

# The Influence of Topical Cyclopentolate Instillation on Peripapillary and Macular Microvasculature Measured by Optical Coherence Tomography Angiography in Healthy Individuals

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## Abstract

**Purpose:** To investigate the influence of topical cyclopentolate 1%, as an anti-muscarinic mydriatic agent, on the peripapillary and macular microvasculature by optical coherence tomography angiography (OCT-A) in healthy adults.

**Methods:** A total of 41 healthy adults without any systemic or ocular disease were enrolled for this prospective consecutive study. All patients underwent OCT-A measurements (OptoVue Inc., Fremont, CA, USA) to assess optic disc status for radial peripapillary capillary network (whole image, inside disc, and peripapillary capillary densities), and superficial and deep capillary plexus whole, foveal, parafoveal and perifoveal densities, and foveal avascular zone (FAZ) densities. Foveal retinal thicknesses and all quadrant retinal fiber layer thicknesses were also assessed. The 4.5 mm × 4.5 mm peripapillary and 6 mm × 6 mm macular OCT-A images were undertaken before and 30 min after instillation of topical cyclopentolate 1% to the right eyes.

**Results:** The mean age of subjects was 38.14 ± 14.10 years. All macular, optic disc, and FAZ densities, foveal retinal thicknesses, average, and all quadrant retinal fiber layer thicknesses were statistically similar between baseline and after administration of topical cyclopentolate 1% ( $P > 0.05$ ).

**Conclusion:** The current study demonstrated that pupillary dilation with topical cyclopentolate 1% seems to have no statistical effect on macular and peripapillary OCT-A measurements of healthy adults.

**Keywords:** Macula, Optic disc, Optical coherence tomography angiography, Retina, Topical cyclopentolate

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## INTRODUCTION

A novel, noninvasive imaging technology, optical coherence tomography angiography (OCT-A) has recently been used in many ophthalmology clinics.<sup>1-5</sup> It has been evaluated in different ocular and systemic diseases to visualize retinal microvasculature in different layers as well as optic nerve head blood flow. Many studies have investigated factors influencing OCT-A findings such as motion artifacts and

image quality,<sup>6,7</sup> age and gender,<sup>8</sup> spherical equivalent and axial length,<sup>9</sup> systemic diseases,<sup>10</sup> and how to apply and assess OCT-A most adequately.

Cyclopentolate is a synthetic anti-muscarinic (parasympatholytic) agent and is available in 0.5% and 1% solutions. It is widely used for patients of all ages in ophthalmologic practice to dilate the pupil before fundus

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and optic nerve examination, surgery, or fundus fluorescein angiography to create cycloplegia before the evaluation of refraction, to relieve the ciliary muscle spasm, and to decrease pain or break posterior synechia in eyes with uveitis.<sup>4</sup> Both retinal pigment epithelium and the choroid have been shown to contain muscarinic cholinergic receptors.<sup>4</sup> Both sympathomimetics and parasympatholytics have vasoconstricting effects, and they may affect the measurements of OCT-A parameters.<sup>5</sup> There are several studies on the influence of topical mydriatics such as tropicamide 1% and phenylephrine hydrochloride 2.5% on quantitative OCT-A parameters.<sup>1-3</sup> Direct and crossover effects of phenylephrine and cyclopentolate on foveal avascular zone (FAZ) and vessel density of macular capillary plexuses via OCT-A were reported very recently.<sup>5</sup> However, in this context, there is no study about the effect of cyclopentolate 1% on OCT-A peripapillary microvasculature. Therefore, we aimed to evaluate the effect of topical cyclopentolate 1% on both peripapillary capillary and macular microvasculature measurements with OCT-A in healthy volunteers.

## METHODS

The data in this study were derived from 41 eyes of 41 healthy adults examined at Hatay Mustafa Kemal University Hospital, Ophthalmology Department. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee (approved by the Ethics Committee of the Hatay Mustafa Kemal University Hospital) and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all individuals included in the study. The optimal sample size was calculated as 41 individuals with alpha value = 0.05 and test power 0.80 to find a difference of results in the groups. Patients with best corrected visual acuity of 20/20, the refractive error between +1.0 and -3.0 diopters, intraocular pressure  $\leq$ 21 mmHg, and axial length between 20 mm and 24 mm were included in the study. The presence of any ocular or systemic diseases such as glaucoma, age-related macular degeneration, uveitis, corneal opacities or dense cataract preventing high-quality imaging, primary hypertension, diabetes mellitus, and thyroid disease or Parkinson's disease were excluded from the study. All B-scans were checked for alignment and segmentation errors. OCT-A images with a signal of  $<8$ , presence of blink artifacts, and images with motion artifacts and de-centered were also excluded. All patients underwent a standard ophthalmic examination including best corrected visual acuity, measurement of intraocular pressure, anterior segment examination, and fundus examination.

The built-in AngioVue software (version 2017.1.0.151 of the RTVue XR Avanti, Optovue Inc., Fremont, CA, USA) automatically segmented each scan. High-definition (HD) retina scans (6 mm  $\times$  6 mm) were undertaken with OCT-A for evaluating vessel densities (%) for whole image,

fovea, parafovea, and perifovea sections of superficial capillary plexus (SCP) and deep capillary plexus (DCP), 300  $\mu$ m wide ring surrounding FAZ area (mm<sup>2</sup>) and foveal density (FD) which was automatically calculated software data, and foveal retinal thickness were measured. Fovea, parafovea, and perifovea were defined as an annulus centered on the FAZ with inner and outer ring diameters of 1 mm, 1-3 mm, and 3-6 mm, respectively. HD optic disc scan (4.5 mm  $\times$  4.5 mm) for radial peripapillary capillary densities including the whole image, inside disc, and peripapillary capillary plexus densities, and average and all quadrant retinal nerve fiber layer thickness (RNFL) were also obtained. The peripapillary region was automatically defined by the software as a 1.0-mm-wide round annulus extending from the optic disc.

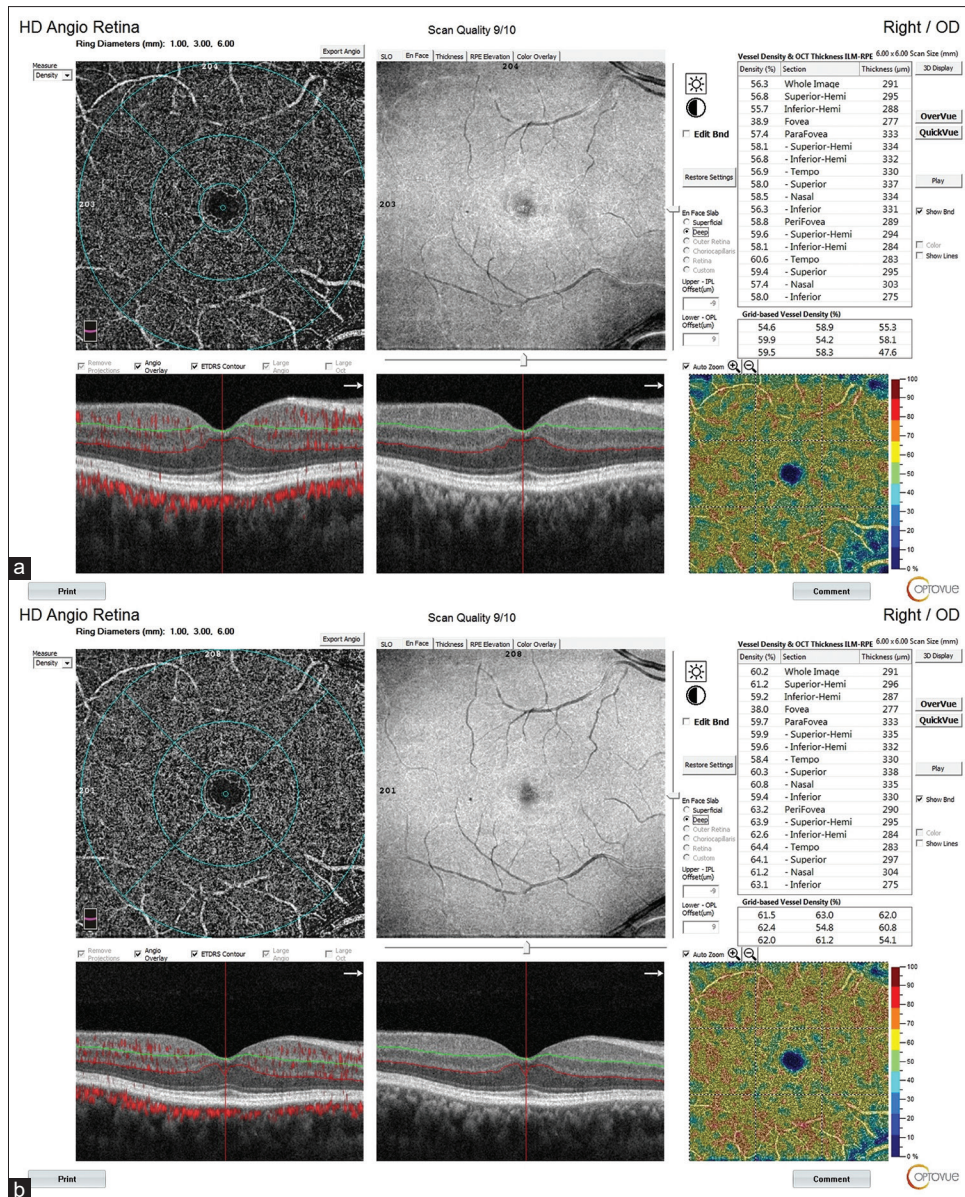
OCT-A imaging was applied in two imaging sessions for each subject under the same conditions in the same location by an expert examiner (once before and once after pupil dilation). All measurements were taken at the same time of day (between 10:00 and 12.00 a.m), and the same expert examiner (A.E.) administered the pupil-dilating drug (cyclopentolate 1%, Sikloplejin®, Abdi İbrahim, İstanbul, Turkey) one time to the right eyes of subjects. The second imaging session was performed 30 min after the administration of cyclopentolate 1% to the right eyes. In addition, the onset of dilation was checked visually by the same examiner (A.E.) before continuing with the second imaging session. Furthermore, subjects had to rest for at least 10 min before imaging was performed, as recommended by Alnawaiseh *et al.*<sup>11</sup>

## Statistical analysis

Statistical analysis was performed using the software SPSS (version 21.0, Chicago, IL, USA). Parametric data were uttered as mean  $\pm$  standard deviation. Demographic data and clinical characteristics for cases and controls were compared using a two-sample *t*-test for continuous variables. Categorical data were expressed as number and percentages. To compare categorical data, the Chi-square test was used. A *P* < 0.05 was accepted as statistically important.

## RESULTS

Nineteen female (46.4%) and 22 male (53.6%) adults were included in the study. The mean age was  $38.14 \pm 14.10$  (18-56) years. The mean refractive error was  $-0.87 \pm 0.32$  diopters. OCT-A images of a subject are shown in Figures 1-3 (before and 30 min after instillation). OCT-A imaging showed no statistically significant difference in SCP and DCP vessel density measurements, FAZ areas, FD, flow area, and foveal retinal thicknesses values after topical cyclopentolate 1% instillation [Table 1]. There were also no significant changes regarding optic disc OCT-A parameters, average, and all quadrant RNFL thicknesses between baseline and after topical cyclopentolate 1% administration [Table 2].



**Figure 1:** The retinal angiography imaging of a subject at baseline (a) and after pupil dilation by topical cyclopentolate 1% (b) periods. The vessel density does not change significantly in the ring diameters (mm) 1.00, 3.00, 6.00 of superficial and deep retinal capillary plexus, measured by optical coherence tomography angiography after pupil dilation by cyclopentolate 1%

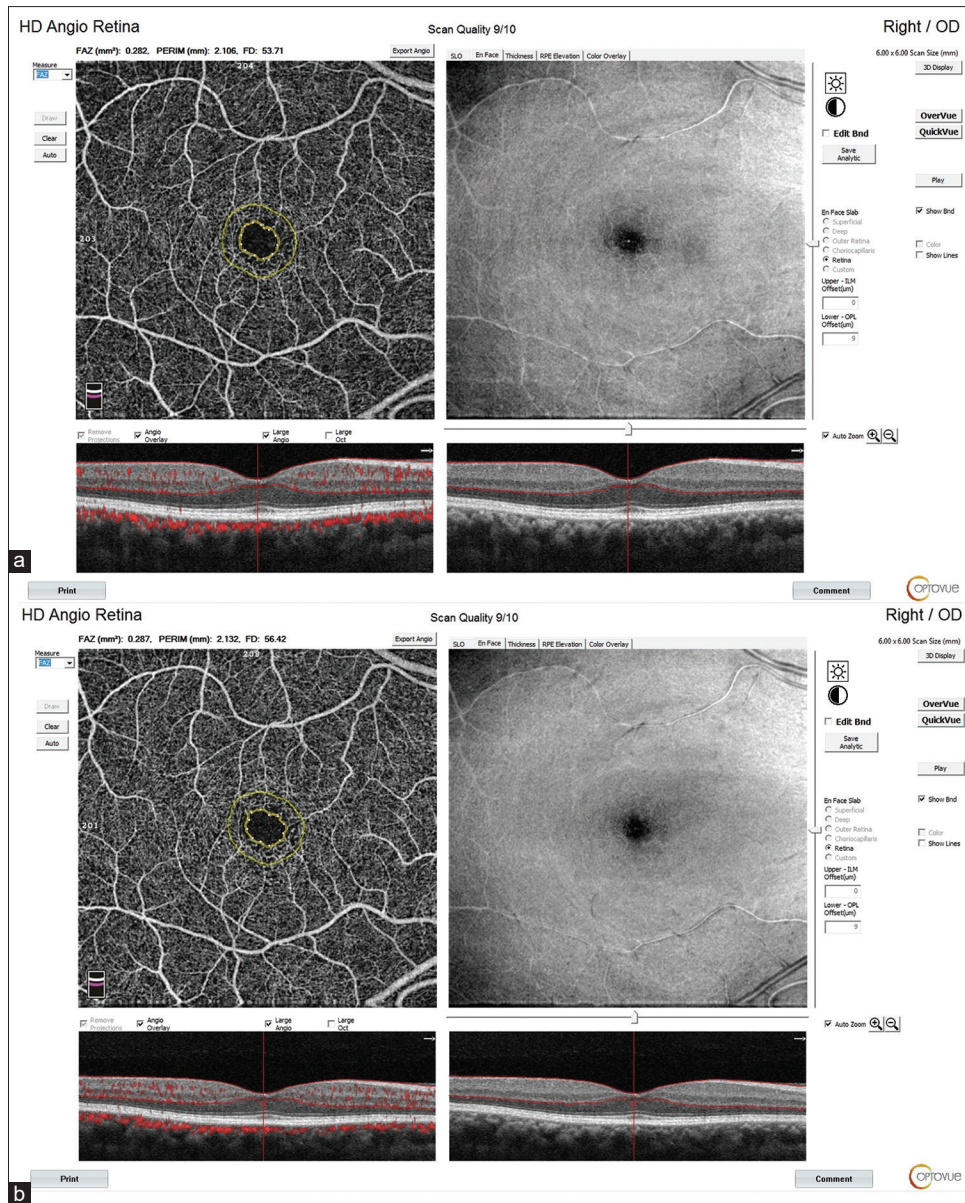
## DISCUSSION

To the best of our knowledge, this is the first study examining both optic disc and macular vascular parameter changes after topical cyclopentolate 1% application by using OCT-A. In this current study, we found no significant change on macular and peripapillary OCT-A measurements of healthy adults after topical pupillary dilation with cyclopentolate 1%.

To obtain the correct assessment of vascular parameters, the image quality of OCT-A is important. Proper retinal fundus examination and imaging require good pupil dilation by pharmacological agents. Small pupil size may cause signal loss of the OCT-A images by shadowing of the corner of the image; however, dilating the pupil with anti-muscarinic

or  $\alpha$ -adrenergic agonists may result in a decrease in retinal circulation and misunderstanding of OCT-A images.<sup>12</sup> There are few studies regarding the effect of topical mydriatic drop on retinal microvasculature in literature. In a study by Cheng *et al.*,<sup>1</sup> a decrease in peripapillary vessel density with topical phenylephrine was reported. However, they did not observe this effect on macular microvasculature. In another study, Hohberger *et al.*<sup>3</sup> reported that topical phenylephrine 5% and tropicamide 0.5% did not affect either macular or peripapillary microcirculation. In our study, different from their study, we found no change on either macular or peripapillary microvasculature by using cyclopentolate 1%. Göker *et al.*<sup>5</sup> determined the influence of phenylephrine and cyclopentolate on FAZ and vessel density of macular capillary





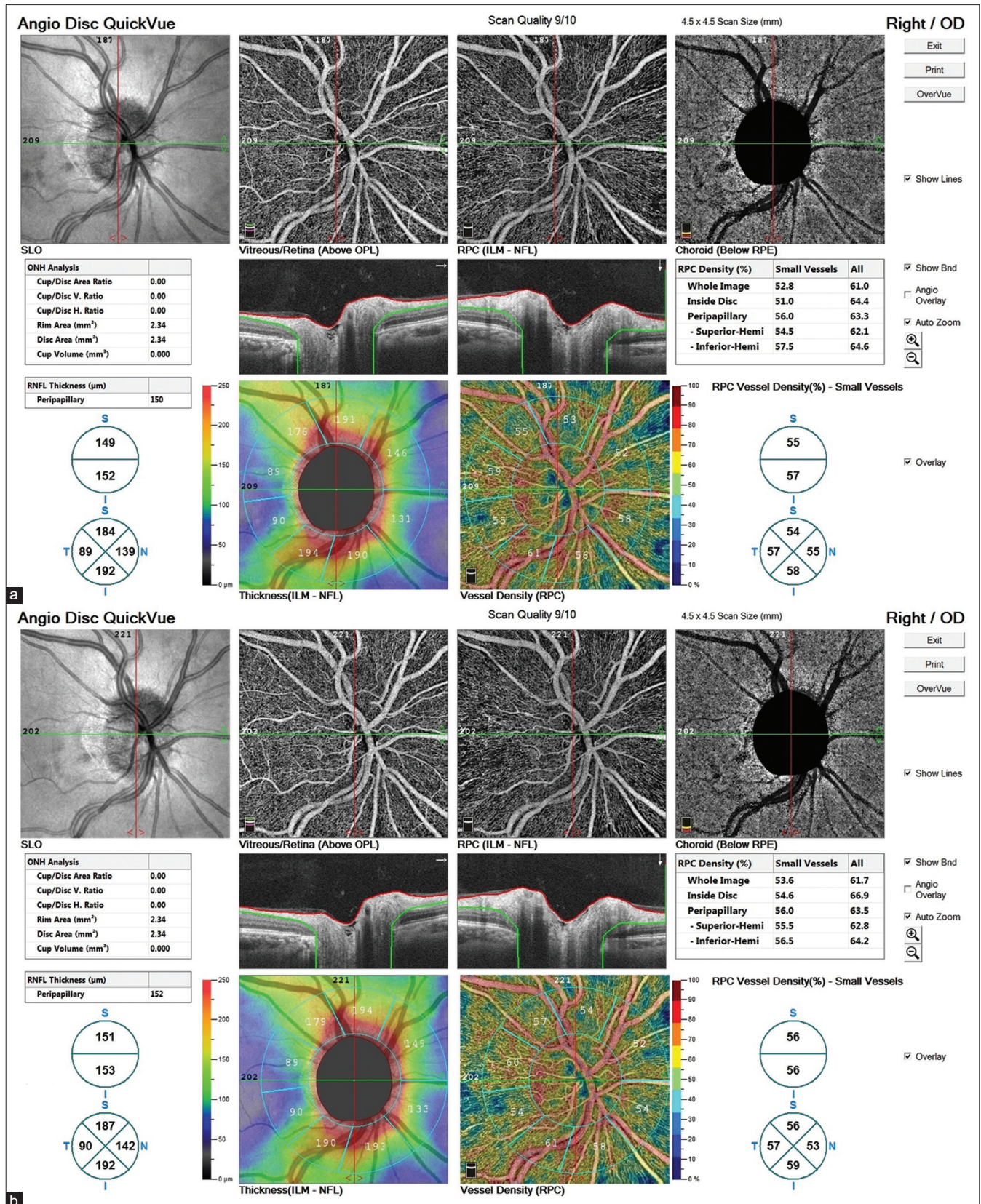
**Figure 2:** Foveal avascular zone densities foveal density of a subject at baseline (a) and after pupil dilation by topical cyclopentolate 1% (b) periods

plexus measurements via OCT-A. The vessel density values in SCP and DCP were found to be significantly decreased after drop instillation in both phenylephrine and cyclopentolate groups in their study. They mentioned that phenylephrine and/or cyclopentolate did not affect the FD-300 values while analyzing the perfusion of the macula. Therefore, evaluation of vessel density in the foveal region via FAZ software of the OCT-A was suggested in their study. However, the sample size of their study consisted of 30 subjects. We speculated that in that study, the decrease in SCP and DCP densities might be due to the relatively small sample size compared to our study. Additionally, they did not evaluate the optic disc OCT-A measurements by these drugs. In our study, we investigated the effect of isolated cyclopentolate 1% on both macular and optic disc OCT-A parameters. There were not significant differences regarding all optic discs, macular, and FAZ variables by OCT-A

between baseline and after cyclopentolate 1% administration in our study.

The advantages of this drug are rapid onset of action and recovery. Cycloplegics are known as anticholinergics that block the action of acetylcholine. Cycloplegics temporarily cause ciliary body paralysis and pupillary mydriasis.<sup>12-17</sup> Systemic absorption of the drug can occur transconjunctivally or by entering the nasolacrimal duct through highly vascular nasal mucosa.<sup>17-21</sup> Furthermore, after topical use, the drug can spread across the globe, and a direct effect through the retinal capillaries can be observed.<sup>21</sup> Systemic toxicity of cycloplegics is dose related. Adverse effects include tachycardia, central nervous system effects (due to stimulation of medulla and cerebral centers) such as restlessness, hallucination, psychosis, hyperactivity,





**Figure 3:** Optical coherence tomography angiographic images of a subject. Peripapillary region at baseline (a) and after pupil dilation by topical cyclopentolate 1% (b)

**Table 1: Comparison of macular parameters by optical coherence tomography angiography**

	Mean±SD		P
	Baseline period (n=41)	After pupil dilation by cyclopentolate 1% (n=41)	
Signal strength	8.68±0.47	8.65±0.63	0.256
FRT (µm)	254±73	253±21	0.403
Superficial vessel density (%)			
Whole image	51.5±2.2	51.3±2.6	0.556
Fovea	22.1±8.1	22.3±7.9	0.629
Parafovea	54.4±2.8	53.8±3.2	0.260
Perifovea	52.5±2.3	52.1±2.5	0.383
Deep vessel density (%)			
Whole image	55.9±4.6	55.9±5.4	0.962
Fovea	39.7±8.7	39.8±8.2	0.790
Parafovea	58.5±3.6	58.9±3.2	0.649
Perifovea	58.0±5.1	57.6±5.7	0.756
FAZ area (mm <sup>2</sup> )	0.26±0.1	0.25±0.1	0.511
FAZ FD	52.20±3.67	54.78±3.75	0.610
Flow area of choriocapillaris (mm <sup>2</sup> )	2.14±0.0	2.17±0.1	0.069
Flow area for outer retina (mm <sup>2</sup> )	0.48±0.2	0.53±0.2	0.287

SD: Standard deviation, FRT: Foveal retinal thickness, FAZ area: Area of 300 µm width around the foveal avascular zone, FAZ FD: Vessel density of 300 µm width around the foveal avascular zone

**Table 2: Comparison of optic disc parameters by optical coherence tomography angiography**

Mean±SD	Baseline period (n=41)	After pupil dilation by cyclopentolate 1% (n=41)	P
Signal strength	8.30±0.46	8.23±0.42	0.159
Radial peripapillary capillary density (%)			
Whole image	50.0±2.3	50.5±2.4	0.202
Inside disc	52.3±4.9	52.6±3.4	0.545
Peripapillary	52.2±3.1	52.2±2.9	0.885
RNFL thickness average (µm)	111.2±11.5	108.6±19.5	0.283
Inferior quadrant (µm)	142.0±0.2	141.1±18.6	0.101
Superior quadrant (µm)	130.2±16.3	129.9±16.3	0.425
Temporal quadrant (µm)	70.9±8.6	70.7±8.5	0.372
Nasal quadrant (µm)	104.4±13.2	101.9±19.9	0.352

SD: Standard deviation, RNFL: Retinal nerve fiber layer

seizures, incoherent speech, and ataxia. Although uncommon, cycloplegics may induce mental and neurotoxic effects such as drowsiness, ataxia, visual hallucinations, tachycardia, restlessness, psychosis, hyperactivity, seizures, and incoherent speech.<sup>17-21</sup> Muscarinic cholinergic receptors were occupied almost completely (more than 99.9%) by aqueous humor and 3%–18% by plasma taken at 55–125 min after the drug application.<sup>18</sup> In another study, its cycloplegic effects begin at 25–75 min after administration of the drop and recovery appears through 6–24 h later.<sup>19</sup> In this study, OCT-A measurements were taken 30 min after the administration of only one drop of cyclopentolate 1%. Ocular side effects may include irritation, lacrimation, allergic blepharoconjunctivitis, and conjunctival hyperemia. None of the patients complained about either ocular or systemic side effects. Furthermore, the child population, which is more vulnerable to systemic side effects, were excluded from our study. Therefore, we did not think the results could be affected for this reason.

Our study was made with healthy humans, but OCT-A is mainly used for patients with diabetic retinopathy, retinal vascular diseases, age-related macular degeneration, and glaucoma in clinical practice. These patients frequently have systemic vascular diseases and may be more sensitive to sympathomimetic effects of topical mydriatic eye drops. Therefore, our results with healthy adults cannot be generalized to all patients with ocular disorders who may have some vascular diseases.

There are several limitations of our study. First, a relatively small number of participants were evaluated. Second, we did not note the iris coloration and pupil size, which could affect the results.<sup>20</sup> Third, we did not note the parameters of a healthy pediatric population because we excluded the subjects under the age of 18 from the study. OCT-A findings may change after topical cyclopentolate 1% application in children. It may be an issue of another study. Finally, Odabaş *et al.*<sup>22</sup> evaluated the repeatability of SCP and DCP vessel density and FAZ



measurements using OCT-A and specified a diurnal change range. Their repeatability study has revealed that OCT-A is a noninvasive and highly reliable method to measure the retinal vessel density and FAZ, and they mentioned that changes in SCP 8% and DCP 10% may be considered real clinical change rather than variation. In our study, the same OCT-A device was used as in their study, and all measurements were taken at the same time of day (between 10:00 and 12.00 a.m), but we could not evaluate the diurnal variations after pupil dilation.

In conclusion, Topical pupillary dilation with topical cyclopentolate 1% seems to have no effect on either macular or peripapillary OCT-A measurements of healthy adults. The use of cyclopentolate 1% may provide reliable results for evaluation of macular and optic disc microvasculature by OCT-A. However, further studies are needed to evaluate the effects of mydriatics on OCT-A measurements of patients with retinal disorders.

### **Compliance with ethical standards**

#### **Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

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Nil.

### **Conflicts of interest**

There are no conflicts of interest.

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