Original Article

Peripapillary choroidal vascularity quantification and characterization in healthy individuals

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Abstract

Introduction: To characterize the peripapillary choroidal vasculature in healthy individuals using the choroidal vascular index (CVI), a previously established more robust tool of measurement of choroidal vascularity than choroidal thickness.
Methods: The peripapillary choroid in healthy individuals was analyzed using optical coherence tomography. OCT B-scan were analyzed using automated binarization, a previously established technique. This separates the choroidal layer into the stromal and vascular areas. Choroidal vascular index (CVI), the vascular area/total area, was computed for each image over the macula and the peripapillary area of the optic disc. Regression analysis and generalized estimating equation (GEE) were used to analyze various demographics, and CVI in the macula and each quadrant of the optic disc.
Results: 58 eyes of 29 healthy individuals were included. Mean age was 42±17 years. Average CVI at the macula was 0.583. Average peripapillary CVI was 0.643 (nasal), 0.598 (temporal), 0.621 (superior) and 0.623 (inferior). Regression analysis of variables demonstrated there was no significant relationship between the demographic variables and macular CVI. However, the analysis demonstrated age and CVI of the peripapillary area were significantly correlated. Further stratification revealed significantly higher CVI in the optic disc in subjects over 45.
Conclusion: Peripapillary CVI in all quadrants is higher than macular CVI in all age groups. CVI significantly increases after the age of 45 in the peripapillary area but not

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macular area. This suggests that stromal area decline is greater than the decline of the luminal area in the choroid at the peripapillary area as age increases.

Key words: Choroid, Peripapillary, Vascularity, Optical Coherence Tomography, Optic disc

Introduction

Vascular supply to the eye is provided by the choroid. Consisting of blood vessels and connective tissue, the choroid, lies between the retina and the sclera. Disruptions in the integrity of the choroid have been implicated in many ocular pathologies.

Optical Coherence Tomography (OCT) has been instrumental in studying choroidal health. Computation of the choroidal thickness (CT) has served as a marker of its vitality and used to study a host of ocular diseases central serous chorioretinopathy, age-related macular degeneration, glaucoma, and including the study of optic neuropathy and optic disc pathologies. (Stanga et al, 2003; Imamura et al, 2009; Chung et al, 2011; Koizumi et al, 2011; Manjunath et al, 2011) Peripapillary choroidal vessels help supply blood to the surface nerve fiber layer and prelaminar part of the optic nerve head (ONH). (Hayreh, 1969) Peripapillary CT has been used to study primary open-angle glaucoma, branch retinal vein occlusions, preterm and full-term infants, high myopic patients, and even in systemic disease such as patients with Parkinson's disease. (Pablo et al, 2017; Song et al, 2017; Kang et al, 2017; Fiess et al, 2016; Garcia-Martin et al, 2017; Abdolrahimzadeh et al, 2017)

However, CT is not a true standard for the vascular supply, since it comprises of the stromal and interstitial layer along with the blood vessels and capillaries. Recently, we reported choroidal vascularity index (CVI), a more robust tool to study the choroid, in various disease such as central serous chorioretinopathy, AMD, high myopia, and dystrophies. (Agrawal et al, 2016a; Ruiz-Medrano et al, 2017b) Using image binarization techniques the choroidal area can be divided into stromal and luminal areas. CVI is ratio of the luminal area to the total choroid area. Others have adopted this technique to study changes at the macula and fovea, discovering luminal area decreases with increasing age, while the stromal area remains stable in healthy individuals. (Agrawal et al, 2016b; Agrawal et al, 2016a; Ruiz-Medrano et al, 2017b) However, none have used to characterize the choroid around the ONH.

Assessment of the peripapillary choroidal vascularity may be beneficial in evaluating ONH blood supply. To further study such diseases around the optic disc with more accurate measurements of choroidal vascular integrity around the disc, we aim to study the peripapillary CVI in the healthy population and compare it with macular CVI.

Methods

Study Population

This was a cross-section, non-interventional study of healthy volunteers from January 2017 to July 2017 at Smt. Kanuri Santhamma Centre for Vitreo Retinal Diseases at L.V. Prasad Eye Institute, Hyderabad. The study was approved by the Institutional Review Board of the Institute and all the methods adhered to the tenets of the Declaration of Helsinki.

Both males and females were included. Inclusion criteria were best-corrected visual acuity between 20/ 20 and 20/25, spherical equivalent (SE) between -3 diopters (D) and +1.5D, no systemic or ocular diseases (other than visually insignificant cataracts). Eyes with poor quality images, peripapillary atrophy, scans with invisible choroidal borders throughout, and

eyes with any history of any retinal diseases in the study or fellow eye or patients with any systemic diseases were not included. Eyes with SE beyond -3 D and +1.5 D were excluded. All patients underwent a comprehensive ophthalmology exam including demographic details, best-corrected visual acuity assessment using Snellen's chart, intraocular pressure assessment using applanation tonometry and fundus examination.

Imaging of the choroid was obtained via swept-source OCT scan using DRI-OCT "Triton" (Topcon Corporation, Tokyo, Japan). The Topcon SS-OCT uses a tunable laser as a light source to provide a 1050nm centered wavelength. The device reaches a scanning speed of 100 000 A-scans per second, yielding 8 and 20 μm axial and transverse resolution in tissue, respectively. Two horizontal and vertical cross-sectional high definition, 9 mm long, scans were obtained at the fovea and center of the optic disc. All images were obtained from 9 am to 12 pm reducing the effect of diurnal variation.

Image Analysis

As reported previously by our group, choroidal stroma and vessel area analysis involved automated binarization of an OCT B-scan and automated segmentation of the binarized choroid layer using a previously validated algorithm. The automated binarization involved preprocessing, exponential and nonlinear enhancement, and thresholding. OCT images were denoised using the block-matching and 3D filtering technique. Thresholding and choroidal segmentation were obtained using a recent method proposed and implemented by previous literature, which reported reproducibility and reliability, for multiple studies. (Ruiz-Medrano et al, 2017b; Vupparaboina et al, 2015; Ruiz-Medrano et al, 2017a)

CVI was computed as the (vascular area/total area). It was computed over the macula and the peripapillary area (1mm rim) of the optic disc. The area posterior to the optic disc, which is devoid of choroidal tissue was manually removed from the scans passing through the scans, to remove any potential bias in CVI measurements. Peripapillary measurements were computed over the four quadrants: nasal, temporal, superior, and inferior quadrants, using vertical and horizontal scans through the disc. Analyzed images can be seen in figure 1 and 2.

Regression analysis was computed for various demographics, and CVI in the macula and each quadrant of the optic disc. Next, the data was stratified by age and analyzed. GEE was used for to compensate both eyes of patients in the study.

Results

A total of 58 eyes of 29 patients with healthy eyes were included in the study. Average age of patients was 42 ± 17 years (range 11 to 67). Mean best-corrected visual acuity was 0.04 ± 0.09 logMAR (Snellen's equivalent 20/20) and mean spherical equivalent of -0.22 ± 0.89. None of the eyes had any previous treatment for ocular disease. Average CVI at the macula was 0.583. Average peripapillary CVI was 0.643 (nasal), 0.598 (temporal), 0.621 (superior) and 0.623 (inferior).

Regression analysis of variables demonstrated age and CVI of the peripapillary area were significantly correlated. Interestingly there was no significant relationship between the demographic variables and macular CVI, or temporal quadrant CVI of the optic disc. In the nasal quadrant of the optic disc, there was a significant relationship between CVI and spherical equivalent. Nasal CVI had marginally significant relationship with sex, with females having lower CVI. In the superior quadrant, there was a significant relationship between CVI and spherical equivalent, and lastly, in the inferior quadrant, there was a significant

relationship between visual acuity and CVI. Results are summarized in table 1.

Considering age was significantly correlated with CVI, data was stratified by age. There was a statistically significantly higher CVI in all quadrants of the optic disc in subjects over 45. Macular CVI was also higher but was not a statistically significant finding. (Table 2)

Table 1: Regression analysis and associated demographics (p-value)

	Age	**Sex**	**Visual Acuity**	**Spherical Equivalent**
Macular CVI	-0.413 (0.001)	-0.017 (0.900)	0.165 (0.215)	-0.212 (0.111)
Nasal CVI	-0.525 (0.000)	-0.260 **(0.049)**	-0.145 (0.278)	-0.296 **(0.024)**
Temporal CVI	-0.290 (0.027)	0.090 (0.500)	0.180 (0.177)	-0.199 (0.133)
Superior CVI	-0.498 (0.000)	0.016 (0.907)	-0.069 (0.606)	-0.329 **(0.012)**
Inferior CVI	-0.519 (0.000)	-0.099 (0.459)	-0.299 **(0.023)**	-0.157 (0.240)

Table 2: Comparison of choroidal vascularity as per age

	</= 45 years old	**>45 years old**	**p-value**
Number of Eyes	30	28	
Male: female ratio	1: 1.1	1: 2.1	0.170
Macular CVI	0.574	0.593	0.088
Nasal CVI	0.6208	0.667	0.000
Temporal CVI	0.587	0.609	0.039
Superior CVI	0.601	0.642	0.000
Inferior CVI	0.602	0.645	0.003

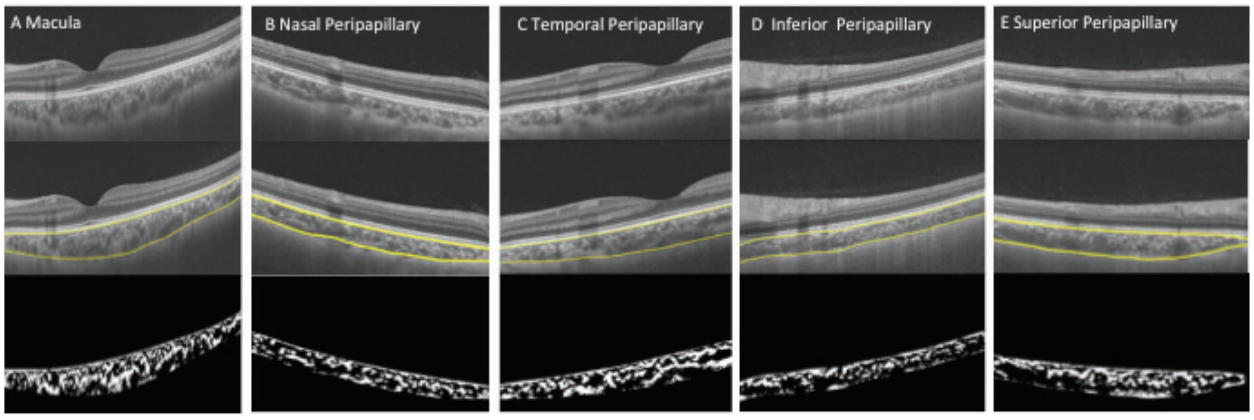

Figure 1: Horiztonal OCT scans where the top image is the initial OCT scan, middle image shows segmentation, and bottom image represents analyzed segmented image. A. OCT through Macula B. OCT through Nasal Peripapillary C. OCT through Temporal Peripapillary D. OCT through Inferior Peripapillary E. OCT through Superior Peripapillary

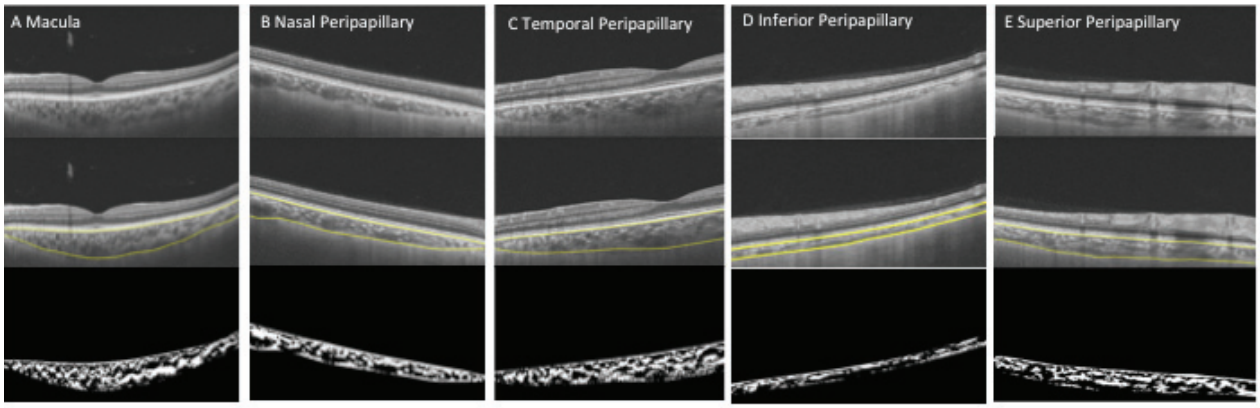

Figure 2 Vertical OCT scans where the top image is the initial OCT scan, middle image shows segmentation, and bottom image represents analyzed segmented image. A. OCT through Macula B. OCT through Nasal Peripapillary C. OCT through Temporal Peripapillary D. OCT through Inferior Peripapillary E. OCT through Superior Peripapillary

Discussion

It is vital to understand nature of the choroidal vasculature, especially around the ONH. Peripapillary choroidal vasculature supplies blood to the surface nerve fiber layer and prelaminar part of the ONH. (Hayreh, 1969) It is a metabolic activity, and vasculature viability have been studied using CT in diseases such as optic neuropathy, non-arteritic ischemic optic neuropathy, and glaucoma. Utilizing CVI, a novel robust measurement of choroidal vascularity, we report CVI around the ONH and macula for healthy individuals.

Numerous studies measuring CT, have demonstrated decreasing CT with age both around the peripapillary and the macula. (Mundae et al, 2017; Huang et al, 2013; Ho et al, 2011; Tanabe et al, 2012; Erbagci et al, 2015; Coskun et al, 2014; Tuncer et al, 2015) Aggarwal et al, has previously demonstrated CVI to be a more robust measurement than CT. (Ruiz-Medrano et al, 2017b) He showed macular CVI demonstrated less variability across age than macular CT. (Ruiz-Medrano et al, 2017b) Our study further confirms this since there is no significant difference between macular CVI in the age groups validating our findings.

Previously studies have shown decreasing CT with age, and no change with gender, refractive error, IOP, BP, axial length in the peripapillary area. (Huang et al, 2013) However, we found an increase in peripapillary CVI with age. Correlating our results with previous literature, we can conclude rate of stromal area decline is greater than the decline of luminal area in the choroid in the peripapillary area. This correlates with the histological and biochemical studies have shown decrease in protease inhibitor, fibrillary collagen, and the amount of interstitial components of the choroid as age increases. (Friedman et al, 1963; Kumar et al, 2014; Sohn et al, 2014) Another theory for increased CVI can be explained secondary to increased demand. Literature supports hypoxic microvasculature damages with increasing age, which occurs from free radical damage. This increase in CVI may be a compensatory mechanism increases blood flow in these areas. No studies in current literature have demonstrated increased choroidal flow with age around the peripapillary area. Further studies need to be done to elucidate why this phenomenon is observed and specifically why it is observed in the peripapillary area but not the macula.

Previous findings have also demonstrated peripapillary choroid thinning greatest in the inferior quadrant of the optic disc. (Erbagci et al, 2015; Tanabe et al, 2012; Ho et al, 2011; Huang et al, 2013) None of the prior literature has established why the inferior quadrant is the thinnest. The proposed theory stems from embryological development. The optic fissure is located on the inferior aspect optic cup and is the last area of the globe to close, and hence may be thinner. (Ho et al, 2011; Tanabe et al, 2012) However, this is not a sound theory as there are dissimilarities between the inferior CT and RNFL layer. We have shown CVI is lowest in the temporal quadrant, and not in the inferior quadrant. This suggests that the thin inferior CT seen in previous literature likely stems from a decrease in the stromal layer, and not the vascular area. Thus, perfusion at the inferior quadrant may still be adequately retained. We found temporal quadrant CVI to be the lowest, which could be due to the watershed supply of vasculature in the temporal quadrant. (Takahashi et al, 1996) Hence, these small peripheral distal capillaries may be contributing to the lower CVI. However, more studies need to be done to confirm this result.

Some other limitations to study must be noted. Our study is limited to healthy eyes, can hence findings cannot be extrapolated any specific pathologies. The study was not controlled for any variables such as intraocular pressure, corneal thickness, that are subject to diurnal variation. However, the study included healthy subjects that had normal blood pressures and ocular pressures. Thus, these variables were not controlled for in our study and may have an effect on perfusion. Lastly, our study revealed CVI to be significantly greater after age 45; however, our sample size is limited and not uniformly distributed among each decade limiting our stratification amongst different ages. Further studies need to be to validate and expand results.

Overall, our study reveals, CVI significantly increases after the age of 45 in the peripapillary area but not macular area in normal healthy subjects. Peripapillary CVI is higher in all quadrants than macular CVI in all age groups. Consider physiological changes, and previous literature this suggests that stromal area decline is greater than the decline of luminal area as age increases in the peripapillary choroid.

References

Abdolrahimzadeh S, Parisi F, Plateroti AM, Evangelista F, Fenicia V, Scuderi G, Recupero SM (2017). Visual Acuity, and Macular and Peripapillary Thickness in High Myopia. Curr Eye Res:1-6.

Agrawal R, Chhablani J, Tan KA, Shah S, Sarvaiya C, Banker A (2016a). Choroidal Vascularity Index in Central Serous Chorioretinopathy. Retina; 36:1646-51.

Agrawal R, Gupta P, Tan KA, Cheung CM, Wong TY, Cheng CY (2016b). Choroidal vascularity index as a measure of vascular status of the choroid: Measurements in healthy eyes from a population-based study. Sci Rep; 6: 21090.

Chung SE, Kang SW, Lee JH, Kim YT (2011). Choroidal thickness in polypoidal choroidal vasculopathy and exudative age-related macular degeneration. Ophthalmology; 118: 840-5.

Coskun E, Okumus S, Gurler B, Yayuspayi R, Oren B, Kaydu E, Comez A, Erbagci I (2014). Choroidal thickness in healthy Turkish subjects. Turk J Med Sci, 44, 56-61.

Erbagci H, Oren B, Okumus S, Kenan S, Celemler P, Erbagci I (2015). Peripapillary choroidal thickness in healthy Turkish subjects. Clin Ophthalmol;9:1393-7.

Fiess A, Christian L, Kolb-Keerl R, Knuf M, Kirchhof B, Muether PS, Bauer J (2016). Peripapillary Choroidal Thickness in Former

Preterm and Full-Term Infants Aged From 4 to 10 Years. Invest Ophthalmol Vis Sci;57:6548-53.

Friedman E, Smith TR, Kuwabara T (1963). Senile choroidal vascular patterns and drusen. Arch Ophthalmol;69:220-30.

Garcia-Martin E, Pablo LE, Bambo MP, Alarcia R, Polo V, Larrosa JM, Vilades E, Cameo B, Orduna E, Ramirez T, Satue M (2017). Comparison of peripapillary choroidal thickness between healthy subjects and patients with Parkinson's disease. PLoS One;12:e0177163.

Hayreh SS (1969). Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. Br J Ophthalmol;53:721-48.

Ho J, Branchini L, Regatieri C, Krishnan C, Fujimoto JG, Duker JS (2011). Analysis of normal peripapillary choroidal thickness via spectral domain optical coherence tomography. Ophthalmology; 118:2001-7.

Huang W, Wang W, Zhou M, Chen S, Gao X, Fan Q, Ding X, Zhang X (2013). Peripapillary choroidal thickness in healthy Chinese subjects. BMC Ophthalmol; 13: 23.

Imamura Y, Fujiwara T, Margolis R, Spaide RF (2009). Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina;29:1469-73.

Kang HM, Choi JH, Koh HJ, Lee CS, Lee SC (2017). Significant Reduction of Peripapillary Choroidal Thickness in Patients with Unilateral Branch Retinal Vein Occlusion. Retina.

Koizumi H, Yamagishi T, Yamazaki T, Kawasaki R, Kinoshita S (2011). Subfoveal choroidal thickness in typical age-related macular degeneration and polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol; 249:1123-8.

Kumar A, Zhao L, Fariss RN, Mcmenamin PG, Wong WT (2014). Vascular associations and dynamic process motility in perivascular myeloid cells of the mouse choroid: implications for function and senescent change. Invest Ophthalmol Vis Sci;55:1787-96.

Manjunath V, Goren J, Fujimoto JG, Duker JS (2011). Analysis of choroidal thickness in age-related macular degeneration using spectral-domain optical coherence tomography. Am J Ophthalmol; 152:663-8.

Mundae RS, Zangwill LM, Kabbara S, Hammel N, Bowd C, Medeiros F, Girkin CA, Liebmann JM, Weinreb RN, Belghith A (2017). A Longitudinal Analysis of Peripapillary Choroidal Thinning in Healthy and Glaucoma Subjects. Am J Ophthalmol.

Pablo LE, Cameo B, Bambo MP, Polo V, Larrosa JM, Fuertes M, Guerri N, Ferrandez B, Garcia-Martin E (2017). Peripapillary Choroidal Thickness Analysis Using Swept-Source Optical Coherence Tomography in Glaucoma Patients: A Broader Approach. Ophthalmic Res.

Ruiz-Medrano J, Flores-Moreno I, Pena-Garcia P, Montero JA, Garcia-Feijoo J, Duker JS, Ruiz-Moreno JM (2017a). Analysis of Age-Related Choroidal Layers Thinning in Healthy Eyes Using Swept-Source Optical Coherence Tomography. Retina; 37:1305-13.

Ruiz-Medrano J, Ruiz-Moreno JM, Goud A, Vupparaboina KK, Jana S, Chhablani J (2017b). Age-Related Changes in Choroidal Vascular Density of Healthy Subjects Based on Image Binarization of Swept-Source Optical Coherence Tomography. Retina.

Sohn EH, Khanna A, Tucker BA, Abramoff MD, Stone EM, Mullins RF (2014). Structural and biochemical analyses of choroidal thickness in human donor eyes. Invest Ophthalmol Vis Sci; 55: 1352-60.

Song YJ, Kim YK, Jeoung, JW, Park KH (2017). Assessment of peripapillary choroidal thickness in primary open-angle glaucoma patients with choroidal vascular prominence. Jpn J Ophthalmol.

Stanga PE, Lim JI, Hamilton P (2003). Indocyanine green angiography in chorioretinal diseases: indications and interpretation: an evidence-based update. Ophthalmology; 110:15-21.

Takahashi K, Muraoka K, Kishi S, Shimizu K (1996). Watershed zone in the human peripheral choroid. Ophthalmology; 103: 336-42.

Tanabe H, Ito Y, Terasaki H (2012). Choroid is thinner in inferior region of optic disks of normal eyes. Retina; 32: 134-9.

Tuncer I, Karahan E, Zengin MO, Atalay E, Polat N (2015). Choroidal thickness in relation to sex, age, refractive error, and axial length in healthy Turkish subjects. Int Ophthalmol; 35: 403-10.

Vupparaboina KK, Nizampatnam S, Chhablani J, Richhariya A, Jana S (2015). Automated estimation of choroidal thickness distribution and volume based on OCT images of posterior visual section. Comput Med Imaging Graph;46(3): 315-27.