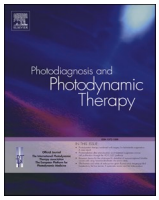
Photodiagnosis and Photodynamic Therapy 50 (2024) 104412

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt



Impact of repeated low-level red-light exposure on choroidal thickness and blood flow in pediatric patients: A SS-OCTA study

Huihang Wang [a,b,c,d], Huifen Zhong [a,b,c,d], Jingjin Zhang [a,b,c,d], Wei Wei [a,b,c,d], Xiaoyuan Cui [a,b,c,d], Weidong Zheng [a,b,c,d,*]

[a] Department of Ophthalmology, the First Affiliated Hospital, Fujian Medical University, Fuzhou, China
[b] Department of Ophthalmology, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou, China
[c] Fujian Institute of Ophthalmology, the First Affiliated Hospital, Fujian Medical University, Fuzhou, China
[d] Fujian Provincial Clinical Medical Research Center of Eye Diseases and Optometry, the First Affiliated Hospital, Fujian Medical University, Fuzhou, China

ARTICLE INFO

Keywords:
Low-level red-light
Choroidal thickness
Blood flow
Children
OCTA

ABSTRACT

Purpose: To evaluate the impact of repeated low-level red-light (RLRL) therapy on choroidal thickness and blood flow in pediatric myopia.

Methods: A three-month trial (April 1, 2023 – September 30, 2023) was conducted involving 44 children (ages 6–16) with myopia. Participants underwent RLRL therapy at home twice daily for five days per week, with each session lasting three minutes. Assessments at baseline, one month, and three months included cycloplegic refraction, best-corrected visual acuity (BCVA), intraocular pressure (IOP), ocular biometrics, swept-source optical coherence tomography angiography (SS-OCTA), slit-lamp, and fundus examinations.

Results: The study included 44 children (average age: 9.79 years; 56.82 % male). RLRL therapy significantly increased subfoveal choroidal thickness (Baseline: 272.82 ± 64.01 μm; 1-month: 297.77 ± 72.94 μm; 3-month: 298.77 ± 77.17 μm, $p = 0.001$), reduced axial length (Baseline: 24.97 ± 1.47 mm; 3-month: 24.88 ± 1.38 mm, $p = 0.002$), and showed a marginal regression in spherical equivalent ($p = 0.055$). Significant elevations in choroidal vessel volume and thickness were noted, with positive correlations intensifying with distance from the fovea.

Conclusion: RLRL therapy shows promise in managing pediatric myopia by increasing choroidal vessel volume and thickness, potentially mitigating myopia progression.

1. Introduction

Global incidence of myopia has risen markedly in recent decades, and nearly half of the world's population (49.8 %) will be affected by 2050 [1]. This trend not only places a substantial economic strain on individuals, families, and communities but also poses significant public health challenges worldwide [2]. The progression of myopia is associated with an increased risk of severe ocular pathologies, including macular degeneration, glaucomatous optic neuropathy, choroidal neovascularization, retinal detachment, and other vision-threatening conditions [3]. Notably, myopic eyes typically exhibit elongation of the axial length (AL) and significant alterations in choroidal thickness and blood flow [4]. Research across both animal and human studies has consistently shown a marked decrease in choroidal thickness and blood flow in myopic eyes [5]. These changes are believed to contribute to scleral hypoxia and extracellular matrix remodeling, playing a crucial role in the onset and progression of myopia [6].

Repeated low-level red-light (RLRL) therapy has emerged as an innovative strategy for managing myopia, with its efficacy and safety being well-documented in recent research [7–10]. A 12-month multicenter randomized controlled trial (RCT) by Jiang et al. has highlighted the therapy's potency, revealing a significant slowdown in axial elongation and myopia progression by 69.4 % and 76.6 %, respectively [7]. Furthermore, RLRL therapy proved superior to low-concentration

Abbreviations: RLRL, repeated low-level red-light; RCT, randomized controlled trial; SER, spherical equivalent refraction; SVS, single vision spectacle; D, diopter; BCVA, best-corrected visual acuity; SS-OCT, swept-source optical coherence tomography; AL, axial length; SD, standard deviation; CI, confident interval; CCT, central corneal thickness; AD, aqueous depth; LT, lens thickness; ChT, choroidal thickness; logMAR, logarithm of the minimum angle of resolution.

* Corresponding author at: Department of Ophthalmology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China.
E-mail address: wdzheng@fjmu.edu.cn (W. Zheng).

https://doi.org/10.1016/j.pdpdt.2024.104412
Received 2 October 2024; Received in revised form 6 November 2024; Accepted 20 November 2024
Available online 21 November 2024

atropine in controlling axial length and myopia progression over a similar timeframe [11]. Additional studies, such as those conducted by Xiong et al., have shown a notable increase in choroidal thickness, peaking within the first month of RLRL treatment [12]. Liu et al. further confirmed these findings in adults, reporting significant reductions in axial length, enhanced choroidal thickness, and improved choroidal circulation after just one month of treatment, though they also noted that choroidal thickening alone did not account for the reduction in axial length [13].

The underlying mechanisms by which RLRL therapy decelerates myopia progression are not fully understood. Existing studies propose that its therapeutic effects could be linked to modifications in the choroid. This study is designed to explore how RLRL treatment influences choroidal thickness and blood flow across various regions in children diagnosed with myopia.

2. Methods

2.1. Study participants

This study, conducted at the First Affiliated Hospital of Fujian Medical University in Fuzhou, China, from April 1 to September 30, 2023, adhered to the ethical guidelines of the Helsinki Declaration. Ethical approval was secured from the hospital's Ethics Committee, with written informed consent obtained from all participants' parents or legal guardians. The study recruited children aged 6 to 16 with myopia, characterized by a spherical refractive error between −10.00D and −0.50D (after cycloplegia) and best-corrected visual acuity (BCVA) at or above 20/20 (Snellen) of study eyes, who were also capable of completing the required examinations. Exclusion criteria included any ocular condition (e.g., corneal lesions, glaucoma, elevated intraocular pressure, anterior chamber infections, lens abnormalities, retinal diseases), strabismus, abnormal binocular vision, a history of eye surgery or trauma, severe systemic diseases, previous myopia treatments, or an inability to cooperate with examinations.

2.2. RLRL procedure

Participants in this study received RLRL therapy twice daily for three minutes per session, five days a week, conducted at home. RLRL serves as an adjunct treatment for myopia in children and adolescents by exposing both eyes to low-intensity red light. Research supports its efficacy and safety in managing myopia [7]. A specifically designed low-intensity red light therapy device (Eyerising, Suzhou Xuanjia Optoelectronics Technology, China), emitting a 650 nm wavelength light at an illuminance of approximately 1600 lux directly through the pupil to the retina, was employed. To maintain standardized procedures and ensure adherence, the device features the ability to record treatment sessions and durations, syncing this data to the backend. This enables professionals to monitor treatment compliance remotely and allows for timely intervention by alerting parents or legal guardians when deviations from the treatment protocol occur.

2.3. Adverse events

Participants who received at least one treatment session were included in the safety analysis. During each follow-up visit, as well as any necessary unscheduled visits, participants and their parents were asked about any side effects. They were specifically questioned about symptoms such as dazzling, temporary glare, flash blindness, and afterimages following the treatment, as well as whether they had experienced illness or hospitalization since the previous visit. All adverse events were recorded, and the data safety monitoring committee made the final assessment on whether the event was related to the treatment.

2.4. Ocular examinations

At baseline and subsequent follow-ups, qualified examiners performed a comprehensive set of assessments on each participant, including measurements of cycloplegic refraction, BCVA, intraocular pressure (IOP), ocular biometrics, swept-source optical coherence tomography angiography (SS-OCTA), slit-lamp, and fundus examinations. IOP was measured pre-ciliary muscle paralysis using a non-contact tonometer (Topcon, Japan), with three readings per eye to calculate an average. Ocular biometric parameters were determined using optical low-coherence reflectometry (Lenstar 900; Haag-Streit AG, Switzerland), retaining three measurements within 0.02 mm variance for average calculation. Ciliary muscle paralysis was induced with tropicamide eye drops across three applications, spaced five minutes apart. After a 20-minute rest with eyes closed, adequacy was assessed based on a pupil diameter of $\geq$6 mm and the absence of light reflex. Refraction was conducted thrice with a computerized auto-refractometer (Topcon, Japan) to determine the average spherical equivalent (SE), calculated as the spherical diopter plus half the cylindrical diopter. Follow-up evaluations were scheduled at 1 and 3 months after initiating RLRL therapy.

2.5. SS-OCTA imaging

Swept-source optical coherence tomography angiography (SS-OCTA) is a non-invasive imaging modality that has become indispensable in ophthalmology, prized for its rapid scanning, high-resolution outputs, consistent repeatability, and non-invasive nature. Empowered by artificial intelligence for refined layer segmentation, SS-OCTA offers precise visualization of vascular structures and dynamic blood flow within the retina and choroid [14]. In this research, the VG200 system (VisionMicro Imaging Technology Co., Ltd., Henan, China) facilitated the SS-OCTA imaging process. Uniformity in examination conditions was ensured by having all scans conducted by an adept operator within a controlled environment, focusing on a 12 × 12 mm area of the macula. Criteria for image analysis included a signal strength greater than 7, absence of artifacts, and accurate segmentation, processed through the device's integrated software. As shown in Fig. 1, utilizing the Early Treatment Diabetic Retinopathy Study (ETDRS) grid, images were segmented into five concentric circles to analyze various choroidal metrics, including subfoveal choroidal thickness (SChT), average choroidal thickness (ChT), choroidal vessel volume (CVV), choroidal vascularity index (CVI), choroidal flow area (CFA), and choriocapillaris blood flow area (CBFA). These parameters measured the vertical distances and volumes within the choroid and choriocapillaris, providing a comprehensive evaluation of vascular health and function.

2.6. Statistical analysis

Statistical analyses were performed using SPSS version 25.0, presenting results as means ± standard deviations. The Shapiro-Wilk test assessed data normality. Temporal changes were analyzed via single-factor repeated measures ANOVA, and Pearson correlation analysis explored relationships between change rates of CVV and ChT. A P-value < 0.05 denoted statistical significance.

3. Results

3.1. Baseline characteristics

A total of 44 participants (88 eyes) were included, comprising 25 males (56.82 %) and 19 females (43.18 %). The average age was 9.79 ± 3.40 years, ranging from 6 to 16 years. Table 1 summarizes the general information of the participants. The average compliance for RLRL at 1 month and 3 months were both above 85 %, ensuring the effective implementation of the treatment.

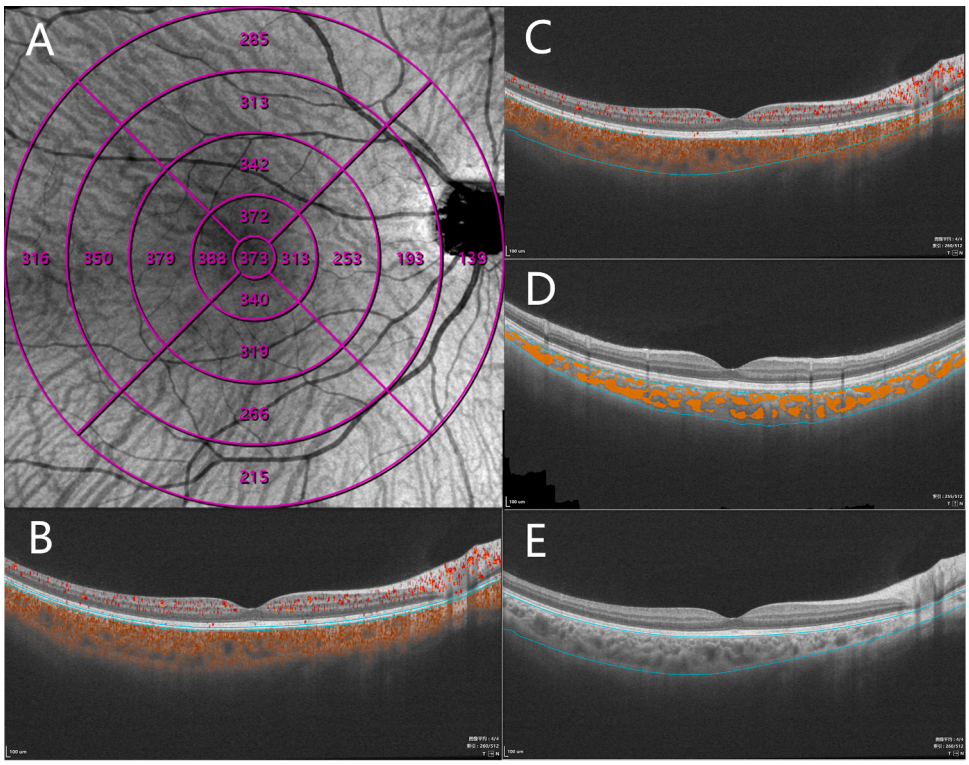


Fig. 1. (A) Calculation of ChT in different areas of the macula using the ETDRS grid (12 × 12mm). (B) The OCT of CFBA, where the red signal at the position of the blue line indicates blood flow in the choriocapillaris layer. (C) The OCT of CFA, where the orange signal between the two blue lines indicates blood flow in the larger vessels of the choroid. (D) The OCT of CVV and CVI, where the orange signal between the two blue lines indicates blood flow in the larger vessels of the choroid. (E) The OCT of ChT, where the vertical distance between the two blue lines represents the thickness of the choroid. ChT=choroidal thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; OCT=optical coherence tomography; CFBA=choriocapillaris blood flow area; CFA=choroidal flow area; CVV=choroidal vessel volume; CVI=choroidal vascularity index.

Table 1
Baseline characteristics of participants.

Subjects	N/Range	Mean ± SD
NO. of participants	44	
NO. of eyes	88	
Sex, male No (%)	25 (56.82)	
Sex, female No (%)	19 (43.18)	
Age (years)	6 - 16	9.79 ± 3.40
Central corneal thickness (μm)	509 - 630	526.23 ± 33.12
Corneal curvature (D)	40.52 - 44.83	43.08 ± 1.23
Anterior chamber depth (mm)	2.96 - 4.37	3.71 ± 0.28
Lens thickness (mm)	3.06 - 3.48	3.35 ± 0.11
Corneal diameter (mm)	11.50 - 13.92	12.12 ± 0.55
Axial length (mm)	22.88 - 28.01	24.97 ± 1.47
Spherical equivalent (D)	−9.875 - 0.625	−3.23 ± 3.16
SChT (μm)	140 - 415	272.82 ± 64.01
Compliance at 1-month (%)	31.82 - 97.62	86.10 ± 18.90
Compliance at 3-month (%)	80.53 - 97.85	92.35 ± 5.63

SChT=subfoveal choroidal thickness; SD=standard deviation.

3.2. Axial length and spherical equivalent changes over time

The top half of Table 2 illustrates the changes in AL and SE following RLRL therapy. AL showed a progressive decrease over the duration of RLRL therapy, with a notable reduction observed at 3 months. Initially, AL decreased from 24.97 ± 1.47 mm to 24.93 ± 1.42 mm after 1 month and further reduced to 24.88 ± 1.38 mm after 3 months ($p < 0.05$). SE did not exhibit significant changes from the baseline to 1- and 3-month post-treatment, yet a downward trend was apparent. A statistically significant difference in SE was noted when comparing the intervals between 1 month and 3 months of treatment ($p < 0.022$). For better visualization, line graphs depicting these trends are provided in Fig. 2.

Table 2
Comparison of AL and SE at baseline and follow-up.

	AL (mm)	SE (D)	ΔAL (mm)	ΔSE (D)
Baseline	24.97 ± 1.47	−3.23 ± 3.16	0	0
1 month	24.93 ± 1.42	−3.33 ± 3.00	−0.04	−0.10
3 months	24.88 ± 1.38	−3.06 ± 3.15	−0.09	+0.17
P_{0-1}	0.026	0.403	–	–
P_{1-3}	0.006	0.022	–	–
P_{0-3}	0.002	0.055	–	–
Younger $_{0-3}(n = 32)$	–	–	−0.024	+0.14
Older $_{0-3}(n = 12)$	–	–	−0.275	+0.24
$P_{Y\text{-}O(0-3)}$	–	–	0.0014	0.15

Δ=Change from baseline; AL=axial length; SE=spherical equivalent; *D*=diopter.

The bottom half of Table 2 shows that after three months, the AL in older patients (aged ≥ 11 years) was significantly shorter compared to younger patients (aged < 11 years) ($P < 0.05$). While the SE also showed a greater reduction in older patients, this difference was not statistically significant.

3.3. Choroidal thickness and blood flow changes

After RLRL therapy, SChT experienced a significant thickening, from 272.82 ± 64.01 μm at baseline to 297.77 ± 72.94 μm at 1 month and further to 298.77 ± 77.17 μm at 3 months ($p < 0.05$).

CVV and ChT across various diameter regions from fovea (0–1 mm, 1–3 mm, 3–6 mm, 6–9 mm, 9–12 mm) exhibited marked increase from baseline to 1 and 3 months of therapy ($p < 0.05$) as detailed in Table 3. Linear regression analysis revealed a significant, positive correlation

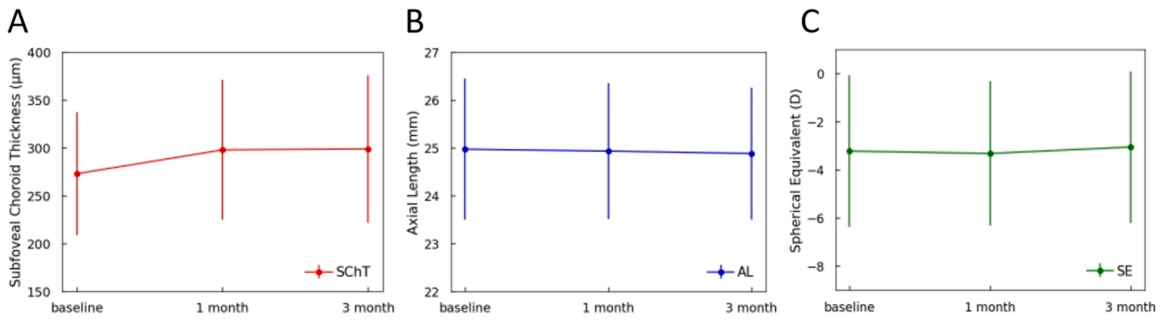


Fig. 2. Change of SChT (A), AL (B) and SE (C) at baseline and follow up after RLRL treatment. SChT=subfoveal choroidal thickness; AL=axial length; SE=spherical equivalent. Data were plotted as mean and standard deviation.

between the growth rates of CVV and ChT, with stronger correlations observed as distance from the central fovea increased, especially notable in regions further from the central fovea (Fig. 3).

Regression analysis on the change rates of CVV and ChT demonstrated that as distance from the central fovea increased, the coefficient of determination (R^2) generally rose, while the bias, mean squared error (MSE), root mean squared error (RMSE), and mean absolute error (MAE) progressively declined (Table 4). These trends underscore that the primary contributor to the increase in ChT was the rise in CVV, a relationship that intensifies in more peripheral regions. Differences in ChT and CVV across the four quadrants followed a pattern of temporal > superior > inferior > nasal (Fig. 4). Post-3-months RLRL therapy, this trend persisted, indicating a gradual increase from the central fovea towards the periphery. The comparative analysis reveals that the increase in ChT slightly surpassed that of CVV within the same quadrant after three months, suggesting that, beyond CVV's influence, other factors such as non-vascular smooth muscle components, extracellular matrix changes, and collagen remodeling within the choroidal stroma could also contribute to ChT enhancement.

Following one month of treatment, CVI experienced a notable decrease from baseline in all regions except the 6–9 mm zone ($p < 0.05$), with the extent of change diminishing as the region's diameter increased, as outlined in Table 3. At the three-month mark, a significant reduction in CVI was observed solely in the 9–12 mm region relative to baseline ($p < 0.05$). Comparisons between the three-month and one-month data points revealed no significant alterations in CVI across all examined regions, indicating a lack of statistical significance ($p > 0.05$).

CFA remained unchanged in all regions after one month of treatment when compared to the baseline ($p > 0.05$). However, by the three-month interval, a significant enhancement in CFA was detected in the 6–9 mm region against the baseline ($p < 0.05$). No noteworthy differences in CFA were observed when comparing data from three months of treatment to one month across all regions ($p > 0.05$).

For CBFA, a significant augmentation was noted in the 1–3 mm region after one month of therapy compared to baseline ($p < 0.05$), as shown in Table 3. Following three months of intervention, the 0–1 mm region showed a marked increase in CBFA relative to the baseline ($p < 0.05$). Yet, when assessing the period from three months to one month of treatment, CBFA changes across all regions did not achieve statistical significance ($p > 0.05$).

3.4. Adverse events

During the initial phase of treatment, only one patient felt that the emitted light was "too strong," leading to poor compliance. However, compliance improved after a period of adjustment. None of the participants reported experiencing symptoms such as dazzling, glare, flash blindness, or afterimages following treatment. Additionally, OCT scans showed no structural damage to the photosensory layer in any of the eyes studied. The BCVA of study eyes did not change, remained at or above 20/20 (Snellen) by the end of the study.

4. Discussion

4.1. Myopia control effectiveness after RLRL treatment

AL and SE serve as principal measures for evaluating the effectiveness of myopia management. An RCT among children with initial stages of myopia, demonstrated that RLRL therapy markedly reduced myopic progression in both AL and SE (with reductions of 0.17 mm and −0.41 D, respectively) [9]. Similarly, studies involving myopic adults have shown that one month of RLRL therapy significantly decreases AL, signifying RLRL's potent impact on myopia across different age groups [13]. In this study, we found that RLRL therapy appeared to be more effective in older patients compared to younger ones, nevertheless, findings on the relationship between AL modifications and variables such as age or initial AL remain further research [15].

In comparison to orthokeratology lenses or low-concentration atropine treatments, RLRL therapy exhibits superior immediate effects in slowing myopia progression. Previous studies have reported that over two years, RLRL therapy reduced AL by 0.48 mm and SE progression by 0.93 D compared to the control group, representing a treatment efficacy of 75 % for both outcomes [10]. Other treatments, for example, atropine 0.05 % produced a 64.5 % reduction in myopia progression over two years [16]. The cumulative reduction in AL for orthokeratology lenses ranges from 0.27 to 0.32 mm, representing a treatment efficacy between 43 % and 63 % [17,18]. These results indicate that repeated low-level red-light therapy may offer better outcomes in myopia control compared to other established interventions.

This study substantiates that 3-month RLRL therapy induces AL reduction and SE regression, validating its utility in myopia management. However, The observation period in this study was limited to three months, which may be insufficient to assess the rebound effect after RLRL therapy cessation. Previous studies have reported a modest rebound effect occurring 6–12 months post-treatment discontinuation, with approximately 20–30 % of patients affected [10]. Longer treatment duration, ideally at least 12 months, followed by gradual reduction rather than abrupt cessation, is recommended to minimize rebound. Future studies should focus on extending observation periods to better understand long-term outcomes and the potential rebound effect in pediatric myopia management. Additionally, this research noted a more rapid response in SChT compared to changes in AL and SE, with no significant alterations from the first to the third month. This suggests that AL reduction may not be exclusively attributed to SChT enhancement, indicating the role of other factors as explored in prior studies [7,13,19].

4.2. Changes in choroidal thickness and blood flow after RLRL treatment

This study revealed notable increases in ChT and CVV across all areas

Table 3
Comparison of choroidal thickness and choroidal blood flow from various regions at baseline and follow-up.

Subjects	Baseline	Δ1 month	Δ3 months	P_{0-1}	P_{1-3}	P_{0-3}
SChT (μm)	272.82 ± 64.01	+24.95	+25.95	<0.001	0.755	<0.001
ChT (μm)						
ChT_{01}	272.82 ± 64.60	+22.63	+22.91	<0.001	0.937	<0.001
ChT_{03}	268.97 ± 61.87	+22.71	+23.14	<0.001	0.895	<0.001
ChT_{06}	260.84 ± 54.69	+21.23	+21.57	<0.001	0.888	<0.001
ChT_{09}	243.08 ± 45.34	+19.73	+21.58	<0.001	0.086	<0.001
ChT_{12}	221.60 ± 37.90	+14.70	+17.18	<0.001	0.021	<0.001
CVV (mm^3)						
CVV_{01}	0.083 ± 0.020	+0.006	+0.008	<0.001	0.345	<0.001
CVV_{03}	0.608 ± 0.146	+0.052	+0.055	<0.001	0.489	<0.001
CVV_{06}	1.818 ± 0.360	+0.148	+0.171	<0.001	0.191	<0.001
CVV_{09}	2.743 ± 0.492	+0.215	+0.266	<0.001	0.013	<0.001
CVV_{12}	3.515 ± 0.601	+0.232	+0.296	<0.001	0.024	<0.001
CVI						
CVI_{01}	0.437 ± 0.070	−0.015	−0.010	<0.001	0.208	0.101
CVI_{03}	0.434 ± 0.066	−0.011	−0.006	0.029	0.182	0.276
CVI_{06}	0.417 ± 0.053	−0.005	−0.002	0.045	0.132	0.571
CVI_{09}	0.402 ± 0.064	−0.012	−0.008	0.085	0.080	0.182
CVI_{12}	0.398 ± 0.055	−0.004	−0.004	0.029	0.868	0.024
CFA (mm^2)						
CFA_{01}	0.79 ± 0.00	−0.01	−0.01	0.429	0.374	0.708
CFA_{03}	6.29 ± 0.03	−0.07	−0.01	0.303	0.344	0.249
CFA_{06}	21.19 ± 0.06	+0.01	+0.01	0.426	0.396	0.885
CFA_{09}	34.88 ± 0.30	+0.02	+0.02	0.205	0.429	0.047
CFA_{12}	47.68 ± 0.78	+0.02	−0.06	0.670	0.258	0.194
CBFA (mm^2)						
$CBFA_{01}$	0.71 ± 0.03	+0.01	+0.01	0.050	0.728	0.034
$CBFA_{03}$	5.63 ± 0.30	+0.08	+0.06	0.017	0.518	0.090
$CBFA_{06}$	18.82 ± 0.93	+0.17	+0.15	0.111	0.824	0.127
$CBFA_{09}$	30.71 ± 1.52	+0.02	+0.10	0.908	0.410	0.334
$CBFA_{12}$	41.94 ± 2.304	−0.02	−0.08	0.823	0.860	0.991

Δ=Change from baseline; SFCT=subfoveal choroidal thickness; ChT=choroidal thickness; CVV=choroidal vessel volume; CVI=choroidal vascularity index; CFA=choroidal flow area; CFBA=choriocapillaris blood flow area.
01: 0–1 mm annular region; 03: 1–3 mm annular region; 06: 3–6 mm annular region; 09: 6–9 mm annular region; 12: 9–12 mm annular region.

following RLRL therapy, aligning with existing literature while expanding the scope to include peripheral areas up to a 12 mm diameter [13]. This broader approach allows for an in-depth examination of choroidal changes extending from the central to peripheral regions, areas previously overlooked in choroidal research.

Previous literature has highlighted the choroid's essential role in the growth and development of the eye [20], particularly in adjusting the retina's position and contributing to vascularization and scleral remodeling. Decreases in choroidal thickness and blood flow have been associated with scleral hypoxia and remodeling, leading to AL growth—a principal contributor to myopia progression [21]. This study suggests that enhancements in ChT and CVV can mitigate scleral hypoxia and remodeling, thus slowing, or possibly reversing, AL growth, offering insight into the mechanisms by which RLRL therapy could control myopia progression. Intriguingly, the findings indicate a more extended response of the peripheral choroid to RLRL than that of the fovea, suggesting that peripheral scleral remodeling might have a more prolonged impact on altering posterior polar retinal curvature and reducing AL. These initial observations highlight the need for further research through extended observation and detailed retinal curvature measurements, setting a new direction for subsequent studies.

After three months of RLRL therapy, no significant differences were observed in ChT and CVV compared to the results after one month. This aligns with findings by Xiong et al. [10], who noted that choroidal thickening peaked at one month, diminishing thereafter. This pattern suggests a dose-dependent response to RLRL therapy, with initial choroidal sensitivity to RLRL leading to maximal increases in ChT and CVV, which gradually decline as this sensitivity diminishes over time without adjustments in therapy dosage.

Utilizing ETDRS rings, we segmented the choroid within a 12 mm diameter around the macular fovea into annular regions and four quadrants (upper, lower, nasal, and temporal). Comparison of data from three months versus one month of treatment showed that while CVV and ChT did not significantly change in most regions, there was a trend towards variation with increased diameter. Notably, after three months, the increase in ChT and CVV was most pronounced in the temporal quadrant, diminishing from the fovea outward, indicating differential choroidal sensitivity to RLRL across quadrants and distances. The foveal choroid exhibited greater responsiveness to RLRL than peripheral areas, with the temporal side showing heightened sensitivity compared to other quadrants. This differential response may be attributed to direct exposure to red light during treatment, concentrating energy centrally and eliciting a quicker, more substantial response in the fovea, while the peripheral choroid reacts more slowly and subtly but continues to respond over a longer duration. Additionally, variations in baseline ChT and CVV across different areas may influence response magnitude. Previous research confirms that the choroid is thickest under the fovea, tapering towards the periphery and among the quadrants, with the nasal side being the thinnest and the temporal side the thickest [22]. Thus, the degree of response to RLRL therapy varies by distance, with increases in ChT and CVV being most significant in the temporal quadrant, illustrating a complex interplay of choroidal sensitivity and baseline characteristics in the RLRL therapy response.

After one month of RLRL treatment, CVI significantly decreased across all regions, with the exception of the 6–9 mm zone. This trend suggests a more pronounced reduction in the proportion of choroidal vascular cross-section subfoveally than peripherally. Despite notable increases in both CVV and ChT, the rise in ChT outpaced that of CVV, implying that while CVV expansion contributes significantly to ChT enhancement, additional factors also play a role. Contrary to these findings, Liu et al.'s study on 98 adults aged 18–35 revealed significant CVI changes within the 0–6 mm region after one month of RLRL treatment [14], diverging from our results possibly due to differences in participant age and choroidal structure between children and adults.

Studies indicate that factors such as choroidal blood vessels, permeable molecules within the choroidal matrix, non-vascular smooth muscle cells, and intrinsic choroidal neurons can influence choroidal thickness [23]. We propose that RLRL treatment not only stimulates choroidal vascular dilation and increased blood flow but also engages other choroidal structural components in the thickening process, resulting in a more substantial increase in ChT than in vascular dilation

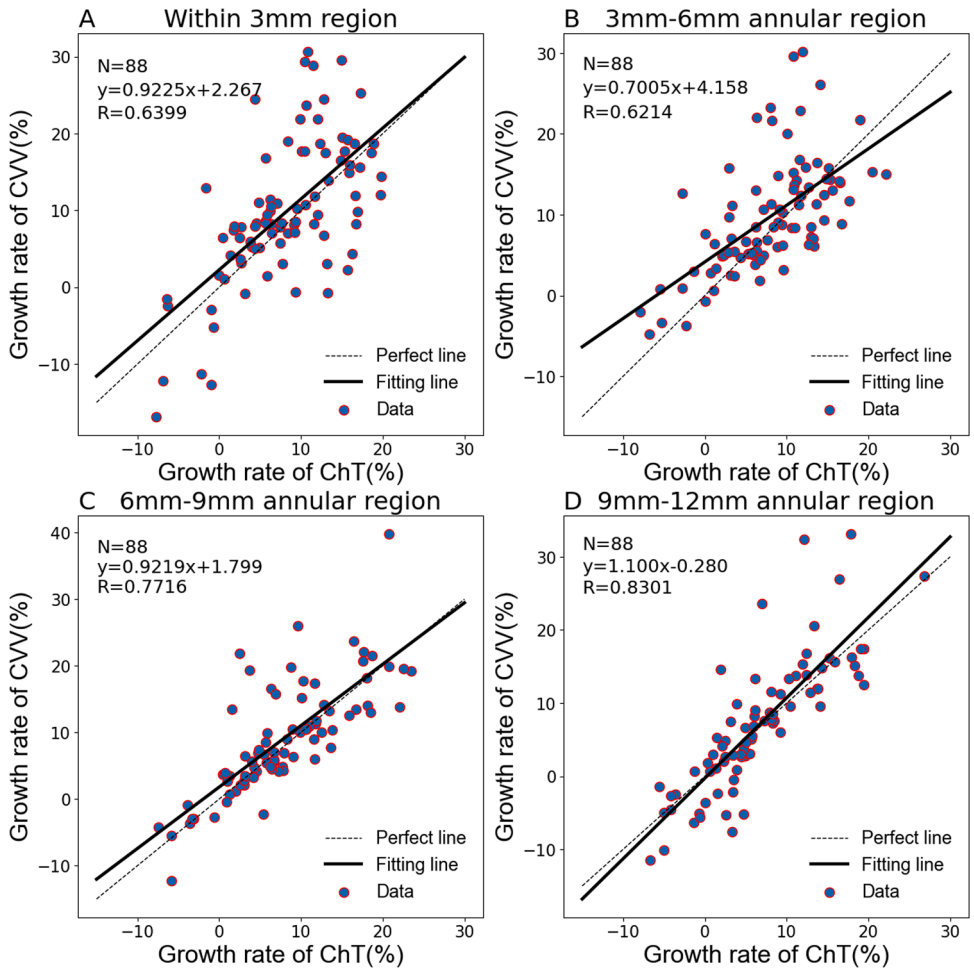


Fig. 3. Scatter plots of ChT growth rate versus CVV growth rate in the 3 mm region (A), 6 mm region (B), 6–9 mm region (C) and 9–12 mm region (D). R represents the correlation coefficient, and the absolute value of R (|R|) indicates the strength of the correlation. $0 \leq |R| \leq 0.2$ indicates very weak or no correlation; $0.2 < |R| \leq 0.4$ indicates weak correlation; $0.4 < |R| \leq 0.6$ indicates moderate strength linear correlation; $0.6 < |R| \leq 0.8$ indicates strong correlation; $0.8 < |R| \leq 1$ indicates a high degree of correlation. ChT=choroidal thickness; CVV=choroidal vessel volume.

Table 4
Correlations between the growth rate of CVV and the growth rate of ChT at various regions.

Region	R	R^2	Bias	MSE	RMSE	MAE
Within 3 mm region	0.6399	0.4094	1.63	54.19	7.36	5.50
3–6 mm annular region	0.6214	0.3861	1.77	36.59	6.05	4.31
6–9 mm annular region	0.7716	0.5953	1.18	30.16	5.49	3.53
9–12 mm annular region	0.8301	0.6890	0.39	26.61	5.16	3.42

Bias refers to the difference between predicted value and actual value.
MSE= mean squared error; RMSE=root mean squared error; MAE=mean absolute error.

alone, thereby leading to a reduction in CVI. The varying contribution of these structural components, particularly in the fovea compared to the periphery, may explain the observed gradient in CVI significance with increasing annular diameter. These hypotheses, derived from clinical data analysis, warrant further investigation through animal studies to elucidate the mechanisms underlying choroidal thickening and distribution differences.

CFA remained largely unchanged, suggesting no significant impact from RLRL treatment, whereas CBFA exhibited a minor increase. The diminishing significance of this increase with larger annular regions indicates a modest effect of RLRL therapy on CBFA, potentially less impactful than on CVV. This observation posits that RLRL primarily targets larger blood vessels, a theory that requires confirmation through

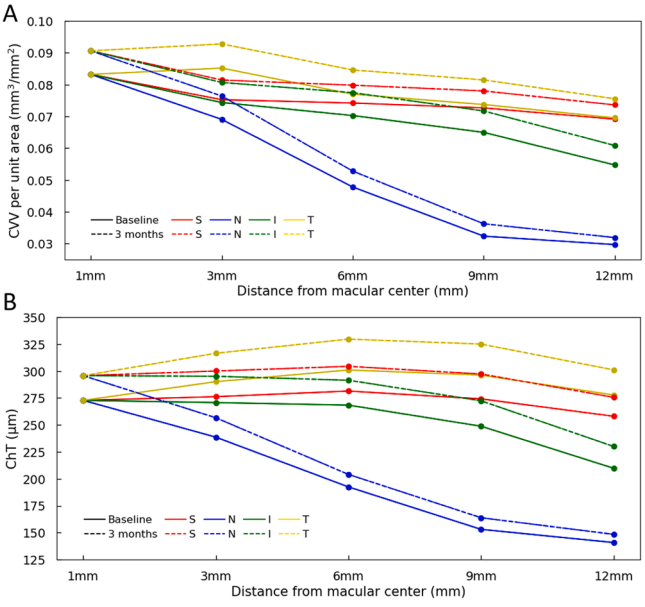


Fig. 4. Trend of CVV (A) and ChT (B)in different quadrants with increasing distance from the central fovea. CVV=choroidal vessel volume; ChT=choroidal thickness.

future cellular or animal studies.

4.3. Safety

Current studies support the safety of RLRL therapy when used appropriately. Over a 12-month period, no significant retinal damage or visual loss was observed [24]. In fact, mfERG results showed improvements in retinal function, and increased reflectance of the ellipsoid zone (rEZR) and photoreceptor outer segment reflectance(rPOSR) reflectance indicated enhanced mitochondrial activity without harm to the retinal pigment epithelium (RPE) [25]. While rare cases of light sensitivity have been reported, the overall evidence suggests that RLRL therapy is safe for managing myopia, with long-term monitoring still recommended.

5. Strengths and limitations

The primary strength of this study is its prospective clinical approach, which facilitated direct observation of the impacts of RLRL therapy on choroidal thickness and blood flow in various zones. Moreover, the utilization of SS-OCTA enabled detailed choroidal imaging. The advanced technology of the built-in software supported automated image segmentation, allowing for precise quantitative assessments of choroidal metrics. Nevertheless, the study is not without its limitations. The follow-up period was relatively short, which limits insights into the long-term effects, durability, and potential rebound phenomena associated with RLRL therapy for myopia management. Additionally, the absence of a control group in the study design restricts the ability to definitively attribute observed changes to the RLRL treatment, thus affecting the precision of the therapeutic effect assessment.

6. Conclusions

In summary, this clinical study substantiates the efficacy of RLRL therapy as a myopia treatment, promoting choroidal thickening through enhanced CVV and reducing AL which collectively decelerates myopia progression. Initial responses to SChT enhancement are predominantly observed in the early phases of RLRL therapy. Conversely, the peripheral choroid demonstrates a more prolonged reaction, in contrast to the foveal choroid, where the response concludes sooner. RLRL therapy also more significantly elevates CBFA under the fovea than in peripheral regions. However, AL reduction is not exclusively linked to increased ChT. The precise mechanisms through which RLRL controls myopia progression remain to be fully understood, necessitating further investigation to uncover these underlying processes.

Statement of Ethics

The study was reviewed and approved by the Institutional Review Board (or Ethics Committee) of Ethics Committee of The First Affiliated Hospital of Fujian Medical University's approved the study protocol (IRB No.[2022] 420). Written informed consent was obtained from participants to participate in the study. Written informed consent was obtained from the participants' parent/legal guardian/next of kin to participate in the study for all minor participants.

Funding sources

This research was funded by the Natural Science Foundation of Fujian Province (2021J05150) and Fujian Provincial Clinical Medical Research Center of Eye Diseases and Optometry (YK-YJZX).

Summary statement

We find initial responses to SChT enhancement are predominantly observed in the early phases of RLRL therapy. The peripheral choroid demonstrates a more prolonged reaction, in contrast to the foveal choroid, where the response concludes sooner. RLRL therapy also more significantly elevates CBFA under the fovea than peripheral regions.

CRediT authorship contribution statement

Huihang Wang: Writing – review & editing, Visualization, Validation, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Huifen Zhong:** Writing – original draft, Investigation. **Jingjin Zhang:** Investigation. **Wei Wei:** Resources. **Xiaoyuan Cui:** Data curation. **Weidong Zheng:** Supervision, Project administration, Conceptualization.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy but are available from the corresponding author upon reasonable reques.

Acknowledgements

None.

References

[1] B.A. Holden, T.R. Fricke, D.A. Wilson, et al., Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050, J. Ophthalmology 123 (2016) 1036.
[2] K.S. Naidoo, T.R. Fricke, K.D. Frick, et al., Potential lost productivity resulting from the global burden of myopia, J. Ophthalmology 126 (2019) 338–346.
[3] A.E.G. Haarman, C.A. Enthoven, J.W.L. Tideman, et al., The complications of myopia: a review and meta-analysis, J. Invest Ophthalmol Vis Sci 61 (2020) 49.
[4] H. Wu, G. Zhang, M. Shen, et al., Assessment of choroidal vascularity and choriocapillaris blood perfusion in anisomyopic adults by SS-OCT/OCTA, J. Invest. Ophthalmol. Visual Sci. 62 (2021) 8.
[5] S. Zhang, G. Zhang, X. Zhou, et al., Changes in choroidal thickness and choroidal blood perfusion in guinea pig myopia, J. Invest Ophthalmol Vis Sci 60 (2019) 3074–3083.
[6] Y.S. Yang, J.W. Koh, Choroidal blood flow change in eyes with high myopia, J. Korean J. Ophthalmol.: KJO 29 (2015) 309–314.
[7] Y. Jiang, Z. Zhu, X. Tan, et al., Effect of repeated low-level red-light therapy for myopia control in children: a multicenter randomized controlled trial, J. Ophthalmol. 129 (2022) 509–519.
[8] L. Zhou, C. Xing, W. Qiang, et al., Low-intensity, long-wavelength red light slows the progression of myopia in children: an Eastern China-based cohort, J. Ophthalmic & Physiolog. Optics: J. British College of Ophthalmic Opticians (Optometrists) 42 (2022) 335–344.
[9] X. He, J. Wang, Z. Zhu, et al., Effect of repeated low-level red light on myopia prevention among children in china with premyopia: a randomized clinical trial, J. JAMA network open 6 (2023) e239612.
[10] R. Xiong, Z. Zhu, Y. Jiang, et al., Sustained and rebound effect of repeated low-level red-light therapy on myopia control: a 2-year post-trial follow-up study, J. Clinical & Experim. Ophthalmol. 50 (2022) 1013–1024.
[11] Y. Chen, R. Xiong, X. Chen, et al., Efficacy comparison of repeated low-level red light and low-dose atropine for myopia control: a randomized controlled trial, J. Translat. Vision Sci. & Technol. 11 (2022) 33.
[12] R. Xiong, Z. Zhu, Y. Jiang, et al., Longitudinal changes and predictive value of choroidal thickness for myopia control after repeated low-level red-light therapy, J. Ophthalmology 130 (2023) 286–296.
[13] G. Liu, B. Li, H. Rong, et al., Axial length shortening and choroid thickening in myopic adults treated with repeated low-level red light, J. Clin. Med. 11 (2022) 7498.
[14] A. Lotery, S. Sivaprasad, A. O'connell, et al., Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for 4 months (VICI): a randomised, double-blind, placebo-controlled trial, J. Lancet (London, England) 395 (2020) 294–303.
[15] Z.H. Lin, Z.Y. Tao, Z.F. Kang, H.W. Deng, A study on the effectiveness of 650-nm red-light feeding instruments in the control of myopia, J. Ophthalmic research 66 (2023) 664–671.
[16] J.C.;. Yam, F.F.;. Li, X. Zhang, et al., Two-year clinical trial of the low-concentration atropine for myopia progression (lamp) study: phase 2 report, Ophthalmology 127 (7) (2020 Jul) 910–919.
[17] J.;. Charm, P. Cho, High myopia-partial reduction ortho-k: a 2-year randomized study, Optom. Vis Sci 90 (6) (2013 Jun) 530–539.

[18] P. Cho, S.W. Cheung, Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial, Invest. Ophthalmol. Vis Sci 53 (11) (2012 Oct 11) 7077–7085.
[19] F. Xiong, T. Mao, H. Liao, et al., Orthokeratology and low-intensity laser therapy for slowing the progression of myopia in children, J. Biomed Res Int 2021 (2021) 8915867.
[20] D.L. Nickla, J. Wallman, The multifunctional choroid, J. Progress in Retinal and Eye Res. 29 (2010) 144–168.
[21] M.J. Lipson, M.M. Brooks, B.H. Koffler, The role of orthokeratology in myopia control: a review, J. Eye & contact lens 44 (2018) 224–230.
[22] Y. Qi, L. Li, F.J. Zhang, Choroidal thickness in chinese children aged 8 to 11 years with mild and moderate myopia, J. Ophthalmol. 2018 (2018) 7270127.
[23] W. Chen, H. Zhang, Y. Zhang, et al., Relationship between Aquaporin-1 Protein Expression and Choroidal Thickness during the Recovery of Form-deprivation Myopia in Guinea Pigs, J. Current eye research 45 (2020) 705–712.
[24] B. Deng, M. Zhou, X. Kong, et al., A meta-analysis of randomized controlled trials evaluating the effectiveness and safety of the repeated low-level red light therapy in slowing the progression of myopia in children and adolescents, Indian J. Ophthalmol 72 (2024) S203–S210.
[25] M. Zhu, Y. Liu, D. Fang, et al., Safety of repeated low-level red-light therapy for children with myopia, Photodiagnosis Photodyn Ther 47 (2024) 104198.