Peripapillary Vessel Density Measurement of Quadrant and Clock-Hour Sectors in Primary Angle Closure Glaucoma Using Optical Coherence Tomography Angiography

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Research Article

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Abstract

**Background:** The purpose of this study was to investigate peripapillary vessel density of primary angle closure glaucoma (PACG) eyes in quadrant and clock-hour sectors, and the diagnostic ability of peripapillary vessel density was also studied.

**Methods:** This was a cross-sectional study on forty-one PACG patients (50 eyes) and twenty-seven healthy subjects (27 eyes). The optic disc was imaged using a 1050-nm-wavelength swept-source optical coherence tomography system (DRI OCT Triton, TOPCON). Peripapillary vessel density was quantified by imageJ software. Characteristics of peripapillary vessel density of quadrant and clock-hour sectors were analyzed, and diagnostic capability was evaluated by areas under the receiver operating characteristics curves (AUCs).

**Results:** Compared to the control group, four quadrants and each clock-hour sectors of peripapillary vessel density of glaucomatous group decreased to different degrees, and vessel density reduced most at 7 o'clock. Except 4 o'clock, there was not any statistical difference between the diagnostic ability of peripapillary vessel density and peripapillary retinal nerve fiber layer thickness. The inferior quadrant peripapillary vessel density had the best diagnostic value (AUCs 0.944), followed by 7 o'clock vessel density (AUCs 0.937), average vessel density (AUCs 0.926) and 7 o'clock RNFL thickness (AUCs 0.922).

**Conclusions:** In PACG, the diagnostic ability of peripapillary vessel density is equivalent to peripapillary retinal nerve fiber layer thickness. Understanding spatial characteristics of peripapillary vessel density in PACG may be helpful for clinical diagnosis and treatment.

**Background**

There is increasing evidence show that vascular factors are closely related to the pathogenesis of glaucoma[1]. In the past, there was a lack of effective non-invasive instruments to study the vascular mechanism of glaucoma.[2–5]. Recently, research on glaucoma by optical coherence tomography angiography (OCTA) showed that the peripapillary vessel density decreased and the peripapillary vessel density had good diagnostic ability for glaucoma [5, 6]. Previous articles used OCTA to study the spatial characteristics of peripapillary vessel density in glaucoma mainly on average and quadrants, and articles focusing on clock-hour peripapillary vessel density were limited[7, 8]. As far as we know, there is currently no article on peripapillary clock-hour vessel density of primary angle closure glaucoma (PACG). Previous studies have proved that the changes of neuroretinal rim in the eyes of glaucoma patients can be diffuse or local. Therefore, understanding the clock-hour spatial characteristics of peripapillary vessel density may help us to further understand the vascular mechanism of glaucoma and improve the diagnostic ability for glaucoma.

We know little about whether optic disc capillary atrophy in glaucoma eye is diffuse or localized. Shin et al. [9] studied peripapillary vessel density in eyes of normal-tension glaucoma(NTG) at clock-hour sectors using OCTA. They found that the superficial and deep vessel density of glaucoma at 7 and 11 o'clock...
positions decreased the most compared with healthy eyes. The diagnostic ability of 7o’clock position was the highest. The mechanism of PACG is different from NTG and primary open angle glaucoma(POAG) [10]. We do not know whether the peripapillary vessel density is the same for PACG.

Therefore, the purpose of this study was to use OCTA to study the quadrant and clock-hour spatial characteristics of peripapillary vessel density in PACG, and also to assess the diagnostic ability of vessel density.

**Materials And Methods**

**Study subjects**

We told each subject the content of the study. Their willingness to participate was recorded and they voluntarily signed the consent form approved by the institutional ethics committee. PACG patient and healthy person were selected from October 2018 to October 2019. All subjects underwent a detailed medical history, best corrected visual acuity (BCVA), intraocular pressure (IOP) measurement, axial length measurement by OA-2000 (Tomey GmbH, Nagoya, Japan), fundus examination, and swept-source optical coherence tomography (OCT) (DRI OCT Triton, TOPCON) examination. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) of subjects were measured before OCTA was measured. The ocular perfusion pressure (OPP) was calculated as the following formula:

\[
OPP = \frac{2}{3}(DBP + 0.42(SBP - DBP)) - IOP \quad [11]
\]

Glaucoma patients also underwent visual field (VF) examination by the static automated white-on-white threshold 24-2 SITA standard strategy (Humphrey Field Analyzer II; Carl Zeiss Meditec). Our study only included reliable visual field examination results (i.e., false-negative errors <15%, false-positive errors <15%, and fixation loss <20%)

The diagnostic criteria for PACG were as follows [12]: 1. the presence of an occluded angle defined as an angle in which >270° of the posterior trabecular meshwork cannot be seen, as verified with gonioscopy. 2. IOP of more than 21 mmHg. 3. optic disc has RNFL damage due to glaucoma. Inclusion criteria for healthy eyes: 1. age: > 18 years old. 2. normal anterior segment and fundus in clinical examination by experts. 3. intraocular pressure ≤ 21 mmHg. 4. no family history of glaucoma. Exclusion criteria for all participants were: 1. diopter ≥ 6.0 D (sphere) and or 3.0 D (cylinder). 2. previous eye surgery and other eye diseases. 3. poor OCT or OCTA image quality score (less than 40 points).

**OCTA imaging acquisition and processing**

All subjects were examined by 4.5×4.5mm OCTA optic disc scans (DRI OCT Triton; Topcon Corporation, Tokyo, Japan). Images were analyzed by an A-scan rate of 100,000 scans per second, wavelength-scanning light centered on 1,050nm, and in-depth digital resolution of 2.6mm [13]. We used OCT angiography ratio analyses (OCTARA) of the device to generate the maps. The system automatically
divided the optic disc into four layers, and the selected layer was Nerve Head layer. Nerve Head layer is
defined as 130um below the internal limiting membrane. Peripapillary vessel density measurement was
calculated in the Nerve Head layer.

We reviewed and filtered images quality after each scan. Images with significant motion artifacts, poor
signal strength (signal strength index <40), or poor image clarity were discarded. We performed the
Phansalkar as adaptive local thresholding methods[14]. This method was used for binarization algorisms
in OCTA images using Image J software (National Institutes of Health, Bethesda, MD) to obtain vascular
signals as a white region and digitize this area. The vessel density value was defined as a proportion of
vessel signal in area of interest[15]. The peripapillary region was 750mm -wide annular region of interest
centered on the optic disc, with an inner diameter of 1.95cm and an outer diameter of 3.45cm[16]. The
peripapillary region was divided into 4 equal quadrants, namely superior, inferior, temporal and nasal
quadrants. The peripapillary region also was divided into the 12 clock-hour sectors. OCTA image
processing steps were shown in Fig 1.

Statistical Analyses

Data analysis was carried out using commercially available software (SPSS ver.13.0; SPSS Inc, Chicago,
Illinois, USA) and MedCalc(ver.15.2.2, Mariakerke, Belgium). We used mean±standard and ratios to
describe all data and the Shapiro-Wilk test to evaluate the normal distribution of continuous variables.
Independent t test and Mann–Whitney test were used to observe the differences between the PACG eyes
and healthy eyes. We calculated and compared the areas under the receiver operating characteristics
curves (AUCs) of average quadrant and clock-hour vessel density and peripapillary retinal nerve fiber layer
(RNFL) to evaluate the diagnostic ability for glaucoma. Pearson correlation analysis and Spearman
correlation test were used to evaluate the correlation between vessel density parameters and related
factors. P-value of <0.05 was taken to be of statistical significance.

Results

Forty-eight PACG patients60 eyes and 33 healthy people33 eyes were enrolled in this study. Ten eyes of
PACG patients and 6 eyes of healthy subjects were excluded due to poor OCTA image quality. Therefore,
41 PACG patients (50 eyes) and 27 healthy subjects (27 eyes) were enrolled. Demographics and clinical
characteristics of study subjects are listed in Table 1. The axial length of PACG eyes was significantly
different from that of healthy eyes(p<0.001), and there were no significant differences in age, sex,
intraocular pressure at examination and ocular perfusion pressure(p>0.05).The VF mean deviation in
PACG eyes was −18.3±9.9db.

Table 1 Demographic and clinical characteristics of the study population
Table 2 shows data of peripapillary vessel density and RNFL thickness on the mean average, quadrant, and clock-hour regions. Compared with the control group, the peripapillary vessel density of glaucoma in all measured sectors decreased to different degrees and the difference was significant ($P < 0.05$), with 7 o'clock decreased most. Except for 3 o'clock ($P > 0.05$), peripapillary RNFL in all measured sectors showed significant difference between the glaucoma group and control group ($P < 0.05$). Three o'clock sector was a less important sector in glaucomatous diagnosis. Fig 2 shows a decrease in infratemporal and supratemporal peripapillary vessel density sectors of glaucoma and atrophy of RNFL thickness in corresponding regions.

**Table 2 Peripapillary retinal nerve fiber layer thickness and peripapillary vessel density in healthy and glaucomatous eyes**
| Parametres | RNFL thickness | | | Peripapillary vessel density | | |
|-----------|---------------|-----------------|-----------------|-----------------|-----------------|
|            | Healthy eyes(n=27) | PACG eyes(n=50) | P value | Healthy eyes(n=27) | PACG eyes(n=50) | P value |
| Average    | 113.0±9.6 | 78.3±26.1 | 0.001* | 54.8±2.5 | 46.0±5.6 | 0.001* |
| Temporal   | 85.4±10.3 | 64.0±18.4 | 0.001* | 54.8±5.4 | 47.1±6.8 | 0.001 |
| Superior   | 142.7±19.2 | 92.9±38.2 | 0.001* | 57.3±2.7 | 48.5±6.6 | 0.001* |
| Nasal      | 76.7±14.5 | 65.7±21.3 | 0.019 | 49.0±5.5 | 42.2±7.2 | 0.001 |
| Inferior   | 147.6±12.9 | 86.8±40.4 | 0.001* | 58.3±3.0 | 46.4±6.5 | 0.001* |
| 9          | 72.1±7.9 | 60.6±14.4 | 0.001* | 50.3±7.1 | 46.4±6.6 | 0.018 |
| 10         | 100.1±14.0 | 69.0±26.6 | 0.001* | 58.4±4.9 | 49.5±7.7 | 0.001* |
| 11         | 148.3±24.8 | 91.2±42.1 | 0.001* | 59.2±3.6 | 47.9±8.9 | 0.001* |
| 12         | 144.8±30.8 | 98.2±43.2 | 0.001 | 56.9±3.6 | 50.1±7.3 | 0.001 |
| 1          | 135.1±23.5 | 89.1±37.5 | 0.001* | 55.9±3.9 | 47.8±6.9 | 0.001* |
| 2          | 90.9±22.2 | 75.4±28.8 | 0.018 | 51.0±5.9 | 44.4±8.4 | 0.001* |
| 3          | 66.7±14.5 | 60.4±19.1 | 0.137 | 46.7±7.0 | 40.6±8.1 | 0.001 |
| 4          | 72.5±12.0 | 60.2±22.8 | 0.003* | 49.5±5.0 | 41.3±8.4 | 0.001* |
| 5          | 123.1±16.2 | 86.2±38.1 | 0.001* | 55.7±4.7 | 44.7±7.9 | 0.001* |
| 6          | 157.9±20.1 | 102.5±46.8 | 0.001* | 58.7±4.1 | 49.0±6.9 | 0.001* |
| 7          | 161.3±25.8 | 82.5±43.2 | 0.001* | 60.4±4.7 | 45.3±8.8 | 0.001* |
| 8          | 82.7±17.0 | 62.0±19.9 | 0.001* | 55.2±6.4 | 45.5±8.1 | 0.001 |

RNFL, retinal nerve fiber layer; PACG, primary angle closure glaucoma

Unless otherwise illustrated, the comparison was made by using independent sample t test.
*The comparison was performed by using the Mann–Whitney test.

AUCs of peripapillary vessel density was between 0.658 in 9 o'clock sector and 0.944 in the inferior quadrant. AUCs of RNFL thickness was between 0.596 in 3 o'clock sector and 0.922 in 7 o'clock sector. Inferior quadrant vessel density had the highest diagnostic ability (AUCs 0.944), followed by 7 clock-hour peripapillary vessel density (AUCs 0.937), average vessel density (AUCs 0.926) and 7 o'clock RNFL thickness (0.922). Except 4 o'clock, there was no statistical difference between the diagnostic ability of peripapillary vessel density and RNFL. The diagnostic ability of 4 o'clock vessel density was higher than that of RNFL (Table 3).

**Table 3 Areas under the receiver operating characteristics curves comparison for glaucomatous discrimination ability between Peripapillary vessel density and RNFL thickness**

| Parameters   | Peripapillary vessel density | RNFL thickness | P value |
|--------------|------------------------------|----------------|---------|
| Optic disc   | AUC 95%CI                    | AUC 95%CI      |
| Average      | 0.926 0.844-0.973            | 0.885 0.792-0.947 | 0.265   |
| Temporal     | 0.814 0.709-0.893            | 0.832 0.729-0.907 | 0.727   |
| Superior     | 0.880 0.786-0.943            | 0.859 0.760-0.927 | 0.655   |
| Nasal        | 0.769 0.659-0.857            | 0.664 0.548-0.768 | 0.054   |
| Inferior     | 0.944 0.866-0.983            | 0.904 0.815-0.959 | 0.290   |
| 9            | 0.658 0.541-0.762            | 0.739 0.626-0.832 | 0.235   |
| 10           | 0.834 0.732-0.909            | 0.843 0.743-0.916 | 0.848   |
| 11           | 0.875 0.780-0.939            | 0.877 0.782-0.941 | 0.968   |
| 12           | 0.796 0.688-0.879            | 0.810 0.705-0.890 | 0.801   |
| 1            | 0.834 0.732-0.909            | 0.856 0.757-0.925 | 0.667   |
| 2            | 0.735 0.622-0.829            | 0.673 0.557-0.776 | 0.202   |
| 3            | 0.714 0.600-0.812            | 0.596 0.478-0.706 | 0.074   |
| 4            | 0.811 0.705-0.891            | 0.675 0.558-0.777 | 0.022   |
| 5            | 0.881 0.788-0.944            | 0.814 0.710-0.894 | 0.161   |
| 6            | 0.881 0.787-0.943            | 0.837 0.735-0.911 | 0.332   |
| 7            | 0.937 0.857-0.979            | 0.922 0.838-0.971 | 0.676   |
| 8            | 0.825 0.721-0.902            | 0.787 0.679-0.872 | 0.487   |
RNFL, retinal nerve fiber layer; AUCs, areas under the receiver operating characteristics curves; CI, confidence interval;

IOP, average RNFL thickness and VF mean deviation were correlated with average peripapillary vessel density. The P value of IOP was close to 0.05, indicating that the correlation between average peripapillary vessel density and average RNFL, VF mean deviation were stronger than any other variables (Table 4).

**Table 4 The correlation between peripapillary vessel density and glaucomatous related factors**

| Peripapillary vessel density |   |   |
|-----------------------------|---|---|
| Age(year)                   | -0.170 | 0.238 |
| Sex                         | 0.041 | 0.863 |
| IOP(mmHg)                   | -0.318 | 0.024* |
| Mean OPP(mmHg)              | 0.141 | 0.329 |
| RNFL thickness(μm)          | 0.750 | 0.001 |
| VF MD(dB)                   | 0.749 | 0.001* |

IOP, intraocular pressure; OPP, ocular perfusion pressure; RNFL, retinal nerve fiber layer; VF MD, visual field mean deviation

Unless otherwise illustrated, correlation analysis was made by using Pearson correlation test.

* Correlation analysis was made by using Spearman correlation test.

**Discussion**

There are limited reports on the peripapillary vessel density in PACG. As far as we know, there is no literature reporting the peripapillary vessel density in clock-hour sector in PACG. In this study, we found that the peripapillary vessel density in the mean average, quadrant, and clock-hour sectors of PACG decreased in different degrees compared with normal eyes. The inferior quadrant vessel density had the highest diagnostic value. Except 4 clock-hour, there was not any statistical difference between the diagnostic ability of vessel density and RNFL.

In this study, the peripapillary vessel density of PACG eyes was significantly lower than that of healthy eyes, which were consistent with the studies of Rao et al. [17] and Wang et al.[18]. Rao et al. [17] used OCTA to report the diagnostic ability of peripapillary average vessel density and (divided into 6 parts) each quadrant vessel density parameters in PACG, which were similar to the diagnostic ability of RNFL.
thicknesses. AUCs of average peripapillary vessel density and the inferotemporal vessel density sector were 0.79 and 0.86 respectively. In this study, the average vessel density of PACG was higher than that reported by Rao et al., while the diagnostic ability of RNFL thicknesses was similar. This study showed that the diagnostic ability of vessel density parameters may be better than that of RNFL thicknesses in PACG, although the difference was not statistically significant. The reason may be that the severity of glaucoma in this study (VF mean deviation was −18.3dB) was much higher than that in Rao et al. (VF mean deviation was −9.2). Previous studies showed that Peripapillary RNFL measured by OCT may not be as effective as visual field examination or macular thickness in monitoring the progression of advanced glaucoma[19, 20]. This result may be partly explained by that RNFL of advanced PACG change slightly, while vessel density continues to decline significantly. In previous studies of PACG, there was no study to evaluate clock-hour vessel density diagnostic ability. In our study, quadrant and clock-hour vascular density had good glaucoma diagnostic ability in all areas.

According to the study on clock-hour sector, we found that the vessel density at 7 o’clock decreased most, and RNFL at 7 o’clock also decreased the most. Previous studies showed that RNFL defects were most often found in infratemporal and supratemporal sectors[21]. Anatomically, RNFL bundles are particularly thick in the superior and inferior quadrants of the optic disc. These areas are particularly vulnerable to glaucoma damage[22]. The sequential relationship between vessel density reduction and RNFL atrophy needs longitudinal study to prove. In our study, the decrease of vessel density was closely related to the decrease of RNFL and the severity of VF mean deviation. This was consistent with the research by Zhang et al[23].

The advantage of this study was that we used imageJ software to calculate the vessel density of each clock sector that matches the clock-hour RNFL sector. We accurately matched clock-hour vessel density sectors and clock-hour RNFL sectors for AUCs diagnostic capability comparison. Our study had some limitations. There was evidence that ocular hypotensive eye drops may affect the hemodynamics of ocular blood flow and retinal vascular autoregulation[24, 25]. PACG eyes were exposed to 0 to 3 anti-glaucoma drugs during OCTA examination. Second, the OCTA algorithm we used included large vessels and capillaries, which might not represent the actual loss of capillaries in specific regions. Third, because our study was a cross-sectional study, we cannot determine the cause-effect relationship between vessel density and structure.

Our research showed that OCTA may provide useful information for glaucoma. The diagnostic ability of vessel density in PACG was equivalent to that of traditional RNFL measurement. Combining the information of vessel density measurement may improve the diagnostic rate of glaucoma. Future research can evaluate the application of this new method in detecting glaucoma changes.

In summary, the diagnostic ability of vessel density in PACG is comparable to that of RNFL thickness. Understanding the spatial characteristics of Peripapillary vessel density in PACG may be helpful for clinical diagnosis and treatment.
Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Joint Shantou International Eye Center (JSIEC) of Shantou University and the Chinese University of Hong Kong (Shantou city, China). The study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects. Ethical approval number: EC20180929(5)-P12

Consent for publication

Written informed consent has been obtained from the patient.

Availability of data and materials

The author confirms that all relevant data are included in the article.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

MZ, YL, SC participated in the design of the study. YL and SC analyzed and interpreted the data. MZ, YL wrote the article. MZ critically revised the article. YL, SC collected the data. MZ, YL reviewed the literature. All authors read and approved the final manuscript.

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**Figures**
Figure 1

OCT-A image processing steps. (A) Image imported into the Image J software. (B) Binary image after local adaptive thresholding. (C) Annular region of interest centered at the optic nerve head. (D) Obtaining vessel density values of each quadrant and clock-hour sector.