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Research article

# Associations between the retinal/choroidal microvasculature and carotid plaque in patients with CAD: An OCTA study

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ABSTRACT

*Background:* To investigate the associations between retinal/choroidal microvasculature and carotid plaque in patients with CAD assessed by optical coherence tomography angiography (OCTA).

*Methods:* This study included 127 CAD patients with and 79 without carotid plaque. Each patient had both OCTA taken and digitized to determine retinal/choroidal thickness, vessel density and flow area and carotid ultrasound for carotid plaque size and stability measurement. The superficial capillary plexus (SCP), deep capillary plexus (DCP), out retina and choriocapillaris vessel density, out retina and choriocapillaris flow area, and full retina thickness were analyzed in the fovea centered 6 × 6 mm area. The association between OCTA measurements and carotid plaque characteristics in patients with CAD were evaluated.

*Results:* The duration of hypertension and diabetes mellitus (DM) was significantly longer in CAD patients with carotid plaque than that without ($p < 0.001$). The mean values for vessel density SCP and DCP (except fovea zone), and choriocapillaris nasal zone were significantly lower in plaque group ($p < 0.05$). Negative correlations between the carotid plaque width and vessel density SCP and DCP (except fovea zone) ($p < 0.05$) were also found in this study.

*Conclusions:* In patients with CAD, carotid plaque, a risk factor and marker of atherosclerosis and stenosis, is significantly and independently associated with retinal and choroidal microvascular changes by OCTA.

## 1. Introduction

Coronary artery disease (CAD), a major part of ischemic heart disease, has become the top cause of morbidity and mortality worldwide [1]. Within the etiological framework of CAD, stenosis and atherosclerosis are firmly established as the chief culprit for causing the disease progression and clinical events [2]. Furthermore, the size of atherosclerotic plaque and accompanying luminal narrowing have long been the key to research on the role in ischemic cardiovascular disease including CAD [3]. It is widely considered that characteristic of carotid plaques is closely associated with the occurrence of CAD because carotid plaques have similar pathologic and physiologic bases as coronary plaques [4]. Previous Multi-Ethnic Study of Atherosclerosis (MESA) reports also demonstrated that

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presence and extent of carotid plaque were closely associated with cardiovascular risk [5]. Meanwhile, carotid plaque burden is also regarded as a surrogate of atherosclerosis and predictor of future atherosclerotic cardiovascular diseases [6]. Thus, measurement carotid plaque and atherosclerosis with ultrasonography may have a potential role in cardiovascular risk stratification, especially for the identification of individuals at higher risk of developing CAD, or other cardiovascular diseases (CVD).

Optical coherence tomography angiography (OCTA), a noninvasive and 3D angiography technique for retinal and choroidal vessels, has gained increasing importance as a fast and non-invasive method for analyzing fundus microvasculature in a wide variety of systemic diseases not only hypertension and diabetes but also neurological diseases [7], autoimmune disease [8], and CVD [9]. Currently, several studies revealed that CAD is an independent related factor of retinal microvascular disease assessed by OCTA in type 2 diabetes patients [10]. Our previous study also discovered that retinal and choroidal microvasculature had changed in CAD patients before they developed any clinical ocular symptoms by OCTA [11]. However, whether there is a direct correlation among fundus microvasculature change, carotid plaque present and CAD occurrence is still controversial.

The purpose of this study is to illustrate the association between carotid plaque size and stability, as assessed by carotid ultrasound, and the retinal/choroidal thickness, vessel density and flow area, as assessed by OCTA, in patients with CAD.

## 2. Methods and materials

This cross-sectional observational research was conducted in the Department of Cardiology, of Ninth People's Hospital, Shanghai Jiaotong University, School of Medicine and Department of Ophthalmology, of Huashan Hospital, Fudan University. The study was approved by the Ethics Committee of our Institution and written informed consent was obtained before screening for all participants.

### 2.1. Subject

The studied group was randomly selected from a consecutive sample of patients in Department of Cardiology, of Ninth People's Hospital, Shanghai Jiaotong University, School of Medicine for cardiovascular disease standard treatments (authors' institution). Inclusion criteria were age from 18 to 80 and definite diagnosis of CAD. Patients underwent coronary angiography, and a diagnosis of CAD was confirmed when coronary artery stenosis exceeds 50%. Two professional cardiologists independently diagnose all patients, with Dr. Jin Wang making the final decision on inclusion based on a synthesis of these assessments. Exclusion criteria were systemic diseases such as renal failure or replacement, heart failure, stroke or other heart diseases that may affect the final result. The inclusion criteria for healthy subjects (control group) involve age and gender-matched individuals without any cardiac conditions that could potentially influence the experiment's outcome, and without diabetes or hypertension. Patients and healthy subjects underwent detailed basic demographic and clinical data collection. Patients were excluded if they had history of retinal and choroidal surgery or treatment, macular pathology such as age-related macular degeneration (AMD), vitreomacular traction (VMT) and epiretinal membrane (ERM). Moderate to high myopia/hyperopia ($\geq \pm 3$ diopters or axial length$\geq$26 mm), severe cataract or glaucoma, dioptric media opacity that may obscure OCTA imaging were also excluded. To obtain real-time data on plaque impact on OCTA, all CAD patients underwent OCTA examination within a week following carotid Ultrasonography. Patients who had received treatments such as thrombolysis or surgery before the OCTA examination were excluded. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Huashan Hospital, Fudan University. Informed consent was obtained from all subjects.

### 2.2. Carotid ultrasonography

Carotid artery examination was performed by the same experienced ultrasonics technician. High resolution ultrasound (Aplio 500, Toshiba, Tokyo, Japan) with high-frequency (7–12 MHz) linear transducer was used to acquire transverse and longitudinal ultrasound images of right/left common and internal carotid arteries. The presence of carotid plaque was defined as protruding lumen, focal carotid wall thickening$>$1.5 mm or local thickening 0.5 mm or $>$50% than surrounding intima-media thickness (IMT). An experienced cardiologist assessed carotid plaque size by obtaining degree of luminal stenosis and maximum plaque thickness. The stability of carotid plaque assessed and defined as stable plaque (hard or medium, echogenic and/or calcific) and unstable plaque (soft or mixed, hypoechoic, echogenic without calcification and/or mix). IMT was not studied in this analysis because several MESA reports demonstrated that carotid plaque is superior to IMT for predicting CVD risk [4,12].

### 2.3. Optical coherence tomography angiography (OCTA) imaging

RTVue XR3 Avanti (Optovue, Fremont, CA, USA) device and Avanti System (version 2017.1.0.155) with Optovue AngioVue software was used for OCT and OCTA examination. A 6 mm $\times$ 6 mm high Angio macular scan centered on the fovea was acquired. Each OCTA en face image contains 304 $\times$ 304 pixels created from the intersection of the 304 vertical and the 304 horizontal B-scans, with the scan quality **>** 6. Full retinal thickness in this study was defined as inner limiting membrane (ILM) to retinal pigment epithelium (RPE) layers. For vessel density, nine areas (overall, fovea, parafovea, superior-hemi, inferior-hemi, superior, inferior, nasal and temporal) were available for analysis in summary. AngioVue OCT software partitioned these zones automatically, then a same examiner may manually artificially adjusted the picture according to actual situation. In addition, AngioVue software automatically segments images into four layers: the superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina, and choriocapillaris, then fitted the designated margins and measured the vessel density. Flow area zone (FAZ) of out retina and choriocapillaris was defined

as a circle with a center fovea and an area of 3.142 $mm^2$. The schematic of the examined layers and zones has been presented in our previous research [11]. The data was reassessed by two blinded independent examiners. The OCTA measurement data of outer retina layer, an avascular layer, was excluded from results [13].

### 2.4. Statistical analysis

Descriptive statistics were demonstrated in mean ± SD of continuous variables and numbers and percentages for categorical variables to present the baseline characteristics of subjects. Independent *t*-test, Chi-squared test and Mann–Whitney *U* test were used to compare the categorical data. To explore the fundus factors significantly associated with carotid plaque, Logistic regression was conducted. Univariate analyses were separately performed for each variable and those with $p < 0.05$ were included in the multivariate analysis. SPSS (version 22.0) was used to perform all statistical analyses (IBM Corporation, Armonk, NY).

## 3. Results

### 3.1. Patient manifestations

We recruited 206 eligible CAD patients in this analysis, thereinto, 127 patients (61.7%) had carotid plaque. There was no statistical difference in terms of age (63.8 ± 8.4 vs. 69.0 ± 9.6 years, $p = 0.14$) and gender ratio (41/38 vs. 79/48, $p = 0.15$) between patients with and without carotid plaque. Baseline characteristics in this study are summarized in Table 1. Patients with carotid plaque had significant longer duration of hypertension (5.52 ± 4.15 vs. 11.07 ± 9.02, $p < 0.001$), and diabetes mellitus (DM) (1.10 ± 2.71 vs. 2.25 ± 5.83 years, $p < 0.001$), while proportion has no significant difference between two groups.

### 3.2. Changes in retinal thickness, vessel density, and flow area with carotid plaque

The fovea, parafovea, superior/inferior hemi, tempo/nasal, superior/inferior area retinal thickness for patients with carotid plaque were all thinner than that without carotid plaque, with no significant differences between two groups ($p > 0.05$) (Table 2).

When comparing patients with or without carotid plaque, the vessel density of all zones showed a significant decreasing trend when carotid plaque presented ($p < 0.05$) in SCP and DCP, except the fovea zone ($p = 0.486, 0.718$). For choroid cap, the differences of only the whole image, fovea and nasal zones were statistically significant. Moreover, similar to vessel density, flow area of choriocapillaris was smaller in carotid plaque patients, while difference had statistical significance (Table 3).

### 3.3. Carotid plaque characteristics and retinal/choroidal microvasculature

1. Carotid plaque stability

For 127 patients with carotid plaque, stable carotid plaque was detected in 66 (51.97%) participants, and unstable carotid plaque was detected in 61 (48.03%) participants. Comparison of retinal/choroidal vessel density and flow area between patients with stable and unstable plaque: unstable group had fewer vessel density and smaller flow area for all zones than stable group. However, there were no statistically significant differences ($p > 0.05$).

2. Carotid plaque size

In the non-parameter estimation analysis, the negative correlation between superficial/deep retina vessel density (except fovea),

**Table 1**
Clinical characteristics of patients with and without carotid plaque.

| Clinical variables | without (n = 79) | with (n = 127) | p value |
|---|---|---|---|
| Age (years) | 63.8 ± 8.4 | 69.0 ± 9.6 | 0.14 |
| Gender ratio (M/F) | 41/38 | 79/48 | 0.15 |
| History of hypertension (Y/N) | 70/9 | 108/19 | 0.47 |
| Duration of hypertension | 5.52 ± 4.15 | 11.07 ± 9.02 | <0.001*** |
| History of DM (Y/N) | 16/63 | 30/97 | 0.57 |
| Duration of DM | 1.10 ± 2.71 | 2.25 ± 5.83 | <0.001*** |
| LVEF (%) | 65.14 ± 1.14 | 62.45 ± 2.11 | 0.62 |

DM: diabetes mellitus.
Without: Without carotid plaque.
With: With carotid plaque.
M/F: Male/Female.
Y/N: Yes/No.
***: $p < 0.001$.
LVEF: Left Ventricular Ejection Fraction.

**Table 2**
Retinal thickness in patients with and without carotid plaque (μm, mean ± SD).

| Areas | without (n = 79) | with (n = 127) | p value |
|---|---|---|---|
| Fovea | 243.19 ± 21.43 | 241.23 ± 23.61 | 0.55 |
| Parafovea | 311.68 ± 18.05 | 307.91 ± 17.69 | 0.14 |
| - Superior Hemi | 312.70 ± 17.69 | 308.37 ± 17.50 | 0.10 |
| - Inferior Hemi | 311.94 ± 21.17 | 307.41 ± 18.84 | 0.11 |
| - Tempo | 303.20 ± 18.16 | 300.40 ± 16.95 | 0.26 |
| - Superior | 315.70 ± 19.52 | 310.95 ± 17.55 | 0.07 |
| - Nasal | 316.39 ± 19.28 | 312.25 ± 19.85 | 0.14 |
| - Inferior | 311.41 ± 17.79 | 307.94 ± 19.33 | 0.20 |

Areas: retinal areas.
Without: Without carotid plaque.
With: With carotid plaque.

**Table 3**
Vessel density and flow area in patients with and without carotid plaque (mean ± SD).

| Areas | without (n = 79) | with (n = 127) | p value |
|---|---|---|---|
| Vessel Density (%) | | | |
| **SCP** | | | |
| Whole Image | 48.86 ± 4.22 | 47.10 ± 5.01 | 0.010** |
| Fovea | 27.86 ± 7.04 | 27.16 ± 7.00 | 0.486 |
| Parafovea | 51.10 ± 5.51 | 49.04 ± 6.17 | 0.016* |
| - Superior-Hemi | 51.46 ± 5.58 | 49.45 ± 6.18 | 0.020* |
| - Inferior-Hemi | 50.74 ± 5.79 | 48.63 ± 6.55 | 0.019* |
| - Tempo | 51.72 ± 6.73 | 50.12 ± 6.07 | 0.080* |
| - Superior | 51.48 ± 5.50 | 49.25 ± 6.86 | 0.011* |
| - Nasal | 50.88 ± 6.02 | 48.77 ± 7.10 | 0.024* |
| - Inferior | 50.32 ± 6.05 | 48.00 ± 7.43 | 0.015* |
| **DCP** | | | |
| Whole Image | 54.33 ± 6.53 | 51.79 ± 7.49 | 0.014* |
| Fovea | 26.94 ± 6.91 | 26.57 ± 7.30 | 0.718 |
| Parafovea | 59.00 ± 6.18 | 56.15 ± 7.50 | 0.003** |
| - Superior-Hemi | 59.21 ± 6.64 | 56.47 ± 7.36 | 0.008** |
| - Inferior-Hemi | 58.79 ± 6.24 | 55.82 ± 8.19 | 0.004** |
| - Tempo | 58.54 ± 7.33 | 56.39 ± 7.12 | 0.039* |
| - Superior | 59.35 ± 7.12 | 56.58 ± 8.70 | 0.014* |
| - Nasal | 59.51 ± 6.10 | 56.06 ± 8.60 | 0.001** |
| - Inferior | 58.60 ± 6.67 | 55.57 ± 9.38 | 0.008** |
| **Outer Retina** | | | |
| Whole Image | 42.07 ± 3.23 | 42.46 ± 3.36 | 0.413 |
| Fovea | 43.89 ± 8.04 | 41.55 ± 7.31 | 0.033* |
| Parafovea | 40.62 ± 4.20 | 41.24 ± 4.60 | 0.328 |
| - Superior-Hemi | 40.22 ± 4.20 | 40.65 ± 4.70 | 0.505 |
| - Inferior-Hemi | 41.03 ± 4.64 | 41.83 ± 4.86 | 0.243 |
| - Tempo | 39.94 ± 5.15 | 40.27 ± 4.98 | 0.651 |
| - Superior | 40.82 ± 4.07 | 41.50 ± 4.98 | 0.313 |
| - Nasal | 40.14 ± 4.93 | 40.58 ± 5.70 | 0.577 |
| - Inferior | 41.58 ± 4.80 | 42.62 ± 5.24 | 0.155 |
| **Choriocapillaris** | | | |
| Whole Image | 65.52 ± 1.94 | 64.82 ± 2.10 | 0.017* |
| Fovea | 63.28 ± 5.94 | 60.84 ± 6.27 | 0.006** |
| Parafovea | 65.12 ± 2.18 | 64.53 ± 2.10 | 0.055 |
| - Superior-Hemi | 65.02 ± 2.43 | 64.42 ± 2.34 | 0.077 |
| - Inferior-Hemi | 65.19 ± 2.24 | 64.65 ± 2.22 | 0.092 |
| - Tempo | 65.45 ± 2.67 | 64.95 ± 2.45 | 0.167 |
| - Superior | 64.81 ± 2.81 | 64.36 ± 2.78 | 0.258 |
| - Nasal | 64.95 ± 2.07 | 64.15 ± 2.42 | 0.016* |
| - Inferior | 65.27 ± 2.50 | 64.67 ± 2.79 | 0.122 |
| Flow Area ($mm^2$) | | | |
| Outer Retina | 1.099 ± 0.177 | 1.080 ± 0.179 | 0.460 |
| Choriocapillaris | 1.861 ± 0.074 | 1.828 ± 0.077 | 0.002** |

Areas: retinal areas.
Without: Without carotid plaque.
With: With carotid plaque.
SCP: superficial capillary plexus.
DCP: deep capillary plexus.
*: $p < 0.05$; **: $p < 0.01$.

outer retina flow area and carotid width remained significant ($p < 0.05$). The results also showed negative correlation between carotid length and superficial/deep retina and choroid cap area but failed to show any statistical significance except parafovea and superior-hemi deep retina ($p = 0.04, 0.04$) (Table 4).

## 4. Discussion

This study demonstrated that decrease in retinal/choroidal microvasculatures (vessel density and flow area) was associated the presence of carotid plaque in CAD. CAD is the most common type of CVD, thus, the result may suggest correlations between macrovascular and microvascular complications. Based on our results, the alterations of retinal/choroidal microvasculatures in OCTA which were implicative of higher risk of coronary or carotid artery stenosis, could be regared as one of fast and non-invasive imaging biomarkers or diagnostic basis for the higher risk of macrovascular such as coronary artery or carotid artery lesions which should require timely and careful monitoring. Besides, systemic diseases such as long-term hypertension and diabetes are also important risk factors for carotid atherosclerosis and plaque formation, our research also supports this viewpoint [9].

Previous research found the pathophysiological processes implicated in the genesis of CVD start developing well in advance of diagnostic, since it has been shown that microcirculatory modifications are thoroughly associated with cardiovascular changes [14].

**Table 4**
Correlation between retinal/choroidal vessel density and flow area with plaque length and width.

| Plaque length (mm) and vessel density (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SCP rowhead | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | −0.144 | −0.079 | −0.149 | −0.158 | −0.139 | −0.164 | −0.128 | −0.129 | −0.096 |
| p | 0.11 | 0.38 | 0.09 | 0.08 | 0.12 | 0.07 | 0.15 | 0.15 | 0.29 |
| **DCP** rowhead | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | −0.162 | −0.089 | −0.185 | −0.183 | −0.159 | −0.161 | −0.164 | −0.127 | −0.163 |
| p | 0.07 | 0.32 | 0.04* | 0.04* | 0.07 | 0.07 | 0.07 | 0.16 | 0.07 |
| **Outer retina** rowhead | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | 0.038 | 0.056 | 0.065 | 0.039 | 0.083 | 0.096 | 0.021 | 0.088 | 0.031 |
| p | 0.67 | 0.53 | 0.47 | 0.67 | 0.35 | 0.28 | 0.82 | 0.33 | 0.73 |
| **Choriocapillaris** rowhead | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | −0.039 | −0.103 | −0.026 | −0.031 | −0.037 | −0.091 | −0.002 | −0.080 | −0.078 |
| p | 0.66 | 0.25 | 0.77 | 0.73 | 0.68 | 0.31 | 0.98 | 0.37 | 0.39 |
| Plaque length (mm) and flow area ($mm^2$) | | | | | | | | | |
| | Outer retina | | | | | Choriocapillaris | | | |
| r | 0.136 | | | | | −0.105 | | | |
| p | 0.13 | | | | | 0.24 | | | |
| Plaque width (mm) and vessel density (%) | | | | | | | | | |
| **SCP** | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | −0.294 | −0.095 | −0.260 | −0.253 | −0.271 | −0.263 | −0.197 | −0.257 | −0.243 |
| p | 0.001** | 0.29 | 0.003** | 0.004** | 0.002** | 0.003** | 0.03* | 0.004** | 0.006** |
| **DCP** rowhead | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | −0.312 | −0.068 | −0.296 | −0.264 | −0.281 | −0.214 | −0.254 | −0.265 | −0.281 |
| p | <0.001*** | 0.45 | 0.001** | 0.003** | 0.001** | 0.02* | 0.004** | 0.003** | 0.001** |
| **Outer retina** rowhead | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | 0.073 | 0.059 | 0.130 | 0.070 | 0.163 | 0.064 | 0.076 | 0.152 | 0.106 |
| p | 0.41 | 0.51 | 0.15 | 0.43 | 0.07 | 0.48 | 0.40 | 0.09 | 0.24 |
| **Choriocapillaris** rowhead | | | | | | | | | |
| | Whole | Fovea | Parafovea | S-hemi | I-Hemi | Tempo | Superior | Nasal | Inferior |
| r | −0.095 | −0.155 | −0.052 | −0.019 | −0.072 | −0.045 | −0.084 | −0.121 | −0.011 |
| p | 0.29 | 0.08 | 0.56 | 0.83 | 0.42 | 0.61 | 0.35 | 0.18 | 0.90 |
| Plaque width (mm) and flow area ($mm^2$) | | | | | | | | | |
| | Outer retina | | | | | Choriocapillaris | | | |
| r | 0.188 | | | | | −0.209 | | | |
| p | 0.03* | | | | | 0.22 | | | |

Whole: Whole image.
S-hemi: Superior hemi.
I-hemi: Inferior hemi.
SCP: superficial capillary plexus.
DCP: deep capillary plexus.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Carotid and coronary arteries represent large vessels, both arteries transport large volumes of blood away from the left ventricle to perfuse vital organs like brain, eye (carotid artery) and cardiac muscle (coronary artery). For similar physiological function, carotid artery structure such as wall thickness, plaque presence, calcification, and regulatory pathway, show a close correlation to coronary artery [15]. Thus, the carotid artery may serve as a surrogate marker for coronary artery vascular health. Generally speaking, carotid intima-media thickness (CIMT) and plaque have been clearly shown to be associated with traditional risk factor (TRF) for CHD [16,17] [18,19]. However, in contrast, carotid plaque, compared with CIMT, had a significantly higher diagnostic accuracy for the prediction of future CAD events [20]. Therefore, in this study, we focused on the relationship between carotid plaque characteristics and fundus microvasculature in CAD patients.

Systemic vascular changes, as well as systemic diseases, such as hypertension and DM, have been linked to retinal or choroidal microvascular changes and alterations in the retinal autoregulation responses [14]. In fact, retinal vascular alterations have also been shown to reflect several systemic processes, such as cumulative responses to ageing, inflammation, endothelial dysfunction and CV risk factors (CVRF) [21]. In addition, the microvasculature of retina is thought to have identical physiological and anatomic features to the cerebral and coronary microcirculation [14]. Embolism originating from carotid or cardiac lesion is the most common cause of retinal vascular occlusion. San-Ni Chen et al. [22] reported patients with ipsilateral carotid plaques and high-grade stenosis or even total carotid occlusion had significant decreased retinal blood perfusion. Another study on patients in Netherlands revealed patients with a retinal neurological event more often had a significant carotid stenosis [23]. Carotid procedures such as angioplasty and stenting for high-grade stenosis have been shown to improve bilateral retinal and choroidal vessel density in the deep capillary plexus [24,25]. Our previous study also discovered vessel density and flow area decreased in CAD patients with coronary artery stenosis before ophthalmologic clinical signs appeared [11]. However, previous studies have not specifically described the impact of carotid plaque or stenosis on each layer of retina and choroid, which OCTA can just recover the defect. In this OCTA study, we discovered that the presence of carotid stenosis and plaque seemed to have a more obvious effect on the decrease of SCP and DCP vessel density, suggesting the superficial and deep retina may be more sensitive to the alters of carotid blood flow. Nevertheless, the "dual blood supply" of fovea (central retinal artery and choroidal vessels) may be the key reason for the insensitivity of carotid blood flow reduction in fovea area. For choriocapillaris, only fovea and nasal area vessel density were affected by plaque, which was much obtuser than retina. We speculated the reason for this phenomenon may be that the nasal choroidal vessel density was the lowest in all zones, which was more sensitive to the reduction of carotid artery perfusion. Previous observer explained by the fact that, retinal and choroidal vasculature has an autoregulatory mechanism, suffering hypoperfusion-induced capillary dropout due to vasoconstriction. However, choroidal vasculature is known to be a passive vascular bed, suggesting that the choroidal vasculature may have a much weaker autoregulatory capacity than that of the retinal vasculature, which also was supported by our view [26–28].

The stability and size of carotid plaque may also be related to the retinal and choroidal microvasculature in our study, while only plaque width was significant. In a study on male diabetic patients, the presence of asymptomatic retinal arteriolar emboli was observed in 20% participants with carotid atheroma, prompting calcified carotid artery atheromas may have significant correlation as evidenced by retinal artery emboli [29]. W.E. Hellings et al. also highlighted the presence of vulnerable properties of plaques (including the presence of intraplaque hemorrhage) within an individual is indicative of vulnerable plaques across the whole arterial system within that individual [30]. In this study, however, there was no significant difference in retinal/choroidal microvasculature between patients with unstable plaque and patients with stable plaque. We speculate that the possible reason may be the peripheral vessels are not affected when the plaque has not fallen off in early stage. Plaque width can be considered as a manifestation of the degree of carotid stenosis. Embolic and hemodynamic mechanisms are both responsible for peripheral vascular such as cerebral vascular attacks in the setting of carotid atherosclerosis. Plaque length and parent vessel diameter, in addition to percentage of stenosis, are likely to be critical determinants of hemodynamic compromise [31]. Modeled by the Poiseuille law, the resistance in a tube to a fluid of viscosity, $\eta$, is equal to $8\ \eta L/\pi\ (d/2)$, where L is the length of a tube and d is the diameter. Therefore, longer (L) and wider (smaller vessel diameters, d) carotid plaques would be expected to increase resistance (R) and decrease blood flow across a stenotic carotid artery [32]. Another article also elaborated important finding that the increased max plaque length strongly predicted not only the CAD presence but also its severity, supporting the hypothesis that max plaque length could be used as an independent indicator of coronary lesions [33]. The influence of carotid plaque width on peripheral vascular may be related to carotid hypertension, leading to multiple vessel wall changes [34]. Our results showed retinal/choroidal vessel density and plaque width had statistical correlation, which indicated fundus microvasculature may be more affected by carotid hypertension than by blood flow resistance. This is really an interesting discovery.

The limitations of this study included predominantly homogenous participants (100% Chinese), relatively small sample size, and lack of long-term follow-up, which may lead statistics bias of research results. More rigorous, extensive and longitudinal research will be innovated in the future. Addition, carotid ultrasonography was the sole method for plaque assessment in this study, which presents a limitation. While it's non-invasive and cost-effective, it doesn't provide the detailed plaque characteristics achievable with high-resolution MRI or CTA. Future studies will consider alternative imaging techniques to better understand the relationship between carotid plaques and retinal vascular alterations.

In conclusion, we hold opinion that this maybe the first study to show that carotid plaque is an independent risk factor for lower retinal/choroidal vessel density and flow area assessed by OCTA in people with CAD, providing novel evidence of an association between coronary artery, carotid artery and retinal/choroidal microvascular.

## Data availability statement

Data associated with our study has not been deposited into a publicly available repository.

## CRediT authorship contribution statement

**Jing Jiang:** Writing – original draft, Funding acquisition, Data curation, Conceptualization. **Jin Wang:** Resources, Project administration, Methodology, Formal analysis, Data curation. **Yucen Wang:** Visualization, Software, Resources, Project administration, Methodology. **Luoziyi Wang:** Methodology, Formal analysis. **Yiwen Qian:** Validation, Supervision. **Zhiliang Wang:** Writing – review & editing, Visualization, Supervision, Funding acquisition, Data curation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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