ARC Journal of Ophthalmology
Volume 4, Issue 2, 2019, PP 1-7
www.arcjournals.org

Diurnal Variation in Flow and Vascular Density of Capillary Plexuses of Retina, Choroid and Optic Nerve Head in Healthy Eye by Using Optical Coherence Tomography Angiography

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Abstract

Purpose: *To evaluate the diurnal variation in quantitative parameters of optical coherence tomography angiography (OCTA) in healthy subjects.*

Methods: *This observational case series was done in normal healthy volunteer (34 eyes from 17 subjects). OCTA of macula (3×3mm and 8×8mm image scan) and optic nerve head (4.5×4.5mm image scan) was done for each participant. Flow and vascular density of macula and optic nerve head in different capillary plexuses were evaluated.*

Results: *The mean age of subjects was 27 years with the range of 24 to 32 years. Significant diurnal fluctuation was observed in choriocapillaris flow under the macular area with the maximum and minimum amount at 8 am and 2 pm respectively. Vascular density of deep capillary plexus also showed significant diurnal variation. Significant diurnal variation was detected in vascular density of peripapillary with the peak at 2 pm and least amount at 8 am.*

Conclusions: *Presence of significant diurnal variation in choriocapillaris flow, vascular density of deep capillary plexus and vascular density of peripapillary area is important in interpretation of OCTA. This may reminds clinicians to perform OCTA at the same time of day to avoid normal diurnal variations and mistakes in interpretation of tests.*

Keywords: *Flow; Vascular density; Healthy eye; Optical coherence tomography angiography; choroidal blood flow.*

1. Introduction

The vasculature and blood flow of retina and choroid may involve in different disorders. The evaluation of choroidal thickness as a significant parameter is important in several diseases. [1] The diurnal fluctuation in choroidal blood flow, choroidal thickness and blood flow of optic nerve head in healthy subjects were documented in previous studies. [1, 2] The differentiation between normal diurnal variation of theses parameters from abnormal variation may play an important role in assessment and cognition of pathologic disorders. Previously diurnal variations in several ocular parameters were documented including intraocular pressure, [3] corneal thickness, [4] and choroidal thickness [1].

Optical coherence tomography angiography, as a non invasive method, can evaluate vascular structure of retina and choroid separately by using motion of blood cells as contrast. [5]

The aim of current investigation was to assess the diurnal variation that might occur in blood flow of retinal capillary and choriocapillaris in healthy subjects by using optical coherence tomography angiography (OCTA). We also evaluated the vascular density in three main capillary plexuses of retina and choroid in different time of the day.

2. Method

This observational cross sectional study was performed in Farabi Eye hospital, Tehran, Iran after approval of institutional and Tehran Medical University ethics committee in March 2017. The principles of Helsinki Declaration were followed in this study. A written informed consent was taken from all subjects of the study.

Healthy subjects without known ocular and systemic disease were included in this study. Inclusion criteria were best corrected visual acuity 20/25 or better and spherical equivalent of refractive error between -1 and +1 Diopter. The exclusion criteria were low imaging quality owing to media opacity or excessive eye motion and repeated blinking, signal strength less than 50, history of intraocular surgeries and any ocular and systemic diseases except low refractive error. After complete ocular examination, the OCTA (RTVue XR Avanti; Optovue, USA) was done 4 times for each subject during 24 hours. Four images were taken at 8 am for first time, at 2 pm for second time, at 8 pm for third time and the last one at 8 am of the next morning for each subject. The imaging was taken without using any mydriatic drops after 5 minutes rest to stabilize the blood flow.

All images were taken by single operator. OCTA image was taken in 3 scans including 3 × 3 mm and 8 × 8 mm scans centered on the fovea for evaluation of macula and 4.5 × 4.5 mm scans with centered on optic disk for evaluation of peripapillary area. Flow was measured inside the circle with 1mm radius and 3 mm radius at 3 capillary plexuses including superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris in 3×3mm and 8×8 mm image scans respectively. According to figure1, vascular density was calculated inside the 2 circles with the diameter of 1 mm and 3 mm (based on ETDRS chart) as whole vascular density (within the large circle), fovea vascular density (within the small circle) and parafoveal vascular density (difference between 2 circles) at SCP and DCP in 3×3 image scan. Flow with the 1mm radius circle centered on optic nerve head (ONH) was calculated in 4.5 × 4.5 mm scan. As shown in figure1, vascular density also calculated in 2 circles on ONH as whole vascular density (inside the large circle), inside ONH vascular density (inside the small circle) and peripapillary vascular density (difference between 2 circles). Signal strength also was evaluated.

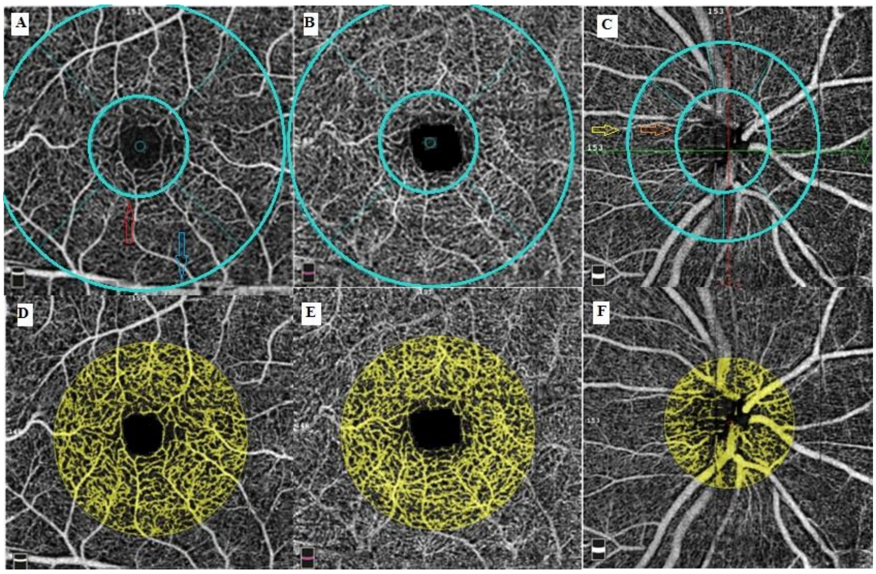

Figure1. *Measurement of quantitative parameters of optical coherence tomography angiography (OCTA). A: vascular density (VD) of superficial capillary plexus as whole VD (within large circle, blue arrow), foveal VD (within small circle, red arrow) and parafoveal VD (difference between 2 circles). B: VD of deep capillary plexus. C: VD of optic nerve head (ONH) as whole VD (inside the large circle, yellow arrow), inside ONH vascular density (inside the small circle, orange circle) and peripapillary vascular density (difference between 2 circles). D: flow of superficial capillary plexus inside the circle with 1 mm radius. E: flow of deep capillary plexus. F flow of ONH.*

3. Statistical Analysis

To present data we used mean, standard deviation and range. To assess the difference in times we used linear mixed model. In this analysis, multiple comparisons were considered by Bonferroni method. All statistical analysis was performed by SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 24.0 Armonk, NY: IBM Corp.). The p-value less than 0.05 was considered as statistically significant.

4. Results

Demographic Data: A total of 34 eyes from 17 healthy subjects (10 male) were analyzed in this study with a mean age of 27.71± 2.14 years and the range of 24 to 32 years. The visual acuity of all subjects was 20/20 by using Snellen chart. The mean spherical equivalent of refractive error was -0.05±0.25.

Signal Strength: For every subject, 12 images were taken. There was a signal strength for each image. The mean amount of signal strength was changed from 68.32±6.14 (range: 53-76) to 80.74±5.00 (range: 69-90).

Diurnal Variation of Quantitative Parameters of OCTA in Macula

The parameters of OCTA in macular area were summarized in table1. The significant diurnal variations were observed in several parameters including flow in choriocapillaris in macular area (8×8mm image), whole vascular density of DCP, foveal vascular density in DCP and parafoveal vascular density of DCP. The other parameters showed insignificant changes during 24 hours (figures 2 and 3). According to figure 2, the flow in choriocapillaris descended from its maximum amount at 8 am first day to its minimum amount at 2 pm respectively. Afterward, it showed an ascending excursion. On the contrary of this diurnal variation in choriocapillaris flow, reverse diurnal variation was observed in both parfoveal vascular density and whole vascular density in DCP. On the other hands, the amount of these two parameters ascended from at least quantity at 8 am first day to maximum quantity at 2 pm and then they showed descending quantity. The foveal vascular density of DCP showed a decline from 8 am of first day to 2 pm and then showed an increasing quantity.

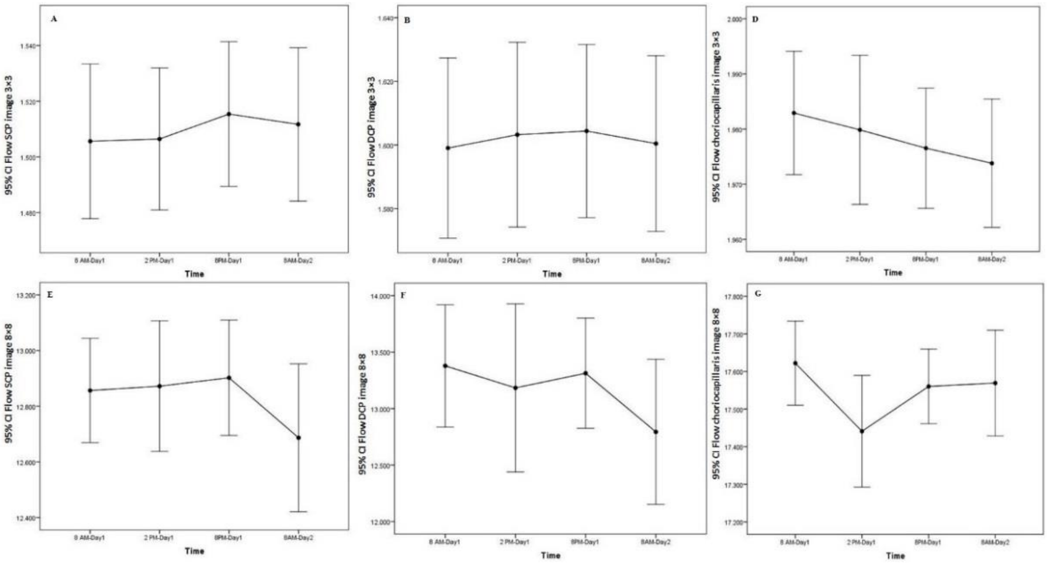

Figure2. *Graphs of diurnal variation of flow in 3 different layers of capillary plexuses of macula including superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris in different times of first day (D1) and second day (D2).*

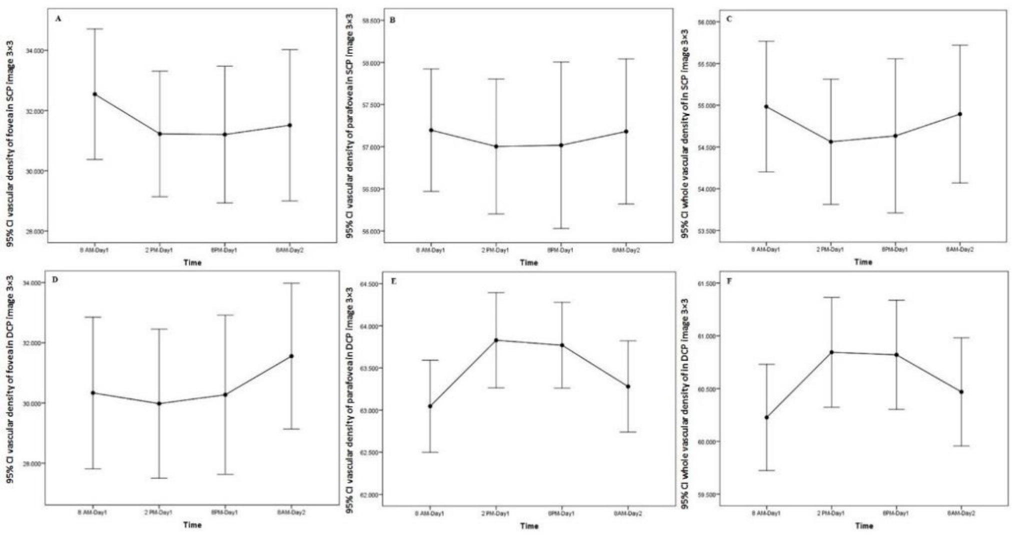

Figure3. *Graphs of diurnal variation of vascular density in superficial capillary plexus (SCP) and deep capillary plexus (DCP) of macula in different times of first day (D1) and second day (D2).*

Diurnal Variation of Quantitative Parameters of OCTA in ONH

Flow and vascular density of ONH were shown in table 2. Insignificant changes were observed over day in flow of ONH, whole vascular density of ONH and vascular density of inside ONH. Based on figure4, peripapillary vascular density increased from 8 am of first day to 2 pm of first day. Afterward, it showed descending quantity. Similar insignificant variations were observed in whole vascular density of ONH.

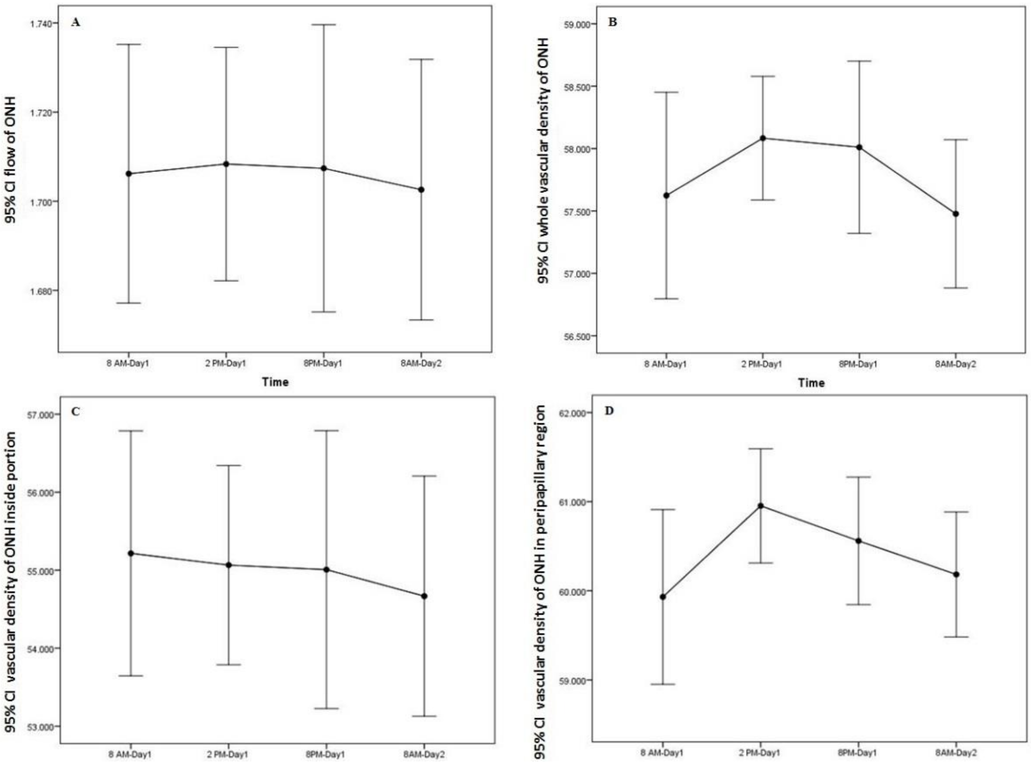

Figure4. *Graphs of diurnal variation of flow and vascular density of optic nerve head in different times of first day (D1) and second day (D2).*

Day to Day Variation of Parameters of OCTA

OCTA images were taken in the second day at 8 am for comparing the flow and vascular density variation and obtaining day to day variation. According to the table 1 and 2, no significant difference was observed in all parameters in 2 consecutive days at the same time.

Table1. *Diurnal fluctuation of flow and vascular density in different capillary layers of retina and choroid in healthy subjects by using optical coherence tomography angiography.*

	Time				P value (diurnal variation)	P value (day to day variation)
	8amD1	2pmD1	8pmD1	8amD2		
Flow in SCP in 3×3mm image	1.506±.080 (1.378-1.649)	1.506±.073 (1.307-1.623)	1.515±.073 (1.360-1.658)	1.512±.079 (1.367-1.680)	0.968	1.00
Flow in DCP in 3×3mm image	1.599±.081 (1.446-1.751)	1.603±.083 (1.325-1.721)	1.604±.078 (1.449-1.729)	1.600±.079 (1.407-1.734)	0.949	1.00
Flow in choriocapillaris in 3×3mm image	1.983±.032 (1.912-2.048)	1.980±.039 (1.860-2.049)	1.977±.031 (1.892-2.029)	1.974±.033 (1.882-2.041)	0.701	1.00
Whole vascular density of SCP	54.98±1.97 (51.27-58.98)	54.56±1.97 (49.59-59.63)	54.63±2.38 (49.18-58.97)	54.89±1.95 (51.96-57.88)	0.920	1.00
Foveal vascular density of SCP	32.54±5.48 (21.59-41.96)	31.22±5.48 (20.81-41.05)	31.20±5.85 (20.40-41.00)	31.51±5.95 (19.69-44.22)	0.388	1.00
Parafoveal vascular density of SCP	57.19±1.83 (52.43-60.12)	57.00±2.10 (51.56-62.35)	57.01±2.54 (51.60-61.74)	57.18±2.03 (53.96-60.70)	0.996	1.00
Whole vascular density of DCP	60.22±1.44 (56.85-62.95)	60.84±1.49 (57.33-64.26)	60.82±1.48 (58.10-63.96)	60.46±1.46 (57.66-63.03)	0.042*	1.00

Foveal vascular density of DCP	30.33±7.21 (16.26-44.68)	29.97±7.09 (16.25-43.05)	30.27±7.58 (16.74-45.77)	31.55±6.94 (16.53-45.79)	0.045*	0.735
Parafoveal vascular density of DCP	63.04±1.56 (60.03-65.78)	63.82±1.61 (61.04-68.14)	63.76±1.45 (61.31-67.04)	63.27±1.55 (60.43-66.68)	0.021*	1.00
Flow in SCP in 8×8mm image	12.856±.537 (11.632-13.857)	12.872±.672 (11.141-14.092)	12.902±.594 (11.396-13.639)	12.687±.762 (11.158-15.195)	0.435	1.00
Flow in DCP in 8×8mm image	13.378±1.552 (8.727-15.932)	13.183±2.133 (6.006-15.873)	13.313±1.399 (9.224-15.772)	12.794±1.840 (7.267-15.121)	0.353	0.935
Flow in choriocapillaris in 8×8mm image	17.622±.320 (16.606-18.158)	17.441±.426 (15.979-18.074)	17.560±.284 (16.353-17.943)	17.569±.403 (16.820-18.539)	0.047*	1.00

*SCP: superficial capillary plexus, DCP: deep capillary plexus, D1: first day, D2: second day, *: statistically significant.*

Table2. *Diurnal fluctuation of flow and vascular density of optic nerve head in healthy subjects by using optical coherence tomography angiography.*

	Time				P value (diurnal variation)	P value (day to day variation)
	8amD1	2pmD1	8pmD1	8amD2		
Flow in ONH	1.706±.083 (1.409-1.829)	1.708±.075 (1.517-1.857)	1.707±.092 (1.369-1.890)	1.703±.084 (1.540-1.883)	0.979	1.00
Whole vascular density of ONH	57.62±2.37 (50.08-61.52)	58.08±1.42 (54.93-60.08)	58.01±1.94 (52.41-60.73)	57.47±1.64 (53.86-60.43)	0.311	1.00
Vascular density inside disc	55.21±4.50 (42.49-66.25)	55.06±3.66 (48.59-64.03)	55.00±5.02 (37.50-65.58)	54.66±4.27 (47.32-66.19)	0.938	1.00
Peripapillary vascular density	59.93±2.81 (51.58-64.55)	60.95±1.83 (56.41-63.81)	60.56±2.01 (55.75-63.65)	60.18±1.94 (56.43-63.40)	0.032*	1.00

*ONH: optic nerve head, D1: first day, D2: second day. *: statistically significant.*

5. Discussion

In this study, significant diurnal variations were detected in choriocapillaris flow in macular area (8×8mm image) and vascular density of DCP (whole, foveal and parafoveal vascular density) by using OCTA. Choriocapillaris flow showed its maximum amount at 8 am then decreased at 2 pm. Afterward it showed an increasing amount toward 8 pm and 8 am of next day. To best of our knowledge, the diurnal variation of flow and vascular density has been reported by using OCTA for the first time. The similar findings were reported in previous study about choroidal thickness. [6-8] Kinoshita et al [6] found significant diurnal variation in choroidal parameters including central choroidal thickness, total choroidal area, luminal area and luminal to total choroidal area (L/C ratio). Maximum and minimum amount were observed at 6 am and 3 pm respectively. [6] This alternation was not observed in choroidal stromal area. [6] Their diurnal variation was approximately similar to fluctuation of choriocapillaris flow in our study. They related variation in choroidal thickness to variation of luminal area. [6] On the other hand, the variation in choroidal thickness was explained with the diurnal varation of blood circulation. [6, 7]

Usui et al [7] found significant correlation between blood pressure and choroidal thickness. On the contrary, no significant correlation was reported between these two parameters by Li et al and Kinoshita et al. [6,9] In the study of Kinoshita et al [6] reported no significant variation in blood pressure and they related this difference with previous studies to lack of variation in diurnal variation of blood pressure. Tan et al [1] reported significant variation in choroidal thickness during day time with the maximum amount at morning and decreasing trend afterward until 5 pm. [1] Chakraborty et al found significant diurnal variation in axial length with maximum and minimum amount at 12:26 and 21:06 respectively. [8] They also found the significant diurnal variation in choroidal thickness on the contrary to axial length changes. [8] They concluded that the main changes in axial length related to alternation of posterior segment. [8] They observed the most and the least amount of choroidal thickness belonged to night and during the day. [8, 10, 11] Lee et al [12] found the significant diurnal variation in choroidal thickness variation with rapid decreased from 8 am to 2 pm similar variation to our result of choroidal flow. They found the variation directly related to baseline choroidal thickness with higher variation in thicker baseline choroidal thickness. [12] Usui et al reported the thinnest and thickest amount of choroidal thickness were at 6 pm and 3 am respectively. [7] The probable explanation of this choroidal fluctuation was related to important role of innervations (sympathetic and parasympathetic) on blood flow of choriocapillaris. [2, 13] The significant diurnal variation was observed in this study and it can be concluded that considering this variation in performing OCTA at same time in different studied subjects is important in interpretation of results.

Diurnal variation in vascular density of DCP was the other interesting finding in this investigation. Whole and parafoveal vascular density of DCP showed an increasing amount from 8 am to 2 pm and decreased both them afterward. In investigation was performed by Tan et al [1], they reported approximately constant retinal thickness with little variation (less than 1 µm) with maximum thickness at 1 pm and minimum thickness at 5 pm and 9 am. [1] Although, the significant alternation was not observed in their variation, but their trend was approximately similar to our results.

The vascular observation in OCTA is based on flow, so the fluctuation in vascular density in retina is explained by alternation in amount of retinal flow. It may be proposed that the alternation in retinal flow is very lower than choroidal flow, so the changes in retinal thickness are very fewer than choroidal thickness alternation. However, the documentation of this theory requires further studies with larger sample size.

We also assessed flow and vascular density of ONH by using OCTA. To best of our knowledge, this was the first report of diurnal variation of flow and vascular density of ONH by using OCTA. Peripapillary vascular density showed significant increasing trend from 8 am to 2 pm and then it showed a decline. Similar insignificant trend was observed in whole vascular density. The considerable diurnal variations of choroidal flow and flow of ONH using laser speckle flow graphy were reported by Iwase et al. [2] They assessed mean blur rate (MBR), as blood flow marker, of choroidal flow and ONH with the least amount at 9 am and most amount at 24. [2] The fluctuation of flow and vascular density of ONH also is appreciable.

No significant difference was observed in all parameters in 2 consecutive days at the same time**.** Similar to our result, no considerable alternations at same time of 2 diverse days in choroidal thickness was reported by Tan et al. [1] It might indicated that the diurnal fluctuation has regular changes from day to day.

Small sample size and limitation in performing OCTA in all times of day or with lower interval were the principle limitations of our study.

It can be concluded that significant diurnal variation in choriocapillaris flow, vascular density of deep capillary plexus and vascular density of peripapillary area is important in interpretation of OCTA. This may reminds clinicians to perform OCTA at the same time of day to avoid normal diurnal variations and mistakes in interpretation of tests.

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Citation: *Ramak Roohipoor et al., Diurnal Variation in Flow and Vascular Density of Capillary Plexuses of Retina, Choroid and Optic Nerve Head in Healthy Eye by Using Optical Coherence Tomography Angiography. ARC Journal of Ophthalmology. 2019, 4(2): 1-7.*