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IMPACT OF PUPIL DILATION ON OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY RETINAL MICROVASCULATURE IN HEALTHY EYES

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Abstract

Purpose: To investigate the effect of pupil dilation using 2.5% phenylephrine and 0.5% tropicamide on quantitative assessment of retinal microvasculature using OCTA.

Methods: OptoVue AngioVue high density (HD) and non-HD OCTA macula and optic nerve head (ONH) images were obtained at 15-minute intervals pre- and post-dilation in 26 healthy participants (mean age: 40.0; 95% CI=33.9, 46.1 years). Superficial macular vessel density (VD) was measured in the whole image (wiVD) and the parafoveal region (pfVD). Optic nerve head capillary density was measured in the whole image (wiCD) and the circumpapillary region

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(cpCD). Differences between pre- and post-dilation densities were assessed using linear mixed effects models to account for within-patient correlation.

Results: Instillation of dilating drops resulted in a small but statistically significant reduction in non-HD ONH wiCD of 0.6%, from a mean of 45.2% (95% CI=41.9%, 48.4%) to 44.6% (41.4%, 47.8%) (*P*=0.046). A similar reduction in non-HD ONH cpCD of 0.8% also was observed, from a mean of 49.3% (45.3%, 53.3%) to 48.5% (44.5%, 52.4%) (*P*=0.025). No post-dilation decreases in macular vessel density or HD ONH capillary density were observed.

Conclusion: Pupil dilation using topical 2.5% phenylephrine and 0.5% tropicamide results in a small but statistically significant reduction in non-HD ONH whole image and circumpapillary capillary densities in healthy eyes. The observed reduction likely is not clinically significant because the observed reduction was within the previously reported range of measurement variability. Further studies should consider investigating these effects in non-healthy eyes with glaucoma and media opacities, as well as older individuals.

PRÉCIS

Small but significant decreases in OCTA-measured circumpapillary capillary density were observed in healthy eyes dilated with 2.5% phenylephrine/0.5% tropicamide. Though likely clinically insignificant, ophthalmologists should consider these changes when interpreting OCTA results from dilated eyes.

Keywords

Optical coherence tomography angiography; optical coherence tomography; vessel density; ganglion cell complex thickness; dilation

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Pupillary dilation is an essential component of non-invasive examination of the retina and retinal vasculature as well as many intra-ocular surgeries. Mydriatic agents such as the sympathomimetic agent phenylephrine and the anti-muscarinic agent tropicamide are commonly used to achieve maximal dilation.[1,2]

The α1-adrenoreceptor family plays a critical role in the regulation of vascular tone and blood flow by mediating the vasoconstrictive effects of endogenous catecholamines and adrenergic agonists like phenylephrine. However, these effects are not limited to the peripheral vasculature. The functional role of α1-adrenoreceptors has been shown in retinal arterioles,[3–5] conjunctival vessels,[6] and anterior ciliary arteries.[7] Studies using laser doppler flowmetry have demonstrated that topical phenylephrine decreases blood velocity in retinal arteries, including those supplying the optic nerve head of rabbits, monkeys, and healthy humans.[8,9]

Muscarinic acetylcholine receptors are involved in various physiologic actions in the eye, such as regulation of intraocular pressure, pupil size, and ocular growth.[10] These receptors also have displayed vasoactive properties by mediating acetylcholine-induced vasodilation in retinal blood vessels, suggesting that interrupting muscarinic receptor communication at the level of the retina could have vascular consequences, potentially affecting vessel density

measurements.[11] A recent study supported this relationship by demonstrating reduced retinal capillary perfusion in healthy human individuals receiving topical 0.5% tropicamide.[12]

These studies have relied largely on laser doppler flowmetry (LDF), a method that is limited by its inability to assess the entirety of the ocular vascular network, specifically the microvasculature. Instead, they have focused on the effect on large vessels of the optic nerve head (ONH) rather than the other vessels supplying the rest of the retina.[13]

Optical coherence tomography angiography (OCTA) is a non-invasive imaging modality that can be used to characterize ocular vasculature and microvasculature in various retinal layers.[14] Several OCTA instruments have recently received FDA approval. OCTA acquisition speed and diagnostic precision are similar to or better than other currently approved ocular imaging modalities.[14,15] Furthermore, OCTA does not strictly require dilation, making it an ideal technique for assessing vascular changes in response to induced mydriasis. However, standard patient flow in ophthalmology clinics often will result in patients being imaged with OCTA after pupil dilation. Additionally, pupillary dilation is commonly employed to enhance the image quality of this technique. Thus, recognizing the effects of common mydriatic agents on ocular blood vessels is important, especially as OCTA is increasingly used for investigating many ophthalmic conditions.

Understanding any influence mydriatic agents may have on ocular vascular measurements is imperative in interpreting clinical results and comparing conclusions from studies utilizing different agents to achieve pupillary dilation. Therefore, the objective in the present study is to evaluate the impact of topical 2.5% phenylephrine and 0.5% tropicamide, dilating agents commonly used during the clinical examination, on the vascular parameters measured by OCTA.

METHODS

Study Subjects

This study included 26 eyes from 26 healthy participants. Participants were recruited from the Hamilton Glaucoma Center and Shiley Eye Institute healthy subject pool, staff, and University of California San Diego School of Medicine students from July 2017 to October 2017. Informed consent was obtained from each participant and the UCSD Human Subjects Committee approved all methodology. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects and to the Health Insurance Portability and Accountability Act. Screening involved the collection of demographic data including date of birth, ethnicity, sex, medical and surgical history, medications, height and weight, heart rate and blood pressure. Study participants underwent a slit lamp and fundus examination to ensure patients had no pre-existing eye disease.

Participants were required to have clear ocular media bilaterally, best corrected visual acuity ≥ 20/40 bilaterally, pre-dilation pupillary diameter ≥ 3mm, intraocular pressure (IOP) < 21 mmHg by Goldmann applanation tonometry, and normal anterior and posterior segments on clinical examination by an ophthalmologist. Individuals were excluded from study if they were pregnant or intending to become pregnant, were lactating, had a history of prior

intraocular surgery or eye disease, including glaucoma, had any medical condition that may affect ocular hemodynamics, including but not limited to diabetes mellitus, hypertension, arrhythmia, or vascular disease. Participants had not consumed caffeine, nicotine or alcohol within the 12 hours prior to study testing.

OCT Image Acquisition

OCT scans were obtained using a commercially available spectral-domain-OCT system (Avanti; Optovue Inc, Fremont, CA. USA) with AngioVue software (version 2017.1.0.144). This system uses an 840 nm super-luminescent diode with a bandwidth of 45 nm, operated at 70,000 A-scans per second. The AngioVue imaging system uses the Split-Spectrum Amplitude-Decorrelation Angiography (SSADA) algorithm, allowing for non-invasive measurement of vessel density using two subsequent aligned OCT images to detect between-image changes in relative voxel position that indicate the presence of flowing blood. OCTA with SSADA has been described in detail elsewhere. [14,16,17]

One eye of each participant was randomly selected for imaging. Three dimensional OCTA macula (3 × 3 mm, 6 × 6 mm, and high density (HD) 6 × 6 mm) and optic disc (4.5 × 4.5 mm and HD 4.5 × 4.5 mm) images were obtained at 15-minute intervals with 2 baseline scans obtained prior to dilation and 2 scans obtained after dilation. Dilation was achieved using one drop of 2.5% phenylephrine and one drop of 0.5% tropicamide in both eyes, and study participants were required a pupil size ≥ 6 mm in order to continue with post-dilation OCTA imaging. Lubricating eye drops were instilled prior to obtaining each image to decrease the possible effect of tear film disruption on image quality.

Hemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate) and IOP were collected prior to each OCTA imaging set. Superficial macular vessel density was measured in the whole image (wiVD) and the parafoveal region (pfVD), and capillary density (after automated removal of large vessels) was measured in the whole image (wiCD) and the parafoveal region (pfCD). Optic nerve head vessel density was measured in the whole image (wiVD) and the circumpapillary region (cpVD), and capillary density (after automated removal of large vessels) was measured in the whole image (wiCD) and the circumpapillary region (cpCD). OCT-derived whole image, parafoveal and perifoveal ganglion cell complex (GCC) thickness measurements obtained from macular images and circumpapillary retinal nerve fiber layer (cpRNFL) thickness measurements obtained from ONH images also were measured.

OCTA and OCT image quality review was completed according to the UC San Diego Imaging Data Evaluation and Analysis (IDEA) Reading Center standard protocol. Images with a scan quality index (SQI) < 4, poor clarity, residual motion artifacts visible as irregular vessel patterns or disc boundaries on the enface angiogram, image cropping or local weak signal due to vitreous opacity, or segmentation errors that could not be corrected were excluded.

Statistical Analysis

The statistical significance of differences in OCT measures pre- and post-dilation was assessed using linear mixed effects models and the Bonferroni-Holm method. Across each

eye, all available measures were included as the dependent variables in these models, with fixed effects for time (pre- or post-dilation) and image quality and a random intercept to account for within-eye correlation. Multi-variable models including fixed effects for gender and age also were performed.

RESULTS

The mean age of participants was 40.0 years (95% CI = 33.9, 46.1, range = 19.6 – 68.6 years) detailed in Table 1. Of the 26 healthy eyes investigated, one eye was excluded due to poor image quality. Pre- and post-dilation measurements from 25 eyes with macula 3 × 3 mm and 6 × 6 mm imaging, 24 eyes with HD macula 6 × 6 mm and ONH 4.5 × 4.5 mm imaging, and 23 eyes with HD ONH 4.5 × 4.5 mm imaging were compared.

The mean non-HD ONH whole image capillary density (wiCD) values pre- and post-dilation were 45.2% (95% CI [41.9%, 48.4%]) and 44.6% (41.4%, 47.8%), respectively (Table 2). The mean reduction between pre- and post-dilation was 0.6% (−1.2%, 0.0%), which was statistically significant ($P = 0.045$). Non-HD ONH circumpapillary capillary density (cpCD) values pre- and post-dilation were 49.3% (45.3%, 53.3%) and 48.5% (44.5%, 52.4%), resulting in a statistically significant reduction of 0.8% (−1.5% to −0.1%), ($P = 0.025$). No significant decrease in post-dilation vessel densities were observed in HD ONH measurements (all comparisons $P \leq 0.287$). Similarly, no significant decrease in post-dilation vessel densities were observed in either the non-HD macula 3 × 3 mm and 6 × 6 mm, or HD 6 × 6 mm scans (all comparisons $P \leq 0.251$).

Average parafoveal GCC thickness increased significantly by 0.5 μm (0.0 μm, 1.0 μm; $P = 0.040$) in non-HD macula 3 × 3 mm scans. A similar significant increase of 0.4 μm (0.0 μm, 1.0 μm; $P < 0.001$) was observed in non-HD macula 6 × 6 mm scans. This effect was not observed in the HD macula 6 × 6 mm scans or in ONH cpRNFL thickness.

Pre- and post-dilation effects within scan type also were explored using the Bonferroni-Holm method of correcting for multiple comparisons. The capillary density reduction previously observed in both non-HD whole image circumpapillary ONH images and circumpapillary images no longer was statistically significant at the $p < 0.05$ level when using this approach (ONH whole images $P = 0.090$; circumpapillary images $P = 0.075$). Only the increase in parafoveal GCC thickness in non-HD macula 6 × 6 mm scans (significant in mixed effects models) was statistically significant ($P = 0.006$).

No relationships between subject age, gender, and quality index of image and differences in pre- and post-dilation vessel density, capillary density, and GCC measures were observed. Similarly, there were no changes in systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, or IOP after administration of the tropicamide and phenylephrine eye drops. See Table 2 for results from all OCT comparisons investigated.

Finally, there was a small decrease in post-dilation SQI for all image types (Table 3). This decrease reached statistical significance for 6 mm high definition macular images only ($P = 0.035$, all other image types $P \geq 0.183$).

DISCUSSION

The current study showed a small but statistically significant decrease in capillary density as measured by non-HD OCTA in the ONH of healthy individuals after application of 2.5% phenylephrine and 0.5% tropicamide. This decrease was not observed in HD ONH scans. Further, small but statistically significant post-dilation increases in OCT derived parafoveal GCC thickness of approximately 0.5 μm and 0.4 μm (an increase of approximately 0.4% of baseline thickness in both cases) also were observed in macula 3 × 3 mm and 6 × 6 mm non-HD images, respectively. These small differences possibly reflect the effect of a larger pupil increasing optical image blur in lower density images resulting in the inability of the instrument to accurately identify the position of the posterior GCC and the IDEA Center personnel to manually correct the segmentation. Finally, we observed a very small decrease in SQI post-dilation, possibly related to study participant fatique.

A recent OCTA study by Cheng et al. observed a 4.63% reduction in non-HD peripapillary vessel density (with no reduction in macula vessel density) in individuals who received a 0.5% tropicamide/0.5% phenylephrine mixture.[18] Hohberger et al., however, did not observe any decrease in retinal vasculature (macula or ONH vessel density) after introduction of 5% phenylephrine and 0.5% tropicamide using high resolution OCTA imaging (Heidelberg OCT Spectralis).[19] A prior study using Canon Laser Blood Flowmetry (LBF) also did not observe changes in vascular reactivity of the major retinal arterioles following the application of 1% tropicamide, combination of 0.8% tropicamide and 5% phenylephrine, or 1% cyclopentolate.[20] The current results do not directly support results from these previous studies, but instead fall somewhere in between, reporting a small reduction in capillary density of the ONH. Possible reasons for reported differences among studies include the use of a different OCTA instruments (Avanti in the current study versus Heidelberg Spectralis by Hohberger et al.), the use of different AngioVue software (version 2017.1.0.144 in the current study versus version 2.0.5.39 by Cheng et al.) and the inclusion of both HD and non-HD scan protocols in the current study. In addition, a different imaging modality altogether (i.e. LBF) was employed by Tsui et al.

It is possible that the small reduction in ONH capillary density post-dilation was the result of optical aberration which could decrease image resolution making some capillaries beyond the detection threshold used by SSADA. Regardless of the differences in magnitude and statistical significance of post-dilation effects between our results and the OCTA results described above, all reported results fall within the limits of OCTA measurement repeatability. Several studies have evaluated the reproducibility of OCTA measurements obtained using Optovue Avanti in healthy and non-healthy eyes. Venugopal et al. observed that intra-session within-subject coefficient of repeatability (CRw) and within-subject coefficient of variation (CVw) of vessel density measurements of HD optic disc scans ranged from 3.0% to 4.9% and from 2.0% to 3.1%, respectively in healthy eyes with similar results in non-HD peripapillary measurements in healthy eyes (from 3.3% to 7.0%, and 2.5% to 4.4%, respectively).[21,22] Other studies have observed similar variability between OCTA measurements representing either a physiologic variability in retinal vascular density of healthy individuals, limits of repeatability of OCTA measurements, or a combination of both.[17,21–23] Variations of retinal vessel diameter in relation to the cardiac cycle also

have been reported.[24] Therefore, although we observed a statistically significant reduction in capillary density surrounding the ONH following instillation of 2.5% phenylephrine and 0.5% tropicamide, the magnitude of the effects observed likely is clinically insignificant.

The observed lack of significant vascular reactivity in the macula and minimal effect on the ONH vasculature could be explained by anatomic and physiologic barriers that prevent topically applied drugs from reaching the posterior segment of the eye at therapeutic levels. Typically, less than 3% of the topically instilled dose reaches the aqueous humor, and an even smaller fraction reaches the posterior segment of the eye in subtherapeutic levels[25], although the percentage reaching the posterior segment may be larger in pseudophakic (or aphakic) eyes. The challenge of drug delivery to the posterior segment of the eye is well understood and documented.[26–28]

Although our study suggests that mydriatic agents have a small impact on non-HD ONH blood flow in healthy individuals that is within reported measures of test repeatability, this may not be the case in people with compromised ocular blood flow, such as patients with diabetes.[29] As OCTA becomes more widely used in assessing diabetic and other diseased eyes, it will be important to consider if unhealthy eyes exhibit a different response to mydriatic agents compared to healthy eyes.[30,31] It is possible that a slight but statistically significant reduction in blood vessel density observed surrounding the ONH could confound OCTA measurements in conditions involving the optic nerve such as glaucoma, potentially resulting in diagnostic misclassification or unwarranted conclusions of disease-related change. Many studies have shown decreases in vessel density in glaucoma eyes and any potential effects that mydriatic agents may have on vessel density measurements may be of significance.[14,32,33]

By only including healthy eyes, we were able to explore the normal physiologic response of retinal vasculature to mydriatic agents but were limited in observing any potential effect that mydriatic agents may have on diseased and pseudophakic or aphakic eyes. Another limitation of this study included testing only a combination of phenylephrine and tropicamide drops in all participants. Without a separate group of individuals receiving either agent alone, we were unable to observe potential effects of each individual agent.

There have been few studies investigating the relationship between mydriatic agents and retinal vasculature using OCTA in non-healthy eyes, particularly with high density scans, that improve the accuracy, speed, and quality of data acquisition. Given that the change in vessel density after dilatation was smaller in the HD scans, dilatation is not likely to effect measurements of microvasculature used for patient management. Future studies are needed to investigate the use of high-density imaging in both healthy and non-healthy eyes.

In conclusion, this OCTA study demonstrated that a combination of topical 2.5% phenylephrine and 0.5% tropicamide in healthy eyes causes a small, but likely clinically negligible, reduction in vessel density of the optic nerve head in the healthy population. While no changes in macular vessel densities were observed post-dilation, small but significant increases in macular ganglion cell complex thickness in non-high-density images were observed.

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Table 1:

Patient Demographics

Total Number of Participants	**n = 25**
Mean Age (years)	40.0 (95% CI = 33.9, 46.1)
Age Range (years)	19.6 – 68.6
Sex	
Female	14 (56.0%)
Male	11 (44.0%)

Table 2:

Mean (95% CI) OCT Measures Pre- and Post-Dilation

	Pre-Dilation Mean (95% CI)	Post-Dilation Mean (95% CI)	Difference Mean (95% CI)	SQI Adj. p-value	Age / Gender / SQI Adj. p-value
Macula 3mm Non-HD					
Whole Image GCC Thickness	106.2 μm (102.4, 110.0)	106.6 μm (102.8, 110.4)	0.4 μm (−0.0, 0.8)	0.080	0.080
Parafoveal GCC Thickness	**112.2 μm (107.8, 116.6)**	**112.7 μm (108.4, 117.1)**	**0.5 μm (0.0, 1.0)**	**0.040**	**0.040**
Whole Image Vessel Density	38.0% (34.2, 41.8)	38.3% (34.6, 42.1)	0.4% (−0.3, 1.0)	0.262	0.265
Parafoveal Vessel Density	40.2% (36.1, 44.3)	40.6% (36.6, 44.6)	0.3% (−0.3, 1.0)	0.327	0.331
Macula 6mm Non-HD					
Whole Image GCC Thickness	97.2 μm (93.3, 101.1)	97.0 μm (93.2, 100.9)	−0.2 μm (−0.6, 0.2)	0.391	0.390
Parafoveal GCC Thickness	**109.1 μm (105.7, 112.5)**	**109.5 μm (106.1, 112.9)**	**0.4 μm (0.2, 0.6)**	**< 0.001**	**< 0.001**
Perifoveal GCC Thickness	97.4 μm (94.0, 100.8)	97.4 μm (94.0, 100.7)	−0.0 μm (−0.3, 0.2)	0.775	0.774
Whole Image Vessel Density	27.3% (22.2, 32.5)	27.3% (22.2, 32.4)	−0.0% (−0.8, 0.8)	0.950	0.924
Parafoveal Vessel Density	29.9% (23.0, 36.7)	29.3% (22.6, 36.0)	−0.6% (−1.6, 0.5)	0.309	0.293
Perifoveal Vessel Density	25.7% (20.2, 31.1)	25.7% (20.3, 31.0)	0.0% (−0.8, 0.9)	0.990	0.985
Macula 6mm HD					
Whole Image GCC Thickness	98.5 μm (94.7, 102.2)	98.6 μm (94.9, 102.2)	0.1 μm (−0.3, 0.5)	0.596	0.595
Parafoveal GCC Thickness	108.5 μm (105.2, 111.9)	108.7 μm (105.4, 112.1)	0.2 μm (−0.0, 0.4)	0.064	0.063
Perifoveal GCC Thickness	98.1 μm (94.9, 101.3)	98.1 μm (94.9, 101.2)	−0.1 μm (−0.3, 0.2)	0.613	0.613
Whole Image Vessel Density	30.8% (26.2, 35.4)	30.8% (26.4, 35.3)	0.0% (−0.7, 0.7)	0.975	0.986
Parafoveal Vessel Density	30.2% (24.0, 36.3)	29.6% (23.7, 35.5)	−0.6% (−1.6, 0.4)	0.251	0.233
Perifoveal Vessel Density	31.0% (26.2, 35.7)	30.9% (26.3, 35.5)	−0.0% (−0.8, 0.7)	0.933	0.929
ONH Non-HD					
Circumpapillary RNFL Thickness	110.3 μm (102.5, 118.1)	110.6 μm (102.9, 118.4)	0.4 μm (−0.8, 1.5)	0.544	0.539
Whole Image Capillary Density	**45.2% (41.9, 48.4)**	**44.6% (41.4, 47.8)**	**−0.6% (−1.2, −0.0)**	**0.045**	**0.046**
Circumpapillary Capillary Density	**49.3% (45.3, 53.3)**	**48.5% (44.5, 52.4)**	**−0.8% (−1.5, −0.1)**	**0.025**	**0.025**
ONH HD					
Circumpapillary RNFL Thickness	113.9 μm (105.1, 122.7)	114.6 μm(105.8, 123.4)	0.7 μm (−0.6, 1.9)	0.287	0.298
Whole Image Capillary Density	44.6% (41.9, 47.2)	44.4% (41.8, 47.1)	−0.1% (−0.6, 0.3)	0.573	0.563
Circumpapillary Capillary Density	50.0% (46.6, 53.4)	50.1% (46.7, 53.5)	0.2% (−0.4, 0.7)	0.592	0.606

GCC, Ganglion Cell Complex; ONH, Optic Nerve Head; RNFL, Retinal Nerve Fiber Layer; HD, High Density; SQI, Scan Quality Index

Parafovea: 1–3 mm of radial scan; Perifovea: 3–6 mm of radial scan

Table 3:

Mean (95% CI) SQI Pre- and Post-Dilation

	Pre-Dilation Mean (95% CI)	Post-Dilation Mean (95% CI)	Difference Mean (95% CI)	p-value
Macula 3mm	7.7 (7.5, 8.0)	7.5 (7.3, 7.8)	−0.2 (−0.5, 0.1)	0.183
Macula 6mm	7.4 (7.2, 7.6)	7.2 (7.0, 7.5)	−0.1 (−0.4, 0.1)	0.239
Macula 6mm HD	**7.6 (7.3, 7.8)**	**7.3 (7.1, 7.5)**	**−0.3 (−0.5, −0.0)**	**0.035**
ONH	7.7 (7.4, 8.0)	7.6 (7.3, 7.8)	−0.1 (−0.4, 0.2)	0.489
ONH HD	7.8 (7.5, 8.0)	7.7 (7.4, 8.0)	−0.1 (−0.4, 0.3)	0.724

SQI, Scan Quality Index; ONH, Optic Nerve Head; HD, High Density