Correlation between Optical Coherence Tomograph Angiography (OCT- A) findings at three to six weeks and functional outcome (modified Rankin Scale – mRS) at three months of onset of acute ischemic stroke due to Extracranial Carotid Artery Atherosclerotic Disease (ECAD)

Biswamohan Mishra
All India Institute of Medical Sciences
Awadh Kishor Pandit (akpandit.med@gmail.com)
All India Institute of Medical Sciences
Rohan Chawla
All India Institute of Medical Sciences
Swati Phuljhele Aalok
All India Institute of Medical Sciences
M V Padma Srivastava
All India Institute of Medical Sciences
Manoj Kumar Nayak
All India Institute of Medical Sciences
Yogeesh PM
All India Institute of Medical Sciences
Manish Salunkhe
All India Institute of Medical Sciences
Ajay Garg
All India Institute of Medical Sciences
Achal Kumar Srivastava
All India Institute of Medical Sciences
Venugopalan Y Vishnu
All India Institute of Medical Sciences
Rohit Bhatia
All India Institute of Medical Sciences
Shubham Misra
All India Institute of Medical Sciences
Ashish Datt Upadhyay
All India Institute of Medical Sciences
Kabiruddin Molla
All India Institute of Medical Sciences

Research Article

Keywords:

Posted Date: March 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1406622/v1

Abstract

Objective

To determine whether Optical Coherence Tomography Angiography (OCTA) findings of retinal and Optic Nerve Head (ONH) can help predict functional outcomes (mRS, modified Rankin Score) in patients with Extracranial Carotid Artery Atherosclerotic Disease (ECAD).

Background

OCTA can image retinal vasculature without the need of contrast injection. Previous studies have evaluated OCTA findings in the pre and post carotid revascularization procedures, however, none have evaluated the utility of OCTA in predicting the clinical outcome in ECAD associated stroke, which we aim to explore in this study.

Methods

For this prospective exploratory study, OCTA findings in patients with ischemic stroke due to ECAD at 3-6 weeks of stroke onset were observed for mRS at three months. OCTA was also performed on risk factors matched controls who did not have carotid artery stenosis and the findings were compared with those of cases.

Results

Twenty-three patients of ECAD stroke (cases arm) and twenty-three risk factor matched controls were enrolled. Mean age was 53.14± 12.28 years and majority were males. There was a significant difference between cases and controls in the Deep Vessel Density (DVD) at macula ($p = 0.0007$) and in the Radial Peripapillary Capillary Perfusion Density (RPCPD) at the Optic Nerve Head (ONH) ($p = 0.0007$). Statistically significant difference was noted in the total superficial vessel density at macula (normal vs abnormal Superficial Vessel Density) in the ipsilateral eye and clinical outcome at 3 months (very good vs poor outcome, mRS 0-1 vs mRS 2-6, respectively ($p= 0.0361$). There was statistically insignificant correlation between the RPCPD at the ONH and National Institutes of Health Stroke Scale (NIHSS) at the time of admission, mRS at discharge, and functional outcome (mRS) at 3 months of stroke onset ($r =0.33$, $r=0.35$, $r=0.39$; $p=0.11$, $p=0.09$, $p=0.06$, respectively).

Conclusion

OCTA findings (total superficial vessel density at macula) at three to six weeks of stroke onset may predict functional outcome at three months in patients with acute ischemic stroke. Further studies involving larger patient cohorts, may help establish OCTA as a new biomarker for predicting and monitoring clinical and functional outcomes in patients with Extracranial Carotid Artery Atherosclerotic Disease, in a fast, non-invasive and reproducible manner.

Introduction

Carotid artery stenosis is a major risk factor for ischemic stroke and is estimated to account for approximately 15% of all ischemic stroke, with Extracranial Carotid Artery Stenosis accounting for 8% of these strokes.[1] MR angiography (MRA), CT angiography (CTA), and Doppler ultrasound are the various imaging modalities used to detect stenosis of the carotid artery. Both CTA and MRA need contrast to delineate the carotid artery and its branches. Accordingly, frequent imaging is usually avoided as it warrants exposure to adverse events of contrast

in addition to radiation risk (in CTA). An imaging modality which can provide accurate and reproducible imaging of the intracranial and extracranial vessels or a surrogate marker of them, with reasonable sensitivity and specificity without using contrast would be desirable.

Ophthalmic artery is the first branch of internal carotid artery, which supplies the retina as central retinal artery.[2] Any flow limitation in the carotid artery is likely to impact perfusion in the retinal microvasculature. Hence imaging the retinal microvasculature may provide an indirect evidence of flow dynamics in the carotid artery (the main supplier of anterior brain circulation). Introduction of Optical coherence tomography (OCT) is considered one of the milestones in retinal imaging.[3]

OCT uses a light source and an interferometer and algorithms to produce images based on the amplitude and the delay of reflected light.[4] To enable non-invasive assessment of retinal blood flow, a new software called OCT angiography (OCTA) was incorporated into the OCT devices in 2006.[5] Multiple cross – sectional A scans of the same location are gathered by the OCTA machine and then computer algorithm detects the differences in amplitude, intensity, phase which helps in generating motion contrast. Motion contrast is based on the principle that, motionless objects do not produce any change in signal contrary to mobile objects. Choroid and retina are stationary tissues, and blood is a moving object (Erythrocytes reflect light due to their biconcave structure). The retinal vasculature can be viewed directly, offering a readily accessible window to monitor vascular and circulatory function. Most importantly, there is no need to inject the contrast and, hence, the possibility to reproduce the examination as many times as the examiner wants.

A growing body of evidence suggests that OCTA can be used to predict retinal vessel abnormalities in dementia, optic disc neuropathies, demyelination, cerebral small vessel disease and inherited degenerative diseases.[3,6] Though two previous studies have evaluated the utility of OCTA in monitoring patients with Carotid Artery Stenosis who underwent CAS,[7,8] no studies till date have evaluated the correlation between OCTA findings in patients with stroke resulting from Extracranial ICA atherosclerotic disease (ECAD) and their functional outcomes. As retina and Optic Nerve head (ONH) are predominantly perfused by ICA, we evaluated whether OCTA findings of retinal and ONH vasculature can help predict clinical outcomes in patients with stroke due to ECAD.

Methods

STUDY OVERSIGHT

Ethics

The present study is an exploratory study involving human participants, and the research was performed in accordance with the Declaration of Helsinki and was approved by the All India Institute of Medical Sciences Institutional Ethics Committee (IECPG -554/26.09.2019, RT -02/28.11.2019), New Delhi, India. The authors confirm that informed consent was obtained from all subjects included in this exploratory study and can be provided on reasonable request to the corresponding author.

Study Setting

This exploratory study was conducted between November 2019 and May 2021 in the Department of Neurology, Department of Neuroradiology and Department of Ophthalmology, All India Institute of Medical Sciences, New

Delhi, a tertiary care hospital in India.

STUDY DESIGN AND PARTICIPANTS

Adult patients more than 18 years of age and diagnosed with symptomatic acute ischemic stroke (AIS) due to ECAD, were eligible for enrolment. AIS was classified as per Trial of Org 10172 in Acute Stroke Treatment (TOAST).[9] Patients with any other cerebro-vascular co-morbidities apart from ECAD ischemic stroke , those with visual loss or visual impairment, or media opacities preventing high-quality imaging and hypertensive retinopathy more than Grade 2, and terminally ill patients on life support measures were excluded. Details of inclusion and exclusion criteria are provided in supplementary appendix.

Risk factor matched viz diabetic, hypertensive, dyslipidaemic subjects without ocular disease of any sort nor any history of previous cerebro-vascular disease were included as controls.

Visual impairment is often defined as a best corrected visual acuity of worse than either 6/12 or 6/18.[10] Accordingly, both in the cases and control arms, patients with best corrected visual acuity (BCVA) worse than 6/18 were excluded from the study.

OUTCOMES

Primary Outcome

1. Correlation between OCTA findings at three to six weeks and functional outcome (mRS) at three months of onset of acute ischemic stroke due to Extracranial Carotid Artery Atherosclerotic Disease (ECAD).

Secondary Outcomes

1. Changes in retinal and optic nerve head (ONH) perfusion using OCTA in patients with ischemic stroke due to extracranial internal carotid artery atherosclerotic disease at three to six weeks of onset of stroke and at three months onset of stroke.
2. Correlation between the retinal and ONH perfusion parameters obtained using OCTA and NIHSS score at the time of onset of stroke, mRS at the time of discharge, mRS at 3 months of stroke onset and change in mRS.

Screening of patients was done during hospitalization and outpatient visits. Eligible patients were enrolled into this exploratory study and their demographic details, vitals, along with the day of onset of stroke, type of stroke, CTA or MRA findings, were noted and a mRS (modified Rankin Score) at the time discharge. The criteria of modified Rankin Score (mRS) used is provided in the Supplementary appendix. The degree of carotid artery stenosis was assessed by two independent neuro-radiologists (M.K.N. and A.G.), and any disparity in results between them was resolved by A.K.P.

Sample size estimation

Satterthwaite's t test assuming unequal variances was used for sample size estimation and considering 10% loss to follow-up, a total of 44 cases and 44 controls were planned for enrolment.

STUDY PROCEDURES

The patients enrolled as cases underwent detailed ophthalmological and OCTA examination at 3-6 weeks of stroke onset using Spectral Domain Cirrus HD-OCT Model 5000 (Carl Zeiss, Meditec, Inc, 5160 Hacienda Drive, Dublin, CA 94568 USA) (Representative images acquired from a case shown in Figure S1). Thereafter, the 3-month functional outcome assessment was carried out by assessing the mRS by telephonic conversation which is validated and has been shown to have a good agreement with face-to-face assessment.[11]

Initially Doppler ultrasound of the bilateral carotid arteries was performed on healthy subjects who were screened for enrolment as control subject. If no stenosis was detected, the subject underwent detailed ophthalmological evaluation and if found eligible, OCTA examination was performed on him by the same ophthalmologist using the same device and enrolled in this exploratory study (Representative images acquired from a control shown in Figure S2).

All the scans of cases and controls were reviewed by two ophthalmologists (R.C. and S.P.A.) and non-qualified images were excluded. The vessel perfusion densities and ONH perfusion data from qualified images were included in the analysis. The detailed methodology of obtaining the OCTA images and the analysis of Deep macula OCTA scans using “ImageJ” software is mentioned in details in the supplementary appendix. [12]

Literature search revealed that there is lack of normative data for OCTA findings in the Indian population. Moreover, since OCTA has recently been introduced into commercial use, so the protocols required for proper selection of OCTA images are also not defined yet. Also, the findings differ as per the technology used to perform OCTA. In the present study analysis of OCTA images was done by using the fovea (Central), parafovea (inner) and whole en face (full), and also the total vessel density at the level of superficial retina and total perfusion density were also analyzed.[7,13,14,15]

The normative data for this study was derived from the risk factors matched controls, using the mean and standard deviation (SD) of the OCTA parameters of the control subjects. The normal range thus obtained was then compared with those of the same parameters of the cases and labelled as normal if the value is was within range or abnormal if the value was outside of this normative range.[13] Thereafter the proportion of patients with very good outcome (defined as patients with mRS 0-1 at three months of stroke onset) or poor outcome (defined as mRS 2-6 at three months of stroke onset) were arranged as per the normality of OCTA parameter and then analyzed.

The eye on the same side as stroke was considered as the “Ipsilateral eye” and the eye opposite to that of side of stroke was considered as the “contralateral eye.”

DATA ANALYSIS AND STATISTICS

Data management was performed using Microsoft Excel 2007 and the statistical analysis was conducted using STATA Version 13 and IBM SPSS® Statistics 22 for Windows (IBM Corporation, Somers, NY, USA). The normality of the data distribution was tested using the Kolmogorov–Smirnov test. After confirmation of the normality, the data was presented either as mean ± SD (if normally distributed) or median and interquartile range (IQR) (if non-normally distributed). Changes at follow-up compared with baseline were assessed using paired sample t-tests or Wilcoxon signed rank test. The two treatment groups were compared using independent Student’s t-tests for normally distributed data otherwise Mann Witney U test was applied. Independent Spearman correlation was used to assess the correlation between OCT-A changes at 3 to 6 weeks and functional outcome (mRS) at 3 months,

mRS at discharge, change in mRS and baseline NIHSS. Fisher Exact Test was used. All inferential statistics was intended to be exploratory, not confirmatory, and was interpreted accordingly. Statistical significance level was set to 0.05.

Results

A total of 69 patients were screened for eligibility, of which 46 cases were excluded for various reasons shown in Figure S3 (flowchart S3a), and finally 23 cases of stroke were enrolled in the study. A total of 46 healthy individuals were screened for potential control subjects. After excluding 23 subjects for various reasons listed in Figure S3 (flowchart S3b), a total of 23 subjects were enrolled as controls.

Baseline characteristics and demographics of the cohort

Overall, the two groups were balanced with respect to baseline characteristics (Table 1). The mean age of the cohort was 52.67 ± 12.40 years and majority were males (35, 76%). Hypertension was the most prevalent risk factor (30, 65.2%). Middle Cerebral Artery territory (MCA) was the most common location site of stroke among the cases (n/N = 19/23, 82.61%). The mean percentage of stenosis in the cases group was 76.67 ± 20.57%. The mean National Institutes of Stroke Scale (NIHSS) at the time of stroke onset score was 8.39 ± 4.45 for the cases group.

The median Best Corrected Visual acuity (BCVA) expressed in log MAR (Minimum Angle of Resolution) was 0.00 (0.00,0.18) for the right eye and for the left eye was 0.00 (0.00,0.18) for the case arm and 0.00 (0.00,0.18) and 0.00 (0.00,0.18) for the same sides, respectively, for the control arm.

The OCTA findings were segregated into 9 parameters for each eye.

Comparison of the OCTA parameters with regards to the total vessel densities (VD) and perfusion densities (PD) showed a significant difference between case arm and control arm in the Deep Vessel Density (DVD), at the level of the macula (case arm = 35.82 ± 9.56 vs control arm = 41.77 ± 5.89; p = 0.0007). Similar difference was seen between the control and case arm (case arm = 42.29 ± 1.89; p = 0.0007 vs control arm = 43.57 ± 1.59) when compared with regards to RPCPD. No significant difference was found when rest of the OCTA parameters were compared between cases and controls (Table 2).

When the comparison was made by the region scanned, the vessel density in the deep retinal OCTA of the macula in patients with ischemic stroke was significantly lower compared with risk factors matched controls (cases arm: 35.93 ± 9.47; control arm: 41.76 ± 5.89; p = 0.01). Significant differences were also found in the RPCPD of the ONH (cases arm: 42.28 ± 1.85; control arm: 43.57 ± 1.59; p = 0.01) (Table S1).

The OCTA parameters between the cases and control arms were also compared segregating into the left and right eyes (Table S2). The VD in the OD (Oculus Dexter, for right) deep retinal OCTA of the macula in patients with ischemic stroke was significantly lower compared with risk factors matched controls (cases arm: 35.26 ± 9.34; control arm: 41.81 ± 6.18; p = 0.01). Significant differences were also found in the perfusion of the OD RPCPD at the ONH (cases arm: 42.71 ± 1.32; control arm: 43.63 ± 1.53; p = 0.04); VD of OS (Oculus Sinister, left) parafovea (cases arm: 15.51 ± 4.54 vs control arm : 18.13 ± 2.06, p = 0.01); VD of OS whole en face (cases arm: 14.37 ± 4.26 vs control arm: 16.85 ± 1.98; p = 0.01) (Table S2).

Similar statistically significant differences were also seen in the PD of the superficial layer at the level of OD parafovea (p = 0.02) and whole en face at OD macula (p = 0.02), in the VD of the OS Deep macula (0.04), and RPCPD of the OS Optic disc (ONH) (p = 0.01) (Table S2). More number of statistically significant findings between cases and controls were observed on the left side (OS) probably because majority of the cases had left sided stenosis related ECAD stroke (Table 1 -baseline characteristics).

Comparison of the OCTA findings of the ipsilateral eye (total values of regions of scan) of cases and clinical and functional outcome.

The mRS outcome at 3 months and change in the mRS at months were plotted against their respective OCTA findings of the Ipsilateral eye (Table 3). mRS outcomes were categorized into very good outcome (mRS = 0–1) and poor outcome (mRS = 2–6). There was statistically significant difference between the normal and abnormal total SVD (abbrev.) at the level of macula in predicting the very good outcome and poor outcome (p = 0.031, Table 3). Rest of the OCTA parameters did not show a statistically significant difference (Table 3) when analysed with respect to mRS outcome. Additionally, there was no statistically significant difference when those same OCTA parameters for the ipsilateral eye were compared with change in mRS (Table 3). However, Comparison of the OCTA parameters with the contralateral eye did not yield any statistically significant association with functional outcomes at 3 months (mRS) (Table 3, bottom).

Comparison of the individual OCTA (Region wise of the scan) findings of cases and clinical and functional outcome.

OCTA parameters of the ipsilateral eye were compared with the NIHSS score at the time of onset of stroke, mRS at the time of discharge, mRS at 3 months of stroke onset. mRS 0–1 at 3 months was achieved in 13/23 patients (56.52%) while mRS score 2–6, at 3 months was achieved in 10/23 patients (43.48%).

There was no statistically significant correlation noticed between the OCTA findings of the ipsilateral eye with NIHSS score at the time of admission, or mRS at discharge, or mRS at 3 months of stroke onset and change in the mRS (Table 4, Fig. 1). However, a mild positive correlation was observed between ONH RPCPD and NIHSS at the time of admission, and also mRS at discharge, and that with mRS at 3 months of stroke onset ($r = 0.33$, $r = 0.35$, $r = 0.39$, respectively), (shown in red dotted rectangle in Fig. 1, and in bold letters in Table 4) but none of these reached a statistical significance (p = 0.11, p = 0.09, p = 0.06, respectively). (Table 4, Fig. 1).

There was no statistically significant correlation noticed between the OCTA parameters of the contralateral eye with NIHSS at the time of admission, or mRS at discharge, or mRS at 3 months of stroke onset and change in mRS, neither was any significant positive corelation noticed. (Table S3, Figure S4).

Discussion

This pilot study is the first to determine the correlation between retinal vessel density and flow density at retina and Optic Nerve Head (ONH) to the functional outcome of the patients at three months by using mRS. Our study showed a significant association of total SVD, an OCTA marker, well correlating with a very good functional outcome at three months in cases with (AIS having ECAD etiology. OCTA is a non-invasive imaging method and can be reproduced as many times as the examiner wants. It enables visualization of the retinal vessels without the need for injecting a contrast.

Since the inception of OCTA into commercial health care use in the late 2016, the technology has been applied to multiple diverse areas of Central Nervous System diseases viz multiple sclerosis, neurodegenerative diseases, dementia cerebral small and Large vessel disease.[16,17]

In cerebrovascular diseases, previous studies had evaluated the utility of OCT in characterising the morphological and functional ocular parameters in patients of carotid artery stenosis and tried to determine any corelation between these parameters and the degree of stenosis.[18,19,20,21]

Lahme et al., 2017, prospectively evaluated the OCTA findings pre and post carotid artery stenting in 25 patients. The cases had a significantly lower flow density in the macula and ONH compared to controls (macula: p = 0.003) (ONH: p = 0.013). After CEA, there was a significant improvement in the flow density in the ONH (p = 0.04).[7] Lee et al., retrospectively studied pre and post-operative OCTA findings in 20 patients of Carotid artery stenosis who underwent Carotid Artery Stenting. No controls were enrolled in the study. Vessel density in the DVC (Deep Vasculature Complex) increased significantly after stent implantation (P = 0.010) in the ipsilateral eye (eye on the side of stenting). In the fellow eye (eye opposite of stenting), there was significant increase in the VD in the SVC (Superficial Vasculature Complex) (P = 0.028) and DVC (P = 0.034). There was no significant change in the RPCPD either in the ipsilateral or contralateral eye group (P = 0.363 and P = 0.878, respectively). However, none of these studies compared the findings of AIS due to ECAD to functional outcomes, which can have a substantial predictive value.[13]

In the present study, comparison of the OCTA parameters with regards to the total vessel densities and perfusion densities showed a significant difference between the case arm and control arm in the DVD, at the level of the macula (p = 0.0007). A similar difference was seen between the control and case arm (p = 0.0007) at the level of RPCPD.

On analysis of data region wise of the scan, the vessel density in the deep retinal OCT angiogram of the macula in patients with ischemic stroke was significantly lower compared with risk factors matched controls (cases arm: 35.93 ± 9.47; control arm: 41.76 ± 5.89; p = 0.01). Significant differences were also found in the RPCPD at the ONH (p = 0.01). Rest of retinal vasculature did not show any significant differences.

Liu et al., 2017, in their study on 87 healthy Chinese adults showed that the right eyes had higher vascular density in superficial, deep retinal capillary and choriocapillaris networks, probably related to dominance.[22] Accordingly, we compared the OCTA parameters of the eyes of our cohort as per laterality (left vs left, right vs right) between the cases and controls.

Therein, a significant difference was seen in various parameters between the cases and controls. The cases had a statistically significant lower VD of the right deep macula retinal (p = 0.01), left deep macula (p = 0.04), left parafovea and left whole en face (p = 0.01), compared to the same side and similar location OCTA angiograms of the controls. Similar differences between cases and controls were found between the perfusion density of the right superficial parafovea (p = 0.02), right whole en face (p = 0.02), perfusion of right RPCPD (0.04), and also left RPCPD (0.01).

There is ample evidence that improved cerebral perfusion following revascularization procedure that has a positive effect on the contralateral cerebral blood flow through the collateral circulation.[23,24,25] Hence the OCTA parameters obtained were compared with the relevant outcomes both for the ipsilateral eye and contralateral eye.

Statistically significant difference was noted in the total vessel density at superficial macula (total SVD, normal vs abnormal) in the ipsilateral eye to clinical outcome at 3 months (very good vs poor outcome, mRS 0–1 vs mRS 2–6, respectively (p = 0.0361). Hence, a normal value of total SVD may have a predictive very good functional outcome at 3 months, however with small sample size, this cannot be stated conclusively and needs larger prospective studies enrolling higher number of patients to establish the association unequivocally.

The status of superficial vessel density assumes significance as they are the distal most vessels of the retina on the blood supply chain and are thus prone to ischemia. The deep capillary plexus are well maintained by proximal blood flow through intricate plexuses as described above.[3] Hence, the statistically significant difference (p = 0.0361) noted between the very good and poor outcome using SVD total as a parameter in the ipsilateral eye assumes more relevance.

On the analysis of the OCTA findings and clinical outcomes, there was no statistically significant correlation noticed between the OCTA parameters of the eye which is in same side as the side of stroke with NIHSS at the time of admission, or mRS at discharge, or mRS at 3 months of stroke onset and change in mRS. However, a mild positive correlation was observed between RPCPD at the ONH and NIHSS at the time of admission, and also mRS at discharge, and that with functional outcome (mRS) at 3 months of stroke onset (r = 0.33, r = 0.35, r = 0.39; p = 0.11, p = 0.09, p = 0.06, respectively).

Limitations

There were several limitations in this study. First, the analysis was conducted on a relatively small sample size. The initial two COVID19 waves in the Indian subcontinent considerably slowed down the recruitment. OCTA needs considerable cooperation for image acquisition and minor degree of movements can cause blurring of the images and artefacts. Lack of cooperation resulted in non-acquisition of OCTA images in 8 of 37 cases (21.6%) who were recruited for OCTA examination and hence had to be excluded. In one study as many as 28% of the eyes could not be imaged due to lack of cooperation, that too in subjects who were fully conscious and did not have any cerebrovascular disease that impaired understanding.[26] Fixation of the eyes is also impaired after an acute stroke, especially if it involves the left frontal eye field area. In the present study, 11 patients were fully cooperative and had a good understanding of the procedure, still could not fix their eyes even for a few seconds to acquire the images. The patients were not matched at the baseline regarding the medications they were taking or the amount of physiotherapy they were getting, which could be a confounding factor to the eventual mRS outcome. This limitation can be avoided in the future studies by ensuring a standardized regime among the patients enrolled in the study and a similar physiotherapy retinue.

Conclusion

To conclude patients with ischemic stroke due to Extracranial Internal Carotid Artery Atherosclerotic Disease (ECAD) showed a lower vessel density in the deep layer of macula (DVD) and in the RPC layer (ONH) perfusion when compared with healthy controls. Total superficial vessel density obtained by OCTA showed statistically significant association with functional outcomes (expressed in in mRS) at 3 months of stroke onset. Further studies involving larger patient cohorts, could help establish OCTA as a new biomarker for predicting and monitoring clinical and functional outcomes in patients with Carotid Artery Stenosis, in a fast, non-invasive and reproducible manner.

Declarations

Acknowledgements: The authors acknowledge Miss Preeti Singh, Miss Rigalla and Miss Hena Fathima, Optometrists, Department of Neuro-Ophthalmology, All India Institute of Medical Sciences, New Delhi, India, for their valuable help in acquisition of OCTA images included in this study.

Author contributions (names must be given as initials)

BM drafted the first manuscript, and was involved in the conception and design of the work; the acquisition, analysis, and interpretation of data, prepared figures and revised the manuscript. AKP and MVPS conceptualised the work, and designed it, were involved in the acquisition, analysis, and interpretation of data, and revised the manuscript. RC, SPA, MKN, YPM, MS, AG, AKS, VVY, RB, SM, ADU, and KM were involed in the the acquisition, analysis, and interpretation of data, and revised the manuscript. All the authors have approved the submitted version and agreed both to be personally accountable for the author's own contributions and ensured that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, have been appropriately investigated, resolved, and the resolution documented in the literature.

Data availability statement (mandatory)

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials. Any further data required will be are available from the corresponding author, [AKP], upon request.

Competing Interests: None declared by any of the authors

Consent to Participate:

The authors confirm that informed consent was obtained from all subjects included in this exploratory study and can be provided on reasonable request to the corresponding author.

Funding: None

Declaration of Interest: None

References

1. Stroke Facts | cdc.gov. Published May 25, 2021. Accessed August 24, 2021. https://www.cdc.gov/stroke/facts.htm
2. Nakaizumi A, Puro DG. Vulnerability of the Retinal Microvasculature to Hypoxia: Role of Polyamine-Regulated KATP Channels. Invest Ophthalmol Vis Sci. 2011;52(13):9345–9352. doi:10.1167/iovs.11-8176
3. Wylęgała A, Teper S, Dobrowolski D, Wylęgała E. Optical coherence angiography: A review. Medicine (Baltimore). 2016;95(41):e4907. doi:10.1097/MD.0000000000004907
4. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Progress in Retinal and Eye Research. 2018;64:1–55. doi:10.1016/j.preteyeres.2017.11.003

5. Makita S, Hong Y, Yamanari M, Yatagai T, Yasuno Y. Optical coherence angiography. Opt Express, OE. 2006;14(17):7821–7840. doi:10.1364/OE.14.007821
6. Lindley RI, Wang JJ, Wong MC, et al. Retinal microvasculature in acute lacunar stroke: a cross-sectional study. The Lancet Neurology. 2009;8(7):628–634. doi:10.1016/S1474-4422(09)70131-0
7. Lahme L, Esser EL, Mihailovic N, et al. Evaluation of Ocular Perfusion in Alzheimer's Disease Using Optical Coherence Tomography Angiography. J Alzheimers Dis. 2018;66(4):1745–1752. doi:10.3233/JAD-180738
8. Lee CW, Cheng HC, Chang FC, Wang AG. Optical Coherence Tomography Angiography Evaluation of Retinal Microvasculature Before and After Carotid Angioplasty and Stenting. Sci Rep. 2019;9(1):14755. doi:10.1038/s41598-019-51382-8
9. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35–41. doi:10.1161/01.STR.24.1.35
10. Maberley D a. L, Hollands H, Chuo J, et al. The prevalence of low vision and blindness in Canada. Eye (Lond). 2006;20(3):341–346. doi:10.1038/sj.eye.6701879
11. Janssen PM, Visser NA, Dorhout Mees SM, Klijn CJM, Algra A, Rinkel GJE. Comparison of telephone and face-to-face assessment of the modified Rankin Scale. Cerebrovasc Dis. 2010;29(2):137–139. doi:10.1159/000262309
12. ImageJ. In: *Wikipedia*.; 2021. Accessed August 24, 2021. https://en.wikipedia.org/w/index.php?title=ImageJ&oldid=1037829363
13. Lee CW, Cheng HC, Chang FC, Wang AG. Optical Coherence Tomography Angiography Evaluation of Retinal Microvasculature Before and After Carotid Angioplasty and Stenting. Sci Rep. 2019;9:14755. doi:10.1038/s41598-019-51382-8
14. You QS, Chan JCH, Ng ALK, et al. Macular Vessel Density Measured With Optical Coherence Tomography Angiography and Its Associations in a Large Population-Based Study. Invest Ophthalmol Vis Sci. 2019;60(14):4830–4837. doi:10.1167/iovs.19-28137
15. Pujari A, Chawla R, Markan A, et al. Age-related changes in macular vessels and their perfusion densities on optical coherence tomography angiography. Indian J Ophthalmol. 2020;68(3):494–499. doi:10.4103/ijo.IJO_521_19
16. Zhang JF, Wiseman S, Valdés-Hernández MC, et al. The Application of Optical Coherence Tomography Angiography in Cerebral Small Vessel Disease, Ischemic Stroke, and Dementia: A Systematic Review. Frontiers in Neurology. 2020;11:1009. doi:10.3389/fneur.2020.01009
17. Kashani AH, Chen CL, Gahm JK, et al. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Prog Retin Eye Res. 2017;60:66–100. doi:10.1016/j.preteyeres.2017.07.002
18. Wang J, Jiang J, Zhang Y, Qian YW, Zhang JF, Wang ZL. Retinal and choroidal vascular changes in coronary heart disease: an optical coherence tomography angiography study. Biomed Opt Express. 2019;10(4):1532–1544. doi:10.1364/BOE.10.001532
19. Sayin N, Kara N, Uzun F, Akturk IF. A quantitative evaluation of the posterior segment of the eye using spectral-domain optical coherence tomography in carotid artery stenosis: a pilot study. Ophthalmic Surg Lasers Imaging Retina. 2015;46(2):180–185. doi:10.3928/23258160-20150213-20

20. Heßler H, Zimmermann H, Oberwahrenbrock T, et al. No Evidence for Retinal Damage Evolving from Reduced Retinal Blood Flow in Carotid Artery Disease. Biomed Res Int. 2015;2015:604028. doi:10.1155/2015/604028
21. Dagdelen K, Dirican E. The assessment of structural changes on optic nerve head and macula in primary open angle glaucoma and ocular hypertension. Int J Ophthalmol. 2018;11(10):1631–1637. doi:10.18240/ijo.2018.10.09
22. Liu G, Keyal K, Wang F. Interocular Symmetry of Vascular Density and Association with Central Macular Thickness of Healthy Adults by Optical Coherence Tomography Angiography. Sci Rep. 2017;7(1):16297. doi:10.1038/s41598-017-16675-w
23. Lareyre F, Nguyen E, Raffort J, et al. Changes in Ocular Subfoveal Choroidal Thickness After Carotid Endarterectomy Using Enhanced Depth Imaging Optical Coherence Tomography: A Pilot Study. Angiology. 2018;69(7):574–581. doi:10.1177/0003319717737223
24. Matsubara S, Moroi J, Suzuki A, et al. Analysis of cerebral perfusion and metabolism assessed with positron emission tomography before and after carotid artery stenting. Clinical article. J Neurosurg. 2009;111(1):28–36. doi:10.3171/2008.09.17663
25. Yun TJ, Sohn CH, Han MH, et al. Effect of carotid artery stenting on cerebral blood flow: evaluation of hemodynamic changes using arterial spin labeling. Neuroradiology. 2013;55(3):271–281. doi:10.1007/s00234-012-1104-y
26. Brouwer NJ, Marinkovic M, Bleeker JC, Luyten GPM, Jager MJ. Anterior Segment OCTA of Melanocytic Lesions of the Conjunctiva and Iris. Am J Ophthalmol. 2021;222:137–147. doi:10.1016/j.ajo.2020.09.009

Tables

Table 1 showing baseline characteristics of the cohort

Parameter	Cases Total N	Cases Mean ± SD or n(%) or Median (IQR)	Controls total N	Controls Mean ± SD or n(%) or Median (IQR)	P value	Total subjects N	Total Mean ± SD or n(%) or Median (IQR)
Age (in years)	23	53.69 ± 12.85	23	51.65 ± 12.14	0.58	46	52.67 ± 12.40
Gender	23		23			46	
Male		20(86.9)		15 (65.3)	0.09		35 (76.0)
Female		3(13.1)		8 (34.7)			11 (24.0)
Family History of stroke	23		23			46	
Positive		6(26.09)		4(17.39)			10 (21.7)
Negative		17(73.91)		19(82.61)			36 (78.3)
Weight(in kg)	23	63.5 ± 8.85	23	66.30 ± 10.39	0.33	46	64.91 ± 9.65
Height(in cm)	23	163 ± 5.59	23	165.26 ± 8.81	0.39	46	164.32 ± 7.35
BMI (in $kg/m^{2)}$	23	23.78 ± 3.48	23	24.25 ± 2.88	0.61	46	24.02 ± 3.17
Systolic Blood Pressure(in mm Hg)	23	143.95 ± 23.39	23	138.34 ±16.32	0.35	46	141.15 ± 20.15
Diastolic Blood Pressure (in mm Hg)	23	84.52 ± 10.08	23	77.34 ± 16.80	0.08	46	80.93 ± 9.76
Wake up stroke	23					23	
Yes		1(4.35)					1(4.35)
No		22(95.65)					22(95.65)

Vascular Area of stroke	23				23	
ACA		1(4.35)				1(4.35)
MCA		19(82.61)				19(82.61)
ACA MCA		3(13.04)				3(13.04)
Vessel Imaging Modality	23		23		23	
CTA		19(82.4)				19(82.4)
MRA		4(17.4)				4(17.4)
Doppler			23(100)		23	23(100)
Predominant side of stenosis	23				23	
Left only		9(39.13)				9(39.13)
Right only		8(34.78)				8(34.78)
Bilateral but more degree of stenosis on the left		4(17.39)				4(17.39)
Bilateral but more degree of stenosis on the right		2(8.70)				2(8.70)
Mean Stenosis of ICAs	23	76.76 ± 20.68			23	76.67 ± 20.57
Mean duration between stroke onset and OCTA examination in days	23	30.3 ± 5.67			23	30.3 ± 5.67
NIHSS	23				23	
Mean		8.48 ± 4.46				8.48 ± 4.46
Median		8 (5,12)				8 (5,12)
Intracranial Stenosis	23				23	
Yes		8(34.7)				8(34.7)
No		15(65.3)				15(65.3)
Hypertension	23		23		46	
Yes		16(69.6)	14(60.8)	0.53		30(65.2)
No		7(30.4)	9(39.2)			16 (34.8)
Diabetes	23		23		46	
Yes		8(34.8)	10(43.4)	0.54		18(39.1)
No		15(65.2)	13(56.6)			28(60.9)
Dyslipidaemia	23		23		46	

Yes		4(17.4)		5(22.8)	0.71	9(19.6)
No		19(82.6)		18(78.2)		37 (80.4)
Smoking	23		23		46	
Yes		7(30.4)		5(21.7)	0.08	12 (26.1)
No		11(47.8)		17(74)		28(60.8)
Former		5(21.8)		1(4.3)		6 (13.1)
Alcohol	23		23		46	
Yes		8(34.8)		4(17.3)	0.95	12(26.1)
No		14(60.8)		18(78.2)		32(69.6)
Former		1(4.35)		1(4.35)		2(4.3)
Tobacco	23		23		46	
Yes		6(26)		4(17.3)	0.55	10(21.7)
No		16(69.7)		19(82.7)		35(76.1)
Former		1(4.35)		0(0.0)		1(2.2)
Fundus	23		23		46	
Normal		20(86.9)		23(100)		43 (93.5)
HTN Grade 1		3(13.1)				3(6.5)
BCVA RE log MAR - Median	23	0.00 (0,0.18)	23	0.00 (0,0.18)	0.68	46	0.00 (0,0.18)
BCVA LE log MAR - Median	23	0.00 (0,0.18)	23	0.00 (0,0.18)	0.45	46	0.00 (0,0.18)
IOP by NCT Right eye (RE)	23	16.9 ± 1.8	23	16.2 ± 2.61	0.33	46	16.58 ± 2.25
IOP by NCT Left eye (LE)	23	17.3 ± 2.0	23	16.6 ± 2.0	0.25	46	17.04 ± 2.04

Table 2 showing the OCTA findings combined for the region in the scan, in comparison between cases and controls

	CASES		CONTROLS		P value
OCTA characteristics	N	Mean ± SD	N	Mean ± SD	
Total Superficial Vessel Density (SVD), in %	23	38.75 ± 9.55	23	41.47 ± 6.6	0.09
Total Superficial Perfusion Density (SPFD) in %	23	70.82 ± 16.09	23	75.35 ± 10.97	0.10
Deep Vessel density (DVD), mm/ m2	23	35.82 ± 9.56	23	41.77 ± 5.89	**0.0007**
RPCPD in %	23	42.29 ± 1.89	23	43.57 ± 1.59	**0.0007**

SVD – Superficial vessel density, SPFD - Superficial Perfusion Density, DVD – Deep Vessel Density, DVD – Deep Vessel Density, RPCPD – Radial Peripapillary Capillary Perfusion Density

Table 3 showing comparison between normal and abnormal OCTA findings to clinical outcomes (mRS at 3 months and change in mRS)

IPSILATERAL EYE								
			mRS at 3 months			Change in mRS		
Region Scanned		OCTA Findings Compared to normal range obtained from control data	Very Good Outcome mRS = 0-1	Poor Outcome mRS = 2-6	P Value	Improved	Static or deteriorated	P value
	Total Superficial Vessel Density (SVD), in mm/m2, N=23	Normal	4	8	**0.0361**	10	2	1.0
		Abnormal	9	2		9	2	
	Total = 23		13	10		19	4	
	Total Superficial Perfusion Density (SPFD) in % N= 23	Normal	4	6	0.22	8	2	1.0
		Abnormal	9	4		11	2	
	Total = 23		13	10		19	4	
	Deep Vessel density (DVD), N=20	Normal	9	6	0.61	13	3	1.0
		Abnormal	2	3		3	1	
	Total =20		11	9		16	1	
	RPC Perfusion density (RPCPD), N=23	Normal	6	5	1.0	8	1	0.63
		Abnormal	7	5		11	3	
	Total = 23		13	10		19	4	

SVD – Superficial vessel density, SPFD - Superficial Perfusion Density, DVD – Deep Vessel Density, DVD – Deep Vessel Density, RPCPD – Radial Peripapillary Capillary Perfusion Density

CONTRALATERAL EYE								
			mRS at 3 months			Change in mRS		
Region Scanned		OCTA Findings Compared to normal range obtained from control data	Very Good Outcome mRS = 0-1	Poor Outcome mRS = 2-6	P Value	Improved	Static or deteriorated	P value
	Total Superficial Vessel Density (SVD), in mm/m2, N=23	Normal	9	5	0.41	12	3	1.0
		Abnormal	4	5		7	1	
	Total = 23		13	10		19	4	
	Total Superficial Perfusion Density (SPFD) in % N= 23	Normal	10	6	0.65	13	3	1.0
		Abnormal	3	4		6	1	
	Total = 23		13	10		19	4	
	Deep Vessel density (DVD), N=20	Normal	11	5	0.61	13	3	0.55
		Abnormal	2	5		6	1	
	Total =20		13	10		19	4	
	RPC Perfusion density (RPCPD), N=23	Normal	4	2	0.66	5	1	1.0
		Abnormal	9	8		14	3	
	Total = 23		13	10		19	4	

SVD – Superficial vessel density, SPFD - Superficial Perfusion Density, DVD – Deep Vessel Density, DVD – Deep Vessel Density, RPCPD – Radial Peripapillary Capillary Perfusion Density

Table 4 Comparison of individual OCTA parameters of the Ipsilateral eye with NIHSS at the time of admission, mRS at discharge, mRS at 3 months of stroke onset and change in mRS

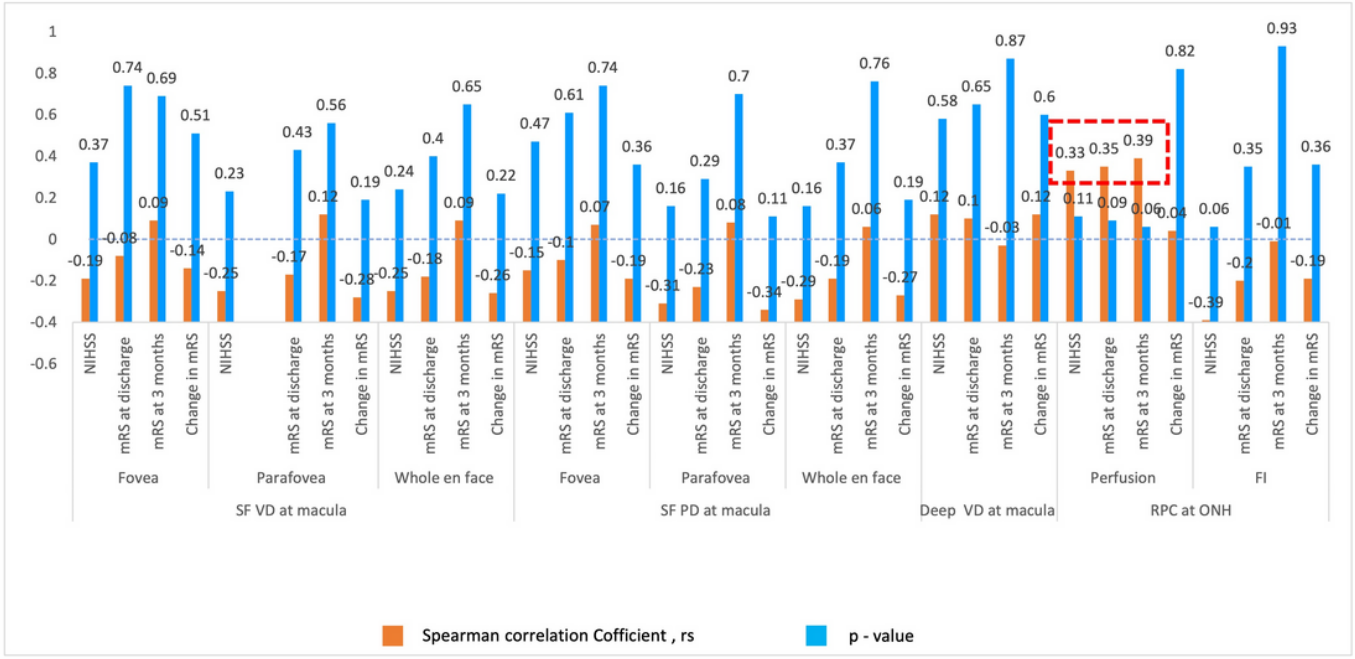
Sl.No.	OCTA findings	OCTA parameters	Baseline and outcomes compared	N	Spearman correlation coefficient (rs)	P value
1	Superficial VD at macula (mm/mm²)	Fovea	NIHSS	23	- 0.19	0.37
			mRS at discharge	23	-0.08	0.74
			mRS at 3 months	23	0.09	0.69
			Change in mRS	23	-0.14	0.51
		Parafovea	NIHSS	23	-0.25	0.23
			mRS at discharge	23	-0.17	0.43
			mRS at 3 months	23	0.12	0.56
			Change in mRS	23	-0.28	0.19
		Whole en face	NIHSS	23	-0.25	0.24
			mRS at discharge	23	-0.18	0.40
			mRS at 3 months	23	0.09	0.65
			Change in mRS	23	-0.26	0.22
2	Superficial PD at macula in %	Fovea	NIHSS	23	-0.15	0.47
			mRS at discharge	23	-0.10	0.61
			mRS at 3 months	23	0.07	0.74
			Change in mRS	23	-0.19	0.36
		Parafovea	NIHSS	23	-0.31	0.16
			mRS at discharge	23	-0.23	0.29
			mRS at 3 months	23	0.08	0.70
			Change in mRS	23	-0.34	0.11
		Whole en face	NIHSS	23	-0.29	0.16
			mRS at discharge	23	-0.19	0.37
			mRS at 3 months	23	0.06	0.76
			Change in mRS	23	-0.27	0.19
3	Deep VD at macula in %		NIHSS	20	0.12	0.58
			mRS at discharge	20	0.10	0.65
			mRS at 3 months	20	-0.03	0.87
			Change in mRS	20	0.12	0.60
4	RPC at ONH	RPCPD in %	NIHSS	23	**0.33**	**0.11**
			mRS at discharge	23	**0.35**	**0.09**

	mRS at 3 months	23	**0.39**	**0.06**
	Change in mRS	23	0.04	0.82
FI	NIHSS	23	-0.39	0.06
	mRS at discharge	23	-0.20	0.35
	mRS at 3 months	23	-0.01	0.93
	Change in mRS	23	-0.19	0.36

VD – Vessel Density, PD – Perfusion density , RPC – Radial Peripapillary Capillary, RPCPD - Radial Peripapillary Capillary perfusion density, ONH – Optic Nerve Head, FI – Flux Index, mRS -modified Rankin score , NIHSS – National Institute of Stroke Severity Score, OCTA – Optical Coherence Tomography Angiography

Figures

Figure 1 showing distribution of spearman coefficient and p- value of the Comparison of OCTA parameters ipsilateral eye with NIHSS at the time of admission, mRS at discharge, mRS at 3 months of stroke onset and change in mRS.



VD – Vessel Density, PD – Perfusion density , RPC – Radial Peripapillary Capillary, ONH – Optic Nerve Head, FI – Flux Index, mRS -modified Rankin score , NIHSS – National Institute of Stroke Severity Score, OCTA – Optical Coherence Tomography Angiography

Figure 1

Showing comparison between OCTA findings of the ipsilateral eye and various outcome measures

Figure 1 showing distribution of spearman coefficient and p- value of the Comparison of OCTA parameters of the ipsilateral eye with NIHSS at the time of admission, mRS at discharge, mRS at 3 months of stroke onset and change in mRS. [x-axis denotes the outcome measures(mentioned vertically) compared with the various OCTA

findings (mentioned horizontally) , y axis denoted the spearman corelation coefficient, rs (in orange colour) and p value (in blue colour)].

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1RepresentativeImageCase.jpg
- FigureS2RepresentativeImageControl.jpg
- FigureS3.jpg
- FigureS4OCTAfindingsCLeye.jpg
- SupplementaryAppendixOCTAstroke.docx
- TableS1OCAstroke.docx
- TableS2OCTAstroke.docx
- TableS3OCTAStroke.docx