



The effects of L-citrulline supplementation on cerebrovascular function during sprint interval training in taekwondo athletes

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ABSTRACT

Background: Sprint Interval Training (SIT), a high - intensity exercise commonly used to improve athletic performance in combat sports, can affect cerebral blood flow. As the maintenance of cerebrovascular health is crucial for athletic performance and recovery, this study aimed to examine the effects of L-citrulline supplementation on cerebrovascular function following SIT in Taekwondo athletes.

Methods: Twenty male Taekwondo athletes (ages 18–30) participated in a double-blind, randomized crossover design. Participants received either 8.8 g of L-citrulline or a placebo (maltodextrin) for 5 consecutive days. The protocol involved four 30-s maximal sprints. Cerebrovascular function was assessed using transcranial Doppler (TCD) to measure changes in the breath-holding index (Δ BHI) and Pulse Index (Δ PI) before and after exercise.

Results: No significant difference was found for average power between conditions ($F = 1.27$, $P = 0.275$, $\eta_p^2 = 0.07$). A significant improvement in cerebrovascular function was observed in the L-citrulline group, with a positive change in Δ BHI ($F = 5.09$, $P = 0.037$, $\eta_p^2 = 0.22$). No significant effect was found for Δ PI ($F = 0.19$, $P = 0.669$, $\eta_p^2 = 0.01$).

Conclusions: L-citrulline supplementation enhanced cerebrovascular function recovery after SIT, suggesting a protective effect for Taekwondo athletes engaged in high-intensity training by promoting cerebral vascular health without affecting performance or peripheral resistance.

1. Introduction

High-intensity exercise, especially Sprint Interval Training (SIT), is receiving more and more attention. SIT has been shown to significantly improve athletes' aerobic capacity, anaerobic capacity, and overall athletic performance by alternating short bursts of maximal-intensity exercise with brief recovery periods. ^{1,2} This high-intensity training mode is particularly suitable for confrontational sports, such as taekwondo, in which athletes need not only excellent muscular strength and endurance, but also quick reaction and explosive power. ^{3,4} However, the high-intensity loading of SIT also puts a greater strain on various body systems, especially the cardiovascular and nervous systems. ^{5,6} During sprint interval training, athletes often experience dramatic heart rate fluctuations, which may lead to changes in cerebral blood flow, thereby affecting neurological function and recovery. ⁷ Intense interval training has been demonstrated to trigger short - term fluctuations in cerebral blood flow, and these fluctuations might potentially influence

the recovery of cognitive and motor functions. ⁸ In addition, research findings indicate that the recovery time of cognitive and motor functions is subject to variation, depending on elements like training intensity, individual fitness levels, and the specific characteristics of the task at hand. ⁹ Furthermore, it has been suggested by relevant studies that cognitive and motor functions are likely to commence their return to the baseline state within a time frame ranging from a few minutes to several hours following training. ⁵ Therefore, it is important to study the changes in cerebrovascular function after high-intensity training, especially in athletes of combat sports, to optimize training effects and improve recovery.

The brain is one of the most critical organs during exercise, and its demand for oxygen and nutrition increases dramatically during exercise. ¹⁰ Especially after high-intensity training, the brain needs to recover quickly to maintain the stability of cognitive and motor functions. Good cerebrovascular health is essential for maintaining recovery from exercise, reducing fatigue and optimizing neurological function. ^{11,12} It has

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been shown that improved cerebral blood flow after exercise accelerates neurological recovery and slows fatigue in the later stages of exercise.¹³ The breath-holding index (BHI) and Pulse index (PI) are widely used to assess functional changes in the cerebral vasculature.¹⁴ These hemodynamic indices can reflect the changes in cerebral blood flow, especially the ability to recover cerebral blood flow after exercise, which is valuable for the assessment of training effects and health management of athletes. Therefore, understanding the effects of exercise on cerebral blood flow and evaluating changes in cerebrovascular function are essential for improving the recovery of athletes and optimizing training protocols.

L-Citrulline, a non-essential amino acid, has garnered significant attention in sports nutrition in recent years. Research indicates that L-citrulline, through its precursor nitric oxide (NO) production, can effectively promote vasodilation, which in turn improves blood flow and supports vascular health.^{15,16} This mechanism not only enhances exercise performance but also accelerates post-exercise recovery, particularly after high-intensity training, with notable effects on the cardiovascular system.¹⁷ Studies have shown that L-citrulline supplementation can reduce muscle fatigue after exercise, improve circulation, and mitigate the buildup of metabolites associated with intense exercise, including lactate and hydrogen ions.^{18,19} While lactate buildup is commonly associated with anaerobic exercise, recent findings suggest that the accumulation of hydrogen ions—resulting from the dissociation of lactic acid—may play a more direct role in muscle fatigue. The accumulation of these hydrogen ions lowers muscle pH, which impairs muscle function and contributes to fatigue. L-citrulline supplementation has been found to help buffer this acidic environment and support improved performance, possibly by reducing the accumulation of these ions during intense exercise, rather than directly affecting lactate concentrations. Moreover, L-citrulline may play a key role in the recovery of cerebral blood flow post-exercise by enhancing blood flow.²⁰ Another study demonstrated that L-citrulline supplementation effectively improved post-exercise hemodynamic indices and facilitated enhanced blood supply after physical exertion.²¹ Therefore, L-citrulline has significant potential to promote cerebrovascular health and facilitate recovery of cerebral blood flow, especially following high-intensity training, by improving cardiovascular function.²² This understanding could provide valuable insight into how L-citrulline helps mitigate both peripheral and cerebral fatigue after exercise. Research has shown that combining L-citrulline with nitrate-rich beetroot extract can improve maximal and endurance strength, as well as aerobic capacity in trained male triathletes. A randomized, double-blind, placebo-controlled trial found that this combination not only boosted performance but also improved recovery.²³ Another study on long-term supplementation showed significant improvements in recovery over time, highlighting the potential of this combination for enhancing endurance and recovery in athletes. These results support the growing evidence of L-citrulline's benefits for performance and recovery in high-intensity training.²⁴

Although a number of studies have examined the facilitating effects of L-citrulline on exercise performance, particularly in endurance sports and strength training,^{25,26} relatively few studies have been conducted on its effects on cerebrovascular function, especially in the context of high-intensity interval training. Most of the existing studies have focused on the effects of L-citrulline on the cardiovascular system and muscle fatigue, while its role in the recovery of cerebrovascular function after exercise has been insufficiently explored.²⁷ There is also very limited research on the effects of high-intensity interval training on cerebrovascular function in specific sports (e.g., taekwondo), which has led to a lack of direct evidence regarding the role of L-citrulline on cerebrovascular recovery. Therefore, this paper aims to fill this research gap and provide a more precise scientific basis by exploring the potential effects of L-citrulline supplementation on the recovery of cerebrovascular function in taekwondo athletes after sprint interval training.

The main objective of this study was to investigate the effects of L-citrulline supplementation on the recovery of cerebrovascular function

in taekwondo athletes after sprint interval training. We hypothesized that L-citrulline supplementation could improve post-exercise cerebrovascular recovery by promoting vasodilatation and increasing cerebral blood flow, as evidenced by improved hemodynamic indices such as Δ BHI. The study aims to provide an in-depth understanding of how L-citrulline supplementation affects cerebrovascular function, further providing theoretical support for recovery and health management in athletes. The study not only provides new insights into cerebral blood flow recovery after high-intensity interval training, but also contributes to the development of a more personalized sports nutrition programmer to optimize performance and health recovery.

Relevance and significance of conducting research: Taekwondo is a high-intensity sport that requires explosive effort, making efficient recovery vital for peak performance. Sprint Interval Training (SIT), a common training method in Taekwondo, involves short bursts of maximal effort with brief rest periods. However, the impact of L-citrulline supplementation on recovery, particularly regarding cerebrovascular function, has not been well studied. L-citrulline, which enhances blood flow by increasing nitric oxide production, has shown benefits in endurance sports, but its effects on recovery in explosive sports like Taekwondo remain unclear. Understanding how L-citrulline influences both peripheral and cerebrovascular recovery in these athletes is important for optimizing recovery and performance strategies. This study is necessary because there is limited research on L-citrulline's effects in high-intensity sports such as Taekwondo. Most existing studies focus on endurance training or peripheral vascular function, with little attention given to its role in cerebrovascular recovery after intense, short bursts of activity. Taekwondo athletes face unique recovery challenges, particularly in maintaining cognitive function during rapid transitions between effort and rest. This research fills an important gap in sports nutrition, providing insights that could help Taekwondo athletes recover more effectively and improve their performance.

2. Methods

2.1. Participants

A total of 20 male Taekwondo athletes aged between 18 and 30 years were recruited for the study. All participants had 3–5 years of competitive experience and had participated in provincial or higher-level competitions, with their demographic characteristics detailed in Table 1. The inclusion criteria consisted of two key requirements: (1) regular participation in Taekwondo training with more than two training sessions per week, and (2) engagement in at least 20-min bouts of vigorous-intensity physical activity on a minimum of three days per week, as verified by the International Physical Activity Questionnaire (IPAQ).

Exclusion criteria were defined as follows: (1) history of cardiovascular, cerebrovascular, or metabolic diseases including hypertension, stroke, or myocardial infarction; (2) current or recent injuries (within past 3 months) affecting physical performance, such as musculoskeletal or joint injuries; (3) diagnosis of neurological or psychological disorders, particularly those experienced in the last 30 days (e.g., chronic headaches, insomnia, or dizziness); (4) regular use of tobacco, alcohol, or recreational drugs; (5) current use of medications affecting vascular function, including β -blockers or other antihypertensive drugs; (6) known allergies to study supplement ingredients; and (7) any medical

Table 1
The demographic characteristics of the participants.

	Mean \pm SD (n = 20)
Age (year)	25.05 \pm 1.73
Training Experience (year)	4.00 \pm 0.65
Body Height (cm)	172.80 \pm 2.75
Body Weight (kg)	68.70 \pm 3.63

condition potentially impairing cerebral blood flow regulation, such as carotid artery stenosis.

Before participation, all individuals signed informed consent forms in accordance with the Declaration of Helsinki. Participants also underwent a brief medical screening to ensure their eligibility for high-intensity physical activity. This study was approved by the Research Ethics Committee of University.

2.2. Experimental design

The study employed a double-blind, two-factor randomized cross-over design. Participants were randomly allocated to receive either L-citrulline supplementation or a placebo (maltodextrin) administered orally for 5 consecutive days. After completing the first intervention phase, a standardized 2-week washout period was implemented to eliminate potential carryover effects, after which all participants crossed over to receive the alternative treatment. This methodological approach allowed each participant to serve as their own internal control, with the complete experimental sequence illustrated in Fig. 1.

2.3. Testing protocol

Participants refrained from eating for at least 8 h prior to the test session and avoided caffeine and prescription medications for at least 12 h before each test. All experiments were conducted in the morning to minimize diurnal variation in performance. Participants were instructed to maintain their habitual diet and exercise routine throughout the duration of the study to avoid confounding effects.

2.4. L-citrulline supplementation

Participants received 8.8 g of L-citrulline daily, divided into four capsules (each containing 2.2 g). The supplementation was taken twice a day: two capsules in the morning and two in the evening, for 5 consecutive days (excluding the testing days).

L-citrulline had been shown to enhance nitric oxide production, promoting vasodilation and improving blood flow. Both acute and chronic supplementation (≥ 7 days) had been reported to significantly improve vascular function and exercise performance. Compliance with the supplementation regimen was monitored daily through participant check-ins to ensure adherence.

2.5. Placebo

The placebo consisted of maltodextrin, identical in appearance and taste to the L-citrulline supplementation, ensuring the blinding of both the participants and the researchers. The dosing regimen and timing were identical to the L-citrulline group.

Participants were instructed to avoid foods or supplements high in L-citrulline or antioxidants during the study period to minimize confounding effects.

2.6. Cycling protocol

The exercise protocol was conducted on a Monark Ergonomic cycle ergometer comprising four 30-s maximal sprints. The session commenced with a standardized 5-min warm-up phase where participants pedaled at self-selected pace without resistance to ensure physiological preparation for high-intensity exertion.

During the sprint trials, participants were instructed to achieve maximal pedaling speed against a predetermined resistance load of 0.075 kp·kg⁻¹ body weight applied to the flywheel. Each maximal effort phase was systematically followed by a 3-min active recovery interval, during which participants maintained free pedaling motion without resistance while permitted to self-regulate their rotational speed (RPM).

Power output quantification was performed through continuous monitoring of wattage production during each sprint interval. The primary performance metric consisted of mean average power calculated from all four sprints within a session. To account for intervention effects, participants completed identical cycling protocols under both experimental conditions (L-citrulline and placebo), resulting in two separate testing sessions per individual across the study duration.

2.7. Cerebrovascular function assessment

Transcranial Doppler (TCD) ultrasound (DWL, Compumedics Germany GmbH, Germany) was used to assess cerebrovascular function. This non-invasive technique allowed for the measurement of cerebral blood flow velocity (CBFV), which was critical for understanding cerebrovascular autoregulation (see Fig. 2).

BHI was measured as an indicator of cerebral vascular reactivity.²⁸ The participants held their breath for three 30-second intervals, with a 2-minute rest between each. Changes in the mean blood flow velocity (MBFV) in the middle cerebral artery (MCA) were recorded during the breath-hold maneuver. The BHI was calculated as follows:

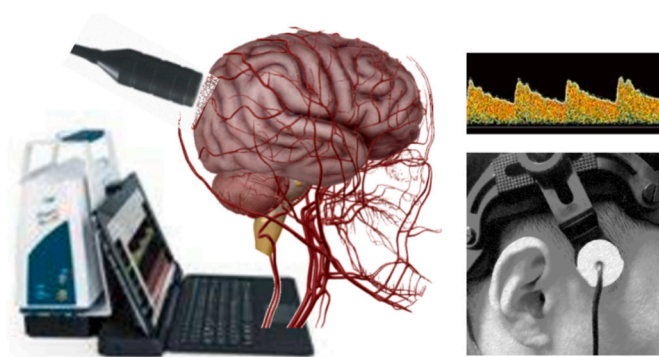


Fig. 2. Cerebrovascular function tests with transcranial Doppler.

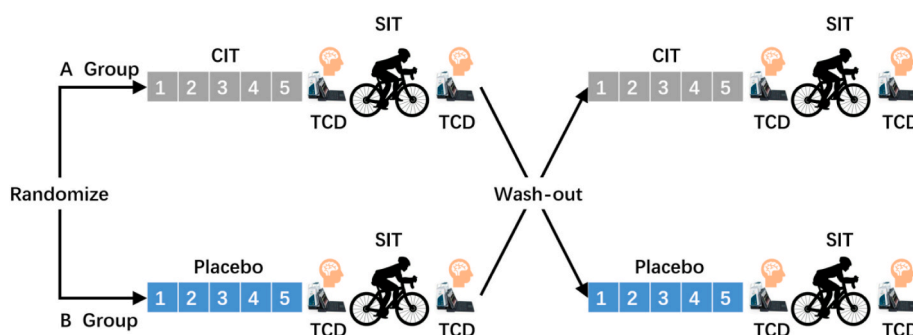


Fig. 1. Flowchart of the study design. Abbreviation: CIT, L-citrulline; SIT, sprint interval training; TCD, transcranial Doppler.

$$BHI = \frac{(MCA \text{ post-breath-hold MBFV} - MCA \text{ baseline MBFV})}{MCA \text{ baseline MBFV}} \times \frac{100}{30}$$

The average of the three BHI values was computed for each participant, and the BHI from both the left and right MCAs was averaged for the final score.

The PI was measured directly from the TCD device's output.²⁸ The PI reflected the peripheral resistance of the cerebral vessels: higher PI values indicated greater vascular resistance, while lower PI values suggested reduced resistance. The PI was measured both before and after exercise, and the difference in PI was calculated to assess the impact of the interventions.

Cerebrovascular function was assessed at two time points: 15 min before and after the cycling exercise. The changes in both BHI (ΔBHI) and PI (ΔPI) were compared between the L - citrulline and placebo conditions.

2.8. Statistical analysis

The data was first checked for outliers using box plots. Descriptive statistics (mean \pm standard deviation) were calculated for all outcome variables. A three - factor linear mixed - effects model was used for statistical analysis. Fixed factors included test condition (L - citrulline vs. placebo), test phase (first vs. second). Random factors included the ID. The dependent variables included the changes in BHI, PI, and peak power output. The significance level was set at $P < 0.05$. Data analysis was performed using SPSS 26.0 software (IBM, Armonk, NY, USA).

3. Results

The study results are summarized in Table 2, comparing indicators under L-citrulline supplementation (CIT) and placebo conditions.

3.1. Average power

No significant difference was found between the CIT and placebo conditions for average power ($F = 1.27$, $P = 0.275$, $\eta_p^2 = 0.07$), nor for the test phase ($F = 0.48$, $P = 0.499$, $\eta_p^2 = 0.03$).

3.2. ΔBHI (change in breath-holding index)

A significant effect of the test condition was observed for ΔBHI ($F = 5.09$, $P = 0.037$, $\eta_p^2 = 0.22$). The CIT group showed a return to baseline BHI, whereas the placebo group decreased (See Fig. 3D). The test phase had no significant effect on ΔBHI ($F = 0.61$, $P = 0.444$, $\eta_p^2 = 0.03$).

3.3. ΔPI (change in Pulse Index)

ΔPI (Change in Pulse Index): No significant effects were found for ΔPI ($F = 0.19$, $P = 0.669$, $\eta_p^2 = 0.01$) or the test phase ($F = 0.05$, $P = 0.821$, $\eta_p^2 = 0.00$).

Table 2
Comparison between indicators under different conditions.

	CIT	Placebo	Test condition			Test phase		
			F	P	η_p^2	F	P	η_p^2
Average power	520.45 \pm 56.83	499.67 \pm 64.88	1.27	0.275	0.07	0.48	0.499	0.03
PRE- BHI	1.66 \pm 0.36	1.66 \pm 0.37	0.00	0.997	0.00	1.99	0.176	0.10
ΔBHI	0.07 \pm 0.22	-0.18 \pm 0.46	5.09	0.037	0.22	0.61	0.444	0.03
POST-BHI	1.73 \pm 0.49	1.48 \pm 0.67	1.64	0.217	0.08	1.88	0.187	0.09
PRE-PI	0.89 \pm 0.07	0.86 \pm 0.07	2.12	0.162	0.11	1.02	0.325	0.05
ΔPI	-0.01 \pm 0.06	-0.00 \pm 0.06	0.19	0.669	0.01	0.05	0.821	0.00
POST-PI	0.88 \pm 0.10	0.86 \pm 0.09	0.47	0.502	0.03	0.27	0.608	0.01

Note: Abbreviation: CIT, L-citrulline; BHI, Breath-Holding Index; PI, Pulse Index. A three - factor linear mixed - effects model was used for statistical analysis.

4. Discussion

In this study, we investigated the effect of L-citrulline (CIT) supplementation on the recovery of cerebrovascular function in taekwondo athletes following Sprint Interval Training (SIT). The results indicated that the L-citrulline-supplemented group showed significant improvements in the respiratory breath-holding index (ΔBHI), suggesting that L-citrulline may facilitate cerebrovascular recovery post-exercise. However, no significant differences were observed in exercise performance (mean power) or peripheral vascular resistance (ΔPI) between the L-citrulline and placebo groups.

The results of this study suggest that L-citrulline supplementation did not directly enhance athletic performance, particularly in terms of power output or explosive strength. This outcome is consistent with prior studies that have highlighted the primary mechanism of L-citrulline as improving blood flow and promoting vasodilation through increased nitric oxide (NO) production. These effects are believed to aid in post-exercise recovery by improving circulation, rather than directly enhancing short-term explosive or strength performance.¹⁵ Specifically, the mechanism by which L-citrulline supports recovery involves enhancing endothelial function and reducing vascular resistance, which could explain the improvement in cerebrovascular function (ΔBHI) observed in our study.²⁹ However, as also suggested in previous research, L-citrulline's effects are more pronounced in endurance training rather than high-intensity interval training (e.g., short sprints), where short-term power output is the focus.³⁰ This aligns with our results, where no significant changes in power output were observed. For taekwondo athletes, the lack of significant improvement in performance indicates that L-citrulline supplementation may not be effective in directly enhancing power output or explosive strength in the short term. However, this does not diminish the potential physiological benefits of L-citrulline, particularly in aiding post-exercise recovery. The significant improvement in ΔBHI points to its role in accelerating cerebrovascular recovery, which could be beneficial in supporting cognitive function and mental clarity, especially following intense training sessions.³¹ The present study's contribution lies in expanding our understanding of L-citrulline's role in recovery beyond peripheral vascular effects, emphasizing its potential impact on cerebrovascular function.

In this study, the L-citrulline-supplemented group showed a significant improvement in the change of ΔBHI , recovering to near-baseline levels, while the placebo group experienced a decline. This suggests that L-citrulline accelerates cerebrovascular recovery after exercise, potentially through its ability to enhance nitric oxide (NO) production, which improves vasodilation and cerebral blood flow. Previous research has mainly focused on L-citrulline's effects on peripheral blood flow or exercise performance during endurance training,³² but its role in cerebrovascular recovery remains underexplored. Our findings provide new insight by demonstrating that L-citrulline may be particularly beneficial for cerebral recovery after SIT.³³ This supports the notion that L-citrulline may improve oxygen delivery to the brain, aiding the recovery of cognitive function such as reactivity, decision-making, and attention, which are crucial for athletes' performance.^{34,35} The

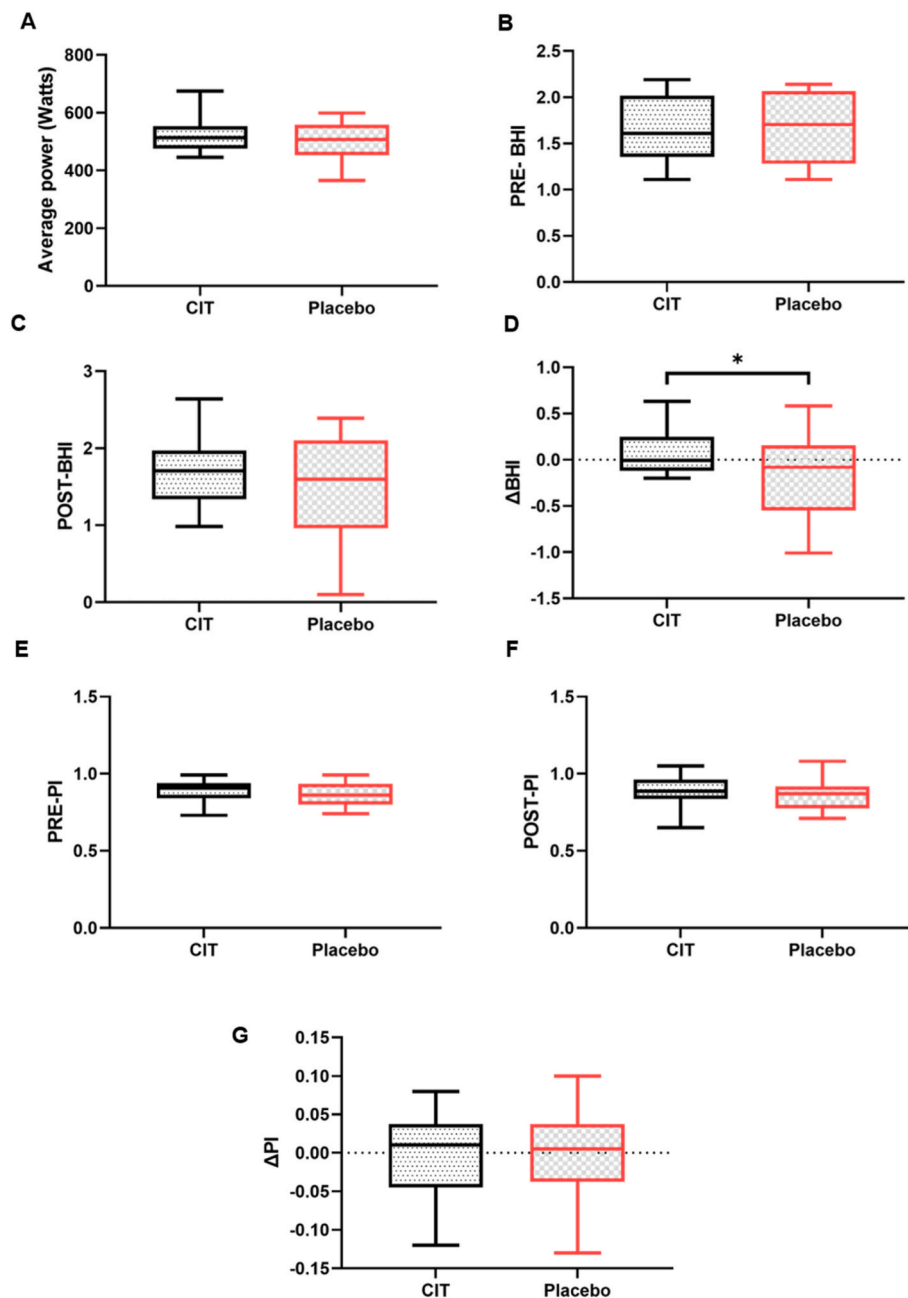


Fig. 3. Comparison between indicators under different conditions. (A) Change (Δ) in average power output. (B) Pre-intervention BHI. (C) Post-intervention BHI. (D) Change in BHI. (E) Pre-intervention PI. (F) Post-intervention PI. (G) Change in PI. Abbreviation: CIT, L-citrulline; BHI, Breath-Holding Index; PI, Pulse Index. A three-factor linear mixed-effects model was used for statistical analysis. * indicates $P < 0.05$.

observed improvement in cerebrovascular function following supplementation is consistent with the role of L-citrulline in promoting vascular health, yet this specific benefit in the context of high-intensity exercise is rarely highlighted in existing literature. This finding has particular relevance for taekwondo athletes, as maintaining high cognitive function after intense training is essential for both the quality of training and competitive performance.³⁶

In terms of Pulse Index (Δ PI), the L-citrulline-supplemented group did not show a significant difference from the placebo group, suggesting that L-citrulline did not have a notable impact on peripheral vascular resistance. This result is consistent with previous studies, where L-citrulline's primary mechanism is thought to improve vasodilatation and blood flow by promoting nitric oxide production, though its effect on peripheral vessels may be more limited, particularly in short-duration,

high-intensity activities.³⁷ One potential explanation for the lack of significant changes in PI could be the specific nature of Sprint Interval Training (SIT). SIT, characterized by repeated short bursts of maximal sprints followed by rest, places distinct demands on the cardiovascular system compared to steady-state or high-intensity interval training (HIIT), which typically involves longer periods of sustained effort. The rapid transitions between work and rest in SIT may not challenge the peripheral vasculature as much as the more sustained, prolonged efforts in endurance-focused or HIIT training.³⁸ This could explain why L-citrulline supplementation did not significantly affect peripheral vascular resistance in this study.³⁹ In endurance events or HIIT, where the circulatory system is engaged for longer durations at elevated intensities, the peripheral vascular system plays a more prominent role in maintaining blood flow and oxygen delivery to the muscles.³⁹ However,

during short bursts of high-intensity work, such as those in SIT, cerebrovascular function may be more critical for ensuring proper oxygen supply to the brain and maintaining cognitive function.⁴⁰ This suggests that while L-citrulline did not significantly impact peripheral vascular resistance, its positive effects on cerebrovascular recovery and oxygen delivery to the brain during short, intense training bouts could be more important. Thus, the lack of significant changes in PI may be attributed to the specific demands of the SIT protocol, emphasizing the need to consider the nature of different training regimens when assessing the effects of supplements like L-citrulline.

Strengths: This study significantly contributes by focusing on cerebrovascular function recovery in taekwondo athletes post - high - intensity training, an under - researched area. By examining L - citrulline's impact on this recovery, it provides novel insights for post - sprint interval training recovery. The use of placebo and supplementation groups minimizes biases, strengthening result reliability. The sample of experienced male taekwondo athletes makes the findings relevant to highly - trained individuals, with practical implications for recovery and performance optimization. The comprehensive analysis of hemodynamic indices like BHI and PI details the physiological mechanisms. Strict dietary control and a standardized design ensure a precise evaluation of L - citrulline's effect, reducing external interferences. Given the lack of research on post - high - intensity interval training cerebrovascular recovery, this study fills a crucial gap, validating L - citrulline's role and guiding future sports nutrition. Highlighting cerebrovascular recovery also broadens the research scope beyond traditional physical metrics, emphasizing the importance of cognitive function in athletes.

Limitations: The main limitation of this study is the small sample size, which included only 20 participants, and therefore the generalizability of the results is limited. Additionally, this study only focused on taekwondo athletes and did not consider other sports or gender differences, which may affect the extrapolation of the results. Future studies could further validate the effects of L-citrulline by increasing the sample size and diversifying the participant population. Additionally, there was a failure to control for other factors that may affect recovery, such as diet, sleep, and stress levels, which may also affect the accuracy of the study results.

5. Conclusion

This study demonstrates that L-citrulline supplementation significantly enhances cerebrovascular recovery in taekwondo athletes following high-intensity sprint interval training, as indicated by the improvement in the breath-hold index. While no direct effect on athletic performance was observed, the results underscore L-citrulline's potential to promote cerebral blood flow and support neurological recovery. This finding addresses the need for effective recovery strategies for athletes engaged in high-intensity training, particularly in maintaining cognitive function and reducing fatigue. By enhancing the recovery of cerebral blood flow, L-citrulline offers a promising nutritional supplement that can optimize the post-exercise recovery process, which is essential for maintaining mental sharpness and improving long-term performance in athletes. Thus, the study not only highlights the importance of cerebrovascular health in the recovery phase but also provides a foundation for future sports nutrition strategies aimed at enhancing both physical and cognitive recovery after intense training.

Author contributions

Aiqin Li (AL) conceived and designed the study, coordinated the data collection, and drafted the manuscript. Haojie Li (HL) performed the statistical analysis and contributed to the interpretation of the results. Jiangang Chen (JC) was involved in the acquisition of data and provided critical revisions to the manuscript. All authors have read and approved the final manuscript and agree to be accountable for the accuracy and integrity of the work. AL takes responsibility for the integrity of the work

as a whole.

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Conflicts of interest statement

All authors declare that they have no competing interests.

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