

Decreased Retinal Microvasculature Densities in Pterygium

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Abstract

Purpose To investigate the retinal vascular network alterations in eyes of patients with pterygium.

Method 18 left eyes from 18 female pterygium patients and 18 left eyes from 18 female healthy control subjects were enrolled. Optical coherence tomography angiography (OCTA) images were generated of the superficial retinal layer (SRL) and deeper retinal layer (DRL) of the macular retina for each eye. The microvascular (MIR) and macrovascular (MAR) densities were calculated and MIR, MAR, and total MIR (TMI) density was compared in the healthy control and pterygium groups.

Results In pterygium group, in the SRL, the vascular density in SMIR (superficial MIR), SR (superior right), IR (inferior right), R (right), SC (superficial central annuli) 1, SC2 and SC3 decreased significantly in the macular area ($P < 0.05$). Furthermore, the vascular density in all those decreased regions except R, was significantly and negatively correlated with the disease course ($r = -0.6038$ to -0.7762 , $P = 0.0008$), and the area size of pterygium ($r = -0.6043$ to -0.9508 , $P < 0.05$). For the DRL, the density of DTMI, DMIR (deeper MIR), SR, IR, R, DC2 and DC3 decreased significantly in macular area of pterygium patients ($P < 0.05$). Furthermore, the vascular density in all those decreased regions was significantly and negatively correlated with the disease course ($r = -0.6901$ to -0.7795 , $P = 0.0015$), and the area size of pterygium ($r = -0.6043$ to -0.9563 , $P < 0.05$). No statistically significant differences and correlation was found in other region density ($|r| \leq 0.47$, $P > 0.05$).

Conclusion OCTA findings suggested that pterygium patients present with decreased retinal MIR density, which was negatively correlated with the disease course and the area size of pterygium.

Introduction

Pterygium is a common disease of the ocular surface involving deposition of a triangular mass of fibrovascular tissue from the bulbar conjunctiva to the cornea, usually occurring on the nasal side, and seriously affecting visual acuity. Its pathological mechanism has not been elucidated. Ultraviolet radiation, wind, and dust generally affect the prevalence of pterygium [1, 2], with an incidence up to 39% among people over 50 years old [3]. Pterygium not only affects the patient's appearance, but also leads to astigmatism, eye irritation, and dry eyes. Furthermore, the recurrence of pterygium can also cause serious complications such as symblepharon and restriction of eyeball movement [3]. Hill et al [1] reported that neovascularization might be involved in the occurrence and development of pterygium, which is further evidenced by Aspiotis et al [4], he reported that the microvascular density from 52 pterygium specimens was significantly increased than that of 7 normal conjunctival tissues analyzed by using the immunohistochemistry staining. Misra et al [5] investigated the changes in visual acuity after pterygium surgery, and found that both unaided and best spectacle corrected visual acuity (BSCVA) were improved significantly in 1 month postoperatively, and the improvement was persistent and maintained for 3 months postoperatively. Therefore, in-depth studies of pterygium are actively demanded for the prevention and recurrence and disease by throwing light on its mechanism with great significance.

The macular area of the human fundus is largely responsible for the human's overall vision, because it is the primary distribution locus for the visual cells and retinal ganglion cells[6, 7]. It is important to understand the coupling between the macular vascular system and the dense macular neurons. The blood flow of pterygium mainly comes from the conjunctival vessels, thus we are wondering whether pterygium pathology will involve the microvessel alterations in the macular area of the fundus. Also whether the altered microvessel will impact the visual acuity has not been reported yet.

Optical coherence tomography angiography (OCTA), based on the principle of frequency division and amplitude decorrelation, has begun to be applied in clinical practice and has been used to detect macular vascular density in glaucoma patients[8]. Penteadó et al [8] by using the OCTA evaluated the macular vascular density in healthy, glaucoma suspect, and glaucoma patients, and found that the macular vascular density in glaucoma was significantly decreased or lost, when compared to the healthy control. Furthermore, they found that Loss of OCT-A macula vessel density is associated with central 10-2 VF defects. Therefore, in this study, we applied the OCTA technique to investigate the retinal microvasculature alteration in pterygium, and the correlation with the disease course and area size of pterygium.

Materials And Methods

This study was approved by the Ethics Committee of Medical school of Nanchang University and performed in accordance with the Declaration of Helsinki principles. A consent form was signed by each subject. In this study, 18 left eyes from 18 female patients with pterygium and 18 left eyes from female healthy controls were enrolled. All subjects were evaluated by a retinal specialist from the First Affiliated Hospital of Nanchang University between 2017 and 2018. The age with all the subjects was between 40-48 years old, with average age of 46 ± 10 .

All patients underwent clinical examination and ophthalmological assessment at the first visits. The inclusion criteria included: (1) female patients first diagnosed with primary pterygium occurring in the nasal side in her left eye; (2) head of the pterygium invaded 2.0-7.0 mm toward the corneal limbus; (3) A disease history of 7-20 years, with an average of 6.70 ± 5.01 years; (4) binocular fixation was good, and the diopter difference between the two eyes not exceed 2 D; (5) intraocular pressure was 11-21 mmHg (1 mmHg = 0.133 kPa) with normal fundus conditions.

The exclusion criteria included: (1) eye surgery or trauma; (2) eye disease or other systemic diseases affecting eye circulation, such as glaucoma, hypertension, diabetes, etc; (3) drug treatment within the past two weeks; (4) fundus examination indicated highly myopic and pathological macular changes (including macular holes, neovascularization, atrophy, et al; (5) severe cataracts, myopia, and patients wearing contact lenses; (6) systemic diseases including mental and central nervous system disorders; (7) pregnancy and lactating women; (8) pseudopterygium. The demographic characteristics and clinical findings of patients with pterygium and healthy controls were summarized in Table 1.

[Table 1]

All subjects underwent a complete ophthalmological evaluations, including:

(1) Slit lamp examination. Slit lamp microscopy was used to examine the anterior segment of the eye, and to detect ocular inflammation, corneal opacity or severe cataracts with image refraction, and the size of any pterygium, and the scope of corneal limbus invasion.

(2) Visual acuity. a logarithmic visual acuity chart was used, and the binocular vision and the best corrected visual acuity was obtained for all of the subjects.

(3) Intraocular pressure. A TDT tonometer (BiCOM, Long Beach, NY, USA) was used to measure intraocular pressure three times. The intraocular pressure measured in both eyes was less than 21 mmHg. The difference between the two measurements was ≤ 3 mmHg, and the average value was calculated.

(4) Dimensional parameters of pterygium include: length (L) [defined as the distance from the corneal limbus to the edge of the pterygium], height (H) [defined as the distance between the relative edge of the pterygium and the corneal limbus], and area (A) [as defined as the surface area of the cornea invaded by pterygium] were calculated using the NIH Image J of the National Institutes of Health, Bethesda, MD, USA [9]. Corneal diameters were measured with digital calipers from 18 patients. The images were calibrated with pixels/mm (mean = 368.12 and standard deviation = 9.74 pixels/mm). The accuracy of the measurements per mm was 0.025 mm. Given the possibility that different corneal diameters have different types of effects on the pterygium, three new parameters were defined and calculated from the length, height, and area of the pterygium by using corneal diameters (D). These parameters included the distance between the edge of the pterygium and the center of the pupil (deduced as $\text{Icntr } D/2-L$), the angle corresponding to the central angle of the pterygium (derived as $[H/2*3.1459] 360$) and the angle derived from pterygium (arfrac) as $(A/[3.14159*D/2]^2)$. The length, height, and area of each pterygium were measured 5 times to generate an average.

To simultaneously visualize the retinal cross sections and microvasculature, OCTA imaging was performed with the RTVue Avanti XR system (Optovue, Fremont, CA). The scan speed was set to 70,000 A-scans/second, with a central wavelength of 840 nm and bandwidth of 45 nm super light-emitting diode [10]. Imaging was performed using angiographic [11, 12] repeated B-scans of 6×6 -mm scan patterns of 216 A-scans (along the x-axis) each at 216 raster positions, focused at the foveal center, and the acquisition time was 3.9 seconds. The superficial and deep microvasculature from the retina may be obtained from the automatic fractionation (FIG. 3). We acquired 6×6 -mm OCTA images by a series of 2 volume scans: 1 horizontal and 1 vertical gratings. For each eye, 3-dimensional 6×6 -mm en-face OCT angiograms were calculated. Motion artifacts were corrected using orthogonal scan alignment algorithm. Density was calculated using SSADA algorithm. The retinal superficial blood flow layer was defined as 3um below the inner limiting membrane to 15um below the inner plexiform layer, and the retinal deep blood flow layer was defined as 15-70um below the inner plexiform layer. The superficial retinal layer consists of ganglion cells and inner plexiform layer, while the deep retinal layer consists of

inner nuclear layer and outer plexus layer. These layers contain the entire retinal vascular system [13] We can better understand the relationship between pterygium and macular vascular density area, and the zoning method for area of macular retinal is shown in figure 1.

[Figure 1]

1.3 Statistical analysis

All data were analyzed by statistical software packages (StatSoft v7.1; Tulsa, OK, USA), and MedCalc software (v10; MedCalc Software, Mariakerke, Belgium). Continuous variables were calculated as the mean \pm standard deviation (SD). Univariate analysis of variance (ANOVA) was used to analyze the microvessel density in each area of each group. Minimum significant differences were used to assess the difference between the two using a specific test. P values < 0.05 were considered to indicate statistically significant differences. The correlation between macular vascular density and the disease course and size of pterygium area was analyzed using Graphpad prism 7.0, and then SPSS 23.0 (IBM Corp, Armonk, NY, USA) was used to plot the working characteristic (Receiver Operator Characteristic, ROC) curves of microvessel density (MVD) in the retinal epithelium to to differentiate between healthy and diseased subjects.

Results

By analysis of the microvessel, macrovascular ring, and microvessel density in superficial layer (Figure 2) and deep layer (Figure 3) between the two groups , we found that the vascular density of SMIR in the pterygium group was decreased significantly when compared to the healthy control group ($P < 0.05$, Figure 2A). Similarly, the vascular density of DTMI and DMIR in deep layer pterygium patients also decreased significantly ($P < 0.05$, Figure 3A) . However, MAR density was not significantly altered in either layer. Using the hemispheric partition and Early Treatment Diabetic Retinopathy Study (ETDRS) method for comparison, we found that the vascular density of SR, IR, and R in superficial layer was decreased significantly ($P < 0.05$, Figure 2B and 2C) , and the vascular density in SR, IR, and R in the deep layer decreased significantly ($P < 0.05$, Figure 3B and 3C) as well. Using the central annuli method for comparison, we found that the vascular density in region of SC1, SC2, and SC3 in the superficial layer was decreased significantly ($P < 0.05$, Figure 2D). For the deep retinal layers, the vascular density in the regions of DC2 and DC3 also decreased significantly ($P < 0.05$, Figure 3D). No statistically significant differences were observed in other regions ($P > 0.05$).

[Figure 2]

[Figure 3]

The retinal vessel density measured by OCTA showed the best sensitivity and specificity to differentiate pterygium from healthy control. In the superficial layer, the SC2 density had the highest positive likelihood ratios in the pterygium group, while SC1 showed the lowest negative likelihood ratio (Table 2). ROC

analysis revealed that SC2 had the highest sensitivity and specificity with the ROC curve 0.85 (95% confidence interval [CI] = 0.72-0.98), and SC1 had the lowest sensitivity and specificity with the ROC curve 0.63 (95% CI of 0.44-0.82) (Table 2). Similarly, in the deep retinal layer, the DC2 density had the highest positive likelihood ratios in the pterygium group, while the IR showed the lowest negative likelihood ratio (Table 2). ROC analysis revealed that DC2 had the highest sensitivity and specificity with the ROC curve 0.85 (95% confidence interval [CI] = 0.72-0.98), and IR had the lowest sensitivity and specificity with the ROC curve 0.72 (95% CI of 0.54-0.89) (Table 2).

[Table 2]

We next investigated the correlation among SMIR, SR, IR, SC1, SC2, and SC3 in the superficial retinal layer with disease course in pterygium group. In the pterygium group, the correlation coefficient of SMIR density and disease course was -0.7662 , and the correlation coefficient of the SR density with disease course was -0.6038 . And the correlation coefficient of IR density with disease course was -0.6234 , and the correlation coefficient of the SC1 density and disease course was -0.7762 . Besides, the correlation coefficient of SC2 density with disease course was -0.7123 , and the correlation coefficient of the SC3 density with disease course was -0.6615 . No correlation in other region density with disease course was found ($|r| \leq 0.47$, $P > 0.05$). These results indicated that decreased macular density in superficial layer of SMIR, SR, IR, SC1, SC2 and SC3 might be negatively correlated with the disease course, suggesting that the longer the disease course, the lower vascular density in those regions.

Besides, we also analyzed the correlation between the vascular density of superficial retinal and the area size of pterygium. Our analyzed data showed that in the pterygium group, the correlation coefficient of SMIR density with the area size of pterygium was -0.9508 , and the correlation coefficient of the SR density with the area size of pterygium was -0.8935 . And the correlation coefficient of IR density with pterygium area size was -0.9359 , and the correlation coefficient of the R density with the area size of pterygium was -0.6043 . Besides, the correlation coefficient of SC1, SC2 and SC3 densities with the area size of pterygium was -0.8217 , -0.8976 and -0.7757 , respectively (Table 2). No correlation in other region density with area size of pterygium was found ($|r| \leq 0.47$, $P > 0.05$). These results indicated that decreased macular density in superficial layer of SMIR, SR, IR, R, SC1, SC2 and SC3 might be negatively correlated with the area size of pterygium, suggesting that the bigger the area size of pterygium, the lower vascular density in those regions.

Furthermore, in deep retinal layer, we also analyzed the vascular densities of deep retinal (deep microvessels), and showed that in the pterygium group, the correlation coefficient of DTMI density with disease course was -0.7003 , and the correlation coefficient of the DMIR density with disease course was -0.6901 . And the correlation coefficient of SR density with disease course was -0.7795 , and the correlation coefficient of the IR density with disease course was -0.7198 . Besides, the correlation coefficient of R, DC2, and DC3 density with disease course was -0.7608 , -0.7504 and -0.7195 , respectively (Table 2). No correlation in other region density with disease course was found ($|r| \leq 0.47$, $P > 0.05$). These results indicated that decreased macular density in deep layer of DTMI, DMIR, SR, IR, R, DC2, and DC3

might be negatively correlated to the disease course, suggesting that the longer the disease course, the lower vascular density in those regions.

Besides, we also analyzed the correlation between the vascular density of deep retinal and the area size of pterygium, and showed that in the pterygium group, the correlation coefficient of DTMI density with the area size of pterygium was -0.9563, and the correlation coefficient of the DMIR density with the area size of pterygium was -0.9508. And the correlation coefficient of SR density with pterygium area size was -0.8935, and the correlation coefficient of the IR density with the area size of pterygium was -0.9359. Besides, the correlation coefficient of R, DC2 and DC3 densities with the area size of pterygium was -0.6043, -0.8976 and -0.7757, respectively (Table 2). No correlation in other region density with area size of pterygium was found ($r=0.47$, $P>0.05$). These results indicated that decreased macular density in deep layer of DTMI, DMIR, SR, IR, R, DC2 and DC3 might be negatively correlated to the area size of pterygium, suggesting that the bigger the area size of pterygium, the lower vascular density in those regions.

Discussion

In this study, we used OCTA to investigate the retinal microvasculature alteration in pterygium. To our knowledge, this was the first study to discover and report that the vascular density decreased in the macular area of patients with pterygium, and the major vascular alterations occurred mainly on the bitamporal side. We further found that the decreased vascular density of the macula was negatively correlated to the disease course and to the area size of pterygium. There is quite few technique used in the study of retinal, choroid, and retrobulbar blood circulation[14, 15]. OCTA has revealed many details of the superficial and deep retinal layers. [17]Many studies have shown that OCTA can be used to diagnose choroidal neovascularization (CNV), age-related macular degeneration (AMD),[18]retinal vein occlusion (RVO), [17]abnormal retinal vessels,[19]and even non-permeable AMD[20]and melanocyte tumors. Thus OCTA could be an important technique for studying the progression, retinal pathology, and complications of pterygium by providing scientific evidences on vascular density alteration.

By using the OCTA technique in pterygium, our results showed that vascular densities decreased in the retinal superficial SMIR, SR, IR, R, and retinal deep DTMI, DMIR, SR, IR, R in pterygium patients. The major decreased region was on the bitamporal side of macula. The annuli partition method showed that vascular density of the superficial SC1, SC2, SC3 in the foveal and deep layer of DC2, DC2 regions, significantly decreased. Zhao et al[21]cthere was a significant increase in retinal vessel density, a decrease in the foveal avascular zone at the macular area after the cataract surgery. Also they found that the retinal vessel density of the parafoveal and perifoveal regions increased significantly at 1week, 1month, and 3 months after the cataract surgery. At 3 months after surgery, there was a mean $6\pm 11\%$ and $3\pm 10\%$ increase in vessel density at the parafoveal and perifoveal regions, respectively (compared with the baseline, which seems consistent with our data. It has been estimated that a cataract might block 18% to 40% of light at different wave-lengths. Zhao et al[21] thought that the increase density in macular vasculature in cataract patients resulted from the increase of light exposure. Thus the possible reason for the alteration in macular vasculature could be the increase in light exposure after cataract

surgery. Our data also supported the hypothesis. Pterygium blocked the light exposure from cornea, which may lead to a reduction in retinal activity and metabolic demands[22, 23], leading to a decreased vascular density. Hardarson et al[24] tried to address this question. However, their results were shown uncertain. Pterygium occurs on the nasal side, which blocks refraction and scattering of light from the refractive stroma in this region, therefore mainly affecting the retina on bitamporal side. On the other hand, the decreased light exposure may be associated with the metabolic changes and the unique vascular pattern of the central fovea. Light vision is accomplished by cone cells, which are also in the highest density in the central fovea. The decreased light exposure leads to a decreased activity of cone cells. Furthermore, the consistency of this location also supports the hypothesis that the decreased light exposure may lead to the decreased density in macular blood vessels.

Our data also showed that in the pterygium group, SC2 and DC2 had the highest positive likelihood ratio, and SC1 and IR had the lowest negative likelihood ratio. And we found that the decreased vascular density was negatively correlated with the disease course, and the size of pterygium area. Pterygium is caused by dysfunction of limbal stem cells and a decrease in the number of stem cells, resulting in an active proliferation and remodeling of conjunctival fibroblasts, and vascularization of connective tissue. The most significantly pathological alterations of pterygium is the proliferation and degeneration of elastic fibers and collagen fibers. But it is not a simple process of proliferation, but an ever-changing process[25]. This obviously pathological alterations indicated that the longer the disease course of the pterygium, the larger size of the pterygium area would develop, therefore blocking more external sunlight into the bitamporal retina. Aspiotis et al [26]reported that pterygium tissues presented with statistically significant higher density of average count of microvessel, when compared to normal conjunctivae, and the angiogenesis-related factors were highly expressed in pterygium tissue. The vascular hypothesis points out that the blood flow of pterygium mainly come from the bulbar conjunctival blood vessels. The blood flow of the bulbar conjunctival blood vessels and the blood flow of the fundus comes mainly from the shared ophthalmic artery. The generation of the pterygium may increase the blood flow in the anterior segment of the eye. Therefore, if the pterygium disease course is longer, or the area size of pterygium is larger, the relatively blood flow of the fundus from the ophthalmic artery would decrease, therefore leading to a decrease in vascular density in the fundus.

Decreased macular vascular density may also affect visual acuity. Hiton[27] reported that after cataract surgery, the increased vascular density in macula was beneficial to the eyes. Our results showed that the visual acuity decreased significantly in pterygium when compared to healthy control (Table 1). But pterygium can also cause corneal alteration[28] leading to a decreased visual acuity, although the posterior corneal surface has been shown to compensate for anterior corneal astigmatism[29-31]. Corneal astigmatism and ocular wavefront aberrations are also found to be related to the area size of the pterygium[32]. Large pterygium may invade the pupillary area and lead to a decrease in visual acuity. Since it is difficult to control these factors, it is not clear whether it is beneficial to the eyes. Surgical removal is still the main therapy for pterygium[33]. After pterygium excision, astigmatism and the wavefront aberration caused by the pterygium on the cornea will be greatly reduced[34-36]. Visual acuity will also be significantly improved. The decreased vascular density in macula will help to understand the

pathophysiological mechanisms involved in the pterygium . This study has some limitations. We did not measure the VEGF. A significant increase of VEGF was reported to occur in pterygium patients[37]. VEGF is mainly produced by fibroblasts. A variety of factors including inflammation, hypoxia, toxic substances, and ultraviolet damage, can affect its expression[37]. The formation of pterygium is accompanied by the growth of activated fibroblasts, the excessive proliferation of extracellular matrix, and inflammation. Whether the production of VEGF will alter the vascular density, we have no answer since no VEGF was tested in the study due to the difficulty in biopsy availabilities. In addition, we also consider that pterygium may lead to low measurements of macular vascular density in healthy eyes, as this can lead to artifact generation, which needs further study.

In summary, this study, by using the OCTA, a convenient and rapid technique to detect the microvessel alteration in the retina macular area in pterygium patients, we first discovered and reported a decreased vascular density in fundus of the pterygium patients. and we further found that the vascular density was negatively correlated to the disease course and the size of the pterygium area. Our data may help to characterize the underlying pathophysiological mechanisms involved in pterygium. The decreased microvessel density in the retina macular area may also help to provide the theoretical basis for the disease prevention, treatment of recurrence and its complications. Besides, it may also provide the important scientific evidences to the clinical oculists for the visual acuity assessment after pterygium removal by surgery. However more studies are still needed to investigate whether the vascular density of the macula would recover after pterygium is removed by surgery.

Abbreviations

DMIR=deep microvessel DRL=deep retinal layer FAZ= foveal avascular zone MAR=macrovascula
MIR=microvessels OCTA=optical coherence tomography angiography SMIR=superficial microvessels
SMAR=superficial macrovascula SRL= superficial retinal layer STMI=total superficial microvessels;
DMAR= deep macrovascular; DTMI=deep total microvessel TMI=total microvasculature I = inferior; IL =
inferior left; IR = inferior right; L = left; R = right; S = superior; SL = superior left; SR = superior right
ROC=receiver operating characteristic SSADA=splitspectrum amplitude-décor-relation angiography CI =
confidence interval DC = deep central annuli SC = superficial central annuli.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request

Authors contributions

Conceptualization of the study: FW, LHY, YS, GPG. Data acquisition and analysis: FW, LHY, WQS, BL, QL, YLM, QY. Manuscript preparation: FW, LHY, YS, GPG. All authors have read and approved the manuscript for publication

Ethical approval and consent to participate:

All procedures performed in the study involving human participants were in accordance with the ethical standards of the First Affiliated Hospital of Nanchang University ethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

We obtained written informed consent for publication from the patients related to details and images.

Competing interests

This was not an industry supported study. The authors declare that they have no competing interests.

References

1. Hill JC, Maske R: **Pathogenesis of pterygium**. *Eye* 1989, **3 (Pt 2)**(2):218.
2. Otsuka J: **[Treatment of pterygium]**. *Ganka* 2011, **10**(3):197-203.
3. Hua Z, Xueping C, Tao W, Xianchai L, Xun L, Jun L, Ning C, Juanjuan L, Xiaodan S, Yongming Y: **Prevalence of and risk factors for pterygium in rural adult chinese populations of the Bai nationality in Dali: the Yunnan Minority Eye Study**. *Guihai Tribune* 2007, **53**(10):6617.
4. Aspiotis M, , Tsanou E, , Gorezis S, , Ioachim E, , Skyrilas A, , Stefaniotou M, , Malamou-Mitsi V, . **Angiogenesis in pterygium: study of microvessel density, vascular endothelial growth factor, and thrombospondin-1**. *Eye* 2007, **21**(8):1095-1101.
5. Misra S, Craig JP, McGhee CN, Patel DV: **A Prospective Study of Pterygium Excision and Conjunctival Autograft With Human Fibrin Tissue Adhesive: Effects on Vision, Refraction, and Corneal Topography**. *Asia Pac J Ophthalmol (Phila)* 2014, **3**(4):202-206.
6. Provis JM, Penfold PL, Cornish EE, Sandercoe TM, Madigan MC: **Anatomy and development of the macula: specialisation and the vulnerability to macular degeneration**. *Clinical & Experimental Optometry* 2010, **88**(5):269-281.

7. Curcio CA, Sloan KR, Kalina RE, Hendrickson AE: **Human photoreceptor topography.** *Journal of Comparative Neurology* 1990, **292**(4):497.
8. Kromer R, Glusa P, Framme C, Pielen A, Junker B: **Optical coherence tomography angiography analysis of macular flow density in glaucoma.** *Acta Ophthalmol* 2019, **97**(2):e199-e206.
9. Vanathi M, Goel S, Ganger A, Agarwal T, Dada T, Khokhar S: **Corneal tomography and biomechanics in primary pterygium.** *Int Ophthalmol* 2018, **38**(2):663-671.
10. Durbin MK, An L, Shemonski ND, Soares M, Santos T, Lopes M, Neves C, Cunha-Vaz J: **Quantification of Retinal Microvascular Density in Optical Coherence Tomographic Angiography Images in Diabetic Retinopathy.** *Jama Ophthalmology* 2017, **135**(4):370.
11. Salz DA, Carlo TED, Adhi M, Moulton E, Choi WJ, Bauman CR, Witkin AJ, Duker JS, Fujimoto JG, Waheed NK: **Select Features of Diabetic Retinopathy on Swept-Source Optical Coherence Tomographic Angiography Compared With Fluorescein Angiography and Normal Eyes.** *Jama Ophthalmology* 2016, **134**(6):644.
12. Yang Y, Wang J, Jiang H, Yang X, Feng L, Hu L, Wang L, Lu F, Shen M: **Retinal Microvasculature Alteration in High Myopia.** *Investigative Ophthalmology & Visual Science* 2016, **57**(14):6020.
13. Kur J, Newman EA, Chan-Ling T: **Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease.** *Progress in Retinal & Eye Research* 2012, **31**(5):377-406.
14. Marta PL, Marco SS, Gema R, Pilar CL, Cristina GG, Elena J, Francisco José MON: **Retrobulbar ocular blood flow changes after orbital decompression in Graves' ophthalmopathy measured by color Doppler imaging.** *Investigative Ophthalmology & Visual Science* 2011, **52**(8):5612-5617.
15. Wu YJ, Wei X, Xiao MY, Xiong W: **Orbital decompression surgery and horse chestnut seed extract improved superior orbital vein blood flow in patients with thyroid-associated ophthalmopathy.** *Journal of Ophthalmology* 2016, **2016**(1):1-8.
16. Edward WA, Slawomir T, Nowińska AK, Michal M, Dariusz D: **Anterior segment imaging: Fourier-domain optical coherence tomography versus time-domain optical coherence tomography.** *Journal of Cataract & Refractive Surgery* 2009, **35**(8):1410-1414.
17. Rodolfo M, Luca DA, Silvio DS, Luca A, Angela DG, Marco C, Leonardo M: **Optical Coherence Tomography Angiography in Retinal Vascular Diseases and Choroidal Neovascularization.** *Journal of Ophthalmology*, 2015, (2015-9-27) 2015, **2015**(4):1-8.
18. Marduel R: **Angio OCT, Dye Less Angiography, A New Approach of Age Related Macular Degeneration (ARMD).** *Advances in Ophthalmology & Visual System* 2015, **2**(2).
19. Sharma P, Sridhar J, Rayess N, Maguire JI: **Optical coherence tomography angiography (OCT-A) of type 2 retinal arteriovenous malformation.** *Canadian Journal of Ophthalmology/journal Canadien Dophthalmologie* 2015, **50**(5):e93-e96.
20. Schwartz DM, Jeff F, Dae Yu K, Zawadzki RJ, Morse LS, Park SS, Fraser SE, Werner JS: **Phase-variance optical coherence tomography: a technique for noninvasive angiography.** *Ophthalmology* 2014, **121**(1):180-187.

21. Zhao Z, Wen W, Jiang C, Lu Y: **Changes in macular vasculature after uncomplicated phacoemulsification surgery: Optical coherence tomography angiography study.** *J Cataract Refract Surg* 2018, **44**(4):453-458.
22. Libre PE: **Intraoperative light toxicity: a possible explanation for the association between cataract surgery and Age-related macular degeneration.** *American Journal of Ophthalmology* 2003, **136**(5):961-961.
23. Pollack A, Marcovich A, Bukelman A, Oliver M: **Age-related Macular Degeneration after Extracapsular Cataract Extraction with Intraocular Lens Implantation.** *Ophthalmology* 1996, **103**(10):1546-1554.
24. Sveinn Hakon H, Samy B, Thora Elisabet J, Thor E, Gisli Hreinn H, Robert Arnar K, James Melvin B, Jon Atli B, Einar S: **Oxygen saturation in human retinal vessels is higher in dark than in light.** *Invest Ophthalmol Vis Sci* 2009, **50**(5):2308-2311.
25. Xu G, Zhou L, Tong U: **[An ultrastructural pathological study of pterygium].** [*Zhonghua yan ke za zhi*] *Chinese journal of ophthalmology* 1996, **32**(6):438.
26. Aspiotis M, Tsanou E, Gorezis S, Ioachim E, Skyrilas A, Stefaniotou M, Malamou-Mitsi V: **Angiogenesis in pterygium: study of microvessel density, vascular endothelial growth factor, and thrombospondin-1.** *Eye (Lond)* 2007, **21**(8):1095-1101.
27. Hilton EJ, Hosking SL, Gherghel D, Embleton S, Cunliffe IA: **Beneficial effects of small-incision cataract surgery in patients demonstrating reduced ocular blood flow characteristics.** *Eye* 2005, **19**(6):670.
28. V Vinod M, Michael P, Jason J: **Pterygia with deep corneal changes.** *Cornea* 2004, **23**(6):635-638.
29. Saw SM, Tan D, . **Pterygium: prevalence, demography and risk factors.** *Ophthalmic Epidemiology* 1999, **6**(3):219-228.
30. Dubbelman M, GI SVDH: **The shape of the anterior and posterior surface of the aging human cornea.** *Vision Research* 2006, **46**(6):993-1001.
31. Dunne MC, Royston JM, Barnes DA: **Posterior corneal surface toricity and total corneal astigmatism.** *Optometry & Vision Science Official Publication of the American Academy of Optometry* 1991, **68**(9):708-710.
32. Tatsuro T, Atsuo T, Tomokazu S, Kazunori M, Masaki S, Yuichi K, Tetsuro O: **Corneal regular and irregular astigmatism assessed by Fourier analysis of videokeratography data in normal and pathologic eyes.** *Ophthalmology* 2004, **111**(4):752-757.
33. Gonen T, Sever O, Horozoglu F, Yasar M, Keskinbora KH: **Endothelial cell loss: Biaxial small-incision torsional phacoemulsification versus biaxial small-incision longitudinal phacoemulsification.** *Journal of Cataract & Refractive Surgery* 2012, **38**(11):1918-1924.
34. Gazzard G, Saw SM, Koh D, Widjaja D, Chia SE, Hong CY, Tan DT: **Pterygium in Indonesia: prevalence, severity and risk factors.** *Br J Ophthalmol* 2002, **86**(12):1341-1346.
35. Lin A, ., Stern G, . **Correlation between pterygium size and induced corneal astigmatism.** *Cornea* 1998, **17**(1):28-30.

36. Fong KS, Balakrishnan V, Chee SP, Tan DT: **Refractive change following pterygium surgery.** *Ciao J* 1998, **24**(2):115-117.
37. Gebhardt M, Mentlein R, Schaudig U, Pufe T, Recker K, Nölle B, Al-Samir K, Geerling G, Paulsen FP: **Differential Expression of Vascular Endothelial Growth Factor Implies the Limbal Origin of Pterygia.** *Ophthalmology* 2005, **112**(6):1023-1030.

Tables

Table 1 Demographic Characteristics and Clinical Findings of Patients with Pterygium and HCs

Condition	Pterygium	HC	t	p-value*
Age[years]	45±11	46±13	-0.16	0.92
Sex[male/female]	0/18	0/18	N/A	>0.99
Best-corrected visual acuity	0.6±0.5	1±1	0.35	0.04
SE-L(diopter)	1.15±1.00	1.25±0.75	0.19	0.83
Astigmatism -L(diopter)	2.50±0.75	1.25±0.75	4.17	0.04
SSI	9±1	9±1	N/A	>0.99
The course of pterygium[years]	6.70±5.01	/	/	/
The Length of pterygium[mm]	6.25±1.65	/	/	/
The height of pterygium[mm]	4.01±1.44	/	/	/
The area of pterygium[mm]	21.69±11.33	/	/	/
Heart rate[beats/min]	69±6	68±7	-0.12	0.95
Systolic blood pressure[mm Hg]	128±15	127±18	-0.21	0.85
Diastolic blood pressure[mmHg]	86±13	85±12	-0.06	0.79
Mean intra-ocular pressure[mmHg]	18±3	15±5	-0.25	0.72

* P <0.05 Independent t-tests comparing two groups

Abbreviations[HC=healthy control; N/A, not applicable;L: left; SE: Spherical equivalent.SSI: Signal strength Index

Table 2 Correlation analysis of density in superficial retinal layer and deep retinal layer with the disease course and the area size of pterygium.

		Fractal Dimension(Dbox)				
		Superficial Microvessels		Deep Microvessels		
		r	p	r	p	
Course of disease(Year)	SMIR	-0.7662	0.0002	DTMI	-0.7003	0.0012
	SR	-0.6038	0.0080	DMIR	-0.6901	0.0015
	IR	-0.6234	0.0057	SR	-0.7795	0.0001
	SC1	-0.7762	0.0002	IR	-0.7198	0.0008
	SC2	-0.7123	0.0009	R	-0.7608	0.0002
	SC3	-0.6615	0.0028	DC2	-0.7504	0.0003
				DC3	-0.7195	0.0008
The area of pterygium	SMIR	-0.9508	<0.0001	DTMI	-0.9563	<0.0001
	SR	-0.8935	<0.0001	DMIR	-0.9508	<0.0001
	IR	-0.9359	<0.0001	SR	-0.8935	<0.0001
	R	-0.6043	0.0079	IR	-0.9359	<0.0001
	SC1	-0.8217	<0.0001	R	-0.6043	0.0079
	SC2	-0.8976	<0.0001	DC2	-0.8976	<0.0001
	SC3	-0.7757	0.0002	DC3	-0.7757	<0.0002

Abbreviations □ DMIR=deep microvessel □ SMIR=superficial microvessels □ DTMI=deep total microvessel □ IR = inferior right; R = right; SR = superior right; CI = confidence interval; SC= superficial central annuli; DC = deep central annuli .

Figures

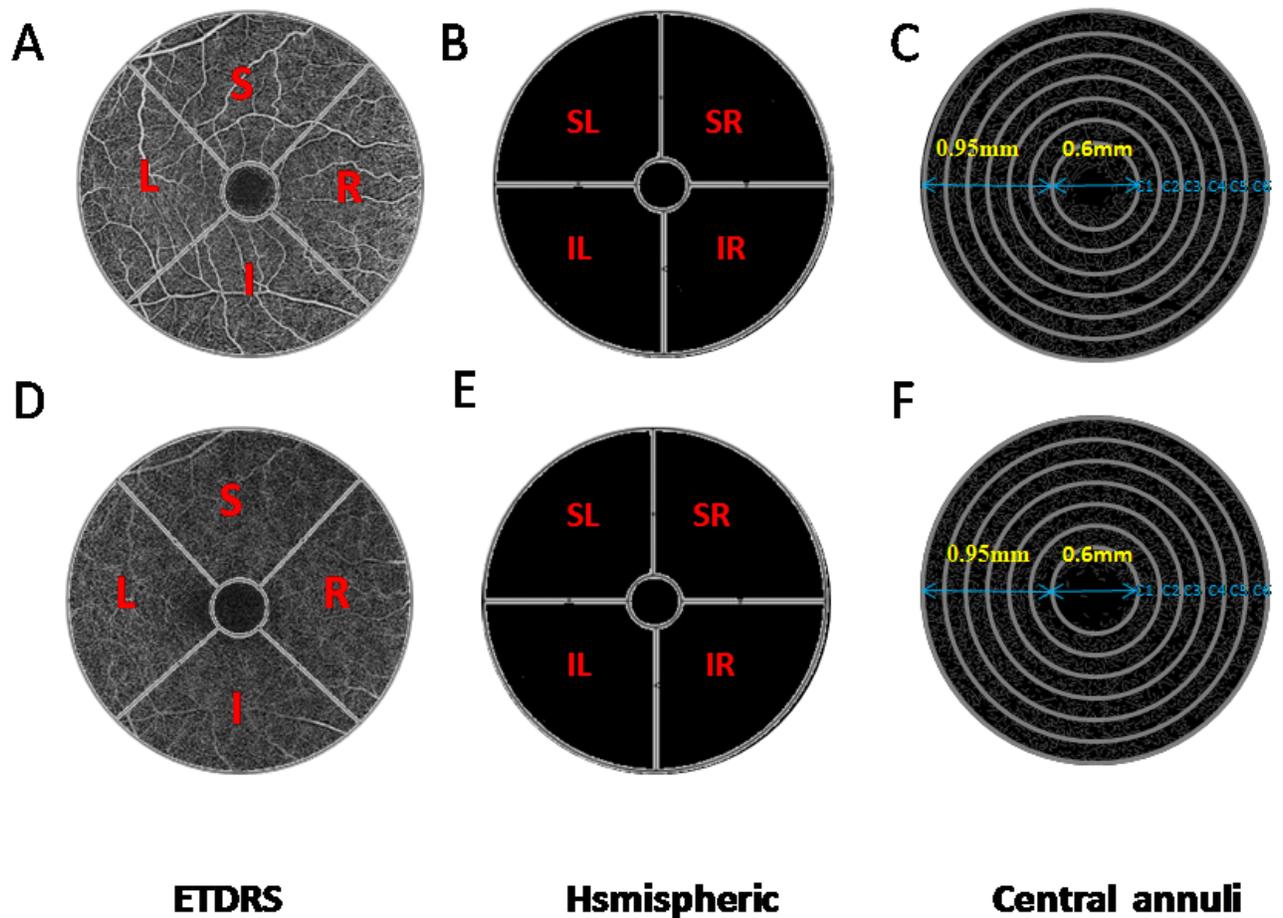


Figure 1

The 6 × 6-mm optical coherence tomography angiography (OCTA) image of the macular region of the retina. A. D image represented the original OCTA image of superficial and deep retinal vascular plexus respectively, based on the ETDRS partition method, which divided the image into 4 quadrants of vertical and horizontal regions, followed by R, S, L, and I. B.E image represented the original image of large retinal vessels in the superficial and deep retina, respectively, based on the hsmispheric partition method, which divided the ring area into 4 quadrants, followed by SR, SL, IL, and IR. C.F images represented the skeletonized microvessel images captured from the superficial and deep retinal vascular plexus, respectively, based on central annuli partition method after removal of the avascular zone (0.6mm diameter of the fovea), a circular region of 0.6 to 2.5 mm in diameter is defined as the ring with bandwidth of 0.95 mm. The annular region is divided into 6 thin rings with a bandwidth of 0.16 mm. Abbreviations I = inferior; IL = inferior left; IR = inferior right; L = left; R = right; S = superior; SL = superior left; SR = superior right

Superfial Microvessels

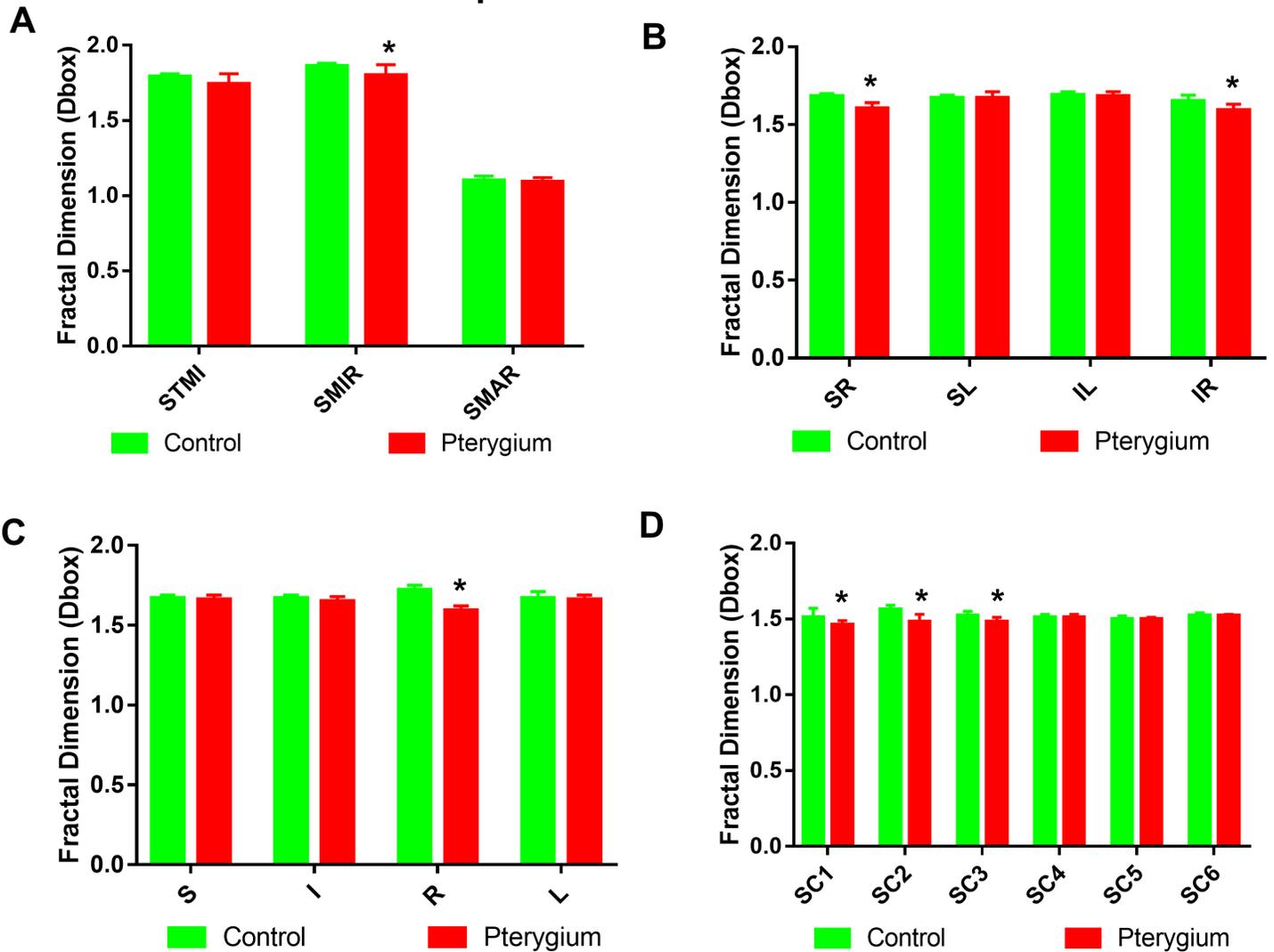


Figure 2

Comparisons of macula retinal vessel density (D box) between pterygium and control subjects in the superficial layer. Compared with the control group, there were significant differences in the densities of SMIR in macular region of pterygium patients ($P < 0.05$), but no statistically differences in densities in the STMI and SMAR region (all $P > 0.05$). In the pterygium group, the microvessel density in SR, IR, R, SC1, SC2 and SC3 region was significantly decreased compared to the control group ($P < .05$). No statistically significant differences was observed in other partitions ($P > 0.05$). * $P < 0.05$ Pterygium vs. Control. Abbreviations: SMIR=superficial microvessels; SMAR=superficial macrovascula; STMI=total superficial microvessels; DMAR= deep macrovascula; IR = inferior right; R = right; SR = superior right. SC = superficial central annuli.

Deep Microvessels

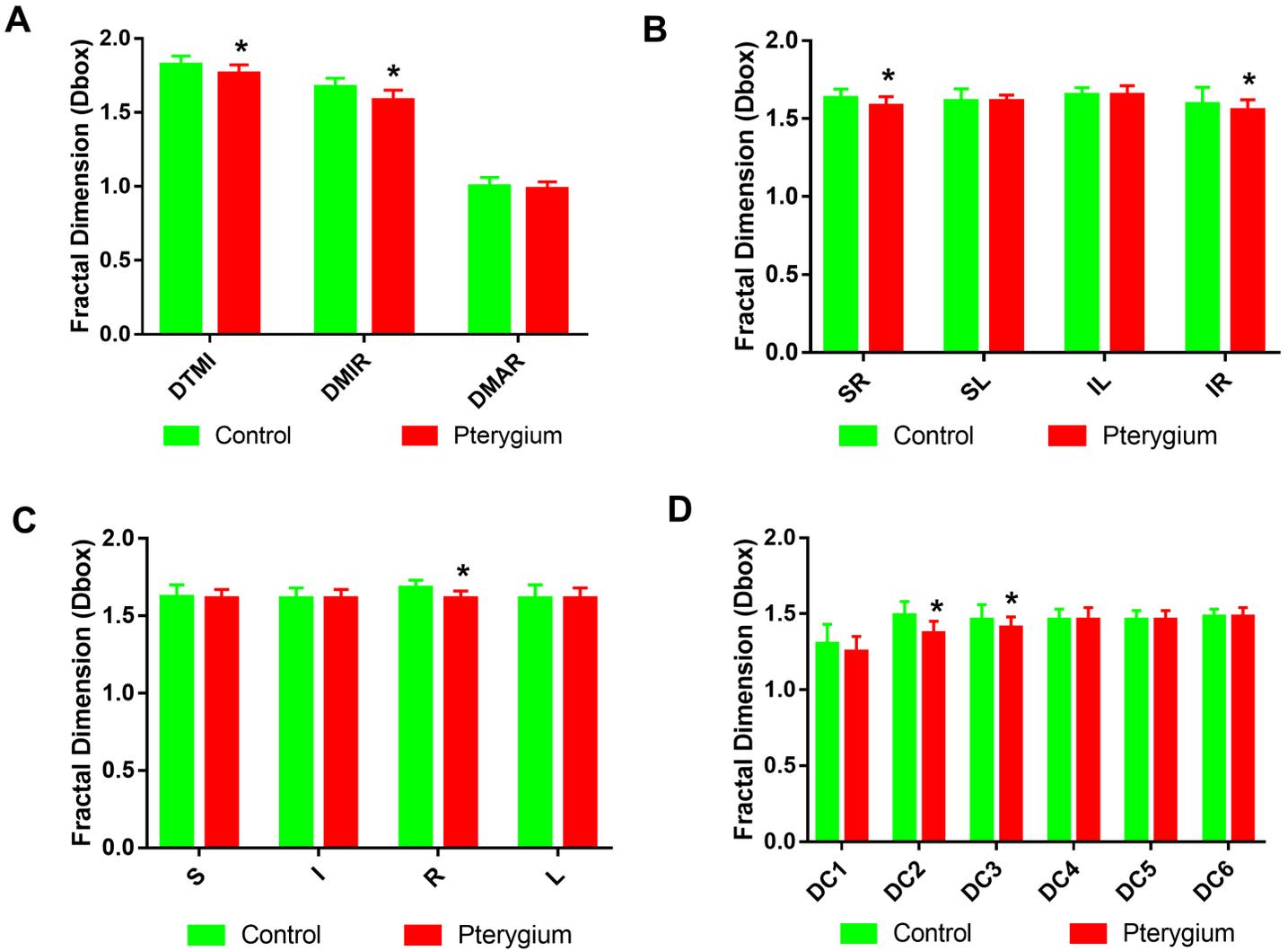


Figure 3

Comparisons of macula retinal vessel density (D box) between pterygium and control subjects in the deep layer. Compared with the control group, there were significant differences in the densities of DTMI and DMIR in macular region of pterygium patients ($P < 0.05$), but no statistically differences in densities in DMAR region (all $P > 0.05$). Meanwhile, the microvessel density of the SR, IR, R, DC2 and DC3 region in the pterygium group was significantly altered ($P < 0.05$). No statistically significant differences were observed in other regions ($P > 0.05$). * $P < 0.05$ Pterygium vs. Control. Abbreviations: DMIR=deep microvessel; DMAR=deep macrovascula; DTMI=deep total microvessel; I = inferior; IL = inferior left; IR = inferior right; L = left; R = right; S = superior; SL = superior left; SR = superior right; DC = deep central annuli

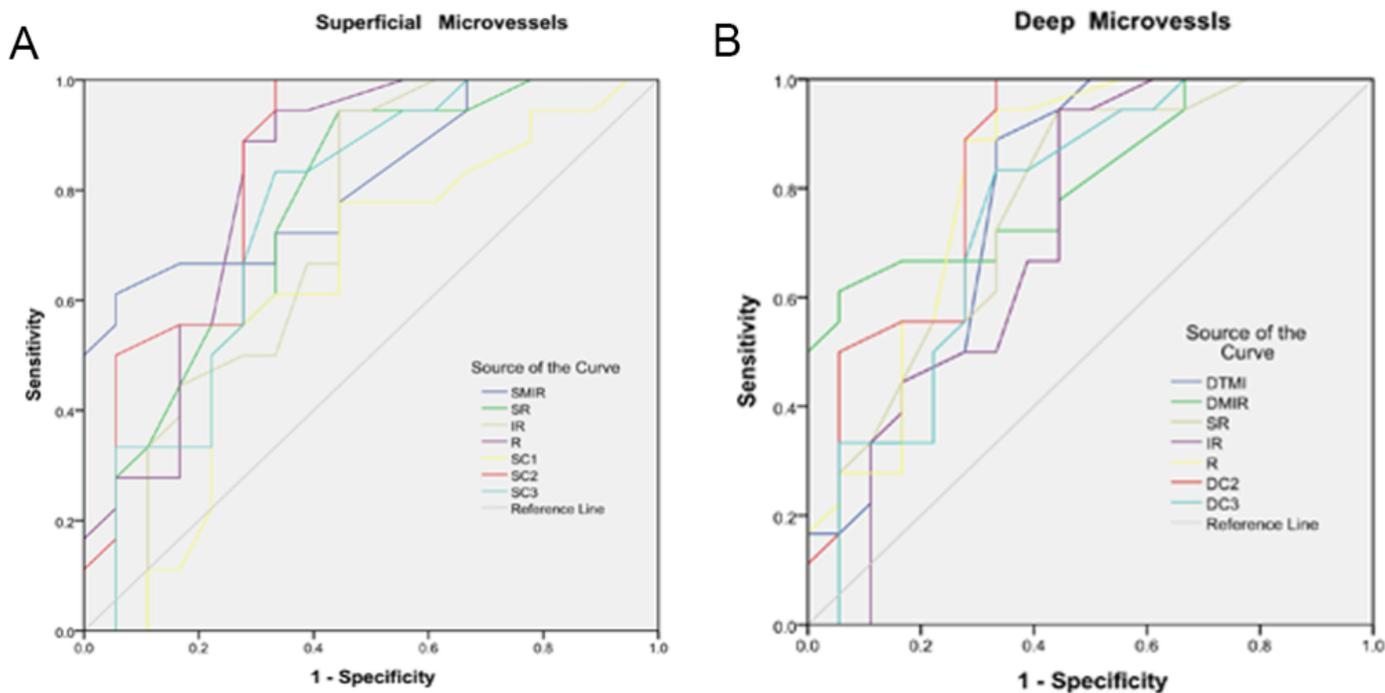


Figure 4

ROC curve analysis of microvessel densities in the superficial and deep layers. A representative of ROC curves obtained with the densities of the superficial layer in pterygium group. The density for largest areas under the ROC curves of the SC2 was 0.85 (95% CI = 0.72-0.98), and the density for lowest areas under the ROC curves of SC1 was 0.63 (95% CI = 0.44-0.82). B, representative of ROC curves obtained with the density of the deep vessel in the pterygium group. The density for largest areas under the ROC curves of the DC2 was 0.85 (95% CI = 0.72-0.98), and the density for lowest areas under the ROC curves of IR was 0.72 (95% CI = 0.54-0.89). Abbreviations: DMIR=deep microvessel; SMIR=superficial microvessels; DTMI=deep total microvessel; IR = inferior right; R = right; SR = superior right; CI = confidence interval; SC1, 2 = superficial central annuli 1, 2; DC 1-2 = deep central annuli 1-2.