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Peripapillary capillary density in acute angle closure crisis and angle closure suspect: A structure, flow and function correlation study

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Abstract

Purpose: to describe peripapillary vascular changes using Optical Coherence Tomography Angiography (OCT-A) in patients with acute angle closure crisis (AACC) and primary-angle closure-suspects (PACS) in comparison to normal controls.

Methods: This cross-sectional/case-control/non-randomized study was conducted at Cairo University Hospitals. It included 21 eyes following AACC, 21 eyes of PACS and 32 eyes of age-matched-controls. Participants underwent visual field (VF) examination, retinal nerve fiber layer (RNFL) assessment using spectral-domain-OCT (SD-OCT), and radial peripapillary capillary density (RPC%) using OCT-A.

Results: There was a statistically significant difference in MD and PSD among the three groups ($p \leqslant 0.001$). There was a significant difference in mean RNFL among the three groups ($p \leqslant 0.001$), this decrease was still present when comparing the AACC group to controls $p = 0.032$. There was a significant decrease in the peripapillary RPC% in all groups $p \leqslant 0.001$. The correlation between structure, function and flow was studied for all groups. Peripapillary RPC% in AACC was positively correlated to MD and peripapillary RNFL ($p \leqslant 0.001$). In PACS, RPC% was positively correlated to RNFL ($p = 0.012$). In controls, RPC% was positively correlated to PSD and peripapillary RNFL ($p \leqslant 0.001$). AUC was 0.8 for the MD, 0.56 for the RPC and 0.38 for the RNFL

Conclusions: Peripapillary vessel density was lower in AACC eyes than in suspects and control eyes. OCT-A parameters could be a more sensitive marker than OCT parameters after an AACC attack as evident on ROC analysis. PACS remains a clinical diagnosis as we could not find any significant differences in OCT or OCT-A parameters between suspects and normal healthy controls.

Keywords

RPC%, acute angle closure crisis, primary angle closure suspect, structure/function/flow correlation

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Background

Optical coherence tomography angiography (OCT-A) is a new technique which allows noninvasive imaging of the optic nerve head (ONH), blood vessels and retina. Many studies reported a reduction in vessel density within the ONH, the peripapillary retina, and the macula in cases of primary open angle glaucoma (POAG).[1–5] Only a few researchers have studied the vessel densities using OCT-A in primary angle closure glaucoma (PACG).[6,7] The fact that PACG accounts for bilateral irreversible blindness in nearly 3.9 million people[8] makes this preventable disease an important field for research.

The mechanism of optic neuropathy in PACG is not fully understood; mechanical compression and vascular insufficiency are the suggested mechanisms commonly implicated in glaucomatous optic neuropathy, with special emphasis on mechanical compression as the main

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mechanism in acute PAC.[9,10] However, previous studies have paid little attention to the vascular factors in PACG.

Radial Peripapillary Capillary (RPC) density has been shown to significantly decrease in POAG cases as well as in PACG[11] when compared to normal healthy individuals. In a study by Zhang et al, the RPC of patients with PACG was significantly lower than the contralateral eye showing no previous attacks of acute angle closure crisis (AACC), and focal capillary dropout was evident in acute PACG eyes.[6] Studies that compared RPC density of PAC disease have either excluded primary angle closure suspect (PACS) or included them in the analysis as primary angle closure disease and therefore have not studied the changes that could occur in PACS eyes as compared to healthy normal controls.[6,7,12]

This study aims to assess the ONH vascular changes as measured by OCT-A in 3 groups of patients; patients who experienced a single attack of AACC in group one, patients classified as primary angle closure suspect (PACS) in group two, and normal controls in group three. The OCT-A findings representing flow will be correlated with retinal nerve fiber layer (RNFL), structural damage as measured by OCT, and functional damage represented in mean deviation (MD) and pattern standard deviation (PSD) as measured by automated perimetry.

Patients and methods

This is a cross-sectional study conducted at Kasr Al Ainy-Cairo University Hospitals. The study was approved by the Research Ethics Committee of the Faculty of Medicine (REC:N-115-2018), Cairo University. Data collection conformed to all local laws and was compliant with the tenets of the Declaration of Helsinki. A written informed consent was obtained from all participants.

A total of 347 study subjects were examined in the glaucoma subspecialty of which 305 subjects were excluded because they did not meet the inclusion criteria ($n=221$), had poor signals on OCT/OCT-A ($n=12$) or declined to participate in the study ($n=72$) (see Appendix 1).

Three groups of patients were included; group 1 included 21 eyes of 21 patients who experienced a single attack of AACC and underwent phacoemulsification, group 2 included 21 eyes of 21 patients diagnosed as PACS who underwent prophylactic laser PI, and group 3 included 32 eyes of 32 normal controls.

Patients with acute angle closure were included if they fulfilled the following criteria; 1 eye had a history of a single attack of AACC, defined by the presence of at least 2 symptoms (such as ocular pain, nausea/vomiting, decreased vision, colored halos), elevated intraocular pressure (IOP) $>$21 mm Hg, and at least 3 findings on clinical examination (e.g. corneal edema, peripheral anterior chamber depth equal to or less than one quarter of the peripheral corneal thickness, gonioscopic confirmation of angle closure, iris bombe, mid dilated vertical oval pupil).[13] All patients had previously undergone phacoemulsification controlling the acute attack with maximum treatment including the administration of hyperosmotic agents.

The angle closure suspect group was recruited if they showed the following criteria[13] (1) a narrow occludable angle with irido-trabecular contact for 270° with no peripheral anterior synechia, (2) normal IOP, and (3) normal optic nerve head examination and perimetry. All selected patients in this group underwent a prophylactic YAG laser PI.

Exclusion criteria included; (1) patients with chronic angle closure glaucoma (CACG), (2) secondary angle closure, (3) evidence of any associated retinal diseases, (4) evidence of previous intraocular surgery, (5) evident refractive media opacity that may hinder imaging quality and (6) the presence of any systemic disease that can affect optic disk perfusion like systemic hypertension or diabetes mellitus.

All participants underwent full ophthalmic examination. IOP was measured using Goldmann applanation tonometry. Gonioscopy was performed using a 4-mirror lens at high magnification (x16) by glaucoma specialists. All participants underwent visual field (VF) examination, OCT and OCT-A.

Patients having AACC presented within 1.09 ± 0.03 days from the onset of the attack, they were hospitalized and received medical treatment to lower IOP prior to phacoemulsification. Surgery was performed within 48 h from admission as soon as the corneal clarity was sufficient to perform phacoemulsification. VF, OCT and OCT-A were done 1 week after the surgery.

Visual field (VF) examination was performed using a Humphrey Field analyzer II, model 720i (Zeiss Humphrey Systems, Dublin, California, USA), with the Swedish interactive threshold algorithm SITA standard 24-2 program. VFs were considered reliable if the fixation losses, and false positive and false negative response rates were all $\leqslant$20%.

OCT angiography (OCT-A) of the optic disk was performed by the same experienced investigator (KA) using an RTVue XR Avanti machine (AngioVue; Optovue Inc., Fremont, CA, USA). The software automatically fit an ellipse to the optic disk margin and the peripapillary region was defined as a 0.75 mm-wide elliptical annulus extending from the optic disk boundary. The Radial peripapillary capillary density was automatically displayed by the machine as a percentage (average, superior average, inferior average, nasal, superior, inferior and temporal quadrants).

The optic disk rim area, cup volume, average RNFL, and the RNFL thickness in superior, inferior, nasal, and temporal quadrants were obtained using the RTVue (Optovue Inc., Fremont, CA, USA) model-RT100 with algorithm version (6.11.0.12).

Table 1. A summary of the IOP, visual field, OCT, and OCT-A parameters[a] among the three groups of patients.

	AACC group Mean ± SD	PACS group Mean ± SD	Control group Mean ± SD	*p*-value
Baseline IOP (mmHg)	44 (±6.2) (on maximum tolerated treatment)	13.9 (±2.32)	13.9 (±2.37)	**≤0.0001***
Post-phaco IOP (mmHg)	22.2 (±14.7) (on no treatment)	13.9 (±2.32)	13.9 (±2.37)	**0.01***
Visual Acuity (LogMAR)	0.7 (±0.6)	0.2 (±0.7)	0.00 (±0.8)	**≤0.0001***
MD	−13.64 (±10.27)	−2.8 (±1.91)	−0.36 (±1.04)	**≤0.0001***
PSD	5.09 (±3.02)	2.08 (±0.81)	1.47 (±0.36)	**≤0.0001***
Peripapillary RPC%	39.2 (±9.64)	52.11 (±3.6)	51.7 (±3.48)	**≤0.0001***
Superior RPC%	36.2 (±12.2)	53.6 (±3.7)	51.3 (±5.4)	**≤0.0001***
Inferior RPC%	45.1 (±7.2)	52.7 (±5.7)	52.7 (±6.3)	**≤0.0001***
Nasal RPC%	36.6 (±13.2)	52.3 (±6.3)	52.2 (±7.2)	**≤0.0001***
Temporal RPC%	40.3 (±9.3)	50.7 (±5.5)	51.1 (±4.8)	**≤0.0001***
Average RNFL	85.87 (±22.4)	97.47 (±10.7)	101.25 (±9.5)	**≤0.0001***
Superior RNFL	101.18 (±28.2)	118.0 (±16.3)	124.68 (±11.0)	**≤0.0001***
Inferior RNFL	102.37 (±30.4)	123.19 (±15.7)	125.5 (±13.1)	**0.001***
Nasal RNFL	70.56 (±24.4)	77.66 (±12.8)	80.19 (±12.0)	0.147
Temporal RNFL	69.18 (±13.7)	70.95 (±6.3)	74.12 (±6.0)	0.137

OCT-A parameters[a]: taken after controlling the attack of AACC as corneal edema precludes imaging with OCT-A; MD: mean deviation; PSD: pattern standard deviation; RPC%: radial peripapillary capillaries percentage; RNFL: retinal nerve fiber layer.
*Significant *p*-values (≤0.05).

For both OCT and OCT-A only patients having a signal strength values between 7 and 10 were included.[14]

Statistical analysis

Descriptive statistics were summarized as mean ± standard deviation for numerical data, frequencies and percentages for categorical data. The ANOVA test and Pearson's moment correlation coefficient were used to compare the means for numerical data and to identify correlations between them. Chi-square test was used to compare categorical data. *P*-values ≤0.05 were considered statistically significant. ROC analysis was used to compare the sensitivity and specificity of the MD, RNFL thickness and RPC in detection of AACC induced changes. Results were interpreted in terms of Area Under the Curve (AUC) and 95% confidence interval (CI). All statistical analyses were performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA).

Results

The study was conducted during the period between August 2018 and December 2018. Three groups of patients were included; group 1 included 21 eyes of 21 patients (15 females and 6 males), group 2 included 21 eyes of 21 patients (19 females and 2 males), and group 3 included 32 eyes of 32 normal controls (16 females and 16 males) (See appendix 1).

The mean (±SD) age of the AACC, PACS and control group was 56.7 ± 6.1 years, 58.8 ± 6.5 years and 57.2 ± 4.3 years, respectively (*p*-value = 0.41).

There was a highly significant difference among the three groups regarding IOP, visual acuity (VA), VF parameters, OCT and OCT-A parameters (*p*-values ≤0.01)as shown in Table 1.

No significant differences were detected between the three groups regarding the nasal and temporal RNFL thickness (*p*-values 0.047 and 0.137 respectively)

These differences were still evident when paired group analysis was performed.

The differences in VF parameters (MD and PSD) were statistically significant between the AACC-PACS, PACS-controls and AACC-controls (*p*-values ≤0.001, ≤0.001 and 0.002 respectively for the MD) (*p*-values 0.001, 0.01 and 0.005 respectively for the PSD).

Similarly, the differences in the average RNFL were statistically significant between the AACC and controls (*p*-values 0.032). The differences in superior and inferior RNFL were statistically significant between the AACC-PACS and the AACC-controls (*p*-values ≤0.033 and 0.018 respectively for the superior RNFL) (*p*-values 0.028 and 0.016 respectively for the inferior RNFL). Also, the differences in the rim area and cup volumes were statistically significant between the AACC and controls (*p*-values 0.036 and 0.026 respectively).

Regarding the OCT-A, the differences in the average, superior and inferior RPC% were statistically significant

Table 2. The mean difference in VF, OCT and OCT-A parameters and their significance.

	AACC-PACS	PACS-control	AACC-control
VF			
• MD **(dB)**	−10.05 (±10.74)	−2.55 (±2.35)	−12.46 (±10.74)
(*p*-value)	**⩽0.001**	**⩽0.001**	**0.002**
• PSD **(dB)**	2.79 (± 3.35)	0.6 (±0.98)	3.3 (±3.14)
(*p*-value)	**0.001**	**0.01**	**0.005**
OCT			
• RNFL (um)	−11.75 (±25.22)	−3.67 (±0.49)	−15.44 (±26.12)
(*p*-value)	0.082	0.26	**0.032**
• Superior RNFL	−18.06 (±30.72	−7.24 (±0.83)	−23.37 (±35.19)
(*p*-value)	**0.033**	0.138	**0.018**
• Inferior RNFL	−21.06 (±34.75)	−1.19 (±0.19)	−22.94 (±33.61)
(*p*-value)	**0.028**	0.52	**0.016**
• Rim area (mm^2)	−0.19 (±0.58)	−0.04 (±0.4)	−0.31 (±0.538)
(*p*-value)	0.19	0.63	**0.036**
• Cup volume (mm^3)	0.11 (±0.29)	0.087 (±0.22)	0.21 (±0.34)
(*p*-value)	0.13	0.084	**0.026**
OCT-A			
• Mean RPCS%	−13.175 (±10.18)*	−0.16 (±5.23)†	−12.78 (±11.11)‡
(*p*-value)	**0.001**	0.889	**⩽0.001**
• Superior	−13.54 (±10.86)	−0.162 (±5.21)	−12.99 (± 11.58)
(*p*-value)	**⩽0.001**	0.88	**⩽0.001**
• Inferior	−13.44 (±9.58)	−0.24 (±5.79)	−13.125 (±11.28)
(*p*-value)	**⩽0.001**	0.852	**⩽0.001**

*Negative values denote lower mean RPCS% in the AACC group.
†Negative values denote lower mean RPCS% in the PACS group.
‡Negative values denote lower mean RPCS% in the AACC group.
Significant results are highlighted in bold.

between the AACC-PACS and the AACC-controls (*p*-values ⩽0.001).

These differences are further illustrated in Table 2.

A correlation between structure/function and flow was studied for the three groups

In the AACC group (Figures 1–3)

There was a positive correlation between the MD and each of the PSD, peripapillary RNFL, RPC%, superior and inferior RPC%, superior and inferior RNFL (p=0.008, 0.011, ⩽0.001, ⩽0.001, ⩽0.001, 0.006, 0.033 respectively). This was not found in the PACS group or in the control group.

Similarly, the peripapillary RPC% showed a strong positive correlation to MD, peripapillary RNFL, RPC superior and inferior in the same group ($p \leqslant 0.001$ for all correlations).

In the PACS group

There was a positive correlation between the peripapillary RPC% and each of the RNFL, RPC superior and inferior (p=0.012, $p \leqslant 0.001$, $p \leqslant 0.001$ respectively).

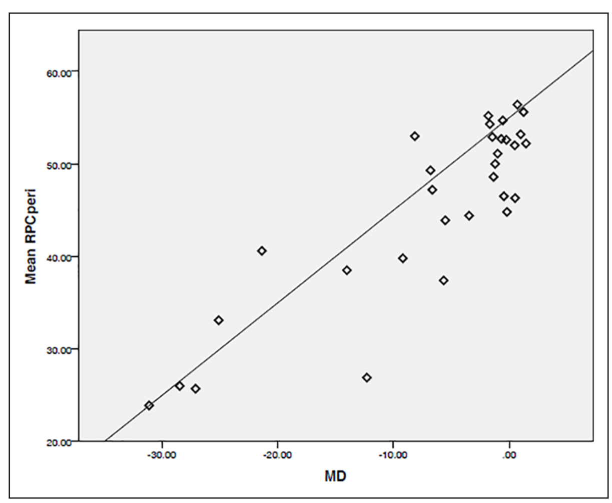

Figure 1. Scatter plot showing strong positive linear correlation between function and flow r=0.86, p < 0.001.

In the control group

There was also a strong positive correlation between the peripapillary RPC% and each of the PSD, peripapillary RNFL, RPC superior and inferior in the same group ($p \leqslant 0.001$ for all correlations).

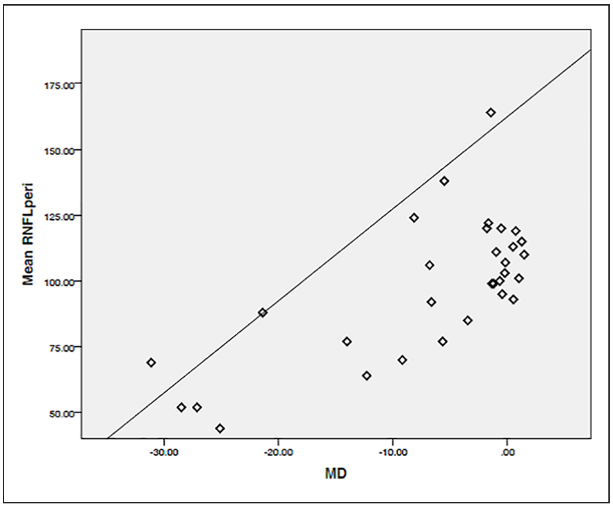

Figure 2. Scatter plot showing positive linear correlation between structure and function $r = 0.67$, $p < 0.001$.

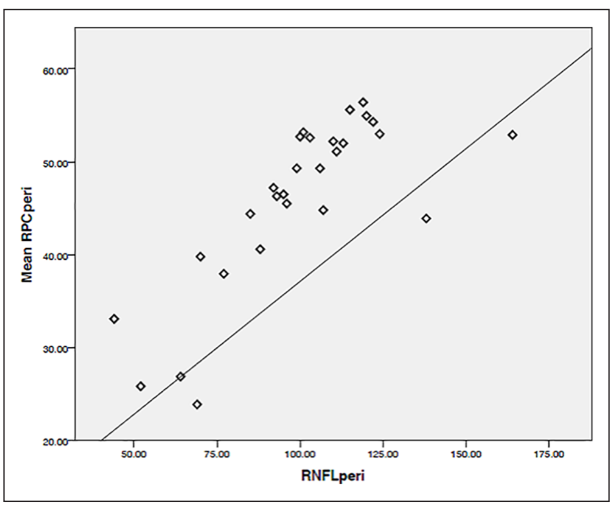

Figure 3. Scatter plot showing strong positive linear correlation between flow and structure $r = 0.78$, $p < 0.001$.

Further illustration for the Function/Structure and Flow relationship is shown in supplemental digital content (SDC1).

ROC analysis

The diagnostic sensitivity/ specificity were compared **between the AACC and control groups regarding** the MD, peripapillary RNFL and peripapillary RPC%. The Area Under the Curve (AUC) for the MD was 0.8 (95% Confidence Interval; CI between 0.6 to 0.98), AUC for the PSD was 0.16 (95% CI between 0.03 and 0.28), AUC for the peripapillary RNFL was 0.38 (95% CI between 0.2 and 0.55) while the AUC for the peripapillary RPC% was 0.56 (95% CI between 0.24 and 0.88); this is further illustrated in Figure 4.

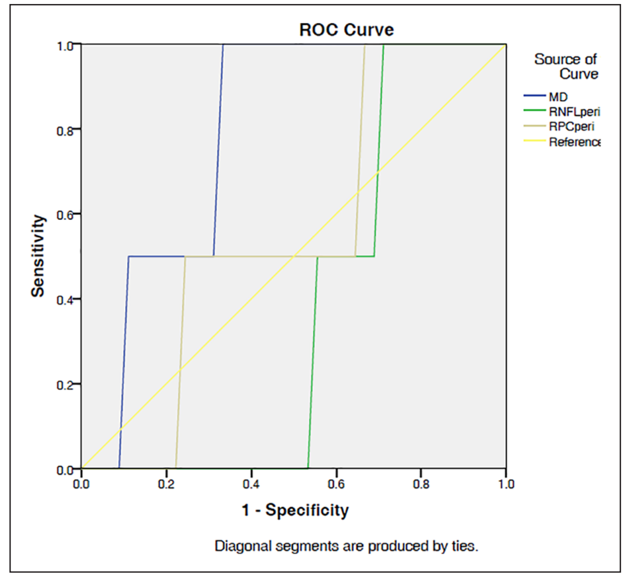

Figure 4. ROC analysis showing the AUC for the MD, peripapillary RNFL and peripapillary RPC%. The diagnostic sensitivity/specificity for the three parameters were compared between the AACC and control groups.

Discussion

The RPC layer is the most superficial retinal capillary layer that supplies the retinal nerve fibers surrounding the optic nerve head. These capillaries have long parallel paths and rare anastomoses, are more vulnerable to high IOP or hemodynamic disorders, and thus may be affected before other retinal capillary networks.[15]

The current study evaluates the RPC perfusion in AACC patients as compared to PACS and normal healthy controls. A significant difference was found in the RPC% among the three groups. In a previous literature review, significantly lower peripapillary OCT-A parameters (vessel density, blood flow index, and flow index) were found in glaucomatous eyes as compared to normal eyes.[16]

Zhang et al. found that the peripapillary microcirculation detected by OCT-A was extensively damaged after an acute primary angle closure attack, as compared to the fellow eye. Yet, they did not compare their results to a normal population nor did they analyze specific quadrants.[6] In our study this damage was still significant as we analyzed the superior and inferior parts as well as each quadrant in the AACC group as compared to the other 2 groups.

Wang and coworkers reported similar results.[12] They found that the AACC eyes had a significantly lower vessel density and worse visual field parameters, but comparable OCT parameters.[12] We found similar results when we compared the AACC to the PACS group.

Roa et al. evaluated the diagnostic ability of peripapillary vessel density measurements in PACG and compared them with the RNFL measurements. They found them to be comparable.[10] They did not compare the AACC group to the PACS as we performed. We found that there was a significant difference in the average RPC as well as in every quadrant RPC between these two groups.

In our study, structural loss was assessed by OCT and a significant difference was found among the three groups in the average RNFL thickness in the superior and inferior quadrants. When we further studied differences among the three groups, the superior and inferior RNFL quadrants showed significant differences between the AACC and PACS ($p = 0.033$, $p = 0.028$ respectively). This finding was also valid when comparing the superior quadrant in AACC to healthy controls ($p = 0.04$).

Roa et al, found a significant difference in the RNFL thickness in the inferotemporal quadrant between primary angle closure and healthy controls, such difference was not noted in our study ($p = 0.08$). This might be explained by the fact that their study included patients with high IOP but no disc damage, and that high IOP may have predisposed to ultra-structural changes.

A possible explanation for the preservation of RNFL thickness in our study may be that retinal edema following the acute attack could have given false higher readings with an impression of preserved OCT parameters.

In this study, the relationship between structural changes (represented by RNFL), perfusion assessed by OCT-A, and functional damage represented by visual field was evaluated. We found a very strong positive correlation between RPC and the MD ($p \leqslant 0.001$, $r = 0.813$) in ACC group, and between RPC and peripapillary RNFL ($p \leqslant 0.001$, $r = 0.826$). The relation between structure and function has long been studied by using OCT and VF,[17,18] but only few studies assessed the vascular perfusion and its relation to function in acute angle closure.[6,7,10]

Zhang et al found a positive correlation between the peripapillary retinal vascular density and the RNFL ($p < 0.0001$). They also found a negative correlation between the peripapillary retinal vascular density and the MD ($p = 0.002$). They could not find such correlations in the unaffected eyes.[6] Similarly, Roa et al showed that the RPC was comparable to peripapillary RNFL in mild and moderate PACG but also failed to demonstrate this in PACS.[10] On the contrary, our study demonstrated a positive correlation between the average RPC and average RNFL in PACS group ($p = 0.012$, $r = 0.537$) and controls ($p \leqslant 0.001$, $r = 0.694$).

In our study, the AUC was highest for the MD (0.8) as compared to the average peripapillary RPC% (0.56) and the peripapillary RNFL (0.38). This might be explained in view that generalized reduction in retinal sensitivity could be evident after an AACC due to edema of the RNFL rather than actual structural loss or flow disturbance. This needs to be further evaluated in future long term studies to determine whether this reduction was temporary or permanent. These values are slightly lower than other studies[9] which might be attributed to our smaller sample size due to more selective inclusion criteria.

Conclusion

MD, PSD, average and inferior RNFL as well as RPC% were lower in AACC than in suspects and controls. AUC was largest in MD and RPC% than RNFL suggesting that both VF and OCT-A parameters could be a more sensitive marker than OCT parameters after an AACC attack. Angle closure suspect with no pressure elevation or structural damage remains a clinical diagnosis as no significant differences were found in OCT or OCT-A parameters between suspects and healthy controls.

Availability of data and material

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

Declaration of conflicting interests

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Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University (REC N-115-2018). Data collection conformed to all local laws and was compliant with the tenets of the Declaration of Helsinki. A written informed consent was obtained from all participants.

Consent for publication

The manuscript does not include any data or images that could lead to the identification of individual participants.

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Supplemental material

Supplemental material for this article is available online.

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