

Retinal microvasculature impairment in patients with congenital heart disease investigated by optical coherence tomography angiography

Cong Li MD¹ | Pingting Zhong MD^{1,2} | Haiyun Yuan MD PhD³ |
Xinran Dong MD PhD¹ | Qingsheng Peng MD^{1,2} | Manqing Huang MD¹ |
Qiaowei Wu MD^{1,4} | Baoyi Liu MD^{1,4} | Minghui Xu MD¹ | Yu Kuang MD¹ |
Xiaomin Zeng MD^{1,4} | Yu Xiao MD^{1,4} | Ying Fang MD¹ |
Honghua Yu MD PhD¹  | Xiaohong Yang MD¹ 

¹Guangdong Eye Institute, Department of Ophthalmology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, School of Medicine, South China University of Technology, Guangzhou, China

²Medical College, Shantou University, Shantou, China

³Department of Cardiovascular Surgery, Guangdong Provincial Key Laboratory of South China Structural Heart Disease, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

⁴The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

Correspondence

Professor Xiaohong Yang and Honghua Yu, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China.
Email: syyangxh@scut.edu.cn (X. Y.) and yuhonghua@gdph.org.cn (H. Y.)

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Abstract

Importance: A high prevalence of retinal abnormalities have been reported in congenital heart disease (CHD), but quantitative analysis of retinal vasculature is scarce. Optical coherence tomography angiography (OCTA) is a noninvasive method to quantitatively assess the retinal microvasculature.

Background: To investigate the retinal microvasculature changes in CHD patients by using OCTA.

Design: Cross-sectional study.

Participants: A total of 158 participants including 57 cyanotic CHD (CCHD) patients, 60 acyanotic CHD (ACHD) patients and 41 control subjects were included.

Methods: All participants underwent a comprehensive ophthalmologic examination, including refraction measurement, intraocular pressure measurement and OCTA.

Main Outcome Measures: Vessel density (VD) was measured within the radial peripapillary capillary (RPC), superficial capillary plexus (SCP) and deep capillary plexus (DCP) of the macula.

Cong Li, Pingting Zhong and Haiyun Yuan contributed equally to this work.

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Results: CCHD patients had significantly lower VD in the RPC, SCP and DCP (all $P < .01$) compared to control subjects, and significantly lower VD in the RPC and DCP (both $P < .05$) compared to ACHD patients. Besides, among the CHD group, VD in the RPC was positively correlated with oxygen saturation (whole image, $\rho = 0.45$; peripapillary, $\rho = 0.48$) and negatively correlated with haematocrit (whole image, $\rho = 0.55$; peripapillary, $\rho = 0.55$) (all $P < .001$).

Conclusions and Relevance: Retinal VD might be a surrogate to reflect the effect of chronic systemic hypoxemia in CHD patients. OCTA could be a convenient and noninvasive tool to evaluate the retinal structure and function in CHD patients.

KEYWORDS

congenital heart disease, hypoxia, retinal vessel density, optical coherence tomography angiography

1 | INTRODUCTION

Congenital heart disease (CHD) is the most common congenital defect, characterized by structural abnormalities of the heart or great vessels and affecting 0.82% of live newborns around the world.¹ Cyanotic CHD (CCHD) is one type of CHD and typically characterized by much severer hypoxia, higher mortality, and poorer quality of life.^{2,3} The effect of chronic hypoxemia is associated with cardiovascular risks,⁴ perioperative bleeding⁵ and multi-system damages in the myocardial blood,^{6,7} kidney function⁸ and retinal microvasculature.⁹

Retina is regarded as a window to the heart and can be non-invasively visualized.¹⁰ The morphologic manifestations of coronary arteries, such as dilatation and tortuosity, have also been observed with similar changes in the retinal vessels in CCHD patients.¹¹⁻¹³ A previous study also found the abnormal oxygen saturation in the retinal vessel could reflect the chronic systemic hypoxemia secondary to CCHD.¹⁴ A possible link between the retina and the heart might exist.^{10,15,16} We considered the assessment of retinal vessels might provide some insights into the effect of hypoxemia in CHD patients. The effects of chronic hypoxemia on retinal vascular morphology have been well documented previously, but the quantitative analysis of retinal vessel density (RVD) in CCHD is poorly explored. Optical coherence tomography angiography (OCTA) is a novel and noninvasive method used for the quantitative and qualitative assessment of retinal microcirculation status.¹⁷ Therefore, we conducted this study to explore the RVD changes measured by OCTA in patients with CHD.

In this study, we aimed to evaluate the RVD changes in patients with CHD and to determine the association between retinal microvasculature and the severity of chronic hypoxia in CHD. We aimed to explore whether

RVD could reflect the effect of chronic systemic hypoxemia and whether RVD could be a surrogate to reflect the microvasculature status in CHD patients.

2 | METHODS

2.1 | Study design and participants

In this cross-sectional and comparative study, CHD patients were consecutively enrolled from June 2018 to September 2019 in the Department of Cardiovascular Surgery in Guangdong Provincial People's Hospital. CHD is defined as a range of cardiac abnormalities, which is presented before birth and attributable to abnormal foetal cardiac development without inherited disorders.^{18,19} Patients with a definite diagnosis of CHD under echocardiography or cardiac catheterization were consecutively included before the cardiac surgery. Oxygen saturation (SaO_2) was measured by pulse oximetry in the finger or toe after a minimum of 5 minutes rests in sitting position on admission. According to the value of SaO_2 , the CHD patients were classified into acyanotic group (ACHD, $\text{SaO}_2 > 90\%$) and cyanotic group (CCHD, $\text{SaO}_2 \leq 90\%$).¹⁸

A control group without ocular disease of any sort were also included. All participants were arranged to undergo a comprehensive ophthalmologic examination, including refraction measurement, best-corrected visual acuity (BCVA) test, intraocular pressure (IOP) measurement using a non-contact tonometer and OCTA.

Exclusion criteria included the following: (a) IOP > 21 mmHg; (b) a history of glaucoma, uveitis, coexisting retinal disease, ocular trauma or other fundus diseases; (c) a history of intraocular surgery; (d) media

TABLE 1 Demographic and clinical characteristics of three groups

	Control (n = 41)	ACHD (n = 60)	CCHD (n = 57)	P value
Age (years)	24 ± 6	25 ± 11	22 ± 11	.083*
Male (%)	13 (31.7)	24 (40.0)	30 (52.6)	.105**
Body mass index (kg/m ²)	19.87 ± 1.38	19.40 ± 3.62	18.04 ± 6.96	.146*
Systolic BP (mmHg)	109 ± 10	114 ± 13	111 ± 9	.052*
Diastolic BP (mmHg)	71 ± 9	72 ± 10	69 ± 10	.340*
SE (diopters)	-1.92 ± 2.02	-2.09 ± 2.49	-2.34 ± 2.75	.737*
BCVA, LogMAR	0.01 ± 0.04	0.03 ± 0.14	0.04 ± 0.13	.332*
IOP (mmHg)	14.27 ± 2.74	14.83 ± 3.29	14.91 ± 2.72	.539*
SaO ₂ (%)	NA	98 (97-100)	83 (75-86)	<.001***
Hb (g/L)	137 (127-141)	135 (125-150)	180 (164-205)	<.001***
HCT (L/L)	0.41 (0.39-0.42)	0.40 (0.38-0.43)	0.53 (0.49-0.61)	<.001***

Note: Quantitative variables are expressed as mean ± SD or median (interquartile range), and categorical variables are expressed as percentages of total.

Abbreviations: ACHD, acyanotic congenital heart disease; BCVA, best-corrected visual acuity; BP, blood pressure; CCHD, cyanotic congenital heart disease; Hb, haemoglobin; HCT, haematocrit; IOP, intraocular pressure; LogMAR: logarithm of the minimum angle of resolution; NA, not available; SaO₂, oxygen saturation; SE, spherical equivalent.

*ANOVA, ** χ^2 test, *** Kruskal-Wallis H test; $P < .05$ is considered statistically significant.

opacities preventing high-quality imaging; (e) a history of any systemic congenital diseases, other than heart diseases.

This study protocol was explained in detail to all participants and written informed consent was obtained. This research adhered to the Declaration of Helsinki and was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital.

2.2 | Optical coherence tomographic angiography

The retinal images were captured with patients' pupil dilated in a dark room by using an OCTA instrument (Version 2017.1.0.151; RTVue-XR Avanti; Optovue, Fremont, California). This instrument uses a light source centred on 840 nm and a bandwidth of 50 nm with an A-scan rate of 70 000 scans per second. The system provides an axial resolution of 5 μ m in tissue and the diameter of the beam spot at the retinal plane around 22 μ m.

The high-definition (HD) modes of optic disc (4.5×4.5 mm²) and macula (6×6 mm²) within the OCTA scans were employed. The parameter measured in the optic disc contained the VD of the radial peripapillary capillary (RPC). The parameter in the macula majorly contained the VD of the superficial capillary plexus (SCP), deep capillary plexus (DCP). Split-spectrum amplitude decorrelation angiography (SSADA) software

TABLE 2 Distribution of primary diagnoses of CHD patients

	ACHD (n = 60)	CCHD (n = 57)
Tetralogy of Fallot	7 (11.7)	12 (21.1)
Ebstein anomaly	21 (35.0)	1 (1.8)
Single ventricle	0	15 (26.3)
Pulmonary atresia	1 (1.7)	9 (15.8)
Transposition of the great arteries	0	7 (12.3)
Heart septal defects	12 (20.0)	6 (10.5)
Double-outlet right ventricle	1 (1.7)	4 (7.0)
Anomalous pulmonary venous connection	6 (11.3)	1 (1.8)
Other	12 (20.0)	2 (3.5)

Note: Values are expressed as percentages of total.

Abbreviations: ACHD, acyanotic congenital heart disease; CCHD, cyanotic congenital heart disease.

algorithm²⁰ was used for the evaluation of VD which was defined by the percentage area occupied by vessels. Furthermore, the system was equipped with three-dimensional Projection Artefact Removal (3D PAR), which could reduce projection artefacts in the deeper layers while maintaining their authentic layout.

RPC is defined as the layer between the outer limit of the retinal nerve fibre layer (RNFL) and the internal limiting membrane (ILM). The software automatically fits a 2 mm diameter circle centred on the optic disc and the

peripapillary region is defined as an area extending between the 2- and 4-mm-diameter elliptical contour lines around the optic disc boundary. Eight sectors were used to describe the peripapillary area, including nasal superior (NS), nasal inferior (NI), inferior nasal (IN), inferior temporal (IT), temporal inferior (TI), temporal superior (TS), superior temporal (ST) and superior nasal (SN). We also analysed the superior-hemi and inferior-hemi values in the study. Capillary density was measured with built-in software that automatically removes larger vessels with diameter $\geq 33 \mu\text{m}$.

In the macular region, SCP and DCP were automatically generated by the software. SCP is defined as the ILM to $10 \mu\text{m}$ above the inner plexiform layer (IPL). DCP is defined as $10 \mu\text{m}$ above the IPL to $10 \mu\text{m}$ below the outer plexiform layer (OPL). The VD of four areas (whole image, fovea, parafovea, perifovea) in the SCP and DCP

were available for analyses. The foveal area of the macula refers to the inner circle with a diameter of 1 mm, the parafoveal area refers to the annular area between the concentric circles with a diameter of 1 and 3 mm, and the perifoveal area refers to the annular area between the concentric circles with a diameter of 3 and 6 mm.

Only images of good quality with a signal strength index (SSI) ≥ 50 were used for further quantitative analysis. If the initial image quality was poor, we repeated the scans until the scan quality of images could meet the requirement.

2.3 | Statistical analysis

The demographic and clinical characteristics were compared among the three groups. Continuous variables

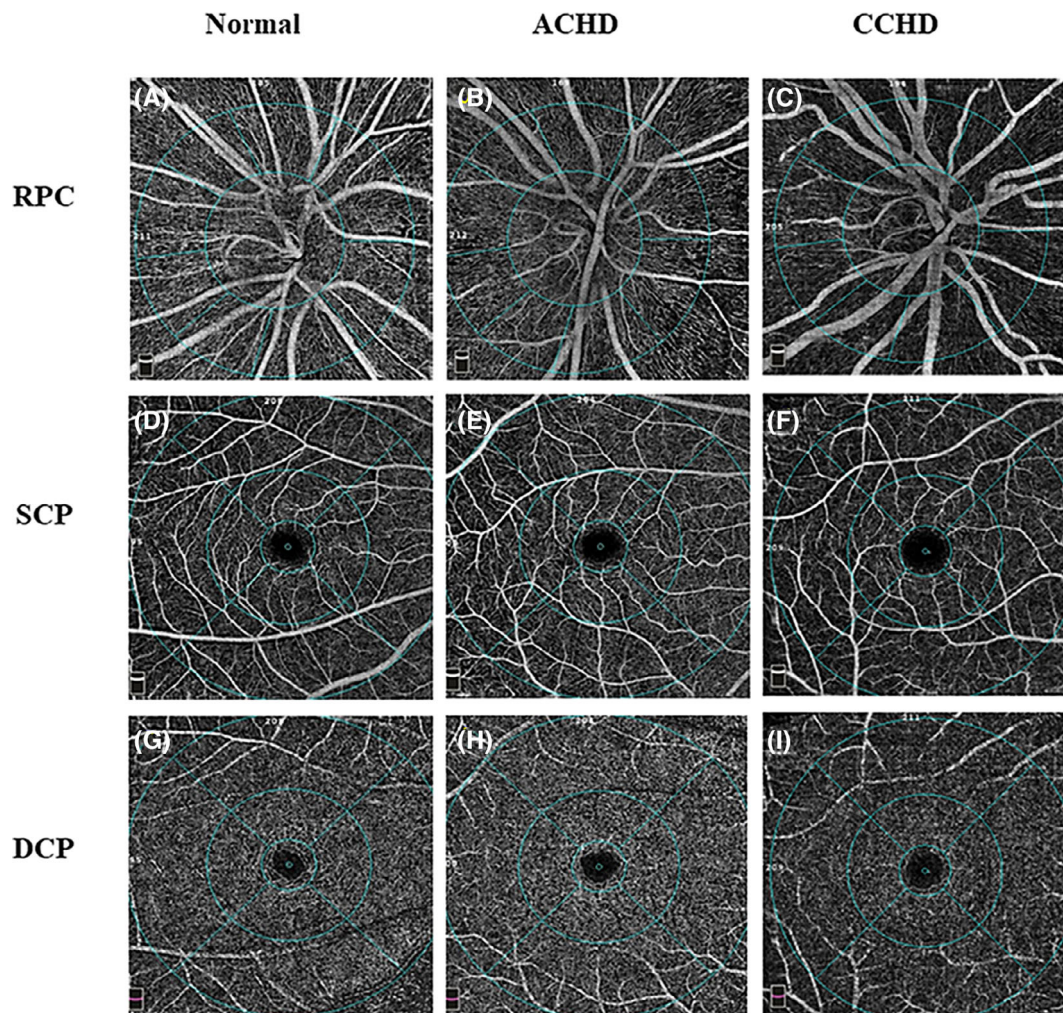


FIGURE 1 OCTA images of vessel density in three groups. RPC angiograms of $4.5 \times 4.5 \text{ mm}^2$ in, A, a normal eye, B, ACHD eye, C, CCHD eye. SCP angiogram of $6 \times 6 \text{ mm}^2$ in, D, a normal eye, E, ACHD eye, F, CCHD eye. DCP angiogram of $6 \times 6 \text{ mm}^2$ in, G, a normal eye, H, ACHD eye, I, CCHD eye. ACHD, acyanotic congenital heart disease; CCHD, cyanotic congenital heart disease; DCP, deep capillary plexus; OCTA, optical coherence tomographic angiography; RPC, radial peripapillary capillary; SCP, superficial capillary plexus

were presented as mean \pm SD or median (interquartile range, IQR). Data distribution was tested using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used for continuous variables when the assumption of normality was met. Otherwise, Kruskal-Wallis H test was used. Categorical variables were presented as numbers and percentages and compared with the χ^2 test. One-way ANOVA was used to compare the differences of RVD among control group, ACHD patients, and CCHD patients. Then pairwise comparisons among the three groups were done using the Bonferroni test. Spearman's correlation analyses were performed to investigate the relationships between RVD and related factors. Multivariable regression analysis was used to determine the driving factors associated with RVD.

Refraction values were converted to spherical equivalent (SE), calculated as spherical dioptic power

plus one-half of the cylindrical dioptic power. For each participant, only one eye with higher SQ was used for the analysis.

All data were analysed using SPSS software (IBM SPSS, Version 25.0, IBM Corporation, Armonk, New York). All *P* values were presented based on two-tailed and *P* < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study population

A total of 117 CHD patients (60 with ACHD and 57 with CCHD) and 41 control subjects were consecutively included in our study. The demographic and clinical characteristics were summarized in Table 1. The

TABLE 3 Retinal vessel density among the three groups

	Control (n = 41)	ACHD (n = 60)	CCHD (n = 57)	<i>P</i> value ^a	<i>P</i> value ^b	<i>P</i> value ^c	<i>P</i> value ^d
SSI (optic disk scan)	76.93 \pm 7.04	76.80 \pm 6.98	76.56 \pm 7.49	.966	1.000	1.000	1.000
RPC density (%)							
Mean	56.22 \pm 2.16	55.47 \pm 2.63	52.90 \pm 3.24	<.001*	.552	<.001*	<.001*
Peripapillary	58.19 \pm 2.43	56.90 \pm 3.01	53.45 \pm 3.99	<.001*	.167	<.001*	<.001*
Superior-hemi	58.78 \pm 2.49	57.21 \pm 3.08	53.93 \pm 4.04	<.001*	.066	<.001*	<.001*
Inferior-hemi	57.53 \pm 2.66	56.57 \pm 3.14	52.94 \pm 4.20	<.001*	.513	<.001*	<.001*
RPC capillary density (%)							
Mean	49.42 \pm 1.91	48.41 \pm 2.53	44.25 \pm 4.15	<.001*	.343	<.001*	<.001*
Peripapillary	51.39 \pm 2.48	49.71 \pm 3.07	44.29 \pm 5.23	<.001*	.102	<.001*	<.001*
Superior-hemi	51.73 \pm 2.71	49.60 \pm 3.26	44.39 \pm 5.30	<.001*	.030*	<.001*	<.001*
Inferior-hemi	51.01 \pm 2.79	49.81 \pm 3.27	44.17 \pm 5.50	<.001*	.461	<.001*	<.001*
SSI (macula scan)	74.60 \pm 6.48	73.64 \pm 5.56	72.34 \pm 4.68	.133	1.000	.147	.620
SCP density (%)							
Mean	51.15 \pm 3.25	50.57 \pm 2.14	49.45 \pm 3.00	.009*	.911	.010*	.095
Fovea	20.70 \pm 6.57	20.47 \pm 6.16	19.39 \pm 7.41	.565	1.000	1.000	1.000
Parafovea	53.96 \pm 4.52	53.39 \pm 2.54	52.70 \pm 3.06	.176	1.000	.200	.781
Perifovea	52.07 \pm 3.21	51.18 \pm 2.34	50.10 \pm 3.27	.005*	.406	.004*	.145
DCP density (%)							
Mean	54.47 \pm 5.31	52.57 \pm 5.48	50.02 \pm 5.61	<.001*	.266	<.001*	.039*
Fovea	37.16 \pm 7.31	35.98 \pm 7.66	35.40 \pm 7.97	.530	1.000	.790	1.000
Parafovea	58.35 \pm 3.68	56.49 \pm 5.23	53.43 \pm 5.24	<.001*	.183	<.001*	.003*
Perifovea	56.08 \pm 5.72	54.10 \pm 5.71	51.29 \pm 6.14	<.001*	.297	<.001*	.031*

Note: Values are presented as mean \pm SD.

Abbreviations: ACHD, acyanotic congenital heart disease; CCHD, cyanotic congenital heart disease; DCP, deep capillary plexus; RPC, radial peripapillary capillary; SCP, superficial capillary plexus; SSI, signal strength index.

^a*P* value for the comparison among CCHD group, ACHD group and control group using one-way analysis of variance.

^b*P* value for the comparison between the ACHD group and control group using post hoc Bonferroni.

^c*P* value for the comparison between the CCHD group and control group using post hoc Bonferroni.

^d*P* value for the comparison between the ACHD group and CCHD group using post hoc Bonferroni.

*Significant statistical difference, *P* < .05.

distribution of primary diagnoses of CHD was shown in Table 2. There were no significant differences among control, ACHD, and CCHD groups in age, sex, body mass index, blood pressure, SE, BCVA and IOP. Significant differences were found in the comparison of SaO₂, haemoglobin (Hb) and haematocrit (HCT) among the three groups (all $P < 0.001$).

3.2 | Intergroup differences of RVD among the three groups

In patients with CCHD, the impairment of retinal vasculature was more evident as a decrease in VD, especially in the RPC and DCP (Figure 1). Comparisons of the VD of different retinal layers were presented in Table 3. There were no significant differences in SSI of optic disk and macula among the three groups (both $P > .05$).

3.2.1 | Radial peripapillary capillary

Among the three groups, patients with CCHD had the significantly lowest VD of the whole image and the peripapillary area in the RPC (all $P < .001$). For the sectors in the RPC, the CCHD patients had significantly lowest VD in all sectors compared to other groups (all $P < .05$). However, the density of these sectors in the RPC did not differ significantly between ACHD patients and control subjects, except for the ST sector ($P = .013$).

3.2.2 | Superficial capillary plexus

The mean VD of the SCP was compared among the three groups. Patients with CCHD had a significantly lower mean VD of the whole image ($P = .010$) and the perifovea area ($P = .004$) in the SCP, compared with the control

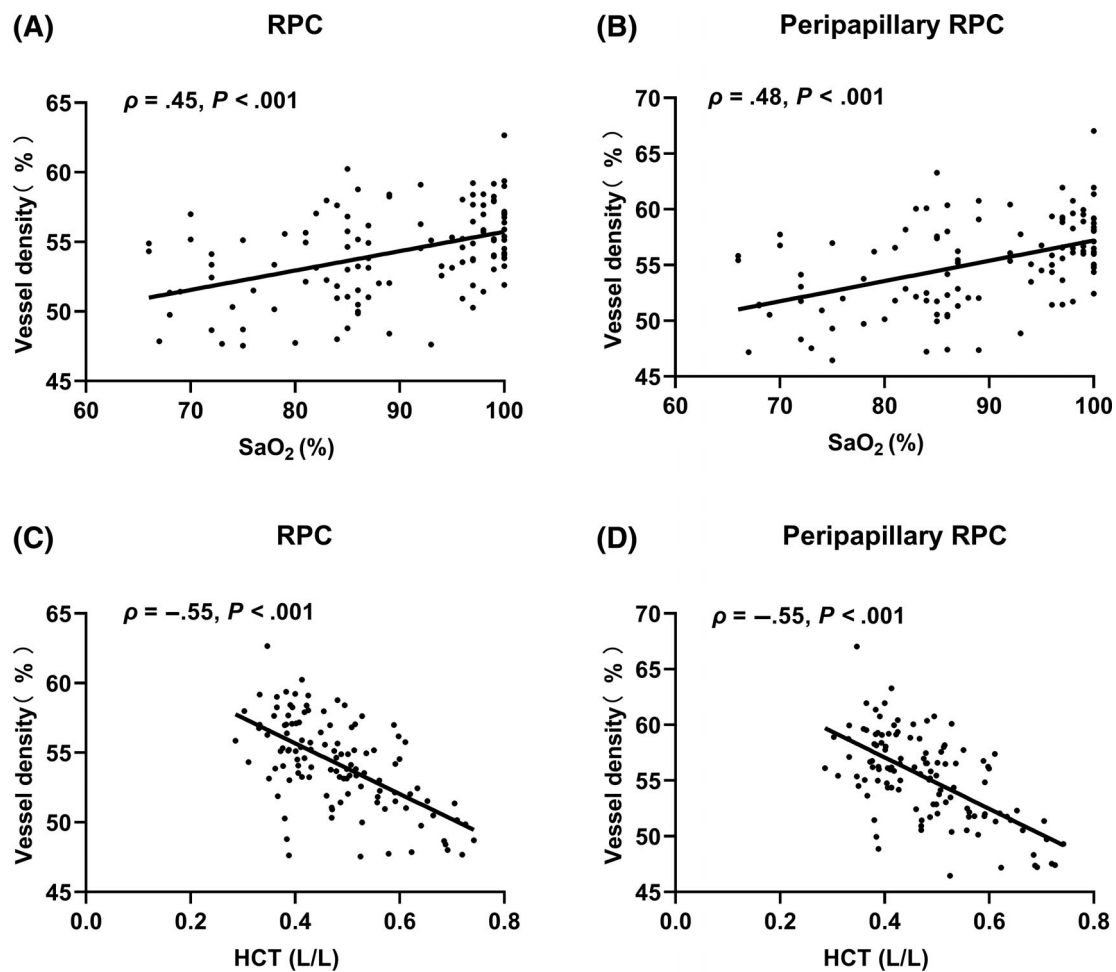


FIGURE 2 Correlation analyses between the VD of the RPC and SaO₂ and HCT. A, The density of RPC and, B, peripapillary RPC were positively correlated with SaO₂. C, The density of RPC and, D, peripapillary RPC were negatively correlated with HCT. HCT, haematocrit; RPC, radial peripapillary capillary; SaO₂, oxygen saturation; VD, vessel density

TABLE 4 Multiple linear regression analysis for retinal vessel density among three groups

	RPC			SCP			DCP		
	β	95% CI	<i>P</i> value	β	95% CI	<i>P</i> value	β	95% CI	<i>P</i> value
SaO ₂	0.03	-0.04 to 0.10	.406	0.02	-0.06 to 0.10	.592	0.06	-0.10 to 0.22	.437
HCT	-16.34	-21.75 to -10.93	<.001*	-10.94	-16.75 to -5.13	<.001*	-14.37	-26.13 to -2.61	.017*

Abbreviations: CI, confidence interval; DCP, deep capillary plexus; HCT, haematocrit; RPC, radial peripapillary capillary; SaO₂, oxygen saturation; SCP, superficial capillary plexus.

*Significant statistical difference, $P < .05$.

subjects. But no significant differences were observed among the ACHD group and the other two groups in the SCP.

3.2.3 | Deep capillary plexus

Analysis of VD in the DCP revealed that the mean VD was the lowest in the patients with CCHD when compared to the ACHD group (in the parafovea $P = .003$, and perifovea $P = .031$), and to the control group (in the parafovea and perifovea, both $P < .001$). There was also no significant difference between the ACHD group and the control group in the DCP.

3.3 | Correlations analysis between OCTA parameters and clinical data

There was a significant positive correlation between SaO₂ and VD in the RPC (in the whole image, $\rho = 0.45$; in the peripapillary, $\rho = 0.48$; both $P < .001$). The negative correlations were shown between HCT and the VD in the RPC (in the whole image, $\rho = 0.55$; in the peripapillary, $\rho = 0.55$; both $P < .001$) (Figure 2). Multiple regression analysis showed that HCT was a driving factor for VD (RPC, SCP and DCP) independent of oximetry oxygen saturation (all $P < .05$) (Table 4).

4 | DISCUSSION

In this study, we evaluated the RVD changes in patients with CHD by using OCTA. Our results indicated that CCHD patients had the lowest VD in the macula and optic disc compared to ACHD patients and control subjects. However, in CCHD patients, the VD reduction in the macula was only revealed in the DCP when compared to ACHD patients. Besides, the RVD was positively correlated with SaO₂ and negatively correlated with HCT among CHD patients.

The RVD most significantly decreased in CCHD patients compared to ACHD patients and control subjects. This alteration might suggest the response to chronic hypoxia in CCHD patients. On the one hand, the chronic severe hypoxemia could stimulate erythropoietin production causing a secondary erythrocytosis and hyperviscosity.^{21,22} On the other hand, high blood viscosity associated with excessively elevated haematocrit would further reduce oxygen supply and tissue perfusion.²³ The multivariable models in the present study indicated that blood viscosity was the driving factor for RVD, independent of oximetry oxygen saturation. Besides, endothelial dysfunction caused by hypoxia has been found in the systemic arteries and retinal vessels in CCHD patients.²⁴ This might be the result of reduced expression of nitric oxide synthase and increased nitric oxide scavenging.^{4,25,26} The impaired endothelial function could significantly reduce endothelium-dependent vasodilation and lead to vasoconstriction.²⁷ Additionally, a previous study also supported the increased arterial stiffness might result in the hypoperfusion of retina in CCHD patients.³

The different capillary layers of the retina might respond differently to the pathologic changes, such as hypoxia and ischemia. The early stage of diabetic retinopathy with the hypoxia in retina was featured by the more significant reduced VD in the DCP.²⁸⁻³⁰ In our research, among the CHD patients, we also found CCHD patients had more significantly reduced VD in the DCP. Anatomically, The SCP is composed of arterioles that are surrounded by smooth muscle cells. However, the DCP consists of vessels smaller and thinner and surrounded by pericytes.³¹⁻³³ Several studies have proved that pericytes were more sensitive to hypoxia.^{32,34} Furthermore, the DCP is far away from the arterioles which are the source of oxygen.³⁵ Hence, the DCP would mostly be affected in case of hypoxia. Functionally, DCP located in a watershed zone of oxygen supply.³⁶ The DCP supplies oxygen to the inner retina and the outer retina, while the SCP only needs to maintain the oxygen stability of the inner retina.³⁷ Therefore, the DCP might be more vulnerable to hypoxia.

In the present study, retinal microvasculature impairment was much severer in CCHD patients than ACHD

patients, indicating that the retinal microvasculature was associated with the severity of chronic hypoxia in CHD. It had been stated previously that higher prevalence of structural and functional ocular abnormalities in the CCHD group than that in the ACHD group.³⁸ CCHD is characterized by unsaturated blood distributed into the systemic circulation and thus presents with much severer hypoxia than ACHD.³⁹ Besides, in our study, the mean SaO₂ of ACHD patients was within normal range and no significant RVD changes were found between ACHD patients and control subjects, which supported the relationship of the lower RVD and severer hypoxia. These findings might have a potential value to estimate the severity of hypoxia in CHD patients and help us to better understand the ocular effects of CCHD.

Our results also indicated that the change of RVD was positively correlated with SaO₂ and negatively correlated with HCT among CHD patients. On the one hand, hypoxia and secondary erythrocytosis could lead to retinal microvasculature impairments and vascular dysfunction.^{24,26,40} On the other hand, studies have proved that retinal vasculature dilation and tortuosity could be significantly relieved after cardiac surgical repair improve hypoxia.^{41,42} To some extent, it might provide a clue that the retinal microcirculation could reflect systemic hypoxia status.^{14,43} Furthermore, retinal microvasculature has been proposed as an easily measured surrogate for systemic circulation and could be a possible marker of vascular damage in CHD patients.

The retina is highly metabolically active tissue and one of the tissues with the highest oxygen consumption in the body.^{44,45} Therefore, the retina is highly sensitive to systemic hypoxemia. It has already been found that RVD was decreased in obstructive sleep apnoea syndrome (OSAS) as a result of chronic systemic hypoxemia.⁴⁶ Similarly, in our study, we also found significantly reduced RVD in CCHD patients. Notably, the retina might be a noninvasive window to evaluate microcirculation status under the condition of chronic hypoxia.

The main strength of our study is using a convenient and noninvasive technology, OCTA, to observe retinal microvascular changes in CHD patients. Nonetheless, there are still several limitations to the present study. Firstly, the number of subjects is limited and this cross-sectional study is unable to evaluate the retinal vasculature impairment with disease progression, further explorations are needed. Secondly, the field of view might be limited in the current technology of OCTA.⁴⁷ Although the 6 × 6 mm² HD mode was chosen, we still could not completely understand the vascular changes in the peripheral retina. Thirdly, some severe CHD patients failed to survive at a young age, so the selection bias inevitably exists.

4.1 | Conclusion

In conclusion, this study has found that CCHD patients had the lowest RVD when compared to ACHD patients and control subjects. RVD might have a potential value to estimate the severity of hypoxia in CHD patients and help us to better understand the microcirculation effect of CCHD. Retinal vasculature could provide a deeper insight into the effect of chronic systemic hypoxemia on retinal structure and function. The results are promising, and further study is warranted.

FINANCIAL DISCLOSURES

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CONFLICT OF INTEREST

None declared.

ORCID

Honghua Yu  <https://orcid.org/0000-0002-0782-346X>

Xiaohong Yang  <https://orcid.org/0000-0001-9466-7591>

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