to extract result data reported only in graphical form (mean  $\pm$  standard deviation).

#### 145 **2.6 Statistical methods**

Statistical analysis was conducted on the included data using RevMan 5.4 software. The outcome measures included in this article are all continuous variables, and the strength data are tested in different units. Therefore, the standard mean difference (SMD) is chosen as the effect measure, while the muscle volume test unit is the same. Therefore, the mean difference (MD) is chosen, and both use a 95% confidence interval (CI) as the effect scale for muscle related indicators. Evaluated the quality of the included literature using RevMan 5.4 software.

Heterogeneity among studies was evaluated using the Higgins  $I^2$  test. Ranges for interpretation of  $I^2$  followed the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org). Values of 30% to 60%, 50% to 90%, and 75% to 100% represent, respectively, moderate, substantial, and considerable heterogeneity. A fixed model effect was set as default in every comparison. If substantial or considerable heterogeneity was detected, a random model effect was adopted. Values of P<0.05 were considered statistically significant.

# 159 2.7 Risk assessment of bias in included literature

The bias risk assessment that was included in the literature had been evaluated using Cochrane Collaboration's RCT bias evaluation tool<sup>41</sup>: 1) The generation of random sequences; 2) Allocation hidden; 3) Blind method between implementers and participants; 4) Blind method for outcome evaluation; 5) The completeness of the result data; 6) Selective reporting; 7) Other sources of bias. The risk of bias was evaluated independently by two researchers. If there was any disagreement, it was resolved through negotiation or discussion with a third researcher before making a decision.

## 167 **3 Research results**

#### 168 **3.1 Description of the included studies**

A total of 1729 references were retrieved, and 512 duplicate references were excluded; Obtain 8 articles by reading the title and abstract; Subsequently, download the full text of the remaining 8 articles, remove 2 articles after reading the full text, and include 6 articles in the meta-analysis. The specific literature screening process is shown in Figure 1.



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Figure 1 Literature Selection Process

# 175 **3.2 Basic characteristics included in the study**

Table 1 displays a sample size of 259 individuals, comprising 154 males and 105 females. Of 176 these, three studies exclusively involved males, one focused solely on females, and two 177encompassed both genders; Subjects' average age spanned from 21.5 to 24.8 years; Six studies 178 179 quantified variable resistance, with the BFR group consistently employing a low load between 25% 180 and 50% 1RM.In two studies, the control group utilized loads varying from low (75% 1RM) to 181 high (100% MVC); Three studies employed a blank control group, another three a non-BER 182 unilateral training control, and two implemented both control types concurrently; Intervention 183 duration ranged from 4 to 10 weeks, with sessions held 2 to 5 times weekly and post-intervention,

184 each study assessed muscle strength and volume.

Table 1         Characteristics of the included studies								
		Sample		Interventio				
Study	Characteristics	Experimental	Control	Method	occlusion Duration pressure		Factors	
Anthony	Healthy young	n=12	n=12	The dominant arms of the	6004	7 weeks (3	Bicep :	
et al,	male with no	$22.6\pm3.3$	22.1±2.5	experimental and control groups	60%	times	1RM, CSA	

2018 <sup>42</sup>	training or injury experience within six months.	(BFR)	(non-BFR group)	were subjected to unilateral biceps curling(50% 1-RM,3x10). The non-dominant arm was used as an untrained control.		/week)	
David et al, 2017 <sup>37</sup>	Healthy young male with no training or injury experience within six months.	n=7 23.8±2.5 (BFR group)	n=8 24.8±2.9( blank control group) n=7 21.5±3(no n-BFR group)	The dominant legs were subjected to 4 sets of unilateral soleus isometric training(25% of MVC,4sete:1x30,3x15). The left leg was used as an untrained control and there is a blank control group.	150 -210 mmHg	4 weeks (3 times /week)	Soleus: MVC, CSA
Ethan et al, 2020 <sup>38</sup>	Healthy young woman with no training or injury experience within six months	n=12 (BFR group)	n=12 (blank control group) n=12 (non-BFR group) (all 22±2)	Randomly assign dominant or non dominant arms for four sets of isokinetic training(30% of peak torque,4sete:1x30,3x15).The opposite arm arm was used as an untrained control and there is a blank control group.	40%	4 weeks (3 times /week)	Biceps : MVIC, CSA
Goncalo et al, 2021 <sup>43</sup>	Young healthy volunteers (females and males), training frequency <2times/week	n=15 22.3±2.9 (BFR group)	n=15 21.9±3.3 (high-inte nsity group)	Perform four sets of plantar flexion training(20% of 1RM/75% of 1RM,4x10) on the right leg. The left leg was used as an untrained control	60%	4 weeks (5 times /week)	Soleus: MVC, RTD, CSA
Haruhiko et al, 2008 <sup>44</sup>	healthy men without prior experience of regular resistance training	n=8 21.6±2.4 (BFR group)	n=7 21.9±4.2 (non-BFR group)	Randomly select the dominant or non-dominant group for four sets of unilateral dumbbell curling(30% of 1RM,3x10), knee extension, and knee bending training(50% of 1RM,2x15), with the opposite side serving as the control group.	160-260 mmHg	10 weeks (2 times /week)	Upper arm and thigh: Equidistant torque, 1RM, CSA
Vickie et al, 2023 <sup>45</sup>	Young healthy volunteers (females and males)with no training or injury experience within six months	n=41(BFR group)	n=47 (non-BFR group) n=44 (blank control group) (all 21.5 ±3.5)	The dominant hands were subjected to four sets of handgrip training(30% /50% of 1RM,4x 2min). The non-dominant hand was used as an untrained control and there is a blank control group.	50%	6 weeks (3 times /week)	Forearm: 1RM, CSA

185 1RM:one-repetition maximum; CSA: cross-sectional area; MVC: maximum voluntary contraction; MVIC: maximum voluntary

186 isometric contraction; RTD: rate of torque development

# 187 **3.3 Study quality and reporting**

Employ the Cochrane bias risk assessment tool for evaluating the referenced literature's quality. A rating of "low risk" for all items in the Cochrane tool indicates an overall low bias risk for the study; If one or two items receive a "high risk" or "uncertain risk" rating, the study is deemed to have a moderate overall bias risk; An assessment of "high risk" or "uncertain risk" for two or more items classifies the study as having a high overall bias risk. Consequently, six articles received a high-risk rating. Figure 2 illustrates the evaluation results.



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Figure 2 Analysis of the risk of bias in accordant with

the Cochrane Collaboration Guidelines

# 197 **3.4 Meta-analysis results**

In the meta-analysis of BFR group vs blank control group induced contralateral muscle strength, three intervention studies were included in the literature, each of which tested muscle strength at different time points, with a total of three comparisons. The meta-analysis results (Figure 3) showed no significant heterogeneity in the study (I2=0%, P=0.73), with a combined effect size of SMD=0.56 and a 95% CI of [0.24, 0.94], indicating a statistically significant difference (P=0.001).



## Figure 3 Forest plot of meta-analysis of the effectiveness of

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BFR in inducing muscle strength CE benefits

In the meta-analysis of BFR group vs unilateral resistance training group induced contralateral muscle strength, 5 intervention studies were included in the literature, and each study tested muscle strength at different time points, with a total of 8 comparisons. The meta-analysis results (Figure 4) showed no significant heterogeneity in the study (I2=36%, P=0.14), with a combined effect size of SMD=0.29 and a 95% CI of [0.06, 0.52], indicating a statistically significant

difference (P=0.01).

		- Evn	erimental		Co	ntrol			Std Mean Difference	Std. Mean Difference
	Study or Subgroup	Mean	SD T	otal I	Mean	SD .	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	Anthony et al , 2018	0.8	0.4	12	0.6	0.3	12	7.8%	0.55 [-0.27, 1.36]	
	David et al , 2017	149	205.12	7	67	233.5	7	4.7%	0.35 [-0.71, 1.41]	
	Goncalo et al , 2021	-0.32	14.93	15	6.93	16.62	15	9.9%	-0.45 [-1.17, 0.28]	· · · · · · · · · · · · · · · · · · ·
	Goncalo et al , 2021	31.15	98.73	15 4	47.54 1	05.77	15	10.2%	-0.16 [-0.87, 0.56]	
	Haruhiko et al , 2008	0.54	6.36	8	1.2	6.58	7	5.1%	-0.10 [-1.11, 0.92]	
	Haruhiko et al , 2008	0.62	1.62	8	1.21	1.37	7	5.0%	-0.37 [-1.39, 0.66]	
	Vickie et al., 2023	2.76	3.36	41	0.8	3.19	47	28.5%	0.59 [0.17, 1.02]	
	VICKIE et al , 2023	2.76	3.37	41	0.95	3.64	47	28.8%	0.51 [0.08, 0.94]	
	Total (95% CI)			147			157	100.0%	0.29 [0.06, 0.52]	
	Heterogeneity: $Chi^2 = 1$	10.93. df	= 7 (P = 0)	.14): 1	$^{2} = 36\%$					
919	Test for overall effect: 2	Z = 2.50	(P = 0.01)							-1 -0.5 0 0.5 1
213										Pavours (experimental) Pavours (control)
214	Figur	ъ.	Fores	st pl	lot of	met	ta-ar	nalvs	is of muscle	strength CE benefits of
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215				В	SFR V	vs un	iilate	eral 1	resistance trai	ining
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217	In the meta-analy	vsis o	f BFR	gro	oup	's bl	ank	cont	rol group ind	uced contralateral muscle volume.
	5			0	1				0 1	,
910	the and any three inter					1		41	literature as	ah of which to stad move als strongeth
210	there are three inter	venu	ion stu	iaie	s inc	lude	μm	the	merature, ea	ch of which tested muscle strength
219	at different time poi	ints_	and th	ere	is a t	otal	of t	hree	comparisons	The meta-analysis results (Figure
210	at anticient time poi	incs,	und un	10	15 44	otui	01 0	mee	comparisons	. The meta analysis results (1 igure
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220	5) showed no signif	fican	t heter	oge	eneity	y in '	the s	study	y (12=0%, P=	0.98), with a combined effect size
	, e				-			-		, , , , , , , , , , , , , , , , , , ,
991	of $MD = 0.01$ and a	050	CLaf	ΓΛ	0600	241	The	d:ff	-	at statistically significant (D-0.6)
$\angle \angle 1$	of $MD = -0.01$ and a	93%	Cro	[-0	.0000	J4].	The	anne	erence was no	of statistically significant ( $P=0.0$ ).
		Expe	rimental		Cont	rol		Ν	lean Difference	Mean Difference
	Study or Subgroup	Mean	SD To	tal M	lean S	D Tot	tal We	eight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	David et al , 2017	0.3	2.2	7 (	0.25 2.4	46	8	0.0%	0.05 [-2.31, 2.41]	
	Ethan et al , 2020	2.14	0.18	24 2	2.14 0.2	26 1	12	9.8%	0.00 [-0.16, 0.16]	+
	Vickie et al , 2023	0.015	0.1	41 0	0.03 0.1	15 4	44 9	0.2% -	-0.01 [-0.07, 0.04]	
										Т
	Total (95% CI)			72		e	64 10	0.0% -	0.01 [-0.06, 0.04]	•
	Heterogeneity: $Chi^2 =$	0.03, d	f = 2 (P =	0.98);	$1^2 = 0\%$				-	
222	Test for overall effect:	Z = 0.5	12 (P = 0.6)	0)						Favours [experimental] Favours [control]
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In the meta-analysis of BFR group vs unilateral resistance training induced contralateral muscle volume, 5 intervention studies were included in the literature, and each study tested muscle volume at different time points, with a total of 7 comparisons. The meta-analysis results (Figure 6) showed no significant heterogeneity in the study ( $I^2=0\%$ , P=0.93), with a combined effect size of

MD=0.01 and a 95% CI of [-0.04, 0.06], and no statistically significant difference (P=0.64).

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	Expe	erimer	Ital	Co	Control			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
Anthony et al , 2018	-0.62	2	12	0.11	2.5	12	0.1%	-0.73 [-2.54, 1.08]			
David et al , 2017	0.3	2.2	7	0.1	1.6	7	0.1%	0.20 [-1.82, 2.22]			
Goncalo et al , 2021	-0.1	3.65	8	-0.1	1.9	7	0.0%	0.00 [-2.89, 2.89] -			
Haruhiko et al , 2008	0.09	1.01	8	-0.16	1.26	7	0.2%	0.25 [-0.92, 1.42]	· · · · · · · · · · · · · · · · · · ·		
Vickie et al , 2023	0.015	0.1	41	0.0035	0.13	47	99.7%	0.01 [-0.04, 0.06]			
Total (95% CI)			76			80	100.0%	0.01 [-0.04, 0.06]	•		
Heterogeneity: $Chi^2 =$	0.84, df	= 4 (P	= 0.93	); $I^2 = 0\%$	0			-			
Test for overall effect:	Z = 0.47	' (P = )	0.64)						-2 -1 0 1 2 Favours [experimental] Favours [control]		

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Figure 6 Forest plot of meta-analysis of muscle volume CE benefits of

BFR vs unilateral resistance training

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# 235 4 Discussion

Few studies comprehensively evaluate the effects of BFR on the CE of muscle strength and volume using quantitative analysis. This article analyzes the effects of BFR group compared to a blank control group and a unilateral resistance training group, focusing on changes in muscle strength and cross-sectional area. The aim is to optimize clinical rehabilitation prescriptions and enhance muscle function in rehabilitation patients and middle-aged or elderly individuals.

By comparing the growth of contralateral muscle strength between the BFR group and the blank control group in three studies, we conclude that BFR significantly induces CE of muscle strength. Based on this, we need to explore whether BFR has an advantage over unilateral resistance training in increasing contralateral muscle strength and if it is worth choosing BFR over conventional unilateral resistance training despite certain risks.

During the meta-analysis comparing BFR group with unilateral resistance training group, three studies<sup>34, 37, 42</sup> indicated a notably greater CE of muscle strength with BFR, whereas two smaller studies<sup>43, 44</sup>yielded contrasting findings. Previous systematic analyses<sup>46, 47</sup> have demonstrated that high-load exercises induce greater CE effects compared to low-load intensity exercises. Among the five studies included, only Goncalo et al.'s study<sup>43</sup> used high-intensity resistance training in the

control group. This could explain why Goncalo et al.<sup>43</sup> reported contrary findings, they compared 251252 the growth of contralateral muscle strength between low-intensity blood flow restriction training 253(20% of 1RM) and high-intensity unilateral resistance training (75% of 1RM) in their study. This 254 indicates that although low-load unilateral training may exhibit greater cross-education (CE) 255compared to low-load unilateral training, it may not be as effective as high-intensity unilateral 256 training. A 2020 meta-analysis highlighted that BFR led to significant improvements in muscle 257 strength, muscle cross-sectional area, and physical function among the elderly compared to blank control groups; with average strength gains ranging from 2.9% to 35.6%, muscle cross-sectional 258 259 area increases ranging from 3.1% to 8.0%, and functional testing improvements ranging from 12% to 28% <sup>10</sup>. However, the report also indicates that while BFR effectively enhances strength in older 260 adults, as demonstrated by Cook et al. study<sup>48</sup>, this increase is not as significant as that achieved 261 through high-intensity unilateral resistance training. This conclusion does not necessarily impact 262 the use of unilateral BFR in clinical rehabilitation. BFR can effectively enhance muscle strength in 263 individuals who cannot tolerate or are contraindicated for high-load training, relieve pain, and 264 prevent muscle atrophy and strength decline in bedridden patients and the elderly. 265

Haruhiko et al.<sup>44</sup> randomly selected either the dominant or non-dominant side for intervention 266 training in the experimental group, whereas other studies focused solely on the dominant hand. But 267 the hemisphere function of the brain has asymmetry, noting higher corticospinal excitability in the 268 dominant hemisphere<sup>49</sup> and shorter transcallosal conduction delay (TCD) <sup>50</sup>. During unilateral 269 movement, the inhibitory effect of the dominant hemisphere on the non-dominant hemisphere 270 271 outweighed the reverse. The dominant hemisphere exhibited greater involvement in non-dominant 272 movement and tended to interfere with mirror movements generated by the non-dominant hemisphere's excitatory output<sup>50-52</sup>. Therefore, despite both limbs bearing equal loads during 273 274 unilateral training, it disproportionately stimulates the dominant side, leading to increased limb 275asymmetry, particularly evident during complex multi-joint exercises. This discrepancy may 276 account for the insignificant difference in CE observed between the BFR group and the unilateral 277 resistance training group.

Based on the above content, we can conservatively conclude that in clinical settings, BFR can be prioritized to induce contralateral muscle strength. For subjects who cannot undergo high-intensity unilateral resistance training to promote contralateral muscle strength recovery, BFR
is a more suitable and effective choice.

282 In practical applications, the magnitude of CE correlates with the muscle strength increment on 283 the trained limb, with the strength increase on the opposite side being approximately 60% of that on the same side<sup>53-55</sup>. Thus, in assessing the CE phenomenon, one can gauge the enhancement in 284 muscle strength on the contralateral side by monitoring the strength increase on the ipsilateral limb, 285 286 facilitating a prompt and convenient evaluation of the therapeutic effect. Furthermore, it allows for 287 a scientific determination of the training volume for the advantaged limb, enhancing the overall 288 efficacy of the rehabilitation plan, thereby increasing the strength of the contralateral muscle and 289 achieving the desired rehabilitative outcome.

Regarding muscle volume, the meta-analysis results indicated no significant difference between the experimental and control groups. Of the three studies comparing with the blank control group, two showed an increase or maintenance in contralateral muscle volume. Similarly, four out of five comparisons with unilateral resistance training reached the same conclusion.

294 Studies indicate that maintaining muscle volume relies on a delicate balance between muscle protein synthesis and degradation<sup>56</sup>. Muscle atrophy occurs when protein degradation surpasses 295 synthesis, and CE has been proven effective in reducing muscle atrophy. Research suggests that 296 the protective effect of CE on skeletal muscle mass depends on synergistically activating protein 297 synthesis pathways and/or inhibiting protein degradation pathways <sup>10</sup>. Another hypothesis is that 298 training the contralateral limb may inhibit protein degradation pathways instead of activating 299 300 protein synthesis pathways. This effect may not be detected under stable conditions of basic 301 protein degradation but can be significant in severe muscle atrophy, thus preventing 302 disuse-induced muscle atrophy. The mechanism underlying increased strength and muscle 303 hypertrophy during BFR remains unclear. Multiple pieces of evidence suggest that this could be 304 due to indirect effects, including the response of muscle cells to swelling and the accumulation of 305 metabolites, possibly triggered by the biochemical stress response and metabolite buildup during 306 exercise. These effects may lead to the recruitment of more type 2 muscle fibers, enhancing 307 muscle activation through fatigue and improving training efficiency. Concurrent metabolic stress 308 response and tissue hypoxia also promote the expression of hypoxia-inducible factor 1  $\alpha$  and vascular endothelial growth factor<sup>57, 58</sup>. Furthermore, muscle fiber swelling facilitates cell protein 309

synthesis via mTOR/S6K1-mediated mammalian targeting pathways and satellite cell migration to
 muscle fibers<sup>59, 60</sup>. The augmentation of these responses ultimately leads to muscle hypertrophy
 and an increase in skeletal muscle capillaries<sup>33, 61</sup>.

Thus, based on previous evidence regarding the effects of CE or BFR on muscle volume, it is plausible that BFR induced CE phenomenon could mitigate or prevent muscle volume atrophy on the disused side.

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#### 317 **5 Conclusion and perspective**

In summary, meta-analysis reveals that BFR can stimulate CE of muscle strength, yet confirmation is pending regarding its effect on muscle volume. Reduced exercise intensity during BFR may enhance neural activation. Coupled with neural mechanism-based cross-migration, rehabilitation training holds distinctive exploratory value for patients with neurological disorders.

This article has limitations. The literature included is publicly available, omitting theses, possibly introducing publication bias. The subjects, all healthy, limit generalization to those with major or chronic diseases. The focus on adults aged 18-30 may not represent older participants' muscle adaptability. CE induced by BFR is intricate, influencing body adaptations differently. Future research requires robust randomized controlled trials for comprehensive investigation.

Currently, there is no clear standard definition for the pressure intensity limit of BFR. Variation 327 in pressure among patients in the literature hinders the establishment of an optimal range. 328 329 Additionally, BFR parameters, including automatic pressure regulation, occlusion time, deflation 330 during rest, and methods for calculating total limb occlusion pressure, require ongoing exploration. 331 BFR offers advantages through neural mechanisms, enhancing motor unit recruitment, and 332 facilitating muscle hypertrophy and strength gains. However, its direct impact on muscle strength 333 and quality is limited, potentially leading to slower progress after initial gains. Future research 334 should investigate CE and BFR mechanisms to enhance theoretical understanding and clinical 335 efficacy in rehabilitation populations.

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