Retinal microvasculature and early cerebral hemodynamics in patients with internal carotid artery stenosis

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Research Article

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Abstract

Purpose: To investigate the relationship between retinal microvasculature and cerebral hemodynamics in patients with internal carotid artery (ICA) stenosis.

Methods: Patients with unilateral moderate or severe ICA stenosis(≥50%) from West China hospital, Sichuan university were enrolled in the current study. The retinal microvasculature was evaluated with the swept-source optical coherence tomography angiography (SS-OCTA). The cerebral blood flow perfusion on bilateral MCA territories measured at the basal ganglia level was assessed by brain CTP. CTP data were postprocessed to generate maps of different perfusion parameters including cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), mean transit time (MTT) and permeability surface(PS). Relative perfusion parameters (rPS, rCBF, etc.) were calculated as the ratio of the value in the contralateral side to that in the ipsilateral side.

Results: In the final analysis, 31 patients were included, of whom 11 patients had a moderate ICA stenosis and 20 with a severe ICA stenosis. A total of 55 eyes were analyzed in the study, 27 eyes from the ipsilateral side (ie, side with stenosis) and 28 eyes from the contralateral side. In the patients with ICA stenosis, there was a strong correlation between the retinal microvascular perfusion of superficial vascular complex (SVC) with rCBV(β=0.239, p=0.03), rCBF(β=0.472, p=0.02) and rPS(β=0.653, p<0.001) after adjustment for age, sex and vascular risk factors. Similar correlations were also found between microvasculture in superficial vascular plexus (SVP) and cerebral perfusion changes. There were no any significant associations of microvascular perfusion in both deep vascular complex(DVC) and deep capillary plexus(DVP) with CTP parameters (all p>0.05).

Conclusions: Assessing retinal perfusion changes in superficial vascular layer(SVC and SVP)with the SS-OCTA as a proxy for early brain hemodynamic compromise could be a potentially valuable tool for early identification subgroups with a high risk of stroke in patients with ICA stenosis.

Introduction

Internal carotid artery(ICA) stenosis or occlusion is associated with a transient ischemic attack (TIA) and ischemic stroke, and the risk increases with increasing severity of the stenosis[1,2]. In addition to the severity of stenosis, hemodynamic compromise in the brain such as cerebral hypoperfusion may further increase its risk[3]. Carotid endarterectomy(CEA) and carotid artery stenting(CAS) have been suggested to reduce future strokes in patients with severe stenosis or occlusion, and also in patients with ≥ 50% symptomatic stenosis[4,5]. However, even in patients with severe stenosis, the 5-year risk of ipsilateral stroke was decreased by just 16%[6], indicating that a subgroup of individuals possibly with asymptomatic carotid stenosis, who have hemodynamic compromise, might benefit from CEA and CAS. Therefore, identifying such high-risk of subgroups reliably is of critical importance in clinical practice.

Recent reports have shown that brain CT perfusion (CTP) is a fast and reliable tool for evaluating cerebral perfusion[7] in patients with acute ischemic stroke and ICA stenosis; importantly, the CT perfusion measurements of cerebral blood flow (CBF) were accurate and stable when compared to xenon CT and $H_2{}^{15}O$ PET[8,9]. In addition, mean transit time (MTT) is the most sensitive and reproducible CT perfusion parameter to detect brain hemodynamic changes in patients with ICA stenosis[10,11]. Although the CTP is a useful imaging tool, it is time-consuming, costly, and has some contraindications (some patients are unable to tolerate CTP because of their allergic to contrast agent or renal dysfunction). Therefore, simpler, inexpensive, reproducible tools for assessing cerebral hemodynamics in patients with ICA stenosis would offer the prospect of identifying individuals with a high risk of stroke and may play a role in personalized and tailored treatment.

The retina shares embryologic origin and microvascular characteristics with the brain and is widely regarded as part of the central nervous system[12]. Moreover, the ophthalmic artery, which supplies blood to the retina, is an important branch of the internal carotid artery; thus, structural changes in the internal carotid artery may affect the vasculature and structure of the retina. Notably, retinal thickness and microvasculature offer a unique route to assess cerebral microstructure and microvasculature changes. Several studies [13–16] suggested that ocular manifestations are related to the changes of carotid artery including the severity of carotid stenosis. However, whether retinal microvasculature abnormalities can reflect the cerebral hemodynamic changes in patients with ICA stenosis remains unknown. Swept-source optical coherence tomography angiography (SS-OCTA) is an in vivo imaging tool that allows noninvasive, high-resolution examination of the retinal microvasculature. This imaging tool has a longer wavelength and a faster scan speed which enables a more accurate three-dimensional image of the retinal microvasculature [17]. Automated segmentation techniques make a quantitative assessment of retinal microvasculature a viable proposition. This offers the prospect of retinal imaging contributing to assessing cerebral hemodynamic changes in patients with ICA stenosis.

Therefore, we aimed to assess the relationship between retinal microvasculature, and cerebral perfusion parameters assessed on CTP in patients with ICA stenosis to understand how accessible and affordable retinal microvascular imaging may contribute as a potential tool for hemodynamic changes in the brain.

Methods

Participants

Patients with unilateral symptomatic or asymptomatic carotid stenosis admitted to the department of neurology, West China Hospital, Sichuan university were recruited for our study since 2020 December 1st. The study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University (2020[922]), and followed the principles of the Declaration of Helsinki. All the participants signed informed consent. The inclusion criteria of our participants were as follows:(1) age ≥ 18 years;(2) patients with unilateral internal carotid stenosis≥ 50% or more as confirmed on CT angiography(CTA) or digital subtraction angiography(DSA);(3) the cerebral perfusion status in the ipsilesional middle cerebral artery(MCA) territory normal, i.e. comparable to the

contralateral side, defined as a relative difference in cerebral blood flow (CBF) ≤ 30% between bilateral MCA territories on CT perfusion (CTP) maps;(4) patients who completed CTP and also could cooperate with SS-OCTA imaging.

In the present study,56 patients were enrolled from 1st December,2020 to 30th November,2021. Patients were excluded as follows:(1) non-atherosclerotic intracranial stenosis (e.g. Moyamoya disease, vasculitis, or dissection); (2) previous known or evidence of arteriovenous malformation or aneurysm; (3) poor SS-OCTA images with signal quality less than 7[18]; (4)with other neurological diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis; (5)with ophthalmic abnormalities that could potentially impact the structure and microvasculature of the retina such as diabetic retinopathy, pre-existing glaucoma, cataract, age-related macular degeneration, optic neuritis, and significant myopia; or (6)previous interventional or surgical procedures in ipsilesional extra- or intracranial arteries.

Data collection

Clinical characteristics

Demographic (age and sex), vascular risk factors (hypertension, diabetes, hyperlipidemia, coronary artery disease, smoking, previous TIA, previous stroke and alcohol consumption information) were collected from the medical records.

Retinal imaging with swept-source optical coherence tomography angiography (SS-OCTA)

With a central wavelength of 1050 nm and a scan rate of 200,000 A-scan per second, the SS-OCTA which contained a swept-source laser was used to image the retina of all participants. The tool was set with an eye-tracking function based on an integrated confocal scanning laser ophthalmoscope to remove eye-motion artifacts. The lateral resolution, axial resolution, and scan depth were 13 μm, 5 μm, and 3mm respectively.

OCTA fundus images were obtained with a raster scan protocol of 512 horizontal B-scans that covered an area of 6 mm^2 centered on the fovea. The proposed OCTA nomenclature segmentation was used in our study. En face angiograms of the superficial vascular complex (SVC), deep vascular complex (DVC), superficial vascular plexus (SVP), intermediate capillary plexus (ICP), and deep capillary plexus (DCP) were generated by automatic segmentation to assess the retinal microvascular perfusion. Segmentation of the SVC and DVC was defined as the inner two-thirds and outer one-third interface of the ganglion cell layer and inner plexiform layer (GCL + IPL) as shown in Fig. 1. The SVP was defined as the microvasculature between the base of the retinal nerve fiber layer (RNFL) to the junction between the inner plexiform layer (IPL) and inner nuclear layer (INL); ICP was defined as the microvasculature between IPL/INL junction to the junction between INL and outer plexiform layer (OPL); DCP was defined as the microvasculature between the INL/OPL junction to 25μm below the OPL as shown in Fig. 1.Microvascular perfusion was used to assess the microvasculature of the macular plexuses and was defined as the total length of perfused microvasculature per unit area in square millimeters (mm_2) in the annulus region of measurement (6 × 6 mm^2 around the fovea).

Computed tomography perfusion (CTP) imaging protocol and postprocessing

All patients were examined by CTP to evaluate the cerebral blood flow perfusion of patients with carotid artery stenosis. CTP imaging was performed on a 64-slice CT scanner (Discovery CT750 HD; GE Medical Systems, Waukesha, Wisconsin) or a 128-row dual-source CT scanner (Siemens SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) depending on device availability. CT scanning was initiated 5 s (GE) or 5 s (Siemens) after a contrast agent bolus(350 mg/mL Omnipaque followed by a saline flush of 45 mL at 5 mL/s), as follows: Jog mode, 80 kVp/150 mAs (GE) and 80kVp/200mAs (Siemens); 26 cycles for 42 s (GE) and 30 cycles for 45 s (Siemens); and 312 slices (GE)and 128 slices (Siemens). Brain standard reconstruction was performed. The gantry angle was parallel to and above the orbital roof to avoid radiation exposure to the lens.

CTP postprocessing

CTP data were transferred to a workstation (IntelliSpace Portal system, Philips Healthcare) to generate perfusion parameter maps of cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), mean transit time (MTT) and permeability surface(PS). The PS was calculated based on Patlak model. Regions of interest (ROIs) were drawn on CTP source images and transferred to corresponding parametric maps. The source images were average images calculated from all phases that could offer accurate anatomical references. Absolute values of CBF, CBV, TTP, MTT and PS in bilateral MCA territories were measured at the basal ganglia level, by drawing symmetrical regions of interest in the two hemispheres on perfusion maps. Any region of old or new infarct was excluded from such measurement. Relative perfusion parameters (rPS, rCBF, etc.) were calculated as the ratio of the value on the contralateral side to that on the ipsilateral side for each ROI.

Statistical analysis

Continuous variables with normal distribution expressed as mean ± standard deviation (SD), while skewed distribution was as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages. Multivariable linear regression models were used to investigate the association between SS-OCTA parameters and perfusion parameters while adjusting for age, gender, and vascular risk factors. All statistical analyses were conducted using the statistical software R version 3.4.1(http://www.R-project.org). The difference was considered statistically significant if the P-value was < 0.05.

Availability of supporting data

The data that support the results of this study are available from the corresponding author upon reasonable request.

Results

Clinical and imaging characteristics

During the study period, 56 patients with unilateral ICA stenosis were enrolled, of whom 14 patients were excluded due to poor quality of CTP scans, 9 patients were excluded due to the relative difference of CBF between bilateral MCA territories≥30%, and 2 patients were excluded due to poor quality of OCTA images. Thus, 31 patients were analyzed in the current study. The mean age was 64.8 ± 10.7 years, and 87.1% were male. Overall, there were 11 (35.5%) patients with moderate ICA stenosis and 20 (64.5%) with severe ICA stenosis. A total of 55 eyes were included in the study, 27 eyes from the ipsilateral side (ie, the side with stenosis) and 28 eyes from the contralateral side. The retinal microvascular parameters were comparable between ipsilateral and contralateral side(Fig. 2, all $p > 0.05$).Detailed characteristics of the patients are presented in Table 1.

Table 1
Baseline characteristics of the 31 ICA stenosis patients

Characteristics	Overall(n = 31)
Age, (mean (SD))	64.77 (10.74)
Male, n(%)	27 (87.1)
Vascular risk factors	
Hypertension, n(%)	19 (61.3)
Diabetes mellitus, n(%)	7 (22.6)
Hyperlipidemia, n(%)	5 (16.1)
Coronary heart disease, n(%)	3 (9.7)
Previous TIA, n(%)	4 (12.9)
Previous stroke, n(%)	9 (29.0)
Smoking, n(%)	21 (67.7)
Drinking, n(%)	16 (51.6)
CT perfusion parameters	
CBV, (mean (SD))	4.23 (1.02)
rCBV, (mean (SD))	1.00 (0.11)
CBF, (mean (SD))	45.53 (15.65)
rCBF, (mean (SD))	1.10 (0.18)
MTT, (mean (SD))	6.77 (1.58)
rMTT,(mean (SD))	0.93 (0.18)
TTP, (mean (SD))	20.75 (2.69)
rTTP, (mean (SD))	0.97 (0.05)
PS, (mean (SD))	13.27 (4.65)
rPS,(mean (SD))	1.02 (0.16)

PS is expressed in mL·100 g-1·min-1; CBF in mL·min-1·100 g-1; CBV in mL·100 g-1; and MTT and TTP are expressed in seconds. r, relative; CBF ,cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; TTP, time to peak;and PS, permeability surface.

Brain and retinal perfusion parameters between moderate and severe ICA stenosis group

Concerning brain perfusion parameters, patients with severe ICA stenosis had significantly higher MTT(mean,7.27 vs.5.86,P = 0.01) and lower CBF(mean,41.45 vs.52.96,P = 0.048) values in the ipsilateral side compared to patients with moderate ICA stenosis(Fig. 3), and the other brain perfusion parameters were not significantly different among the two groups(Fig. 3). We did not find any significant correlations between the severity of ICA stenosis and SS-OCTA parameters of the eyes on the ipsilateral side (Fig. 4-A) and contralateral side (Fig. 4-B; all $p > 0.05$).

Correlation between SS-OCTA parameters and brain perfusion

After adjustment for confounders, the perfusion of SVC showed a significant correlation with rCBV($\beta = 0.239$, $p = 0.03$), rCBF($\beta = 0.472$, $p = 0.02$) and rPS($\beta = 0.653$, $p < 0.001$) in patients with ICA stenosis. Likewise, the perfusion of SVP was also found to be significantly related to rCBF($\beta = 0.731$, $p = 0.01$) ,rMTT($\beta=-0.615$, $p = 0.006$)and rPS($\beta = 0.784$, $p = 0.002$).In addition, the perfusion of ICP showed a significant association with rPS($\beta = 0.805$, $p = 0.02$) in multivariate linear regression analysis. DVC and DCP did not show any significant correlation ($P > 0.05$) with CTP parameters as shown in Table 2.

Table 2
Correlation between perfusion of SVC, DVC and brain perfusion in multivariate linear regression analysis*

	SVC			DVC			SVP			ICP			DCP	
	β	95%CI	P	β	95%CI	P	β	95%CI	P	β	95%CI	P	β	95%CI
rCBV	0.239	(0.024, 0.453)	0.03	0.070	(-0.146, 0.285)	0.52	0.228	(-0.094, 0.550)	0.16	0.224	(-0.215,0.663)	0.31	0.191	(-0.232,0.
rCBF	0.472	(0.080, 0.865)	0.02	0.134	(-0.265, 0.532)	0.50	0.731	(0.166, 1.296)	0.01	0.651	(-0.145,1.450)	0.11	0.637	(-0.125,1.
rMTT	-0.292	(-0.602, 0.018)	0.06	-0.017	(-0.325, 0.291)	0.91	-0.615	(-1.043, -0.187)	0.006	-0.486	(-1.101,0.128)	0.12	-0.460	(-1.050,0.
rTTP	-0.016	(-0.120,0.089)	0.76	-0.033	(-0.132, 0.066)	0.51	-0.110	(-0.258, 0.038)	0.14	-0.078	(-0.282,0.125)	0.44	-0.099	(-0.299,0.
rPS	0.653	(0.336, 0.969)	< 0.001	0.079	(-0.280, 0.437)	0.66	0.784	(0.295, 1.272)	0.003	0.805	(0.113,1.498)	0.02	-0.010	(-0.717,0.

*adjusting for age, sex, vascular risk factors(hypertension, diabetes, hyperlipidemia, coronary artery disease, smoking, previous TIA, previous stroke and alcoh consumption information) and degree of stenosis; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; rTT time to peak; and rPS, relative permeability surface; SVC, superficial vascular complex; DVC, deep vascular complex; SVP, superficial vascular plexus; ICP, inter capillary plexus; DCP, deep capillary plexus.

Discussion

Carotid stenosis affects the structure and microvascular of the retina. However, whether microvascular changes of the retina reflect brain hemodynamic changes in patients with carotid stenosis remains unknown. Our study shows a novel association of microvascular changes in SVC and SVP with brain perfusion among patients with unilateral carotid stenosis of more than 50%. We suggest that the retinal microvasculature may reflect early hemodynamic changes caused by carotid stenosis. Therefore, OCTA may be used as a potential noninvasive quantitative screening tool for the assessment of early cerebral hemodynamic compromise, which may have a prospect for identifying subgroups with a high risk of stroke in patients with moderate and severe ICA stenosis.

ICA stenosis causes retinal hemodynamics[19]. However, whether microvascular changes in the retina could be indicator of early changes in brain hemodynamics among patients with ICA stenosis remains unclear. To the best knowledge, our current report is the first to show a significant correlation between perfusion changes in the retina and brain in ICA stenosis patients. Given the homology between the retinal and cerebral microvasculature, concomitant cerebral hemodynamic changes in ICA stenosis might extend to the retina, causing changes in the microvascular network. Similarly, reports using different OCTA machines showed patients with ICA stenosis have significantly decreased superficial vasculature densities compared with controls[20,21]. It suggested the superficial vessels of the retina are sensitive to ischemic injury[21], which are the main blood flow channel and responsible for the arterial circulation of the retina[22,23,24]. That may help to explain why we only found microvascular changes in superficial vascular layer(SVC and SVP) significantly related to brain hemodynamic changes.

Previous reports using different imaging modalities have shown that the superficial vessels of the retina are significantly altered in patients with cerebrovascular diseases[25–27] and may be a potential risk indicator of ischemic stroke[28]. Since ICA stenosis causes cerebral hypoperfusion[29], accounting for 30%-50% ischemic strokes in Asia[30], it is plausible that changes in the superficial vessels may give clues to the occurrence of ischemic stroke.

In our study, patients with severe ICA stenosis showed a higher MTT and lower CBF in the ipsilateral side compared to moderate ICA stenosis(Fig. 3). It is consistent with others reports that the severity of ICA stenosis is related to cerebral hypoperfusion, which may have a higher risk of ischemic stroke or recurrence[31,32]. However, our data did not show any significant differences between severity of ICA stenosis and retinal microvascular changes(Fig. 4). It may suggest brain hemodynamics occurs earlier than retinal changes in patients with moderate and severe ICA stenosis. Reports on retinal microvasculature changes in patients with carotid artery stenosis compared with controls have been inconsistent[33–35]. Little research has investigated the retinal perfusion changes in different severity of ICA stenosis, especially between moderate and severe ICA stenosis. Longitudinal studies with larger sample sizes are needed to investigate this.

In addition, we did not find any significant differences in retinal microvascular between ipsilateral and contralateral eyes. During stenosis, ipsilateral circulation may rely on contralateral circulation for support (a compensatory mechanism), which may explain the insignificant difference between the contralateral and ipsilateral retinal microvasculature. Given the small sample size of the subjects in the study, future studies with larger sample sizes are needed.

We are aware that our study labors under several limitations. Since our study was a cross-sectional study, it is also not certain when the retinal perfusion change occurs, whether the retinal perfusion changes in patients with ICA stenosis could be an indicator for predicting a broad spectrum of neurological disorders such as ischemic stroke, transient ischemic attack, and vascular dementia. Future studies with follow-up data were needed to explore this. In addition, bias might be caused by the small number of patients in the moderate stenosis group. The future study will expand the enrollment group, especially those in the mild and moderate stenosis group.

Conclusions

In conclusion, our study provides the first evidence that the retinal microvasculature is correlated with brain hemodynamics in patients with moderate and severe ICA stenosis. Despite the preliminary nature of the study, our results pave the stone for future extensive investigations on whether the retinal microvascular changes assessed by SS-OCTA could be a potential biomarker to identify early brain hemodynamic compromise and predict future stroke risks in ICA stenosis.

Declarations

Ethics approval and consent to participate

The study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University (2020[922]), and followed the principles of the Declaration of Helsinki. All the participants signed informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available due to patient privacy and ownership issues but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Junfeng Liu drafted and analyzed the manuscript. Jincheng Wan and William Robert Kwapong collected the data. Wendan Tao and Chen Ye and Ming Liu revised the paper. Bo Wu supervised the research.

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Figures

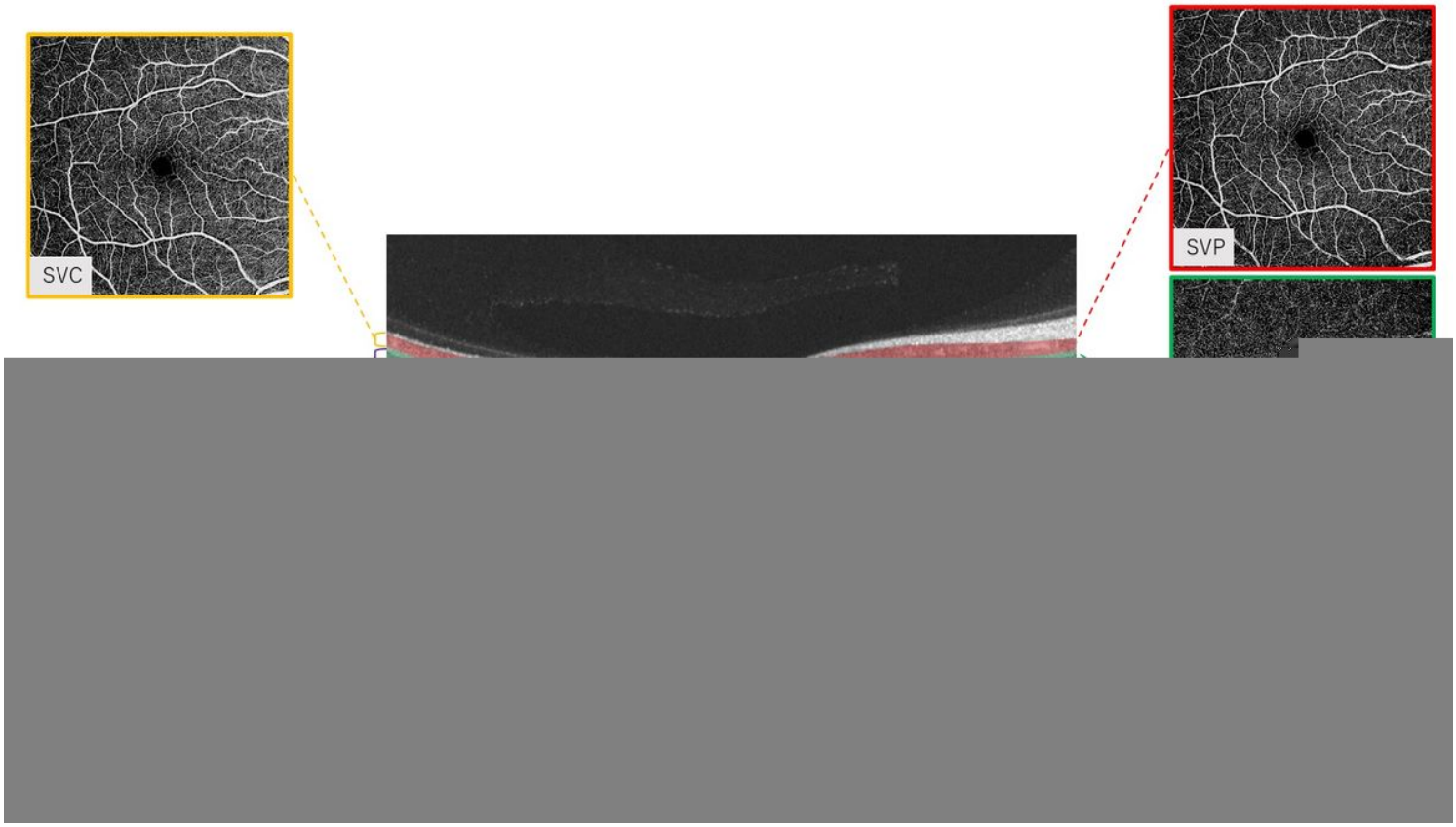


Figure 1

Segmentation of the two macular complexes in the fovea.

SVC: superficial vascular complex, DVC: deep vascular complex, SVP: superficial vascular plexus, ICP: intermediate capillary plexus; DCP: deep capillary plexus

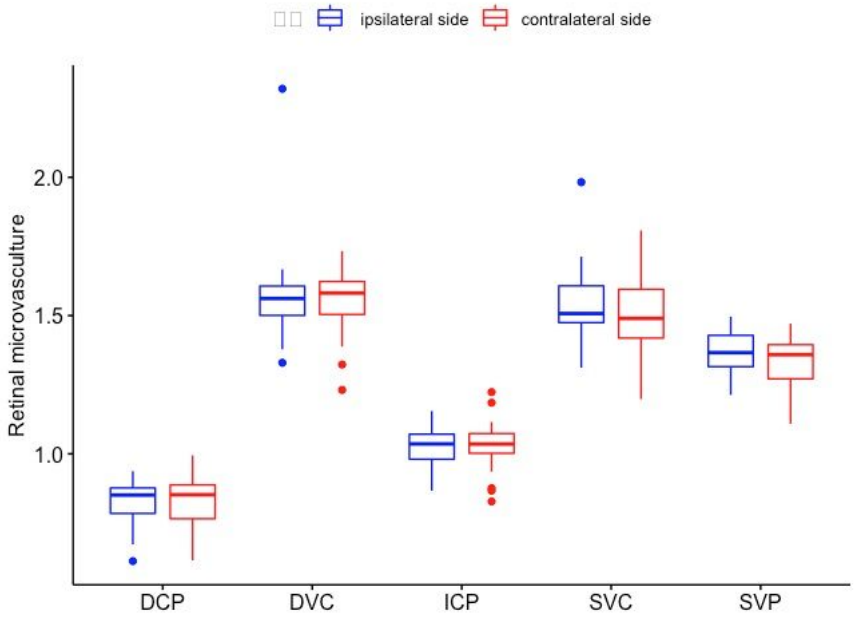


Figure 2

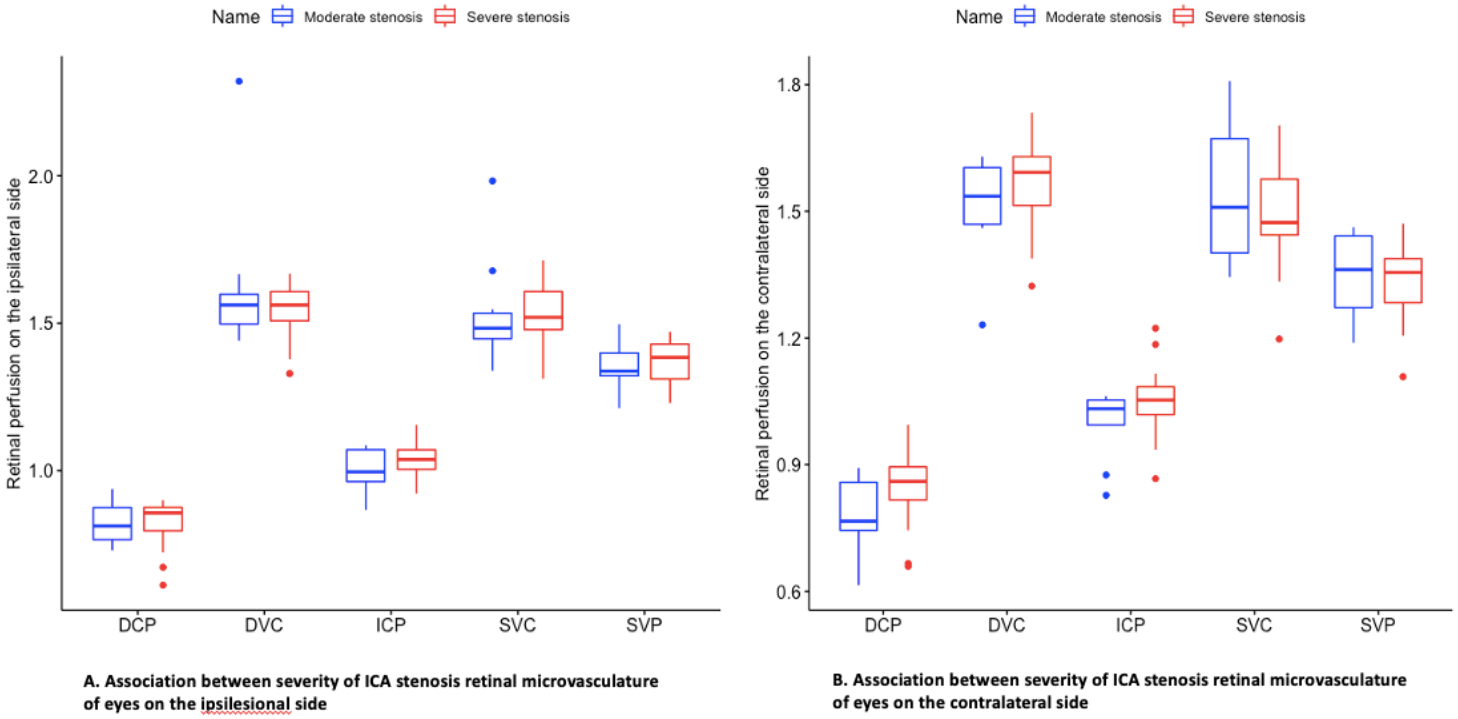
The differences of retinal parameters of eyes on ipsilateral and contralateral side

SVC, superficial vascular complex; DVC, deep vascular complex; SVP, superficial vascular plexus; ICP, intermediate capillary plexus; DCP, deep capillary plexus

Figure 3

The differences of CTP parameters between patients with moderate and severe internal carotid artery stenosis.

CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; TTP, time to peak; and PS, permeability surface



A. Association between severity of ICA stenosis retinal microvasculature of eyes on the ipsilesional side

B. Association between severity of ICA stenosis retinal microvasculature of eyes on the contralateral side

Figure 4

The association between the severity of internal carotid artery stenosis and retinal microvasculature.

SVC, superficial vascular complex; DVC, deep vascular complex; SVP, superficial vascular plexus; ICP, intermediate capillary plexus; DCP, deep capillary plexus; ICA, internal carotid artery