Optical coherence tomography angiography of the macular retina in primary angle closure glaucoma

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Abstract

Background: To detect the macular vessel density (MVD) changes in primary angle closure glaucoma (PACG) and to investigate the correlation between MVD and other glaucomatous changes. Methods: A case-control study. Eyes of 22 PACG patients with an episode of acute primary angle closure (APAC) in one of the two eyes. Structural OCT scans were used to obtain peripapillary retinal nerve fiber layer (RNFL), macular ganglion cell complex (GCC) thickness and C/D area ration. OCT angiography (OCTA) was used to measure MVD. Results: In the control group, the dense macular blood vessels were visible on OCTA the macular vessels were sparse in the case group, and with an enlarged fovea avascular zone. There was a reduction in MVD in the case group compared with the controls (P<0.01). No correlations between MVD, VF mean deviation (MD), C/D area ratio, GCC thickness or RNFL thickness were found in the control group. In the case group, the Pearson correlation analysis showed that MVD was significantly correlated with BCVA (r=0,65, P=0.001), GCC (r=0.50, P=0.018) and VF MD (r=-0.54, P=0.009). In the case group, the multiple stepwise regression analysis, in which MVD were considered the dependent variables, showed that BCVA and GCC were significant predictors. Conclusions: Macular microvascular network attenuated and MVD reduced significantly caused by APAC. MVD was strongly linked to BCVA and GCC.

Background

Glaucoma is characterized by the progressive loss of retinal ganglion cells (RGC), neuroretinal rim thinning of the optic nerve head (ONH), and accompanied with VF loss [1]. Broadly speaking, RNFL thinning around the ONH could serve as an early indicator of RGC loss in glaucoma. RGC and RNFL measurements have high accuracy in diagnosing glaucoma has been demonstrated in former studies[2,3]. Besides that, there are increasing studies comfirm that vascular insufficiency of optic nerve has been implicated in pathogenesis of glaucoma [4,5]. Published investigations using OCTA have shown significant correlations between vessel density and other glaucomatous structural and functional parameters [6-9].

However, few studies concerned the retinal microvasculature in macular area in glaucoma so that was still unclear. Chen et al. found that the diagnostic accuracy of the macular superficial vessel density was equal to peripapillary RNFL and macular GCC thickness [10].

In our previous studies, we have reported peripapillary retinal vessel density (RVD) was lower after APAC [11]. Sequentially, the purpose of this study was to investigate macular perfusion with OCTA and evaluate the potential relationship of MVD measurements with other glaucomatous structure and function changes in PACG after APAC.

Methods

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (PUMCH) and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Participants

22 unilateral acute PACG patients, who visited the ophthalmology department of PUMCH, from Apr. to Sep. in 2016 were enrolled. The inclusion and exclusion criteria refer to the principles decribed in our previous study[11].

Examination

Ophthalmic examination included BCVA, IOP, slit-lamp examination, fundus examination, gonioscopy and VF examination. Circumpapillary RNFL (cpRNFL), GCC thickness, C/D area ratio and MVD were assessed with SD-OCT.

Retina angiography examinations were performed in all participants within the same visit by a single experienced ocular specialist. The scan sizes of optic disc and macular area were 4.5 ×4.5 mm and 3.0 × 3.0 mm. The fovea avascular zone (FAZ) was delineated and measured automatically. MVD was defined as the percentage area occupied by blood vessels in the macular region. Signal strength index (SSI) below 60 were excluded from analysis.

Statistical Analysis

Normality of quantitative data was evaluated with Kolmogorov–Smirnov normality test. BCVA was converted to a log of the minimum angle of resolution (logMAR) for statistical analysis, BCVA data are shown as medians, the other measurements are presented as mean ± standard deviation (SD). The nonparametric Wilcoxon test was used to compare BCVA, and paired-samples *t* test was used to compare other parameters between two groups. The correlation analysis was used to determine the relationships between MVD and MD, C/D area ratio, cpRNFL, GCC and IOP in the both groups. Multiple stepwise regression analysis was performed to analyze the effect among MVD and other variables, such as BCVA, C/D area ratio, GCC and RNFL. Statistical analyses were performed with SPSS version 20.0 software (SPSS for Windows, Chicago, IL, USA). Statistical significance was defined at $P < 0.05$.

Results

Baseline clinical parameters

44 eyes of 22 subjects which fulfilled the above inclusion criteria were included in the analysis，22 PACG eyes after APAC formed the case group, 22 contralateral eyes without attack formed the control group. 17 females (77.3%) and 5 males (22.7 %), with a mean age of 66.7±7.4 years (range, 54-83 years). In the case group, 2 eyes were on 1 local IOP lowing medication, travoprost once daily was used in 1 eye, brinzolamide three times daily was used in another eye. 12 eyes had underwent phacoemulsification surgery, 5 of them had received trabeculectomy before. Among unaffected eyes, none required glaucomatous surgery or anti-glaucoma medication, 4 eyes had undergone phacoemulsification surgery. Laser peripheral iridotomy (LPI) was performed on all eyes in the both groups. The median study assessment time was 22 months (range, 7days-32 months) after APAC attack.

Median of BCVA, the mean and range of IOP，VF MD , GCC, RNFL thickness and C/D area ratio are listed in Table 1.The significant differences were found on these parameters between two groups except for IOP, this could be due to a proper treatment after APAC attack. Compared to unaffected eyes, acute PACG eyes were demonstrated

with more serious VF loss and poor BCVA. Structural evaluation also identified increscent C/D area ration and loss of GCC and RNFL thickness in acute PACG eyes (P<0.001).

Comparison of macular retinal angiograms

The *En Face* OCTA scan provided detailed images for both macular microvascular and vessel density on different levels. Example images on superficial retina of two groups are shown (Figure 1). The *En Face* OCTA shown that unaffected eyes had a denser microvascular network compared to acute PACG eyes which was visibly attenuated and with different degrees of macular microvascular network atropy, enlargement of intercapillary spaces and FAZ area. The contour of FAZ became irregular and the perivascular space Dilated. Pseudo-color images of vessels also visually displayed a lower VD in PACG eyes.

The posterior-pole macular area was automatically categorized into several regions and vessel density in the different area were measured. The values of acute PACG eyes' vessel density in the superficial were significant lower than that of unaffected eyes (P<0.05). FAZ area was also significantly less than that of unaffected eyes. (Table 2)

In acute PACG eyes, correlation analysis showed that the vessel density was significantly correlated with VF MD, BCVA and GCC, but not with IOP, C/D area ratio and RNFL thickness (Table 3，Figure 2). GCC was significantly correlated with RNFL thickness and VF MD. In the control group, there was no correlation between the MVD and GCC, VF MD, IOP, BCVA, C/D area ratio, or RNFL thickness.

In the multivariate stepwise regression analysis where MVD was considered as the dependent variable, GCC and BCVA were the dominant explanatory variables, however, C/D area ratio, IOP, VF MD and RNFL thickness were not significant explanatory variables. When the dependent variable was BCVA, MVD was the dominant explanatory variable. Meanwhile, when the dependent variable was GCC, MVD and RNFL were the dominant explanatory variables，which suggested MVD was much more strongly linked to BCVA and GCC than any other parameters, MVD is a relatively strong indicator of BCVA severity (Table 4).

Discussion

In current clinical work, doctors usually focused on features suggesting neural tissue loss on the ONH and surrounding area to assess the glaucomatous structural changes. However, in addition to the changes that occur in ONH and cpRNFL, another retinal region, macula has been proposed to be a potential location for glaucoma evaluation [12]. There is hardly any large vessel in macula, and which shape is generally less variable than ONH. Additionally, RGCs are located intensively within macula [13]. Meanwhile, RGC cell body exists is large enough that any such loss should theoretically be easiest to detect in macular region [14]. These are the reasons that we focus on macular area in this study.

Formerly，GCC thickness is the only data that investigators could get in previous studies which concerned on macular area. Vessels and blood flow in macular, which can reflect macular function, were not available before the appearance of OCTA. OCTA can provide value of MVD by its included software automatically. So in our current study, we measured the MVD by OCTA in a group of patients with unilateral APAC. In eyes with history of APAC, we observed that changes of morphological characterstics and vessel density in macular were similar to the results obtained by our team about the changes on peripapillary retina using OCTA [11]. Meanwhile, MVD in

control eyes was similar to that in healthy subjects [15], which suggested the attenuated microvascular network in the case group was caused by APAC.

Few studies concerned the vascular morphology and blood perfusion in PACG. Gao et al. reported PACG individuals had narrower retinal arteries and veins by measuring of retinal vessel diameter from digitized photographs [16]. It is deduced that ocular blood flow may be temporarily blocked by mechanical oppression, and microcirculation system would re-open and regenerate after IOP was controlled. However, in our study, we found that macular microcirculation system is irreversible damaged which can be interpreted as even IOP was lowered to normal level and keep stable for years. It is further demonstrated in our study that blood flow decrease was not temporary manifestation under extremely high IOP but a result of extensive damage of microvascular system.

We observed that MVD was markedly linked to BCVA and GCC than any other glaucomatous parameters, suggesting that a more prominently reduced MVD is associated with more severe visual impairment. FAZ and visual acuity have the close correlation, and significant capillary dropout from FAZ region may cause severe visual loss. So we considered the macular microvascular network atropy, depressed MVD, enlargement of intercapillary spaces and FAZ area might be the indicator of poor visual prognosis in patients with attack of APAC.

Several studies have shown that macular measurements have good glaucoma diagnostic capabilities as RNFL and ONH parameters[15,17]. Kim et al. reported that the macular GCC and cpRNFL thicknesses showed similar diagnostic performances in detecting different severity of glaucoma[18].Therefore, we believe the close correlation between the MVD and GCC thickness suggests that MVD meatured by OCTA might also be useful in monitoring the progression, severity and prognosis of glaucoma, further studies are required to draw the conclusion.

In the present investigation, we chose the patients with unilateral PACG, whose one eye had symptoms of APAC attack while the follow eye with no APAC evidence, as subjects for study. Self-control study might eliminate the effect of age, gender, and systemic disease which may interfere the conclusion about vascular factor in the pathological process of glaucoma, and made results of our study more reliable [19].

There are several limitations in our study. First, the relatively limited number of patients enrolled. Second, more eyes had cataract extraction or trabeculectomy history in case group. There is no data about influence of these surgeries on MVD. Third, the time sequence of macular microcirculation abnormalty and other glaucomatous change could not be concluded in present study. Finally, all the examination and measurements were operated in a non-masked fashion. Because OCTA give the report automatically, it is deduced that the effect of mask on measurements may be limited.

Conclusions

Till now there is limited data on morphological and quantitative macular perfusion in PACG after APAC using OCTA. In our study, macular retinal perfusion could be visualized and quantitative analysis in a group of patients with unilateral PACG. We found a strong link among the MVD, BCVA and GCC thickness. OCTA shows great potential for quantitative analysis of optic and retina flow, and there is increasing interest in assessing how

macular perfusion measurement with OCTA may help in the prognostic indicating for disease course and follow-up of glaucoma, which might further enhance the utility of OCTA in glaucoma detection.

Abbreviations

APAC: acute primary angle closure BCVA: best-corrected visual acuity FAZ: fovea avascular zone GCC: ganglion cell complex LPI: laser peripheral iridotomy MD: mean deviation MVD: macular vessel density ONH: optic nerve head OCTA: optical coherence tomography PACG: primary angle closure glaucoma RGCs: retinal ganglion cells RNFL: retinal nerve fiber layer SD: standard deviation VF: visual field

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects after an explanation of the nature of the study before entry into this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors’ contributions

YZ, CW, and YZ wrote the main manuscript text and prepared all figures. SHZ, QZ and GWC oversaw the project and assisted with the writing of the manuscript. ALB, LL and YZ performed ophthalmic examinations. All authors reviewed the manuscript.

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Tables

Table 1. Comparison of BCVA, IOP、VF MD , GCC, RNFL and C/D area ratio between two groups[a]

Variable	Acute PACG eyes	Contralateral eyes	*P* Value
Median BCVA	20/32 (0.2LogMar)	20/20 (0.0LogMar)	0.001
IOP（mmHg）	14.66±5.32	15.95±3.22	0.101
VF MD（dB）	13.46±6.64	2.57±2.36	0.000
GCC（μm）	77.6±12.8	103.5±22.3	0.000
RNFL（μm）	71.5±18.5	102.1±18.5	0.000
C/D area ration	0.61±0.19	0.40±0.16	0.000

Abbreviations: BCVA, best-corrected visual acuity; IOP, intraocular pressure; VF MD, visual field mean deviation intraocular pressure; GCC, ganglion cell complex; RNFL, retina nerve fiber layer

[a] Unless otherwise indicated, data are given as mean ± standard deviation

Table 2. Comparison of vessel density and FAZ area between two groups

Vessel Density （%）		Acute PACG eyes	Contralateral eyes	*P* Value
Superficial retina	Whole	45.30±3.86	50.88±3.88	0.000
	Fovea	23.72±4.07	26.42±6.15	0.013
	ParaFovea	47.99±4.24	53.28±3.67	0.000
	Superior	48.22±4.16	52.86±4.04	0.000
	Inferior	47.77±4.52	53.70±3.63	0.000
	Tempo	48.19±3.86	52.77±3.85	0.000
	Superior	47.28±5.38	52.76±4.56	0.000
	Nasal	48.41±4.31	52.89±3.86	0.000
	Interior	48.09±4.94	54.72±3.91	0.000
FAZ area（mm^2）	Whole	0.43±0.13	0.37±0.13	0.001

Table 3. The correlation coefficients among the MVD and other glaucoma parameters in acute PACG eyes.

Variables	MVD	GCC	RNFL	VA	IOP	VF MD	C/D Area Ratio
GCC	0.500（0.018）						
RNFL	0.323（0.143）	0.891（0.000）					
BCVA	0.656（0.001）	0.158（0.483）	0.004（0.985）				
IOP	-0.399（0.066）	-0.300（0.175）	-0.238（0.287）	-0.029（0.897）			
VF MD	-0.543（0.009）	-0.759（0.000）	-0.749（0.000）	-0.349（0.111）	0.279（0.208）		
C/D Area Ratio	-0.368（0.092）	-0.694（0.000）	-0.794（0.000）	-0.031（0.891）	0.410（0.058）	0.667（0.001）	
Age	-0.326（0.139）	-0.269（0.227）	-0.254（0.253）	-0.329（0.135）	-0.091（0.686）	0.219（0.328）	0.142（0.529）

Table 4. Multivariate stepwise regression analysis factors affecting MVD, BCVA and GCC in acute PACG eyes.

	MVD	GCC	RNFL	BCVA	IOP	VF MD	C/D area ration	R^2
MVD		0.407（0.013）	-0.389（0.380）	0.592 （0.001）	-0.191 （0.284）	-0.039 （0.887）	0.526 （0.313）	0.735
BCVA	0.766 （0.007）	0.018 （0.969）	-0.238 （0.648）		0.113 （0.617）	-0.346 （0.288）	-0.327 （0.610）	0.629
GCC	0.537（0.023）		0.814（0.000）	0.154（0.133）	-0.094（0.385）	-0.210（0.178）	0.034（0.843）	0.844

Figures

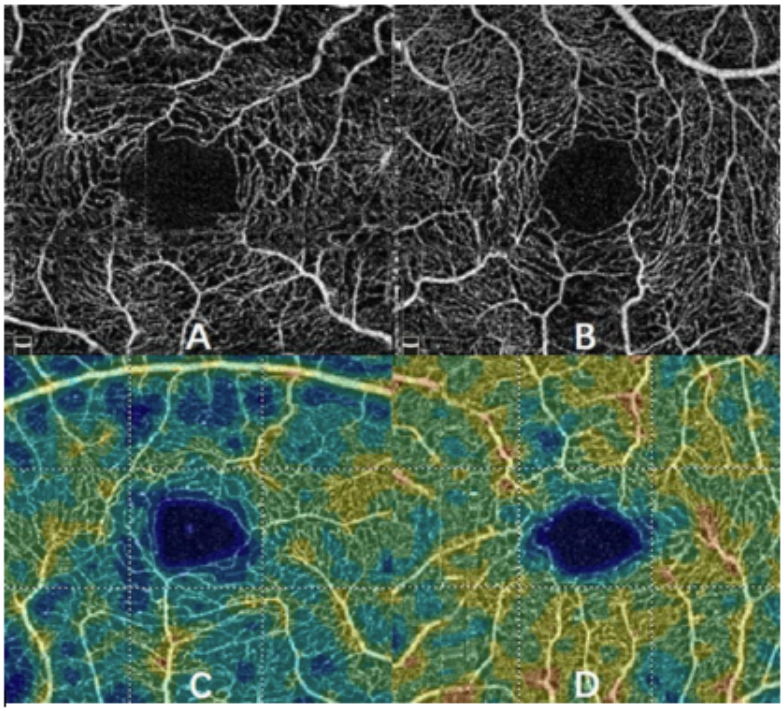

Figure 1

Macular microvascular network on superficial retina of the acute PACG eye (A) and the contralateral unaffected eye (B) in a patient. In unaffected eye, a dense blood vessels network was visible on OCTA. This network was attenuated, and with enlargement of intercapillary spaces and FAZ area in acute PACG eyes. Pseudo-color images of vessels on superficial retina of acute PACG eye (C) showed a lower vessel density than the contralateral eye (D).

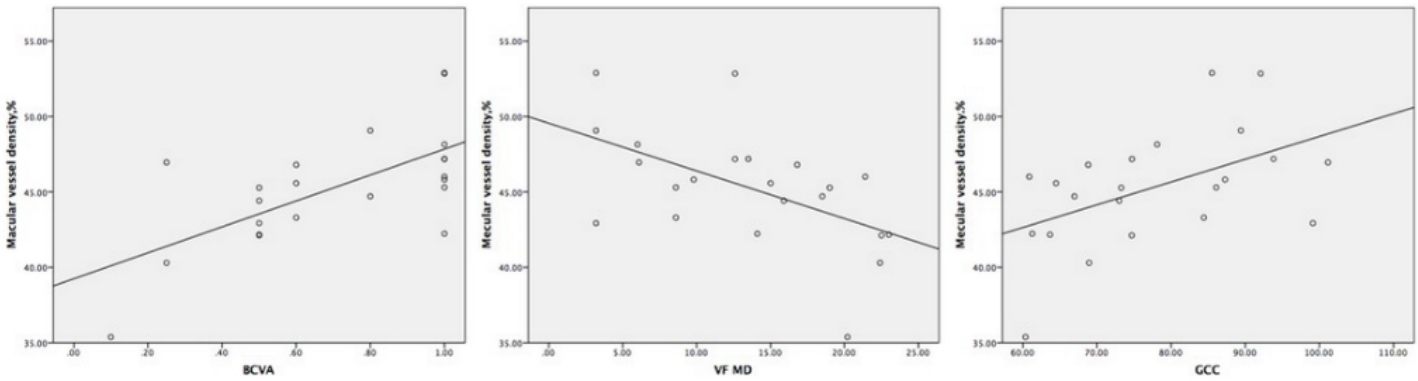

Figure 2

Correlation of MVD with BCVA□VF MD and GCC in acute PACG eyes. Simple linear regression showed a negative correlation of MVD with the VF MD and a positive correlation with the BCVA and GCC in acute PACG eyes.