



## Original Research Article

## Correlation between choroidal vascularity index, flow pattern and neovascular activity in treatment naive eyes of age related macular degeneration

Sunil Ganekal<sup>1,2,\*</sup>, Varun Ganekal<sup>1</sup><sup>1</sup>Dept. of Ophthalmology, Davangere Netralaya, Davangere, Karnataka, India<sup>2</sup>Mayo Clinic, Jacksonville, Florida, US

## ARTICLE INFO

## Article history:

Received 09-01-2022

Accepted 24-01-2022

Available online 29-06-2022

## Keywords:

OCT angiography

Choroidal neovascular activity

AMD

## ABSTRACT

**Purpose:** To study the correlation between choroidal vascularity index, flow pattern and neovascular activity in treatment naive eyes of age related macular degeneration.**Materials and Methods:** Cross-sectional analysis of 46 treatment naive eyes diagnosed with exudative age related macular degeneration. All patients underwent spectral domain optical coherence tomography, fluorescein angiography, indocyanine green angiography and OCTA. The Choroidal Vascularity Index (CVI) and OCTA vascular features at initial and last visit were analyzed after anti vascular endothelial growth factor (VEGF) treatment. These changes were correlated with the disease activity on SD-OCT and OCTA.**Results:** Mean age was  $66.34 \pm 7.2$  years. Mean sub foveal choroidal thickness was  $215.39 \pm 102.378 \mu\text{m}$  at baseline and  $198.42 \pm 101.049 \mu\text{m}$  at 3 months ( $p=0.07$ ). The mean CVI was  $63.73 \pm 5.28\%$  at baseline &  $64.59 \pm 4.87\%$  at 3 months ( $p=0.754$ ). Pattern of network on OCTA was sea-fan in 20(43.5%), medusa head in 8(17.4%), indistinct in 18(39.1%) at baseline and sea-fan in 6(13%), medusa head in 6(13%), indistinct in 28(60.9%) and mixed in 6(13%) at 3 months. The signs of activity on OCT changes after 3 months ( $p=0.001$ ). On OCTA 36 eyes had active network at baseline & 34 eyes had inactive network at the last follow up ( $p=0.001$ ).**Conclusion:** Choroidal vascularity Index showed no correlation with various patterns of CNV and showed no significant change with anti VEGF treatment. Post treatment network patterns showed no significant correlation with the OCT activity even though the OCTA showed an active network.This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.For reprints contact: [reprint@ipinnovative.com](mailto:reprint@ipinnovative.com)

## 1. Introduction

Optical coherence tomography angiography (OCTA) is a new, noninvasive imaging technique that plays an important role in clinical practice.<sup>1,2</sup> Optical coherence tomography angiography (OCTA) has become an alternative imaging method of the retinal and choroidal vascularity within the past decade. Like ordinary optical coherence tomography (OCT), OCTA provides B-scans of the retina, but OCTA additionally offers rapid, high-resolution, repeated, and

accurate visualization of blood flow without injection of a contrast agent, which provides indirect representation of the vascular morphology of the retina and choroid.<sup>3</sup> OCTA has been shown to be effective in the detection of CNV.<sup>1,4</sup> Executed studies with different spectral domain OCTA (SD-OCTA) devices (840 nm wavelength, max. 70,000 A-scans/second) for the detection of choroidal neovascularization (CNV) revealed a far-flung sensitivity between 32% and 89.2% and a specificity between 67.7% and 100%.<sup>5</sup> Deeper tissue penetration and faster scanning rate with SS-OCTA leads to a better visualization of microvascular retinal structures compared with SD-OCTA.

\* Corresponding author.

E-mail address: [drgsunil@yahoo.com](mailto:drgsunil@yahoo.com) (S. Ganekal).

Lumbroso et al. and Muakkassa et al. used OCTA to detect changes in CNV after anti-VEGF treatment.<sup>6,7</sup> Furthermore, with recent developments in equipment and software, OCTA can now measure the size of CNV, so that it can be compared before and after anti-VEGF treatment. Hence we took up this study to evaluate the CNV activity and change in flow patterns of treatment naive exudative AMD by using OCTA. We also analyzed the CVI and CNV flow remodeling response to anti-VEGF therapy as mentioned in methodology.

## 2. Materials and Methods

Cross sectional study of 46 treatment naïve eyes with exudative age related macular degeneration (AMD) which had active CNV of type 1, type 2 and mixed type. All patients were enrolled from August 2019 to April 2020. The study was approved by the institutional review board and was in accordance with declaration of Helsinki. Various parameters at baseline and after 3 months follow up were compared. The diagnosis of exudative AMD was made in each case by clinical examination, SD-OCT, fundus fluorescein angiography, indocyanine green angiography and OCTA (Spectralis HRA; Heidelberg Engineering, Germany) at the baseline. Any patient with previous anti VEGF therapy, Polypoidal choroidal vasculopathy, secondary causes of CNV & eyes in which a good quality OCTA could not be acquired were excluded from the study. We calculated the CVI using the Image J software (version 1.49; National Institutes of Health, Bethesda, MD, USA). CVI gives a measure of the structural changes in the choroid. A central OCT scan passing through the fovea at baseline and after 3 months follow up, was taken for image binarization. We used a protocol proposed by Sonoda et al<sup>1</sup> with few modifications described by Agarwal et al.<sup>2</sup> OCT image was imported in Image J software. Niblack auto local threshold tool was used to binarize the OCT image. Binarizing an image makes the scleral interface with the choroid sharper. Polygon selection tool was used and 4000 $\mu$ m of choroid under the CNV was selected from retinal pigment epithelium to the choroid sclera junction then added to the region of interest manager. Image was then converted to RGB (red, green, blue) color and color threshold tool was used. Total choroidal area (TCA) and the luminal area (LA) were calculated. CVI was obtained by dividing LA by TCA. (Figure 1)

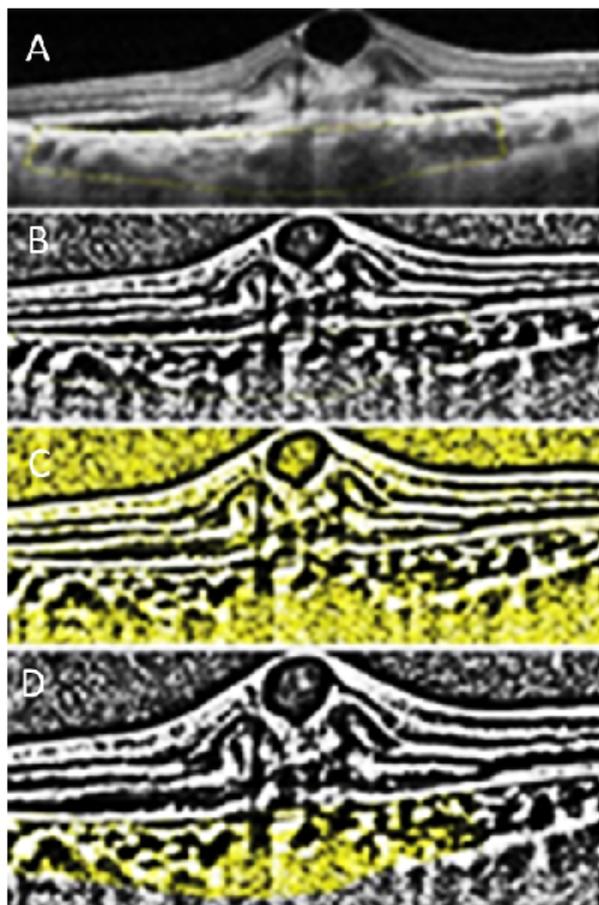
OCTA was obtained with Spectralis HRA device (Heidelberg Engineering, Germany). Protocol covered 15<sup>0</sup> x 15<sup>0</sup> area of the macula centre acquiring high resolution scans with 11  $\mu$ m cuts. The best CNV network area was manually selected for image analysis. 4 types of CNV networks were identified based on previous studies (Figure 2).<sup>3-6</sup> “Sea-fan” pattern showed a peripheral feeder vessel, thin branching and surrounding halo. “Medusa” pattern had a central feeder vessel with circular peripheral anastomosis

and peripheral halo. “Indistinct” pattern showed no feeder vessel but had thin branching & surrounding halo. “Pruned vascular tree” showed only the main branch but no thin branching. The total lesion area was taken from the enface image obtained along with the OCTA. Vascular area was calculated from Image J software. OCT was taken using the same device, 20<sup>0</sup> x 20<sup>0</sup> degree scan of the macula consisting of 49 horizontal line scans with a spacing of 120 $\mu$ m. Choroid was imaged using enhanced depth imaging (EDI) mode. Subfoveal choroidal thickness (SFCT) was manually calculated using the inbuilt caliper tool of the OCT device. Statistical analysis was performed using SPSS version 16.0. Descriptive analysis of the population’s characteristics was carried out. Results of continuous variables are reported as mean and SD and of categorical variables are reported as count and percentages. The differences between quantitative variables were analyzed using Wilcoxon signed rank test and Paired t test. The differences between categorical variables were analyzed using McNemar’s test. Spearman correlation coefficient was used to find the correlation between the two variables. P-value <0.05 was considered as significant for all the comparisons.

## 3. Results

Mean age was 66.34 $\pm$  7.2 (range 52 to 84 years). A total of 46 eyes of 44 patients with exudative AMD were included and there were 22 men and 22 women. They received a total of 2.75  $\pm$  0.38 injections at the final follow up. The initial BCVA was 0.74  $\pm$  0.56 logMAR and the final BCVA was 0.48  $\pm$  0.3 logMAR (p = 0.003). The Subfoveal choroidal thickness at baseline was first 215.39 $\pm$ 102.378  $\mu$ m and at final examination it was 198.42 $\pm$ 101.049 (p = 0.07), decrease of 16.97  $\mu$ m. The baseline CVI was 63.73 $\pm$ 5.28% and 64.59 $\pm$ 4.87% at final examination (p = 0.754). At baseline CNV showed 8 (17.4%) medusa pattern, 20 (43.5%) seafan pattern, 16 (34.8%) indistinct and 2(4.3%) mixed pattern. At final follow up 6 (13%) medusa, 6(13%) seafan, 28 (60.9%) indistinct and 6 (13%) mixed patterns of CNV were seen. OCT at baseline showed activity in 46 (100%) eyes. Final visit 20 (43.5%) had signs of activity and 26 (56.5%) showed no signs of activity (p=0.01). OCTA at baseline, 36 (78.3%) showed active CNV network and 10 (21.7%) had inactive network. OCTA at final visit, 12 (26.1%) had active network and 34 (73.9%) had inactive network (p=0.01). The total CNV lesion area was 4.42  $\pm$  3.16 mm<sup>2</sup> at baseline and 3.24  $\pm$  2.21 mm<sup>2</sup> at final examination (p = 0.05). The total vascular area of CNV network was 0.66  $\pm$  0.634 mm<sup>2</sup> at baseline and 0.52  $\pm$  0.44 mm<sup>2</sup> at final visit (p= 0.12). As all the eyes were treated with anti- VEGFs we noted intrinsic changes in the flow patterns after 3 months with 60.9% (28/46) eyes showing an indistinct type of network and absence of the feeder vessel in 52.2% (24/46) eyes (p=0.20) (Figure 3). There was a significant change in OCTA activity with 34/46

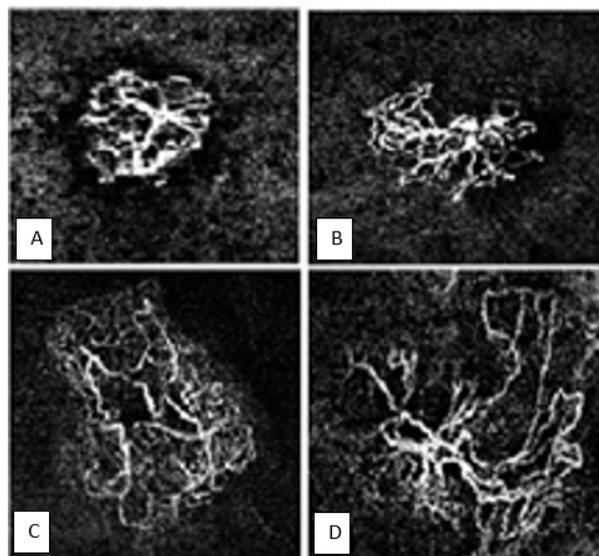
eyes showing inactive networks after 3 months ( $p < 0.01$ ). Flow patterns in these inactive networks were dominated by indistinct pattern (26), mixed pattern (6) and sea fan pattern (2). The total lesion area correlated positively to the vascular area both at baseline ( $p = 0.005$ ) and after 3 months ( $p = 0.023$ ).



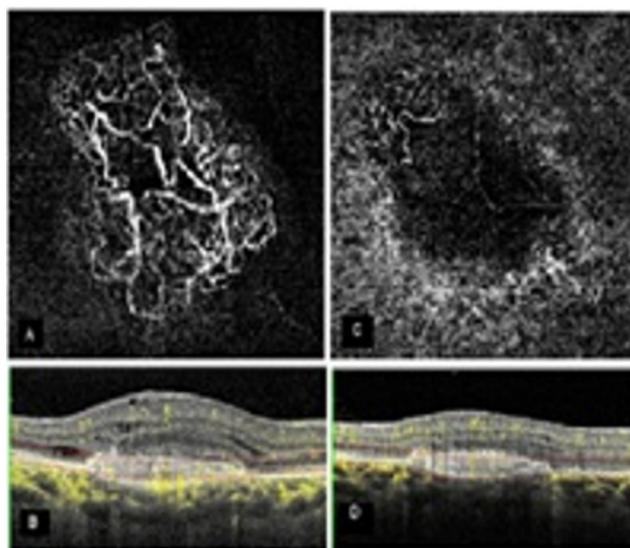
**Fig. 1:** CVI calculation in a patient with exudative AMD. SD-OCT scans were imported into image J software and cropped. **A)** The area of choroid underneath the CNV was manually selected using the polygon selection tool and the area was saved. **B, C, D)** Image was then converted

#### 4. Discussion

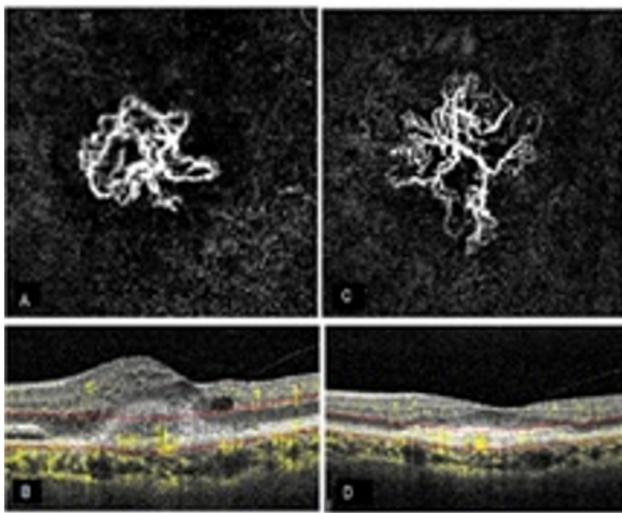
In our study, we tried to evaluate the CNV activity and change in flow patterns of treatment naive exudative AMD by using OCTA and analyzing the CVI. CNV flow remodeling in response to anti-VEGF therapy has been describe previously.<sup>8,9</sup> By starting anti-VEGF therapy Lumbroso et al<sup>8</sup> have demonstrated vascular remodeling changes which include decrease in the caliber of the smaller branches within 24 hours of injection and a maximum decline in the flow between 6 to 12 days. This phase



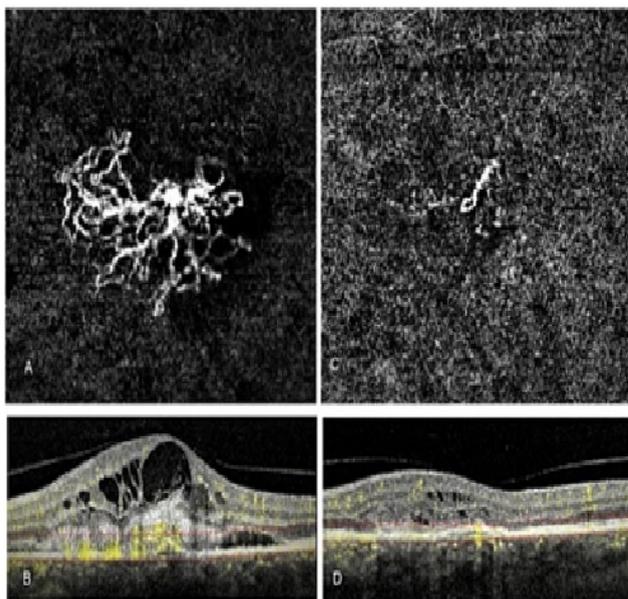
**Fig. 2:** Different CNV patterns in OCTA. **A)** “Medusa” pattern, showing a central feeder vessel. **B)** “Seafan” pattern with eccentric feeder vessel. **C)** “Indistinct” pattern with no feeder vessel. **D)** “Pruned vascular tree” showing only the main vascular trunk with no thin branches



**Fig. 3:** Showing decrease in both OCT and OCTA activity **A)** “Indistinct” pattern of CNV & **B)** SD-OCT showing signs of activity. **C)** Resolution of the CNV network. **D)** OCT shows just a uniform sub-retinal hyper reflective material and no intra retinal fluid



**Fig. 4:** A) “indistinct” pattern of CNV on OCTA at baseline. B) Corresponding OCT shows activity with intra retinal fluid and sub retinal mixed reflective material. C) OCTA showing an active network but (D) OCT shows no signs of activity at 3 months follow up



**Fig. 5:** A) “sea fan” pattern of CNV with B) signs of active exudation on OCT at baseline. C) At 3 months the network has decreased in size and D) OCT activity also has decrease

**Table 1:** Demographic and clinical features

Characteristics	Summary Details
Total no: of eyes	46
Total no: of patients	44
Mean Age	66.34 (7.2)
Gender(M:F)	(22:22)
<b>Total no. of Injections 2.75 (0.38)</b>	
Initial BCVA	0.74 (0.56)
BCVA Final	0.48 (0.3)
Initial SFCT	215.39(102.378)
SFCT final	198.42(101.049)
Initial CVI	63.73(5.28)
CVI final	64.59(4.87)
Initial Trans luminal Area(TLA)	4.42 (3.16)
TLA final	3.24 (2.21)
Initial OCTA VA	0.67 (0.632)
OCTA VA final	0.51 (0.430)

**Table 2:** Assessment of type of network– baseline & post treatment 3 months

Type of Network	Baseline, n (%)	Final visit, n (%)
Medusa	8 (17.4)	6 (13.0)
Sea fan	20 (43.5)	6 (13.0)
Indistinct	16 (34.8)	28 (60.9)
Mixed	2 (4.3)	6 (13.0)

is followed repopulation phase 20 to 50 days later. Vascular remodeling phenomenon like arteriogenesis and angiogenesis were studied by Spaide et al in CNV.<sup>10</sup> Coscas et al. demonstrated that the different CNV patterns detected on OCTA had some correlation with the treatment decisions by multimodal imaging.<sup>11</sup> We attempted studying the choroidal characteristics may affect the flow through the CNV after anti-VEGF therapy.

In the present study mean SFCT decreased from 215.39  $\mu\text{m}$  to 198.42  $\mu\text{m}$  after 3 months showing a decrease of 16.97  $\mu\text{m}$ . SFCT decreases by approximately 4  $\mu\text{m}$  per year during normal aging process.<sup>12</sup> The decrease in SFCT in our study was due to the decrease in the disease activity. This decrease in the SFCT has been described to be either due to decreased choroidal hyperpermeability<sup>13</sup> or secondary vasoconstriction.<sup>14</sup> Anti-VEGF decreases the blood flow to the CNV network. The pre and post procedure SFCT was not able to predict the final disease activity on OCT and OCTA. So in this study SFCT as a biomarker was inadequate to predict the disease activity pre and post treatment with anti VEGF's.

The CVI was 63.73 at baseline and 64.59 at the final visit. The change noted was insignificant. In our study there was no correlation between the type of CNV, the pattern of flow in the CNV & CVI at baseline and at final visit. The VEGF levels are more in the area close to the CNV. But the CVI and SFCT show case changes that are present in the choroid spread across the posterior pole in general.<sup>15</sup> It is difficult to

conclude whether the choroidal changes involve the whole choroid or only the area around the CNV. Unlike the SFCT, CVI is a more stable indicator of choroidal circulation. The shorter follow up time may be the reason why CVI did not show any significant changes in this study.

The present study baseline CNV flow analysis revealed medusa, sea-fan, indistinct and mixed pattern in all the patients (46/46) at the baseline. These networks had the basic features to be classified as “immature” networks.<sup>16</sup> We analyzed the CNV lesion area, the CNV vascular area and the type of vascular flow patterns. The CNV flow patterns showed high fluctuation in the total area and vascular area in networks with active flow patterns. Hence the lesion size can be taken as a marker for therapeutic response in treatment naïve age related macular degeneration. OCT surprisingly showed no sign of activity in some eyes which had features of active network (Figure 4). These included medusa head in 2, indistinct in 18 and mixed pattern in 6 eyes. Signs of exudation on OCT were also noticed in eyes which have inactive networks (Figure 5). The type of flow patterns were analyzed individually for the type of CNV, lesion area and vascular area, which found no significant correlation between them.

OCTA with no CNV network is known to be associated with clinical and OCT inactivity.<sup>17</sup> However cyclic CNV variations during follow-up have been studied by Lombroso et al. who mentioned the CNV cycle to be 62 days long.<sup>18</sup> Huang et al. showed CNV flow shut down by 2 weeks after injection, then recurrence of flow signals by 4 weeks and OCT activity by 6 weeks,<sup>19</sup> Based on the above findings we assume that the CNV networks initially respond to the anti VEGF injections by contraction of lesion area and then later the flow through them changes to develop into mature networks. Anti VEGF therapy initially decreases the choroidal thickness and as the effect wears off the choroidal thickness increases, to thin again as therapy is restarted.<sup>20</sup> In this study CVI was analyzed after the development of CNV. Cyclic CNV changes may explain why certain eyes had no OCT features of disease activity even though the OCTA showed an active CNV network. Limitations of this study include its retrospective nature with a small sample size and short follow up period. Angiography was not repeated at the final visit so the leakage from CNV networks with no OCT activity could not be commented. Absence of a control group, manual measurements used in OCT and OCTA analysis were some other limitations. These can be addressed in future studies with larger sample size.

As far as we know this is the first study which has studied the CNV activity combining CVI and flow patterns on OCTA. Choroidal neovascular lesion area is a good biomarker of treatment response. The cyclic variations of CNV have to be kept in mind before making treatment decisions. Using OCT alone in follow up of CNV can miss cases which can reactivate in the future. Cases with OCTA activity and dry OCT scan needs to be followed up more

frequently. CVI remains a stable indicator of choroidal circulation when compared to SFCT. So studies employing CVI can help to further understand the long term vascular remodeling seen in CNV. These new parameters may help in individualized follow-up and treatment of CNV.

## 5. Source of Funding

None.

## 6. Conflict of Interest

The authors declare no conflict of interest.

## References

1. DeCarlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). *Int J Retina Vitreous*. 2015;1. doi:10.1186/s40942-015-0005-8.
2. Jia Y, Bailey ST, Hwang TS, McClintic SM, Gao SS, Pennesi ME, et al. Quantitative optical coherence tomography angiography of vascular abnormalities in the living human eye. *Proc Natl Acad Sci U S A*. 2015;112(18):2395–2402.
3. Jia Y, Tan O, Tokayer J, Potsaid B, Wang Y, Liu JJ, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express*. 2012;20(4):4710–25.
4. Mastropasqua R, DiAntonio L, DiStaso S, Agnifili L, DiGregorio A, Ciancaglini M, et al. Optical coherence tomography angiography in retinal vascular diseases and choroidal neovascularization. *J Ophthalmol*. 2015;2015:343515. doi:10.1155/2015/343515.
5. Liang MC, DeCarlo TE, Bauman CR, Reichel E, Waheed NK, Duker JS, et al. Correlation of spectral domain optical coherence tomography angiography and clinical activity in neovascular age-related macular degeneration. *Retina*. 2016;36(12):2265–73.
6. Lombroso B, Rispoli M, Savastano MC. Longitudinal optical coherence tomography-angiography study of type 2 naive choroidal neovascularization early response after treatment. *Retina*. 2015;35(11):2242–51.
7. Muakkassa NW, Chin AT, DeCarlo T, Klein KA, Bauman CR, Witkin AJ, et al. Characterizing the effect of anti-vascular endothelial growth factor therapy on treatment-naïve choroidal neovascularization using optical coherence tomography angiography. *Retina*. 2015;35(11):2252–9.
8. Kuehlewein L, Sadda SR, Sarraf D. OCT angiography and sequential quantitative analysis of type 2 neovascularization after ranibizumab therapy. *Eye (Lond)*. 2015;29(7):932–5.
9. Lombroso B, Rispoli M, Savastano MC, Jia Y, Tan O, Huang D. Optical coherence tomography angiography study of choroidal neovascularization early response after treatment. *Dev Ophthalmol*. 2016;56:77–85.
10. Spaide RF. Optical coherence tomography angiography signs of vascular abnormalization with antiangiogenic therapy for choroidal neovascularization. *Am J Ophthalmol*. 2015;160(1):6–16.
11. Coscas G, Lupidi M, Coscas F, Francais C, Cagini C, Souied EH. Optical coherence tomography angiography during follow-up: qualitative and quantitative analysis of mixed type I and II choroidal neovascularization after vascular endothelial growth factor trap therapy. *Ophthalmic Res*. 2015;54(2):57–63.
12. Wei WB, Xu L, Jonas JB, Shao L, Du KF, Wang S, et al. Subfoveal choroidal thickness: the Beijing Eye Study. *Ophthalmology*. 2013;120(1):175–80.
13. Lowe J, Araujo J, Yang J. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. *Exp Eye Res*. 2007;85(4):425–30.
14. Hood JD, Meininger CJ, Ziche M, Granger HJ. VEGF upregulates eNOS message, protein, and NO production in human endothelial

- cells. *Am J Physiol*. 1998;274(3):1054–8.
15. Wei X, Ting DSW, Ng WY, Khandelwal N, Agrawal R, Cheung CMG. Choroidal vascularity index: a novel optical coherence tomography based parameter in patients with exudative age-related macular degeneration. *Retina*. 2017;37(6):1120–5.
16. Miere A, Butori P, Cohen SY, Semoun O, Capuano V, Jung C, et al. Vascular remodeling of choroidal neovascularization after anti-vascular endothelial growth factor therapy visualized on optical coherence tomography angiography. *Retina*. 2019;39(3):548–57.
17. Liang MC, Carlo TED, Bauman CR. Correlation of spectral domain optical coherence tomography angiography and clinical activity in neovascular age-related macular degeneration. *Retina*. 2016;36:2265–2273.
18. Lumbroso B, Rispoli M, Savastano MC. Longitudinal optical coherence tomography-angiography study of type 2 naive choroidal neovascularization early response after treatment. *Retina*. 2015;35(11):2242–51.
19. Huang D, Jia Y, Rispoli M, Tan O, Lumbroso B. Optical coherence tomography angiography of time course of choroidal neovascularization in response to anti-angiogenic treatment. *Retina*. 2015;35(11):2260–4.
20. Kim YK, Park SJ, Woo SJ, Park KH. Choroidal thickness change after intravitreal anti-vascular endothelial growth factor treatment in retinal angiomatous proliferation and its recurrence. *Retina*. 2016;36(8):1516–26.

### Author biography

**Sunil Ganekal**, Medical Director  <https://orcid.org/0000-0002-7879-6155>

**Varun Ganekal**, Research Assistant

**Cite this article:** Ganekal S, Ganekal V. Correlation between choroidal vascularity index, flow pattern and neovascular activity in treatment naive eyes of age related macular degeneration. *Indian J Clin Exp Ophthalmol* 2022;8(2):198-203.