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Short-term anatomic response of the choroid to tropicamide in myopic patients

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Abstract

We aimed to investigate how tropicamide alters subfoveal choroidal thickness (SFChT) and choriocapillaris flow density (CD) and determine the predictive factors of choroid thickness and vascular density in myopic eyes. This retrospective study was conducted from September 2018 to March 2019. SFChT was measured with enhanced depth spectrum-domain optical coherence tomography. The choriocapillaris was imaged using optical coherence tomography angiograms. Ocular parameters were measured thirty minutes before and after 1% tropicamide instillation. Twenty-five eyes of 15 patients (mean age 38.12 ± 6.35 years old and refractive error-8.57 ± 3.37 D) met the study criteria. The baseline linear regression model showed an association of thinner choroid with older age (P = .027) and high myopic patients (P = .001). Tropicamide substantially increased SFChT (P = .001), but had no significant influence on CD (P = .526). Moreover, SFChT variation after tropicamide instillation positively correlated with diopter changes in spherical equivalent (P = .005) and percentage changes in CD (P = .046). In myopic eyes, choroidal layer thickened substantially in response to tropicamide. The increase of SFChT only correlates with variations in spherical equivalent and CD. Short-term tropicamide installation altered both choroid thickness and choroid microvasculature, which implies an interplay among choroidal volume, perfusion, and ciliary muscle tone.

Abbreviations: BCVA = best corrected visual acuity, CD = choriocapillaris flow density, CT = choroidal thickness, EDI-SD OCT = enhanced depth spectrum-domain optical coherence tomography, IOP = intraocular pressure, IRR = inter-rater reliability, KAC = Krippendorff alpha coefficient, OCTA = optical coherence tomography angiography, RPE = retina pigment epithelium, SE = spherical equivalent, SFChT = subfoveal choroidal thickness.

Keywords: choriocapillaris flow density, choroidal thickness, myopia, optical coherence tomography angiography, tropicamide

1. Introduction

The choroid, a highly vascular layer of the posterior uveal tract, provides oxygen and essential nutrients to outer retinal layers, including the hyper-metabolic photoreceptors and retina pigment epithelium (RPE).[1] The choroid thus plays a pivotal role in normal ocular function.

With enhanced depth imaging modality of spectral domain optical coherence tomography (EDI-SD OCT), cross sectional layers of the retina can be visualized and subtle changes of choroidal thickness (CT) can be detected.[2] Previously, researchers have linked changes in CT to age, ethnicity, and refractive errors.[3] CT changes have also been described in a number of ocular diseases. Thinner choroidal layer was associated with myopic chorioretinopathy[4] and age-related macular degeneration,[5] while thicker choroid was seen in the pachychoroid disease spectrum.[6,7]

Choroid tissue is dynamic in nature. For instance, choroid layer significantly thickens 5 minutes after exercise[8] and thins 5 minutes into accommodative tasks. Notably, during accommodation, variations in subfoveal choroidal thickness (SFChT) have only been shown as significant in myopes but not in emmetropes.[9] It is unknown why subfoveal choroidal tissue in myopes reacts differently from emmetropes during accommodative tasks.

Mydriatic agents also dynamically alter the thickness of choroid. For instance, atropine transiently increases CT in emmetropes, an effect associated with the myopic control mechanism.[10,11] However, different mydriatic agents have disparate impacts on the choroid. For instance, while atropine is observed to increase CT, tropicamide decreases CT.[12–14] The reason why the choroid responds divergently to different mydriatics is probably due to the disparate behavior of the choroid between emmetropes and myopes.

Choroidal perfusion is essential for understanding choroid normal physiology and disease pathology. Since choroid perfusion is challenging to directly quantify, choriocapillaris flow density (CD) is used as a reference value for choroidal perfusion.

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The dataset used for analysis are available from the corresponding author Dr Chun-Ting Lai under reasonable request. All data used were included as tables and graphs in current study.

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Optical coherence tomography angiography (OCTA) allows the fine quantifications of choriocapillaris.[15] Interestingly, Al Shiekh et al,[16] discovered reduced retinal microvasculature and choriocapillaris density in myopic eyes with OCTA. The retinal and choroidal perfusion deficit observed in myopes was also observed in earlier studies using different imaging modalities.[17] However, dynamic changes in CT have not been correlated to perfusion changes and its relation to disease remains a mystery.

Given that myopia has been associated with both reduced CT during accommodative tasks[9] and decreased choroid perfusion, myopes serve as a unique model for understanding how outer stimuli affect the choriocapillaris and choroid volume. To the best of our knowledge, there have been no published studies examining the effect of mydriatics on CT and perfusion in myopic eyes. Hence, in this study, we aim to examine the variations of SFChT and CD with the latest technique of EDI-SD OCT and OCTA before and after 1% tropicamide instillation in myopic eyes.

2. Methods

2.1. Subjects

This is a retrospective case series study conducted at Department of Ophthalmology of the China Medical University Hospital in Taiwan. Myopic patients were enrolled from September, 2018 to March, 2019, by retina specialists according to the following inclusion criteria: patients who requested a complete fundus exam and had a diagnosis of myopia with a spherical equivalent (SE) refractive error less than −1.00 D. A history of systemic disease or ocular surgery, including laser intervention, helped forming exclusionary criteria.

We also excluded eyes with retinal breaks or other retinopathy discovered during fundus exam. EDI SD-OCT images revealing discernible choroid-scleral junction and suboptimal OCTA images with a scan quality Q value less than seven were excluded as well. Forty eyes from 20 participants were initially enrolled; however, after excluding 1 eye with retina breaks, 4 others with peripheral retinal degenerations, and ten eyes with poor image qualities, data analysis was based on 25 eyes from 14 patients. The study protocol was approved by Institutional Review Board of China Medical University Hospital and written informed consent was obtained from all participants. This study conformed to the tenets of the Declaration of Helsinki.

2.2. Assessments

To determine the effect of 1% tropicamide (Mydriacyl) on macular and choroid parameters, patients underwent complete ophthalmologic examination both prior to and after tropicamide administration. Baseline ophthalmologic exam comprised of LogMAR (Snellen) visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with noncontact air puff tonometer (Topcon CT-80 model; Topcon Corporation, Tokyo, Japan), and macular, choroidal thickness, and CD measurement with OCT and OCTA. After acquiring baseline parameters, a drop of tropicamide as instilled once on both eyes and pupil light reflex was checked to ensure adequate mydriasis. Thirty minutes after initial dose of tropicamide, parameters of best corrected visual acuity, IOP, choroidal thickness, and CD were remeasured.

2.3. Measurement of SFChT

Choroidal thickness scan was performed with EDI combined SD-OCT (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany; wavelength for scan: 870 nm). Two experienced ophthalmologists (Dr Chun-Ting Lai and Dr Wang I) were masked to patient data and independently measured SFChT. SFChTs were manually measured from the outer portion of the hyper-reflective line (corresponding to the retinal pigment epithelium) to the inner surface of the sclera on EDI-SD OCT.

2.4. Measurement of CD

Choriocapillaris OCTA image was obtained with a spectral-domain OCT device (RTVue-XR Avanti, version 2017.1.0.151; OptoVue, Inc., Fremont, CA), with split-spectrum amplitude decorrelation angiography. OCTA detects motions of erythrocytes and generated angiographic images through motion contrast imaging of high-resolution volumetric blood flow without the need of contrast media infusion. It operated on an A-scan rate of 70,000 scans per second and utilized a light source of 840 nm and bandwidth of 45 nm.[16,18] OCTA thus allows for the characterization of superficial and deep capillary plexus as well as the choriocapillaris and have been applied in studies of retinal and choroid vasculature. However, its resolution of deeper and larger choroidal vessels of Sattler and Haller layers was hindered by RPE, so only in areas of RPE atrophy were deeper vessels better visualized.[19]

The $6 \times 6\,mm^2$ scan was centered on the fovea with 2 consecutive and cross-sectional B scans obtained. Individual B scans consisted of 400 A scans. Motion artifacts from axial motion and transverse saccadic movements were corrected by capturing 2 orthogonal imaging volumes. The choroid vasculature was processed with an intensity-based algorithm into en face OCT angiograms. CD was calculated as caliber per area and converted to binary pixels of black and white using Otsu threshold plug ins and quantified with Image J software (CD represented as % of area).[18,19]

2.5. Statistical analysis

Demographic characteristics and pre-post analysis of choroid thickness and flow parameters a presented as frequency (percentage) for categorical variable and mean ± standard deviation or percentage of area for continuous variables. A paired *T*-test was applied for pre-post analysis of SFChT and CD. A simple linear regression model was adopted for correlation analysis, with SFChT or CD changes as dependent variables and other measured parameters as independent variables.

To validate the manual measurements of SFChT by 2 ophthalmologists, the Krippendorff alpha coefficient (KAC) was applied for inter-rater reliability (IRR) calculations. An alpha value more than 0.8 is customary for the IRR to be consider substantial, while a value <0.667 is unacceptable. We adopted the macro instructions that were written by Hayes et al,[20] for conducting KAC calculations in Statistical Package for the Social Sciences .

All statistical significance tests were 2 tailed with *P*-value < 0.05 and statistical analysis was conducted with Statistical Package for the Social Sciences version 22.0 for Windows.

3. Results

3.1. Demographic data at baseline and after tropicamide instillation

Twenty-five eyes of the 14 patients met the study criteria, with an average age of 38.12 years and a SE refractive error of −8.57D. Prior to pupil dilatation, baseline SFChT and CD were 160.76 + 88.78 μm and 49.30 + 4.03 %, respectively. Thirty minutes after tropicamide instillation, SFChT averaged 172.66 μm, while CD averaged 48.96%. Of note, male subjects had thicker SFChT (*P* = .027) and denser CD (*P* = .001) before mydriasis (Table 1). Other demographic data and ocular features are summarized in Table 1. The IRR was substantial among the 2 ophthalmologists,

with respective KAC alpha value being 0.949, 0.938 for SFChT before and after pupil dilation, and a value of 0.897 for SFChT variations.

3.2. Baseline SFChT were thinner in elderly and those with less myopic refractive error

As in Table 2, a simple linear regression model was used to investigate the relationship of baseline SFChT with other ocular parameters. Preliminary calculations were performed to ensure no violations of the assumption of normality and linearity. Baseline SFChT was significantly thinner in elder patients; P = .027, adjusted R^2 = 0.161, correlation = 0.443 (Table 2; Fig. 1A). Conversely, SFChT was thicker in eyes with less myopic refractive error; P = .001, adjusted R^2 = 0.356, correlation = 0.619 (Table 2; Fig. 1B). Other baseline ocular parameters were not significant predictors of SFChT (Table 2).

Table 1

Basic demographics and ophthalmological data of patients.

	All patients (N = 14), eyes (n = 25)	*P* value
Age, yr	38.12 + 6.35	
Gender		
Male, n (%)	13 (52%)	
BCVA (LogMAR)	0.078 + 0.135	
(Snellen)	20/24 + 20/27	
IOP (mm Hg)	16.44 + 2.50	
Spherical equivalent		
Baseline SE	−8.57 + 3.37	
Post-Mydriacyl SE	−8.24 + 3.52	
Macular thickness	265.40 + 16.62	
Subfoveal choroidal thickness (μm)		
Baseline SFChT	160.76 + 88.78	
Post-Mydriacyl SFChT	172.66 + 93.34	.001†,**
Baseline SFChT (μm) between gender		
Male	197.40	
Female	121.00	.027‡,*
CD (% of area)		
Baseline CD	49.30 + 4.03	
Post-Mydriacyl CD	48.96 + 4.51	.526†
Baseline CD between gender (% of area)		
Male	51.80	
Female	46.59	<.001‡,***

BCVA = best-corrected visual acuity, CD = choriocapillaris flow density, IOP = intraocular pressure, SE = spherical equivalent, SFChT = subfoveal choroidal thickness.
†Comparison of SFChT and CD prior to and after Mydriacyl instillation with paired-*T* test.
‡Comparison of baseline SFChT and CD between different genders with paired-*T* test.
*Statistical significance of P < .05.
**Statistical significance of P < .01.
***Statistical significance of P < .001.

Table 2

Simple linear regression between baseline SFChT and other predictor variables.

	BaselineSubfoveal choroidal thickness		
Factors	***r* (correlation)**	**Adjusted R^2**	***P***
Age	0.443	**0.161**	**.027***
Pre SE	0.619	**0.356**	**.001*****
IOP	0.198	−0.003	.343
CD	0.380	0.108	.061

CD = choriocapillaris flow density, IOP = intraocular pressure, Pre SE = spherical equivalent before Mydriacyl instillation, SFChT = subfoveal choroidal thickness.
*Statistical significance of P < .05.
***Statistical significance of P < .001.

3.3. Baseline CD decreased with age, while increased with less myopic refractive error

In terms of choroidal vasculature and ocular parameters, CD negatively correlated with age; P = .001, adjusted R^2 = 0.346, correlation = 0.611 (Table 3; Fig. 1C), but positively correlated with every diopter increase in SE; P < .001, adjusted R^2 = 0.413, correlation = 0.662 (Table 3; Fig. 1D).

3.4. After tropicamide instillation, SFChT were correlated with variations in CD and SE

Thirty minutes after tropicamide instillation, SFChT showed a significant increase in thickness, with a P value of .001 (Table 1) in paired-*T* test. Linear regression analysis showed significant increases in thickness changes of SFChT for every diopter change in SE; P = .005, adjusted R^2 = 0.269, correlation = 0.547 (Table 4; Fig. 2A). After pupil dilation, though changes in percentage of CD failed to attain significance in paired-*T* test (P = .526) (Table 1), linear regression revealed thickness changes of SFChT that were positively correlated with changes in CD, with P = .046, adjusted R^2 = 0.126, correlation = 0.403 (Tables 4 and 5; Fig. 2B). However, only SFChT change was a predictor of CD change (Table 5).

4. Discussion

Prior to pupil dilation, the subfoveal choroidal layer appeared thinner in older and highly myopic patients (Table 2; Fig. 1A). Males had thicker choroid layers, an observation consistent with a previous study in a healthy Asian population.[21] Apart from gender, other parameters such as best corrected visual acuity, IOP, macular thickness, and CD were not predictors of SFChT (Table 2) in our study. This was compatible with previous epidemiologic studies of choroidal thickness in healthy subjects,[3] which makes our subsequent analysis of SFChT changes more accountable for how myopic eyes differ in response to stimuli.

In this study, the subfoveal choroidal layer of myopic eyes significantly thickened in response to tropicamide (P = .001). We propose that blockage of accommodation by tropicamide and antagonism of muscarinic receptors contribute to the increase in choroidal thickness. The choroid being contiguous with the ciliary body, it is possible that cycloplegics may exert similar local effects on choroidal tissues. Early study in primates found that tendons from the ciliary muscle extend to regions of the anterior choroid. Moreover, ciliary muscle fibers are derived from the corneoscleral spur and insert at Bruch membrane.[22] Drexler et al,[23] postulated that during ciliary body contraction, there is a forward pulling of the choroid, inducing a transient elongation of axial length. Consistent with Drexler hypothesis, Woodman et al,[9] further discovered thinning of choroid during accommodation. Hence, many have proposed that the contracting forces from the ciliary muscle transmit to the choroid and mechanically reduce choroidal thickness.[1,9,13,24,25] Our observation of choroidal thickening might as well be a result of 1% tropicamide blocking the accommodative ciliary muscle tone and hindering the associative choroidal contraction.

The antagonism of muscarinic receptors could be an additional factor that contributes to choroidal thickening after mydriatic application. For instance, Nickla et al,[1,26] observed that in animal studies, anti-muscarinic agents seemed to decrease nonvascular smooth muscle tone and cause thickening of choroid. Moreover, in experimental studies in which the parasympathetic nerve was resected, there was convincing thickening of choroidal tissue in chickens.[1,26] Nickla et al,[11] also discovered that atropine and other anti-muscarinics cause an increase in choroid thickness in chickens while preventing myopia progression. They hypothesized that cholinergic agents affected the

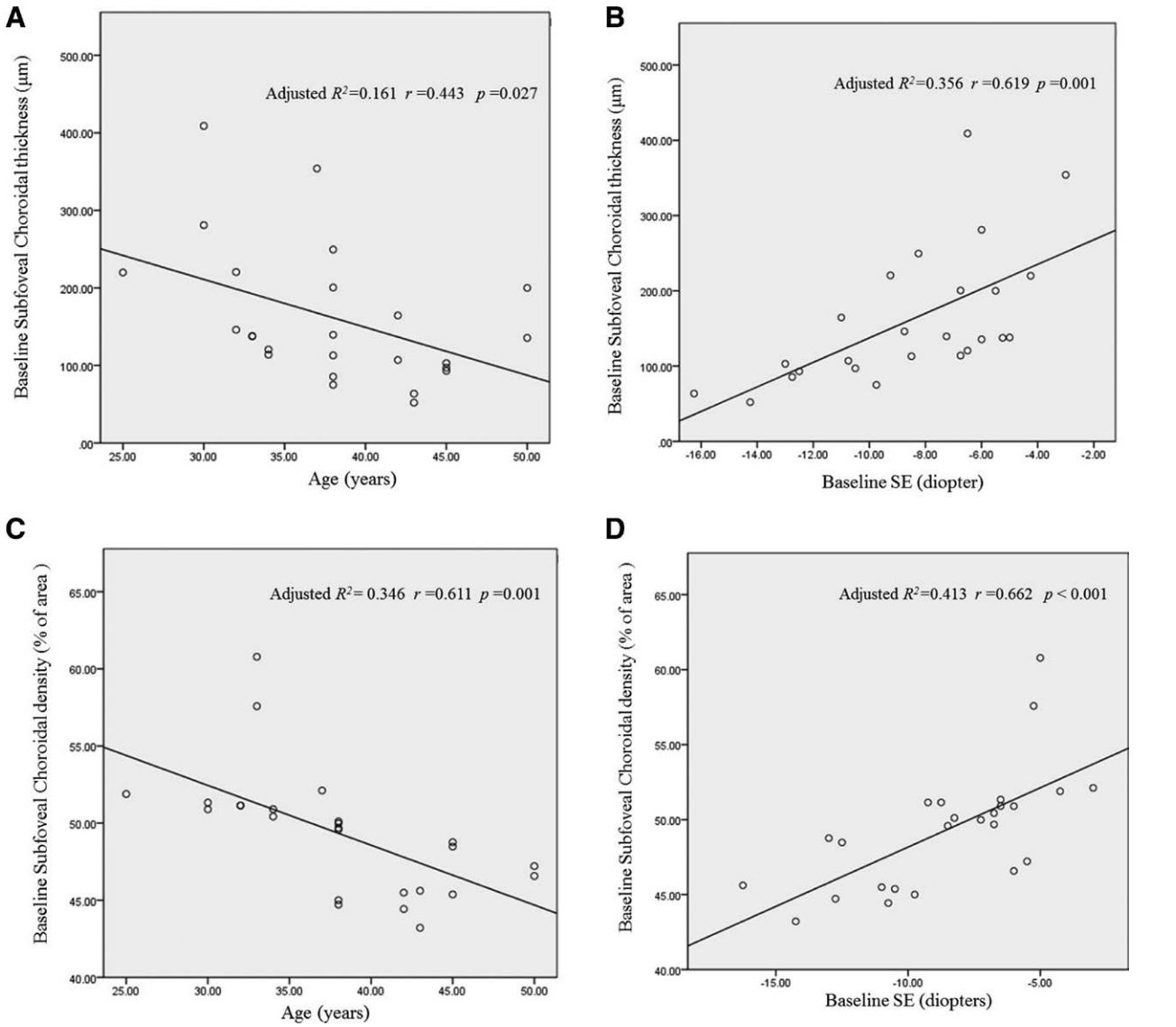

Figure 1. Simple regression model for baseline SFChT (μm) and CD (% of area) with respect to age and baseline SE in myopic patients. (A) SFChT negatively correlated with age (the regression line of baseline SFChT (μm) = 396.502 – 6.184 × Age, P = .027, adjusted R^2 = 0.161, correlation = 0.443). (B) However, SFChT positively correlated with SE (the regression line for baseline SFChT (μm) = 300.324 + 16.285 × SE (diopters); P = .001, adjusted R^2 = 0.356, correlation = 0.619). (C) CD negatively correlated with age (the regression line for baseline CD (% of area) = 64.08 – 0.39 × Age, P = .001, adjusted R^2 = 0.346, correlation = 0.611), (D) while CD positively correlated with SE (the regression line for baseline CD = 56.08 + 0.79 × Baseline SE (diopters), P < .001, adjusted R^2 = 0.413, correlation = 0.662). CD = choriocapillaris density, SE = spherical equivalent, SFChT = subfoveal choroidal thickness.

Table 3

Simple linear regression between baseline CD and other predictor variables.

	BaselineCD		
Factors	***r* (correlation)**	**Adjusted R^2**	***P***
Age	0.611	**0.346**	**.001*****
Pre SE	0.662	**0.413**	**<.001*****
IOP	0.349	0.083	.088
SFChT	0.380	0.108	.061

CD = choriocapillaris flow density, IOP = intraocular pressure, Pre SE = spherical equivalent before Mydriacyl instillation, SFChT = subfoveal choroidal thickness.
***Statistical significance of P < .001.

Table 4

Simple linear regression results of variations in SFChT and other ocular parameters after Mydriacyl.

	After MydriacylSubfoveal chorodial thickness variations		
Factors	***r***	**Adjusted R^2**	***P***
Age	0.230	0.012	.268
Baseline SE	0.385	0.111	.058
Post-dilation SE	0.424	0.144	.035
SE change	0.547	**0.269**	**.005****
IOP	0.201	–0.001	.336
Baseline SFChT	0.232	0.013	.265
Baseline CD	0.320	0.064	.119
CD change	0.403	**0.126**	**.046***

CD = choriocapillaris flow density, IOP = intraocular pressure, SE = spherical equivalent, SFChT = subfoveal choroidal thickness.
*Statistical significance of P < .05.
**Statistical significance of P < .01.

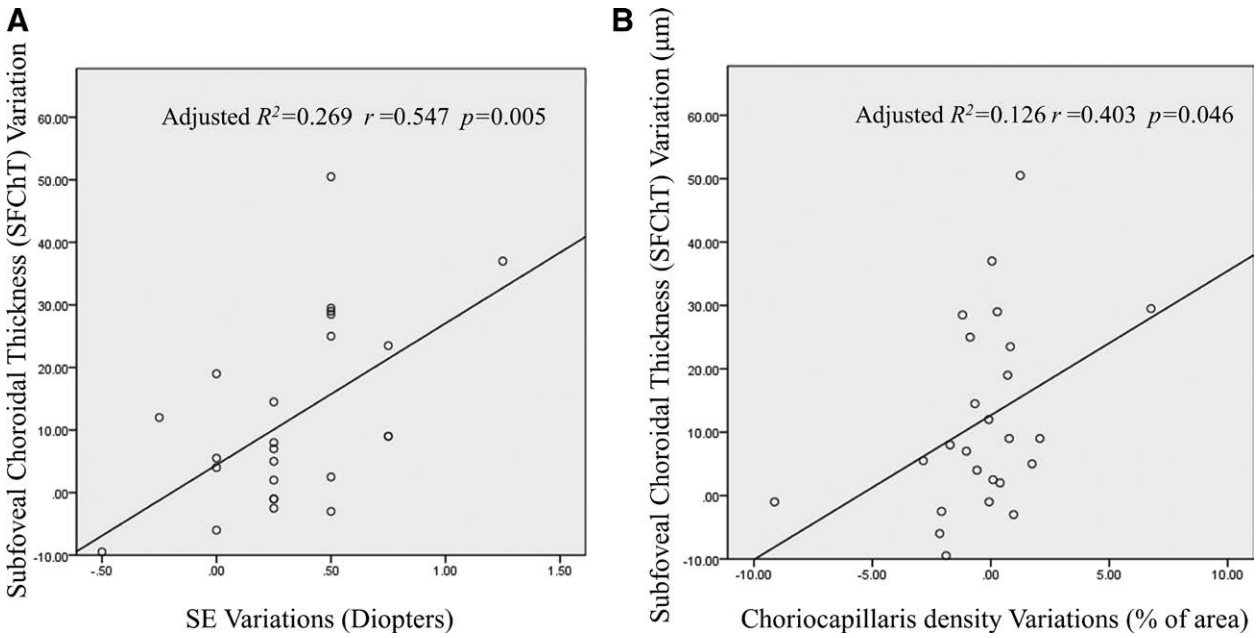

Figure 2. Simple regression model for SFChT (μm) with respect to variations in SE and CD after tropicamide use in myopic patients. (A) SFChT positively correlated with SE variations (the regression line for SFChT (μm) = 4.43 (μm) + 22.64 × SE variations (diopter change); P = .005, adjusted R^2 = 0.269, correlation = 0.547). (B) SFChT positively correlated with CD (the regression line for SFChT (μm) = 12.67 (μm) + 2.28 × CD variations (change in % of area); P = .046, adjusted R^2 = 0.126, correlation = 0.403).

Table 5

Simple linear regression results of changes in CD and other ocular parameters.

	After MydriacylCD change		
Factors	***r***	**Adjusted R^2**	***P***
Age	0.165	−0.015	.43
Baseline SE	0.080	−0.037	.705
Post-dilation SE	0.045	−0.041	.832
SE change	0.312	0.058	.129
IOP	0.020	−0.043	.926
Baseline SFChT	0.019	−0.043	.956
SFChT change	**0.403**	**0.126**	**.046***
Baseline CD	0.134	−0.025	.524

CD = choriocapillaris flow density, IOP = intraocular pressure, SE = spherical equivalent, SFChT = subfoveal choroidal thickness.
*Statistical significance of $P < .05$.

parasympathetic plexus and induced nonvascular smooth muscle contraction, which led to efflux of fluid from the choroid stroma, resulting in a thinner choroid.[11] Nevertheless, considering that choroid vessels are not in vertical alignments with the choroid smooth muscle and small lacunae in the choroid stroma serve as a fluid reservoir, it is possible for muscle contraction to facilitate choroid filling. Cholinergic agonists, under this theory, would paradoxically thicken the choroid.[1,24] Further studies are warranted to discuss how autonomic nerve plexus regulate nonvascular smooth muscle contraction and tissue perfusion.

While debates of the physiological mechanisms of flexible choroid linger, experimental studies have reported conflicting effects of mydriatics on the parafoveal and subfoveal choroidal layers in healthy populations.[11,13,24] For instance, atropine, as an anticholinergic, thickens the choroidal layer,[24] while, Mydrin-P, a combination of tropicamide and phenylephrine, either thins CT or causes no significant changes in emmetropes.[12,13] Yuvaci et al,[27] speculated that the discrepancy in results was a result of the combination of anti-cholinergics and sympathomimetics, considering that both types of agents possibly affect nonvascular smooth muscles and intrinsic choroidal nerves differently. Therefore, to investigate the effect of anti-cholinergics by themselves, we have chosen tropicamide to avoid the effect of sympathomimetics. However, in studies that apply the same single agent, such as that of Mwanza et al,[28] and Li et al,[29] contrasting results still persist. One possible explanation is that the demographic data of most experimental studies involve emmetropes, but it is recognized that emmetropes have less dynamic responses of the choroid during accommodative tasks.[9] Since blocking accommodation potentially accounts for the transient coordination of choroidal thickness, we supposed that more consistent results of mydriatics would be reported in a myopic population.

Our study added to the literature by identifying a positive correlation between the variations in SFChT and diopter changes of SE and percentage changes of CD (Tables 4 and 5; Fig. 2). With SE being a positive predictive factor of choroidal thickness, this might confirm the aforementioned biomechanical effect of mydriatics inducing relaxation of choroidal smooth muscles and affecting choroidal volume. On the other hand, we observed that thicker subfoveal choroids were correlated with increased choriocapillaris density after accommodation (Fig. 2B). This positive relevance of CT and CD might indicate that a thickened choroid may not impair choriocapillaris circulation, which differs from what is observed in pachychoroid disease. Pachychoroid diseases that involve diffuse or focal thickening of the choroid, however, have reduced choriocapillaris perfusion due to compression from larger dilating vessels in Haller layer.[6,30] Judging from how CD reacts to choroidal thickness changes in myopes in our study, the mechanism of how choroid volume of myopic eyes affect perfusion might be disparate from that of pachychoroid disease.

Unexpectedly, OCTA revealed no significant variations in subfoveal CD after tropicamide use. In a subset analysis of our data, however, twelve eyes actually had increased CD after tropicamide instillation. This raised the question of whether tropicamide could increase choriocapillaris density in some patients but not others, and whether tropicamide would benefit

some myopic patients by increasing choriocapillaris perfusion. Further studies with larger cohorts are warranted to address perfusion changes of choriocapillaris.

Our study is limited in sample size and may be insufficient to represent the possible heterogeneous responses of SFChT and CD in a greater myopic population. The sample size was inadequate for achieving statistical power with multiple regression as proposed by Green et al, so simple linear regression was preferred in our study.[31] Axial length change may have influences on SFChT change or CD change,[2] but it was not recorded in our study. However, axial length change after pupil dilation was not significant, demonstrated by several studies focusing on IOL power calculation before or after pupil dilation.[32–34] Moreover, Tsai et al, had investigated the effect of short-term tropicamide on axial length, but failed to demonstrate significant difference in axial length before and after tropicamide installation.[35] Nonetheless, the role of baseline axial length in association with SFChT change or CD change after pupil dilation was not examined in previous studies and is a topic of interest to explore. In our study, the manual measurements of choroid thickness might be inadequate to fully denote changes in CT. However, the quantifying methodology of CT is limited, so previous studies have adopted the same manual calibration of choroid.[12,13,24,25,28] Despite concerns of manual calibration, we as well as other studies report a high reproducibility in IRR measurements of choroid parameters.[2,36]

In conclusion, tropicamide significantly altered the SFChT after 30 minutes in myopic eyes. Choroid thickness alternation was only associated with diopter changes of SE and percentage changes of CD. We established an interrelation among changes of SFChT, SE, and subfoveal CD, and the changes in these parameters might serve as biomarkers for denoting changes in choroidal volume, perfusion, and ciliary muscle tone after tropicamide use. Our study is the first to report the dynamic changes of choroidal layer and its interrelation with choroid microvasculature and ciliary tone after anticholinergic treatment in myopia. Larger prospective studies are necessary to elucidate the interplay of choroid volume, perfusion, and ciliary muscle tone.

Author contributions

CTL contributed to the conception and design of the study. CJL, CTL, IW, CHC, WLC, JML, PTT, NYH, WCW, HB and YYT, all participated in data acquisition. CJL, CTL and CYL analyzed and interpreted the data set. CYL and CTL drafted the manuscript. CJL, CTL and HB supervised and revised the manuscript to meet academic standards. All authors have approved the final manuscript and take responsibility for the integrity and accuracy of this study.

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