CHARACTERISTICS OF THE FOVEAL MICROVASCULATURE IN CHILDREN WITH MARFAN SYNDROME

An Optical Coherence Tomography Angiography Study

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Purpose: To investigate the characteristics of foveal microvasculature in children with Marfan syndrome (MFS).

Methods: Ninety eyes from 45 MFS patients and 76 eyes from 38 healthy individuals of age-matched, sex-matched, and axial length-matched were enrolled. Characteristics of the superficial capillary plexus including the vessel density, perfusion density, and foveal avascular zone were analyzed by optical coherence tomography angiography.

Results: The vessel density and the circularity index of the foveal avascular zone were significantly decreased in the MFS group compared with the controls ($P = 0.017$ and $P = 0.004$ respectively). In MFS group, the central vessel density ($P = 0.003$) and perfusion density ($P = 0.001$) were negatively correlated with the best-corrected visual acuity. The foveal avascular zone area was correlated with the aortic diameters ($P = 0.001$) and the paratemporal perfusion density was correlated with the ejection fraction ($P = 0.003$). Moreover, the paratemporal perfusion density and the circularity index of foveal avascular zone were found to be correlated with the aortic Z-score ($P < 0.001$ and $P = 0.003$ respectively).

Conclusion: Retinal microvascular decrease and its correlation with best-corrected visual acuity and cardiac functions were observed in the MFS group. The optical coherence tomography angiography may help to characterize the underlying pathophysiology features of MFS and enable early detection and prevention of vascular changes in MFS.

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Marfan syndrome (MFS) is an autosomal dominant disease that affects the connective tissue. It was estimated that in every 100,000 people, 2 to 3 individuals are suffering from MFS. Marfan syndrome is caused by a mutation in the gene that codes fibrillin-1 (FBN1), which is associated with several skeletal and vascular abnormalities, and a varied range of ocular manifestations, including ectopia lentis (EL).

Fibrillin-1 is the most abundant elastic microfibril present in human eyes. Fibrillin-1 can also be found in vascular smooth muscle cells and vascular endothelium contributing to regulation of blood flow. In the systemic circulation, structural cardiovascular abnormalities such as aortic dilation are the primary complication in MFS. However, the mechanism of how FBN1 regulates the microvascular blood flow in the retinal vascular system is not well understood.

As we all know, the branch of the internal carotid artery, ophthalmic artery supplies blood to the eye, therefore, perturbations in the coronary macrocirculation and microcirculation, in addition to genetic predisposition, can be reflected by the retinal microvasculature. Moreover, microvascular endothelial dysfunction is an early event in the development of cardiovascular disease and assessment of retinal microvasculature provides valuable information that helps to determine the health of endothelium. In particular, optical coherence tomography angiography (OCTA) visualizes the retinal blood vessel and evaluates the retinal microvasculature in a noninvasive...
manner. Retinal fundus images are used in the detection of subtle, early microvascular variation, prediction, and examination of the target organ damage in vascular diseases.

Little is known about the characteristics of foveal microvasculature in the eyes of patients with MFS. Detailed images of retinal vascular layers are required to understand the association between retinal microvascular changes and MFS. In this study, we investigated different parameters of macular microcirculation in children with MFS including foveal avascular zone (FAZ) parameters, macular vessel density (VD), and perfusion density (PD) based on OCTA. These parameters of the eyes in the MFS group were compared with age-, sex-, and axial length (AL)-matched control eyes, and their correlation with other clinical functional or structural data such as best-corrected visual acuity (BCVA), OCT indices, degrees of ectopia lentis (EL), aortic size, Z-score, and ejection fraction (EF) were analyzed.

Methods

Patients

This cross-sectional observational study was conducted in Zhongshan Ophthalmic Center over 6 months in the period from August 2019 to August 2020. The study was approved by the Ethical Committee of Zhongshan Ophthalmic Center. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all 18-year-old patients or from the legal guardian for those who were less than 18 years old.

Eighty-eight patients consented to the study. Fifty patients with proven MFS according to Ghent-2 criteria and aged between 5 and 18 years were included in this study. Only eyes with AL between 21.0 mm and 26.0 mm were included. Healthy subjects were matched for age, sex, and AL, and then included as controls. Patients with retinal detachments repaired with a scleral buckle, known glaucoma or other retinal diseases were excluded from this study. Patients with ocular surface disorders such as corneal opacity or severe dryness that affect the OCTA image quality were also excluded from this study.

All patients undertook a routine ocular examination, including BCVA, (expressed as logarithm of the minimum angle of resolution [logMAR] units), slit-lamp biomicroscopy, noncontact tonometer, indirect ophthalmoscopy and AL measurement (IOL Master, Carl Zeiss Meditec, Jena, Germany), 1% tropicamide with 2.5% phenylephrine, or 1% cyclopentolate were used for all patients. For the calculation of the spherical equivalent (SE), we used only phakic or pseudophakic eyes. We also excluded phakic eyes with severe EL requiring aphakic correction. Spherical equivalent was calculated as the sum of the spherical plus half of the cylindrical error. Owing to insufficient signal strength, 5 of 50 patients were excluded for macular data. The degree of EL was classified into three broad groups according to previous reference.

Optical Coherence Tomography Measurements

Cirrus HD-OCT instrument (Carl Zeiss Meditec, Dublin, CA) was used to perform SD-OCT imaging. A total diameter of 6 mm from nine subfield areas of the Early Treatment Diabetic Retinopathy Study was quantified by a macular cube scan. Central macular thickness (CMT) refers to the thickness of the central 1-mm diameter. The macular cube in a 512 × 128 combination mode of scan was used to measure the CMT. The ganglion cell-inner plexiform layer thickness was determined using the ganglion cell analysis algorithm. We analyzed the retinal nerve fiber layer (RNFL), CMT and the average thickness of macular ganglion cell-inner plexiform layer.

Optical Coherence Tomography Angiography Measurements

Optical coherence tomography angiography (Cirrus AngioPlex 5000 software V.10.0, Carl Zeiss Meditec, Dublin, CA) with a scanning mode of 3 × 3 mm was used to acquire images for all subjects. All subjects were scanned at the first visit or 3 months after surgery when the inflammation had resolved. Scans with significant artefacts (such as large floaters, segmentation errors, and blinking or motion artefact) or signal strength lower than eight were excluded.

This study analyzed the superficial capillary plexus. The superficial capillary plexus was autosegmented by the built-in software (AngioPlex, V.10.0). Image segmentation of superficial capillary plexus was
assessed and manually adjusted to reduce the segmentation errors.

The superficial retinal layer was imaged from the internal limiting membranes of the retina to the inner plexiform layer. In this study, the central foveal area is defined as the small circle 1 mm in diameter and centered at the fovea; the foveal area is defined as the large circle with 3 mm in diameter and centered at the fovea; and the parafoveal area is defined as the annular area in which the large circle without the small central circle. The inner ring was further divided into 4 equal quadrants (superior, inferior, nasal, and temporal) for subregion analysis (Figure 1). The VD is defined as the sum of the length of vessels in a particular area, and it is shown as \( \text{mm}^{-1} \) including whole fovea superficial capillary VD, central foveal superficial VD, and parafoveal superficial VD. The PD is defined as the percentage of the area occupied by the vessels in a particular area, and it is shown as \( \text{mm}^2/\text{mm}^2 \) including whole fovea superficial capillary PD, central foveal superficial PD, and parafoveal superficial PD. The center of the FAZ was also detected including the FAZ area, FAZ perimeter, and FAZ circularity index (CI). The OCTA data were acquired by the software automatically (AngioPlex, version 10.0). The BCVA and refraction data of all participants were recorded. All the examinations in this study were performed by one experienced technician using the same machine.

**Echocardiography**

Patients in the MFS group were examined with a full ultrasound system (Philips EnVisor C-HD; Philips Co, Best, The Netherlands) at baseline for a complete echocardiographic study. Aortic root diameters and left ventricular EF were measured following the current guidelines.\(^8\) The parasternal long-axis view was used to acquire aortic measurements. The aortic root was measured from the largest diameter within the sinuses of Valsalva. All echocardiographic images were acquired and analyzed by a single observer in a blinded manner. Aortic Z-score was calculated using the Colan formula\(^9\) according to recommendations of the Marfan Foundation. Aortic Z-score with correction for body height was used in the regression analysis because of its best clinical performance.\(^10\)

**Statistical Analysis**

All the numerical information was statistical analyzed by the SPSS version 22.0 (SPSS, Chicago, IL). The Kolmogorov–Smirnov test of normality was used. The differences of demographic characteristics and OCTA parameters between MFS group and healthy group were analyzed using the generalized estimating equation analysis. The correlation between the OCTA measurements and other clinical, functional, or structural data was analyzed. Each OCTA measurement was analyzed independently from the other measurements. Areas under the receiver operating characteristics curves (AUCs) were calculated and assessed as described previously.\(^11\) The desired overall \( \alpha \) level was 0.05; when multiple outcomes were compared between the groups, the \( \alpha \) level was adjusted through Bonferroni’s correction.

![Fig. 1. A representative OCTA image (A–C) of a 5-year-old boy with Marfan syndrome and a 11-year-old healthy boy (D–F).](image)
Results

Baseline and Demographic Data

Clinical characteristics of participants are summarized in Table 1. A total of 90 eyes from 45 MFS patients (25 men and 20 women) from 5 to 18 years old (mean 8.38 ± 3.55 years) were investigated. Seventy-six eyes of age- and sex-matched, healthy participants (20 men and 18 women, aged 7.97 ± 2.14 years) were also included in this study as control subjects. The AL was 24.74 ± 1.97 mm in the MFS group and 24.29 ± 1.35 mm in the control group (P = 0.366). The age, sex distribution, intraocular pressure (IOP), refractive error, and AL were similar in both groups. We confirmed the significant difference between the BCVA (logMAR [Snellen]) of MFS groups and healthy controls (0.31 ± 0.26 [20/41] vs. 0.00 ± 0.02 [20/20], P = 0.009).

Retinal Nerve Fiber Layer, Central Macular Thickness and Ganglion Cell-Inner Plexiform Layer Thickness

The MFS patients had 98.24 ± 11.98 μm RNFL, 244.5 ± 10.13 μm CMT, and 80.48 ± 10.86 μm ganglion cell-inner plexiform layer thickness, which were all relatively thinner than the controls (100.94 ± 8.61 μm in RNFL, 252.78 ± 14.40 μm in CMT, 83.29 ± 5.74 μm in ganglion cell-inner plexiform layer thickness) although with no statistical difference (P = 0.092, P = 0.096, P = 0.236, respectively, Table 2).

Vessel Density

The full superficial foveal VD was 20.29 ± 2.27 mm⁻¹ in the MFS group, which was confirmed significantly lower than those in healthy group by mixed factorial analysis (21.79 ± 0.99 mm⁻¹, P = 0.017, Table 3). The VD of parafoveal, nasal, and inferior values in the inner ring in MFS patients were 21.40 ± 2.26 mm⁻¹, 21.48 ± 2.59 mm⁻¹ and 21.13 ± 2.72 mm⁻¹, which were lower than that in the normal controls, although these were not significantly different after multivariate analysis.

Perfusion Density

The central superficial PD of MFS group (0.20 ± 0.06) was lower than that in the healthy group (0.23 ± 0.05) although these were not significantly different after multivariate analysis (Table 2).

Foveal Avascular Zone Characteristics

The CI of FAZ in patients with MFS (0.64 ± 0.11) was significantly higher than in the healthy controls (0.70 ± 0.08, P = 0.004) (Table 3).

Correlation Between Optical Coherence Tomography Angiography Indices and Other Clinical Functional or Structural Data

The correlations between the OCTA parameters and other parameters in MFS group, including age, gender,
Table 2. Quantitative Analysis Results of the Vascular and Structure Parameters in Patients With MFS and Normal Controls

|                     | Patients          | Control          |
|---------------------|-------------------|------------------|
| VD, mm⁻¹            |                   |                  |
| Full area           | 20.29 ± 2.27      | 21.79 ± 0.99     |
| Central area        | 11.56 ± 3.31      | 13.35 ± 2.77     |
| Para                | 21.40 ± 2.26      | 22.88 ± 0.95     |
| Inner ring          |                   |                  |
| Nasal               | 21.48 ± 2.59      | 23.03 ± 1.04     |
| Temporal            | 21.42 ± 2.46      | 22.71 ± 1.06     |
| Superior            | 21.48 ± 2.46      | 22.97 ± 1.15     |
| Inferior            | 21.13 ± 2.72      | 22.80 ± 1.30     |
| Perfusion density   |                   |                  |
| Full area           | 0.37 ± 0.04       | 0.38 ± 0.02      |
| Central area        | 0.20 ± 0.06       | 0.23 ± 0.05      |
| Para                | 0.39 ± 0.07       | 0.40 ± 0.01      |
| Inner ring          |                   |                  |
| Nasal               | 0.39 ± 0.05       | 0.40 ± 0.02      |
| Temporal            | 0.39 ± 0.04       | 0.40 ± 0.02      |
| Superior            | 0.39 ± 0.04       | 0.41 ± 0.02      |
| Inferior            | 0.38 ± 0.05       | 0.40 ± 0.02      |
| FAZ Area, mm²       | 0.25 ± 0.08       | 0.21 ± 0.10      |
| Perimeter, mm       | 2.20 ± 0.48       | 1.91 ± 0.45      |
| Circularity index   | 0.64 ± 0.11       | 0.70 ± 0.08      |
| RNFL, μm            |                   |                  |
| Average             | 98.24 ± 11.98     | 100.94 ± 8.61    |
| Superior            | 113.52 ± 23.41    | 124.28 ± 15.32   |
| Inferior            | 129.88 ± 18.28    | 128.82 ± 14.95   |
| CMT, μm             | 244.54 ± 10.13    | 252.78 ± 14.40   |
| Ganglion cell layer thickness, μm | 80.48 ± 10.86 | 83.29 ± 5.74 |
| Vertical C/D ratio  | 0.38 ± 0.17       | 0.41 ± 0.19      |

Data are presented as the mean ± SD.

BCVA, IOP, AL, degrees of EL, aortic diameters, Z-scores, and EF, are listed in Tables 4–6.

The central VD (β = 0.088, P < 0.001) and central PD (β = 0.001, P = 0.001) were found to positively correlate with the CMT. The central VD (β = −3.248, P = 0.003) and PD (β = −0.061, P = 0.001) were also found to negatively correlate with BCVA.

Moreover, the FAZ area were correlated with the aortic diameters (sinuses of Valsalva) (β = −0.011, P = 0.001). The paratemporal PD and the CI of FAZ were all correlated with the Z-score (β = 0.020, P < 0.001; β = 0.039, P = 0.003). The paratemporal PD were also found to be correlated with EF (β = 0.002, P = 0.003). In addition, lower paratemporal VD and PD were both found to be significantly associated with male sex and decrease central VD and PD were also found to be correlated with longer AL (all P < 0.003).

**Diagnostic Ability of Vessel Density and Perfusion Density**

The AUCs of VD and PD in various locations are presented in Figure 2. Para-area VD showed the best diagnostic performance with AUC of 0.770 followed by full-area VD (AUC: 0.760) and parainferior area VD (AUC: 0.750).

**Discussion**

Marfan syndrome is mostly caused by mutations in genes controlling the synthesis of FBN1. Large-vessel arterial complications in patients with MFS were well described. In MFS patients, leaky heart valves impairs forward flow of blood and can induce structural modifications of the arterial wall and reduces vessel wall compliance. Specific MFS cases with aneurysm formation have been reported, suggesting that small arteries may be affected in this disorder. Therefore, patients with MFS may have changes in the vessel wall of microvasculature.

The retina is one of the end organs that shares many vascular, structural, and physiological properties with the cerebral and coronary circulations. Moreover, retinal vessels are easily accessible compared with other end organs offering direct access for evaluation of the microvasculature. Optical coherence
Table 3. Retinal Vascular Parameter Differences Between MFS Versus Control Subjects by Univariate and Multivariate Logistic Regression Analysis

| Parameter                          | Full-Area VD |                             | Full-Area PD |                             |
|-----------------------------------|--------------|------------------------------|--------------|------------------------------|
|                                   | Univariate   | Multivariate                | Univariate   | Multivariate                |
|                                   | β (95% CI)   | P                            | β (95% CI)   | P                            |
| MFS vs. control                   | −1.692 (−2.426 to −0.959) | 0.000                        | −1.020 (−1.853 to −0.186) | **0.017**                    |
| Age, years                        | −0.102 (−0.266 to 0.063) | 0.226                        | −0.898 (−1.667 to −0.130) | 0.022                        |
| Sex (male/female)                 | −1.017 (−1.859 to −0.175) | 0.018                        | −2.607 (−6.451 to 1.236)  | 0.184                        |
| BCVA (logMAR [snellen])           | −4.013 (−6.813 to −1.212) | 0.005                        | −0.059 (−0.105 to −0.012) | 0.014                        |
| SE, diopter                       | 0.041 (−0.073 to 0.155)   | 0.479                        | 0.000 (−0.001 to 0.002)   | 0.648                        |
| Intraocular pressure, mmHg        | 0.071         | 0.082                        | 0.001 (5.904E-5 to 0.002) | 0.039                        |
| AL, mm                            | 0.246 (−0.150 to 0.642)   | 0.224                        | 0.002 (−0.005 to 0.008)   | 0.616                        |
| CMT, μm                           | 0.031 (0.014 to 0.048)    | 0.000                        | 0.000 (0.000 to 0.001)    | 0.001                        |
| Ganglion cell layer, μm           | 0.043 (−0.061 to 0.147)   | 0.420                        | 0.001 (−0.001 to 0.003)   | 0.369                        |
| Average RNFL, μm                  | −0.020 (−0.015 to 0.056)  | 0.265                        | 0.000 (0.000 to 0.001)    | 0.451                        |
| Inferior RNFL, μm                 | 0.008 (−0.013 to 0.029)   | 0.471                        | 0.000 (0.000 to 0.000)    | 0.327                        |
| Superior RNFL, μm                 | 0.016 (−0.006 to 0.037)   | 0.165                        | 0.000 (0.000 to 0.000)    | 0.503                        |
| vCD (%)                           | −0.991 (−3.738 to 1.755)  | 0.479                        | −0.991 (−3.738 to 1.755)  | 0.479                        |

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|                      | Full-Area PD                          | FAZ Circularity Index                      |
|----------------------|---------------------------------------|-------------------------------------------|
|                      | Multivariate                          | Univariate                                | Multivariate                          |
|                      | $\beta$ (95% CI)  | $P$          | $\beta$ (95% CI)  | $P$          | $\beta$ (95% CI)  | $P$          |
| BCVA (logMAR snellen)]| $-0.047$ (-0.112 to 0.018) | 0.155           | $-0.118$ (-0.192 to -0.044) | 0.002           | $-0.035$ (-0.111 to 0.040) | 0.359           |
| SE, diopter)         | $0.001$ (-0.001 to 0.002) | 0.300           | $-0.003$ (-0.006 to 0.001) | 0.185           | $0.005$ (0.000 to 0.010) | 0.032           |
| Intraocular pressure, mmHg | $0.001$ (-0.001 to 0.002) | 0.300           | $0.006$ (0.001 to 0.012) | 0.022           |                    |                |
| AL, mm              | $0.000$ (-3.300E-5 to 0.000) | 0.067           | $0.011$ (-0.003 to 0.025) | 0.111           |                    |                |
| CMT, $\mu$m         | $0.000$ (-0.002 to 0.003) | 0.753           | $0.000$ (-0.002 to 0.001) | 0.640           |                    |                |
| Ganglion cell layer, $\mu$m | $0.000$ (-0.002 to 0.001) | 0.640           |                    |                |                    |                |
| Average RNFL, $\mu$m | $-0.001$ (-0.002 to 5.816E-5) | 0.063           |                    |                |                    |                |
| Inferior RNFL, $\mu$m | $6.250E-5$ (-0.001 to 0.001) | 0.897           |                    |                |                    |                |
| Superior RNFL, $\mu$m | $-0.087$ (-0.448 to 0.751) | 0.103           |                    |                |                    |                |

* $P$ value significant after applying the corrected alpha threshold of 0.017; Bold indicates significant values.
Table 4. Correlations Between Baseline Characteristics and Vascular Density in MFS Patients Using Generalized Estimating Equations for Logistic Regression Analysis

|                       | Central VD | Para-Area VD | Full-Area VD | Para-Nasal-Area VD |
|-----------------------|------------|--------------|--------------|--------------------|
|                       | β (95% CI) | P            | β (95% CI)   | P                  | β (95% CI)         | P          |
| Age, years            | -0.660 (-0.971 to -0.355) | <0.001*      | 0.151 (-0.146 to 0.448) | 0.320              | 0.060 (-0.232 to 0.352) | 0.686      | 0.159 (-0.253 to 0.570) |
| Sex (male %)          | -1.650 (-3.182 to -0.120) | 0.035        | -2.196 (-3.607 to -0.784) | 0.002*             | -2.141 (-3.545 to -0.743) | 0.003*     | -2.793 (-4.771 to -0.815) |
| BCVA (logMAR [Snellen]) | -3.248 (-5.426 to 1.070) | 0.003*       | -0.973 (-2.685 to 0.738) | 0.265              | -1.230 (-2.920 to 0.461) | 0.154      | -1.970 (-4.685 to 0.744) |
| SE, D                 | -0.048 (-0.146 to 0.049) | 0.329        | -0.062 (-0.139 to 0.015) | 0.113              | -0.059 (-0.136 to 0.019) | 0.137      | -0.130 (-0.255 to -0.005) |
| Intraocular pressure, mmHg | -0.080 (-0.265 to 0.105) | 0.396        | 0.023 (-0.191 to 0.198) | 0.794              | 0.018 (-0.153 to 0.189) | 0.839      | 0.111 (-0.097 to 0.319)  |
| AL, mm                | 0.709 (0.381 to 1.037)    | <0.001*      | 0.057 (-0.243 to 0.357) | 0.710              | 0.131 (-0.165 to 0.428) | 0.384      | 0.178 (-0.259 to 0.616)  |
| CMT, μm               | 0.088 (0.046 to 0.130)    | <0.001*      | -0.005 (-0.038 to 0.028) | 0.768              | 0.006 (-0.028 to 0.040) | 0.740      | -0.041 (-0.097 to 0.016) |
| Ganglion cell layer, μm | 0.070 (-0.043 to 0.182)  | 0.227        | 0.087 (-0.046 to 0.219) | 0.201              | 0.086 (-0.046 to 0.218) | 0.201      | 0.075 (-0.074 to 0.224)  |
| vCVD (%)              | 1.583 (-2.110 to 5.276)   | 0.401        | -1.247 (-3.735 to 1.242) | 0.326              | -0.983 (-3.475 to 1.509) | 0.440      | -0.181 (-4.105 to 3.744) |
| Average RNFL, μm      | -0.053 (-0.167 to 0.060) | 0.359        | 0.029 (-0.077 to 0.135) | 0.593              | 0.021 (-0.079 to 0.121) | 0.682      | 0.071 (-0.055 to 0.197)  |
| Superior RNFL, μm     | 0.023 (-0.025 to 0.072)   | 0.347        | -0.011 (-0.048 to 0.026) | 0.577              | -0.007 (-0.043 to 0.029) | 0.714      | -0.014 (-0.059 to 0.031) |
| Inferior RNFL, μm     | 0.050 (-0.010 to 0.110)   | 0.100        | 0.012 (-0.046 to 0.070) | 0.680              | 0.015 (-0.040 to 0.070) | 0.588      | 0.002 (-0.062 to 0.065)  |
| Degree of lens dislocation (%) (severe) | 1.859 (-1.980 to 5.697) | 0.343        | -0.731 (-3.985 to 2.522) | 0.660              | -0.393 (-3.470 to 2.685) | 0.803      | 0.563 (-4.681 to 5.807)  |
| Aortic diameter sinuses of Valsalva, mm | 0.200 (-0.085 to 0.486) | 0.169        | -0.232 (-0.513 to 0.049) | 0.105              | -0.187 (-0.466 to 0.092) | 0.188      | -0.202 (-0.546 to 0.143) |
| Z score               | -0.150 (-0.880 to 0.580)  | 0.687        | 0.723 (-0.404 to 1.486) | 0.063              | 0.632 (-0.125 to 1.389) | 0.102      | 0.493 (-0.378 to 1.364)  |
| EF                    | 0.089 (-0.018 to 0.197)   | 0.103        | 0.09 (0.003 to 0.117)   | 0.042              | 0.094 (0.006 to 0.182)  | 0.036      | 0.076 (-0.028 to 0.180)  |

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Table 4.

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Nasal-Area VD      |            |         |            |         |            |         |
| VCD (%)                 | 0.288      | 0.002   | 0.038      | 0.038   | 0.042      | 0.004   |
| Average RNFL, μm        | 0.268      | 0.003   | 0.002      | 0.002   | 0.240      | 0.033   |
| Superior RNFL, μm       | 0.444      | 0.314   | 0.034      | 0.034   | 0.300      | 0.053   |
| Inferior RNFL, μm       | 0.599      | 0.005   | 0.005      | 0.005   | 0.696      | 0.062   |
| Degree of lens dislocation (%) | 0.188     | 0.241   | 0.241      | 0.241   | 0.128      | 0.217   |
| Aortic diameter sinuses of Valsalva, mm | 0.817 | 0.126 | 0.205 | 0.205 | 0.205 | 0.205 |
| Z score                 | 0.132      | 0.099   | 0.089      | 0.089   | 0.077      | 0.073   |
| EF                      | 0.154      | 0.026   | 0.021      | 0.021   | 0.037      | 0.037   |

*p value significant after applying the corrected alpha threshold of 0.003. Bold indicates significant values.

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Temporal-Area VD   |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Superior-Area VD   |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Inferior-Area VD   |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Nasal-Area VD      |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Temporal-Area VD   |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Superior-Area VD   |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Inferior-Area VD   |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |

**Table 4. Continued**

| Area VD                  | β (95% CI) | P       | β (95% CI) | P       | β (95% CI) | P       |
|-------------------------|------------|---------|------------|---------|------------|---------|
| Para-Nasal-Area VD      |            |         |            |         |            |         |
| VCD (%)                 |            |         |            |         |            |         |
| Average RNFL, μm        |            |         |            |         |            |         |
| Superior RNFL, μm       |            |         |            |         |            |         |
| Inferior RNFL, μm       |            |         |            |         |            |         |
| Degree of lens dislocation (%) |         |         |            |         |            |         |
| Aortic diameter sinuses of Valsalva, mm |         |         |            |         |            |         |
| Z score                 |            |         |            |         |            |         |
| EF                      |            |         |            |         |            |         |
Table 5. Correlations Between Baseline Characteristics and Perfusion Density in MFS Patients Using Generalized Estimating Equations for Logistic Regression Analysis

|                         | Central PD | Parafoveal PD | Full-Area PD | Paranasal-Area PD |
|-------------------------|------------|---------------|--------------|-------------------|
|                         | \( \beta \) (95% CI) | \( P \) | \( \beta \) (95% CI) | \( P \) | \( \beta \) (95% CI) | \( P \) | \( \beta \) (95% CI) | \( P \) |
| Age, years              | \(-0.013 (-0.018 to \textcolor{red}{0.001}^*\) | 0.195 | \(0.003 (-0.002 to 0.007)\) | 0.615 | \(0.004 (-0.003 to 0.010)\) | 0.281 |
| Sex (male%)             | \(-0.024 (-0.002 to 0.078\) | 0.011 | \(-0.029 (-0.052 to -0.007)\) | 0.13 | \(-0.04 (-0.072 to -0.008)\) | 0.013 |
| BCVA (logMAR [Snellen])| \(-0.061 (-0.052 to \textcolor{red}{0.001}^*\) | 0.155 | \(-0.018 (-0.042 to 0.007)\) | 0.065 | \(-0.039 (-0.081 to 0.002)\) | 0.064 |
| SE, D                   | \(-0.001 (-0.042 to 0.310\) | 0.310 | \(-0.001 (-0.002 to 3.393E-5)\) | 0.058 | \(-0.001 (-0.002 to 8.205E-5)\) | 0.71 | \(-0.002 (-0.004 to -0.001)\) | 0.005 |
| Intraocular pressure, mmHg | \(-0.001 (-0.002 to 0.404\) | 0.404 | \(0.001 (-0.002 to 0.004)\) | 0.675 | \(0.002 (-0.001 to 0.006)\) | 0.179 |
| AL, mm                  | \(0.009 (-0.002 to \textcolor{red}{0.001}^*\) | 0.582 | \(0.001 (-0.006 to 0.003)\) | 0.996 | \(0.001 (-0.007 to 0.008)\) | 0.861 |
| CMT, \(\mu m\)         | \(0.001 (-0.006 to \textcolor{red}{0.001}^*\) | 0.253 | \(-7.26E-05 (-0.001 to 0.000)\) | 0.760 | \(-0.001 (-0.002 to 1.693E-5)\) | 0.055 |
| Ganglion cell layer, \(\mu m\) | \(-0.026 (-0.001 to 0.330\) | 0.330 | \(0.001 (-0.001 to 0.004)\) | 0.194 | \(0.001 (-0.001 to 0.004)\) | 0.422 |
| vCD (%)                 | \(-0.002 (-0.001 to 0.452\) | 0.452 | \(-0.029 (-0.075 to 0.018)\) | 0.225 | \(-0.023 (-0.069 to 0.023)\) | 0.331 | \(-0.010 (-0.084 to 0.065)\) | 0.802 |
| Average RNFL, \(\mu m\) | \(-0.001 (-0.075 to 0.254\) | 0.769 | \(0.000 (-0.001 to 0.002)\) | 0.894 | \(0.001 (-0.001 to 0.003)\) | 0.427 |
| Superior RNFL, \(\mu m\) | \(0 (-0.001 to 0.000)\) | 0.714 | \(-6.13E-05 (-0.001 to 0.001)\) | 0.833 | \(0.000 (-0.001 to 0.001)\) | 0.783 |
| Inferior RNFL, \(\mu m\) | \(0.001 (-0.001 to 0.048\) | 0.647 | \(0.000 (-0.001 to 0.001)\) | 0.488 | \(0.000 (-0.001 to 0.001)\) | 0.821 |
| Degree of lens dislocation (%) (severe) | \(0.029 (-0.001 to 0.400\) | 0.747 | \(-0.003 (-0.050 to 0.044)\) | 0.904 | \(0.040 (-0.033 to 0.114)\) | 0.282 |
| Aortic diameter sinuses of Valsalva, mm | \(0.004 (-0.008 to 0.074\) | 0.057 | \(-0.003 (-0.007 to 0.001)\) | 0.143 | \(-0.003 (-0.009 to 0.002)\) | 0.260 |

(continued on next page)
Table 5. (Continued)

| Central PD | Parafoveal PD | Full-Area PD | Paranasal-Area PD |
|------------|---------------|--------------|-------------------|
| β (95% CI) | P              | β (95% CI)   | P                 |
| β (95% CI) | P              | β (95% CI)   | P                 |
| β (95% CI) | P              | β (95% CI)   | P                 |

| Z score    | 0.003 (0.000 to 0.002) | 0.013 (0.001 to 0.025) | 0.011 (0.001 to 0.023) | 0.007 (0.007 to 0.022) | 0.310 |
| EF         | 0.001 (0.000 to 0.002) | 0.001 (0.000 to 0.002) | 0.011 (0.002 to 0.027) | 0.007 (0.007 to 0.022) | 0.597 |

| Paratemporal-Area PD | Parasuperior-Area PD | Parainferior-Area PD |
|---------------------|----------------------|----------------------|
| β (95% CI)          | P                    | β (95% CI)          | P                    |

| Age, years          | 0.001 (0.000 to 0.006) | 0.556               | 0.004 (0.000 to 0.010) | 0.231               | 0.001 (0.000 to 0.007) | 0.863 |
| Sex (male%)         | -0.034 (-0.054 to -0.014) | **0.001***           | -0.023 (-0.052 to 0.007) | 0.134               | -0.018 (-0.051 to 0.014) | 0.270 |
| BCVA (logMAR [Snellen]) | -0.016 (-0.042 to 0.010) | 0.238               | 0.01 (0.029 to 0.048) | 0.629               | 0.051 (-0.095 to -0.008) | 0.020 |
| SE, D               | -0.001 (-0.002 to 2.562E-5) | 0.055               | -0.002 (-0.004 to 0.000) | 0.078               | 0.001 (-0.001 to 0.002) | 0.530 |
| Intraocular pressure, mmHg | 0.002 (-0.001 to 0.004) | 0.226               | 0.000 (-0.004 to 0.004) | 0.945               | 0.001 (-0.004 to 0.003) | 0.708 |
| AL, mm              | -0.004 (-0.008 to 0.001) | 0.086               | 0.001 (-0.006 to 0.008) | 0.793               | 0.003 (-0.009 to 0.003) | 0.300 |
| CMT, μm             | -0.001 (-0.001 to -9.281E-5) | 0.020               | 0.000 (-0.001 to 0.001) | 0.483               | 0.001 (-0.002 to 0.000) | 0.106 |
| Ganglion cell layer, μm | 0.002 (0.000 to 0.003) | 0.076               | 0.002 (-8.743E-5 to 0.004) | 0.061               | 0.001 (-0.001 to 0.004) | 0.300 |
| vCD (%)             | -0.007 (-0.061 to 0.048) | 0.812               | -0.058 (-0.136 to 0.020) | 0.146               | -0.048 (-0.127 to 0.031) | 0.234 |
| Average RNFL, μm    | 0.000 (-0.001 to 0.002) | 0.850               | 0.001 (-0.002 to 0.003) | 0.696               | -0.001 (-0.003 to 0.002) | 0.663 |
| Superior RNFL, μm   | 0.000 (-0.001 to 0.000) | 0.476               | 0.000 (-0.001 to 0.001) | 0.537               | 6.14E-05 (0.000 to 0.001) | 0.875 |
| Inferior RNFL, μm   | 0.001 (0.000 to 0.001) | 0.262               | 0.000 (-0.002 to 0.001) | 0.658               | 0.000 (0.000 to 0.002) | 0.156 |
| Degree of lens dislocation (%) | -0.067 (-0.141 to 0.007) | 0.075               | -0.067 (-0.158 to 0.023) | 0.145               | 0.039 (-0.057 to 0.135) | 0.422 |
| (severe)            |                      |                    |                      |                    |                      |       |
| Aortic diameter sinuses of Valsalva, mm | -0.005 (-0.008 to -0.001) | 0.016               | -0.005 (-0.010 to 0.001) | 0.091               | -0.003 (-0.008 to 0.003) | 0.358 |
| Z score             | 0.020 (0.010 to 0.029) | <**0.001***         | 0.013 (-0.001 to 0.027) | 0.064               | 0.010 (-0.005 to 0.025) | 0.207 |
| EF                  | 0.002 (0.001 to 0.003) | **0.003***          | 0.000 (-0.001 to 0.002) | 0.644               | 0.001 (-0.001 to 0.002) | 0.497 |

*P value significant after applying the corrected alpha threshold of 0.003. Bold indicates significant values.
Table 6. Correlations Between Baseline Characteristics and FAZ in MFS Patients Using Generalized Estimating Equations for Logistic Regression Analysis

|                          | FAZ Area                          | FAZ Perimeter                          | FAZ Circularity Index                          |
|-------------------------|-----------------------------------|----------------------------------------|------------------------------------------------|
|                         | \( \beta \) (95\% CI) \( P \)     | \( \beta \) (95\% CI) \( P \)         | \( \beta \) (95\% CI) \( P \)                  |
| Age, years 0.021 (0.015 to 0.028) | 0.012 (0.054 to 0.149) \(*\) \( <0.001^* \) | 0.004 (0.015 to 0.022) \( P \)        |
| Sex (male%) 0.024 (0.011 to 0.059) | 0.017 (0.179 to 0.212) \( P \)       | 0.051 (0.008 to 0.110) \( P \)         | 0.090 |
| BCVA (logMAR [Snellen]) 0.011 (0.055 to 0.633) | 0.160 (0.141 to 0.462) \( P \)       | 0.297 (0.020 to 0.074) \( P \)         | 0.359 |
| SE, D -0.001 (0.003 to 0.146) | -0.009 (0.021 to 0.002) \( P \)      | 0.119 (0.002 to 0.005) \( P \)         | 0.491 |
| Intraocular pressure, mmHg 0.003 (0.002 to 0.230) | 0.015 (0.021 to 0.062) \( P \)      | 0.330 (0.009 to 0.105) \( P \)         | 0.602 |
| AL, mm -0.022 (0.030 to 0.001) | -0.096 (0.153 to 0.039) \( P \)     | 0.013 (0.027 to 0.000) \( P \)         | 0.086 |
| CMT, \( \mu \text{m} \) -0.003 (0.004 to 0.002) | -0.017 (0.023 to 0.011) \( P \)     | 0.002 (0.001 to 0.004) \( P \)         | 0.142 |
| Ganglion cell layer, \( \mu \text{m} \) 0.001 (0.003 to 0.582) | 0.005 (0.021 to 0.012) \( P \)      | 0.585 (0.002 to 0.006) \( P \)         | 0.393 |
| vCD (%) -0.039 (0.104 to 0.233) | 0.015 (0.470 to 0.500) \( P \)     | 0.952 (0.211 to 0.019) \( P \)         | 0.031 |
| Average RNFL, \( \mu \text{m} \) 0.004 (0.001 to 0.004) | 0.013 (0.004 to 0.031) \( P \) | 0.131 (0.004 to 0.010) \( P \)         | 0.105 |
| Superior RNFL, \( \mu \text{m} \) -0.002 (0.003 to 0.005) | -0.008 (0.016 to 0.001) \( P \)  | 0.074 (0.002 to 0.001) \( P \)         | 0.173 |
| Inferior RNFL, \( \mu \text{m} \) -0.002 (0.003 to 0.011) | -0.006 (0.016 to 0.003) \( P \) | 0.191 (0.002 to 0.005) \( P \)         | 0.075 |
| Degree of lens dislocation (%) 0.028 (0.090 to 0.643) | 0.219 (0.590 to 1.028) \( P \) | 0.596 (0.153 to 0.151) \( P \)         | 0.323 |
| Aortic diameter (sinuses of Valsalva, mm) -0.011 (0.018 to 0.005) | -0.038 (0.006 to 2.824) \( P \) | 0.093 (0.014 to 0.027) \( P \)         | 0.020 |
| Z score 0.024 (0.008 to 0.041) | 0.060 (0.172 to 1.136) \( P \)     | 0.286 (0.039 to 0.065) \( P \)         | 0.003* |
| EF -0.001 (0.003 to 0.684) | -0.005 (0.026 to 0.016) \( P \) | 0.645 (0.004 to 0.009) \( P \)         | 0.073 |

*P value significant after applying the corrected alpha threshold of 0.003. Bold indicates significant values.

dysfunction in patients with cardiovascular risk factors and MFS patients have reduced rotational flow in the aorta and impaired function of left ventricle. The results of our study reveal that patients with a larger ascending aorta diameter and left ventricular dysfunction correlates with impairment of retinal blood flow, which indicated that aortopathy in patients with MFS parallels retinal vascular defects. Indeed, despite the fact that severity of aortic disease is the most important diagnostic and prognostic factor determining outcome in this disease, accurate measurements are often difficult to obtain especially in children. Some echocardiographic parameters are affected by increased interobserver and intraexamination variability. However, recent studies have shown a high repeatability and reproducibility of OCTA examination. An OCTA evaluation is easy to perform, objective, and complication free and could be a promising biomarker supporting diagnosis or in providing prognostic information. In addition, retinal microvasculature has been proposed as an easily measured surrogate for systemic circulation. Previous studies in patients with congenital heart disease and coronary heart disease also found a decreased retinal VD compared with normal controls. Therefore, the OCTA examination may provide a great future opportunity for the early recognition of cardiovascular damages in children with MFS.
Importantly, we found that central VD and PD were negatively correlated with BCVA. It has been shown that almost half of the MFS patients had amblyopia in spite of good conservative management. Our finding suggests that the retinal PD and VD may correlate with the occurrence and development of visual outcomes in MFS patients. Visual acuity was found to be associated with FAZ circularity and vessel diameter index in amblyopic eyes and in patients with spontaneously regressed retinopathy of prematurity. In diabetic retinopathy, decreased VD was also found to be associated with a reduction in the visual function. Nevertheless, VD was not correlated with VA in normal children. Therefore, whether foveal microvasculature itself or in combination with other parameters can contribute to the complex function of visual acuity remained to be investigated.

In this study, the reduction of macular central VD and central PD in MFS patients were also found to be positively correlated with the CMT, suggesting that changes in the vasculature network that supports the inner retina could lead to structural consequences. A previous study suggested that a reduction in the retinal blood supply to inner retinal neurons may cause cell death and ischemia. At the same time, most OCT parameters were found to be correlated with OCTA parameters in healthy participants 5 to 80 years old. Finally, we found that the AL was correlated with the superficial vasculatures. In myopic eyes and many healthy controls, the retinal vessel density was reduced. We and others confirmed that the superficial macular vessel density was higher in girls than in boys. On the contrary, some studies found the opposite result. More evidence is required to investigate the sex discrepancy in the retinal vessel density.

Microvascular alterations can be an early sign for certain diseases and correlated with functional parameters. It is worthy to note that the identification of early microvascular impairment may indicate which patients seem to have higher risk of developing cardiovascular diseases and should be more frequently monitored. To investigate how accurate the OCTA parameters can be in the diagnosis of children with MFS, we examined 14 different potentially discriminatory features. We found that the para-area VD (AUC: 770) had the best diagnostic efficacy in distinguishing a healthy eye from an MFS one; however, the diagnostic value of this finding needs to be determined in a larger sample study. Both large retinal vessels and capillaries build up the superficial retinal capillary network whose metrics had been showed to have a good diagnostic performance in systemic diseases such as diabetes mellitus, hypertension, and cardiovascular disease. A future longitudinal study is required to investigate the cause-and-effect relationship between MFS and OCTA metrics and any such possible relationship.

The limitations of this study are that this is single-center study with monoracial background (all subjects were from China), a relatively small sample size, and a lack of long-term follow-up, which may have increased the bias of the study. More extensive and longitudinal studies are necessary to verify these results.

This study confirmed that young MFS patients have morphological changes in the macular microvasculature. Alterations of microvascular flow were associated with visual acuity, CMT, aorta size, Z-score, and EF, suggesting that the inner retina of MFS patients had vascular changes which were structurally, functionally and systemically associated with MFS. In general, our results highlight the capability of OCTA to accurately characterize retinal microvascular network changes in MFS patients enabling further understanding of the pathogenesis of arterial disease in MFS. Therefore, OCTA and quantitative OCTA metrics, such as VD,
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PD, and FAZ, could be a reliable, objective, and automated tool in the recognition and evaluation of MFS. Further randomized trials with larger patient groups and additional systemic parameters could shed more light on this issue.

Key words: foveal microvasculature, Marfan syndrome, optical coherence tomography angiography.

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