Optical Coherence Tomography Angiography of The Macular Microcirculation in Acute Primary Angle Closure Treated With Phacoemulsification

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Abstract

Purpose

To measure the changes of macular microcirculation in cases with unilateral acute primary angle closure (APAC) who were managed by phacoemulsification.

Methods

Patients with unilateral APAC and managed by phacoemulsification were enrolled. The contralateral unaffected eyes were served as fellow group, and normal individuals were recruited as control group. Optical coherence tomography angiography (OCT-A) was performed to analyse the macular whole image vessel density (wiVD) and parafoveal vessel density (pfVD). The retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thicknesses were assessed using spectral-domain optical coherence tomography.

Results

A total of 36 APAC patients and 35 eyes from 35 normal individuals were recruited. In the APAC eyes, the mean wiVD ($42.1\% \pm 3.7\%$) and pfVD ($45.2\% \pm 3.8\%$) in the superficial layers (wiVD-SL and pfVD-SL) were both significantly reduced, compared to fellow eyes ($45.7\% \pm 3.1\%$, $48.7\% \pm 3.1\%$) and control eyes ($44.4\% \pm 4.7\%$, $47.4\% \pm 5.1\%$) ($P < 0.05$). They were all statistically correlated with RNFL, GCC, visual field pattern standard deviation (PSD), and mean deviation (MD).

Conclusion

The macular OCT-A parameters including wiVD-SL and pfVD-SL were significantly reduced in the eyes with APAC compared the fellow unaffected eyes and normal control eyes. They were correlated well with RNFL, GCC, PSD and MD. The macular vessel density parameters may help monitor the progression of APAC.

Introduction

Acute primary angle closure (APAC) is an ocular emergency and a subtype of primary angle closure glaucoma (PACG). Sudden elevated intraocular pressure (IOP), ocular pain and headache are the typical symptoms of APAC. Delayed progressive retinal ganglion cells (RGCs) loss, which is the pathology underlying optic nerve damage can still occur even after the acute episode remission.¹ Gradual reductions of retinal nerve fiber layer thickness (RNFL) and vessel density (VD) in the optic nerve head

(ONH) in eyes with APAC have been studied in several literatures.²⁻⁵ However, the underlying mechanisms of progressive RGCs loss after remission in APAC is still unclear.

The two major mechanisms of glaucoma are mechanical compression⁶ and vascular insufficiency.⁷ The mechanical compression theory is generally acceptable, and acute elevated IOP mainly contributes to RGCs loss in APAC.⁶ With the development of optical coherence tomography angiography (OCT-A), studies showed significant reductions of VD in the ONH in APAC.²⁻⁵ These suggest that vascular insufficiency may also play a critical role in the pathogenesis of APAC. Nevertheless, most of these studies focused on the ONH changes and the glaucomatous damage to the macula has been underestimated for a long time.

Macular region contains up to 30% RGCs of the whole retina, and the macular ganglion cell complex (GCC) greatly relies on the macular capillary network. There is growing evidences that macula damage in glaucoma is common until recently with the rapid development of OCT and OCTA. The diagnostic accuracy for glaucoma can be improved if GCC in the macular area is also focused,^{8,9} and the macular VD change was reported to be sensitive since it could be detected in series examinations even when no evident changes in GCC thickness were observed.¹⁰

One study reported the macular VD reduction in APAC eyes when compared with the fellow eyes, while the examinations were performed immediately after acute attack of angle closure.¹¹ The RNFL thickness did not show differences with the fellow eyes since the measurements were influenced by the retinal edema.¹¹ Therefore, in order to eliminate the influence of retinal edema caused by acute attack, we conducted this study in APAC eyes at least 3 months after acute attack. Moreover, the APAC eyes in previous studies were managed by different strategies, including laser peripheral iridotomy (LPI), trabeculectomy, phacoemulsification or glaucoma medications.^{2,11} Phacoemulsification is effective in treating APAC to reduce IOP, glaucoma medications, and improve visual acuity.¹² Hence, to further reduce the impact of different surgeries on the ocular microcirculation, we only included APAC eyes treated with cataract extraction and phacoemulsification.

Based on the advantage of the OCT-A in studying the retinal microvasculature, this study aimed to compare the macular VD changes in the eyes with APAC, the fellow unaffected eyes and normal control eyes. The relationships between the macular VD parameters and the RNFL, GCC, and visual function were also investigated to enrich the understanding of the pathogenesis of APAC.

Methods

Patients

In this case-control study, patients who were diagnosed as APAC and managed by phacoemulsification were included in this study. An APAC episode was diagnosed based on the criteria published in our previous study.¹³ The inclusion criteria were as follows: (1) the fellow eye was unaffected with normal

visual field (VF) and no signs of glaucomatous optic neuropathy; (2) their IOP values were not more than 21 mmHg without glaucoma medications when examinations were performed; (3) VF results were reliable with a false positive error rate of < 15%, a false negative error rate of < 25%, and fixation loss not more than 33%. The patients were excluded for the following reasons: (1) a history of uveitis, trauma, retinal disease or intraocular surgery except laser peripheral iridotomy (LPI) or phacoemulsification; (2) poor quality of optical coherence tomography (OCT) or OCT-A scans with poor clarity, poor segmentation, signal strength index (SSI) of < 48, and motion artifact. The APAC eyes consisted the case group, the fellow group was constituted of contralateral unaffected eyes, and the normal eyes served as the control group. This study was in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board of Eye hospital, Wenzhou Medical University.

Examinations

All enrolled participants underwent a complete ophthalmic examination, including slit-lamp examination, IOP measurement and best-corrected visual acuity (BCVA). Visual field examinations were performed using Humphrey 24 – 2 perimetry. The RNFL and GCC thicknesses were assessed using spectral-domain optical coherence tomography (SD-OCT, RTVue-XR Avanti; Optovue, Inc, Fremont, California, USA).

Optical Coherence Tomography Angiography

Optical coherence tomography angiography was performed, using AngioVue (RTVue XR AVANTI, Optovue, Fremont, CA, USA) software (version 2017.1.0.155), to quantify the macular vessel density and FAZ area. The AngioVue software produced high resolution 3-dimensional OCT angiograms by using motion contrast technique and the split-spectrum amplitude-decorrelation algorithm angiography (SSADA). It measures the different reflectance amplitudes between consecutive B scans of the red blood cells motion and provides a non-invasive retinal vasculature characterization. The vessel density was calculated as the percentage of the area covered by the microvasculature and large vessels in a particular area.

In this study, parafoveal vessel density (pfVD) was measured in 3 mm x 3 mm OCT-A centered on the fovea with a 1.5 mm wide circular annulus. The whole en face image vessel density (wiVD) was analyzed over the entire macular scan area. The superficial layer of pfVD (pfVD-SL) in the region extending from the inner limiting membrane (ILM) to 10 μ m above the inner plexiform layer (IPL) was evaluated. The deep layer of pfVD (pfVD-DL) was calculated from 10 μ m above IPL to 10 μ m below the outer plexiform layer (OPL). The pfVD was divided into superior, inferior, temporal and nasal sectors. The foveal avascular zone (FAZ) area and perimeter without capillaries were automatically measured from the central macula via the FAZ assessment function. The ratio of the FAZ perimeter and the perimeter of a circle with an equal area is defined as the FAZ acircularity index (AI).

Statistical Analysis

The results were analyzed by SPSS software version 23 (SPSS Inc., Chicago, IL) and Medcalc 19.1 (MedCalc Software Ltd, Ostend, Belgium). The normality of the numeric parameters was evaluated using the Shapiro-Wilk test. Analysis of variance (ANOVA) followed by Bonferroni test was used to compare

mean measurements between APAC eyes, fellow eyes and normal control eyes. Categorical variables were compared using the chi-squared test. The correlations between the normally distributed factors were analyzed by Pearson correlation and the non-normal distributions were evaluated by Spearman correlation. The diagnostic abilities of vessel density and the glaucoma parameters were evaluated using receiver operating characteristic (ROC) curves. Data are presented as mean $\pm$ standard deviation (SD). Statistical significance was set at $P < 0.05$.

Results

After excluding 9 cases due to poor OCT-A image quality (6 cases), and poor visual field examination performance (3 cases), 36 patients (36 pairs of eyes) with unilateral APAC and 35 normal individuals (35 eyes) were included for analysis (Table 1). The peak IOP during acute attack of angle closure in eyes with APAC was 52.4 ± 7.1 mmHg. The interval between the acute attack and phacoemulsification was 4.8 ± 4.0 days and the disease course between acute attack and OCT-A examination was 17.9 ± 13.0 months. No significant differences were found in age, gender, and presenting IOP at OCT-A examination (IOPe, all $P > 0.05$) among the three groups. The axial length (AL) in the APAC eyes and fellow eyes were significant shorter than in the normal control eyes (both $P < 0.05$). The VCDR were significant larger, BCVA and VF results were worse in APAC group than in fellow group and normal control group (all $P < 0.05$). The APAC eyes also had thinner GCC and RNFL than fellow eyes and control eyes (both $P < 0.001$).

Table 1 Characteristics of APAC Eyes, Their Fellow Eyes and Normal Controls

					<i>P</i> Value	<i>P</i> Value	<i>P</i> Value
					APAC VS.	APAC VS.	Fellow VS.
Characteristic	APAC	Fellow	Control	<i>P</i> Value	Fellow	Control	Control
Number of eyes	36	36	35	-	-	-	-
Age, y	62.7±7.8	62.7±7.8	60.4±4.7	0.363	-	-	-
Sex, F/M	31/5	31/5	27/8	0.319	-	-	-
IOPe, mmHg	13.9±3.5	14.4±3.2	14.1±3.3	0.805	0.512	0.758	0.731
Axial length, mm	22.2±0.7	22.3±0.7	22.6±0.8	0.057	0.927	0.034	0.042
VCDR	0.7±0.2	0.5±0.2	0.5±0.2	□ 0.0001	□ 0.0001	□ 0.0001	0.648
BCVA, LogMAR	0.08±0.09	0.05±0.08	0±0	□ 0.0001	0.315	□ 0.0001	0.001
MD, dB	9.5±7.6	2.9±1.5	2.9±1.4	□ 0.0001	□ 0.0001	□ 0.0001	1
PSD, dB	5.5±3.1	2.7±1.1	2.7±1.1	□ 0.0001	□ 0.0001	□ 0.0001	0.984
GCC thickness, μm	83.9±11.9	101.5±9.6	98.5±6.7	□ 0.0001	□ 0.0001	□ 0.0001	0.189
RNFL thickness, μm	78.2±14.4	104.1±8.4	104.0±8.5	□ 0.0001	□ 0.0001	□ 0.0001	1

APAC = acute primary angle closure; IOPe = intraocular pressure when OCTA examination; AL = axial length; VCDR = vertical cup-to-disc ratio; BCVA = best-corrected visual acuity; MD = mean deviation; PSD = pattern standard deviation; GCC = ganglion cell complex; RNFL = retinal nerve fiber layer

Table 2 shows the comparison of the macular microcirculation among three groups. The wiVD in the superficial layer (wiVD-SL), global and sectoral pfVD-SL were all significantly lower in the APAC eyes when compared with the fellow eyes and normal control ($P < 0.05$ for all, Figure 1). No differences were found in the vessel densities of the deep layer, FAZ measurements including FAZ area, perimeter and AI among the three groups ($P > 0.05$ for all, Table 2).

Table 2 Comparison of Macular Parameters among APAC Eyes, Fellow Eyes and Normal Controls

					<i>P</i> Value	<i>P</i> Value	<i>P</i> Value
	APAC	Fellow	Control		APAC VS.	APAC VS.	Fellow VS.
Characteristic	N = 36	N = 36	N = 35	<i>P</i> Value	Fellow	Control	Control
Superficial layer, %							
wiVD	42.1±3.7	45.7±3.1	44.4±4.7	0.001	0.0001	0.014	0.182
pfVD-SL, %							
Average	45.2±3.8	48.7±3.1	47.5±4.8	0.001	0.0001	0.018	0.204
Temporal	44.2±3.9	47.3±3.3	46.6±4.6	0.004	0.001	0.027	0.303
Superior	46.1±4.5	49.5±3.4	48.4±5.7	0.009	0.003	0.039	0.344
Nasal	44.5±4.2	47.5±3.7	46.3±4.5	0.009	0.003	0.033	0.4
Inferior	46.1±4.1	50.6±3.1	48.6±5.5	0.0001	0.0001	0.016	0.056
Deep layer, %							
wiVD	48.7±3.6	49.8±3.6	49.4±3.6	0.425	0.196	0.42	0.631
pfVD-DL, %							
Average	51.4±3.3	52.6±3.4	52.2±3.7	0.396	0.172	0.388	0.619
Temporal	51.4±3.5	52.7±3.4	52.3±3.6	0.319	0.138	0.328	0.618
Superior	51.5±3.8	52.8±3.5	52.3±3.8	0.333	0.146	0.333	0.631
Nasal	51.6±3.3	52.6±3.6	52.6±3.7	0.359	0.215	0.217	0.996
Inferior	51.3±3.9	52.2±4.0	51.2±4.7	0.546	0.353	0.961	0.332
FAZ							
Area, mm2	0.4±0.1	0.4±0.2	0.4±0.1	0.369	0.711	0.173	0.318
Perimeter, mm	2.5±0.5	2.5±0.5	2.4±0.3	0.381	0.511	0.166	0.461
Acircularity index	1.15±0.04	1.14±0.04	1.14±0.04	0.617	0.624	0.327	0.62
Avg SSI	67.1±6.5	68.4±7.5	68.7±8.4	0.602	0.386	0.383	0.989

APAC: acute primary angle closure; wiVD: whole en face image vessel density; pfVD-SL: superficial layer of parafoveal vessel density; pfVD-DL: deep layer of parafoveal vessel density; FAZ: foveal avascular

zone; SSI: signal strength index

The correlations between macular microvascular parameters and traditional four measurements including RNFL, GCC thickness, MD and PSD in the APAC eyes were tested. The parameters of wiVD-SL and pfVD-SL were positively correlated with the mean RNFL and GCC thickness in APAC eyes ($P < 0.01$ for all, Table 3). Also, they were all negatively correlated with the VF PSD and MD ($P < 0.01$ for all, Table 3).

Table 3 Correlations for Macular Vessel Densities in APAC Eyes

Variables	wiVD-SL	pfVD-SL
mean RNFL	$r = 0.64, P = 0.001$	$r = 0.623, P = 0.001$
mean GCC	$r = 0.641, P = 0.001$	$r = 0.616, P = 0.001$
MD	$\rho = -0.488, P = 0.003$	$\rho = -0.439, P = 0.007$
PSD	$\rho = -0.543, P = 0.001$	$\rho = -0.506, P = 0.002$

APAC: in acute primary angle closure; wiVD-SL: whole en face image vessel density in the superficial layer; pfVD-SL: superficial layer of parafoveal vessel density; RNFL: retinal nerve fiber; GCC: ganglion cell complex; MD: mean deviation; PSD: pattern standard deviation

r: Pearson's correlation coefficient; ρ : Spearman's correlation coefficient.

From the ROC curves, the wiVD-SL, pfVD-SL, RNFL and GCC thicknesses all showed optimal area under the ROC curve (AUC) to differentiate eyes with APAC from the fellow eyes ($P < 0.05$ for all, Figure 2). The diagnostic abilities for the macular vessel densities of wiVD-SL (76.0%) and pfVD-SL (75.1%) were both statistically lower than the diagnostic abilities of GCC (89.8%) and RNFL (91.4%, all $P < 0.01$).

Discussion

Studies have reported that macular GCC loss is involved in early glaucomatous damage.¹⁴ Since the macula area is one of the most metabolically active tissues in humans and its oxygen requirement is derived from multiple capillary supplies, the changes in the macular VD after APAC episodes are thought to be related to the pathophysiology of RGC loss in APAC.^{15,16} In the present study, the macular vessel densities were significantly reduced in the indices of wiVD-SL, and pfVD-SL in the APAC eyes, and strong correlations were found between the wiVD-SL, pfVD-SL and traditional glaucoma diagnostic parameters.

The macula has the highest density of RGCs, and reduced macular VDs were firstly reported in POAG eyes when compared with normal subjects.^{17,18} The changes in macular VD were then also observed in PACG, that there were pfVD and wiVD reductions in the superficial vascular plexus when compared with healthy eyes.¹⁹ In our study, we further provide the information of macular VD reductions in APAC eyes,

and these suggest that although in different glaucoma types, the macular vessel density changes may share some similarities.

The superficial vascular complex supplies the inner retina from the nerve fiber layer to the inner part of the IPL. The deep vascular layers supply part of the IPL and the middle retinal layers without retinal ganglion cells.^{20,21} In our study, we scanned the deeper macular vessels and observed that the pfVD-DLs were not significantly different among the APAC eyes, fellow eyes and normal controls. Therefore, only superficial macular vessel supplies were greatly affected in APAC eyes. This finding of unchanged pfVD-DL in APAC suggests that deep vascular plexus is not susceptible in acute IOP elevation. This is similar to the findings in the POAG eyes.¹⁷ Hence, the macular vessel densities in superficial layers provide more important information for glaucoma than in the deep layers.

FAZ, another macular microcirculation parameter, has been regarded as a representative indicator of retinal capillary non-perfusion. Specifically, the enlargement of FAZ was correlated with decreased visual acuity, and the irregular shape of FAZ could contribute to capillary occlusion, and hemodynamic disturbance.^{22–24} In our study, no statistical differences were found in FAZ area, perimeter and AI among the APAC eyes, fellow eyes and normal controls. In the study of Liu et al., they also demonstrated no differences of FAZ area and perimeter among the three groups, while they found that circularity was lowest in APAC eyes, followed by the fellow eyes and normal control eyes.¹¹ The reason may be due to the retinal edema caused by the acute attack of angle closure, since they investigated the macular microcirculation immediately after acute attack had been resolved. The irregularity of FAZ may also contribute to the reduced visual acuity of APAC eyes in acute phase apart from corneal edema induced by IOP elevation.

The correlations of the vessel density parameters with traditional glaucoma parameters in APAC eyes depends on the disease course specifically the time interval between the OCTA examination and acute attack was resolved. The results in our study were consistent with those in the study of Zhang et al.² In the study of APAC conducted by Zhang et al, cpVD was related to RNFL, GCC, and VF MD.² Nonetheless, Wang et al. illustrated that the ONH vessel densities in APAC eyes were only correlated with VF PSD and MD but not with RNFL and GCC thicknesses.³ This is due to the different time intervals between the OCTA examination and acute attack of angle closure, which determines whether the retinal edema was eliminated and the structural parameters were reduced in the APAC eyes. We performed the OCT-A examination at least 3 months after acute attack, and retinal edema was disappeared. The time interval in the study of Zhang et al. ranged from 7 days to 2 years, although retinal edema was still present in some cases, the mean RNFL and GCC thicknesses in his study were significantly reduced compared with the fellow eyes.² However, Wang et al. conducted it immediately after acute attack was resolved, and the RNFL and GCC thicknesses were not significantly different between APAC eyes and fellow eyes when the OCT-A examination was performed.³

Comparing the diagnostic abilities of macular VD indices, the diagnostic abilities were consistent with Rao's report, which showed that the diagnostic abilities of macular vessel densities were lower than those of the structural parameters such as RNFL and GCC.¹⁹ Nevertheless, it is not clear why the diagnostic ability of the structural measures, especially GCC, is better than that of the macular OCT-A. Takusagawa et al. reported comparable diagnostic abilities of the macular superficial vascular complex and the GCC thickness.¹⁷ They accounted this to the larger scan area of the macular VD (6 mm × 6 mm) than in the traditional small scan (3 mm × 3 mm).¹⁷ Since approximately half of RGC soma are located in the macula and the metabolic requirements from the regional capillary plexuses are high, RGCs are prone to be more sensitive to microcirculation dropout in the macula. A larger scan area of the macula may be more accurate in reflecting the diagnostic ability of macular VD.

This study has a few limitations. First, the current scan was limited to an area of 3 mm × 3 mm. A larger macula area of 6 mm × 6 mm which should yield a higher diagnostic accuracy for macular VD measurements, should be used in future studies. Second, this is a cross-sectional study and the macular VD was examined 3 months after APAC to eliminate the influence of retinal edema. Hence, the early stage information of macular VD after APAC episode was lacking. Further research is necessary to determine the sequence of VD and the structural changes to elucidate the role of vascular perfusion in the disease mechanism of APAC.

In summary, statistically significant attenuations of macular wVD and pfVD in the superficial layer were observed in APAC eyes. These parameters were correlated with RNFL, GCC, VF MD and PSD. The diagnostic abilities of the macular VD indices were lower than those of the structural measures of RNFL and GCC thicknesses. Nevertheless, they may still be useful for monitoring the progression of APAC.

Declarations

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Authors' contributions: Nie L, Wen SM, Shen LJ and FU L designed this study; Fang J, Liu JB, and Wang J provided and collected the data; Yu GS and FU L analysed and interpreted the data; Nie L, Chan YK and FU L wrote and revised the paper. All authors read and approved the final manuscript.

Conflicts of interest: Fu L, None; Chan YK, None; Fang J, None; Liu JB, None; Wen SM, None; Shen LJ, None; Wang J, None; Yu GS, None; Nie L, None.

Availability of data: The datasets used in this study are available from the corresponding author on reasonable request.

Ethical approval: This study was in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board of Eye hospital, Wenzhou Medical University.

Informed consent: Informed consents were obtained from all participants. They signed the informed consents and agreed to publish their data and photographs.

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Figures

Figure 1

Macular vessel densities in APAC eyes with corresponding GCC thickness and visual field (A0-D0) compared with fellow eyes (A1-D1) and normal control eyes (A2-D2). pfVD-SL: superficial layer of parafoveal vessel density; pfVD-DL: deep layer of parafoveal vessel density; APAC: in acute primary angle closure; GCC: ganglion cell complex.

Figure 2

Receiver operating characteristic curves of the wiVD-SL pfVD-SL, RNFL, and GCC. wiVD-SL: superficial layer of whole en face image vessel density; pfVD-SL: superficial layer of parafoveal vessel density; GCC: ganglion cell complex; RNFL: retinal nerve fiber layer.