Changes in Optic Nerve Head Vessel Density After Acute Primary Angle Closure Episode

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PURPOSE. To evaluate the changes in circumpapillary vessel density (cpVD) and retinal nerve fiber layer (RNFL) thickness after an acute primary angle closure (APAC) episode.

METHODS. Twenty-eight patients (28 pair of eyes) with unilateral APAC and 39 normal subjects (64 eyes) were included in this prospective, observational study. cpVD as measured by optical coherence tomography angiography and RNFL thickness as measured by spectral-domain optical coherence tomography were compared at 6 weeks after an APAC episode between affected, unaffected, and normal eyes. cpVD and RNFL thickness at 1 week and 6 weeks after APAC were also compared in APAC eyes in qualified images.

RESULTS. At 6 weeks, cpVD was significantly lower in APAC eyes (57.3% ± 6.8%), compared to control eyes (63.6% ± 3.4%) (P < 0.001). There was diffuse microvascular dropout with greater vessel density loss in the superonasal sector. APAC eyes had thinner RNFL globally and in each sector (except temporal and nasal sectors) than in fellow and normal eyes at 6 weeks. cpVD in the affected eyes was significantly greater at 1 week (56.8% ± 5.3%) than values at 6 weeks (55.5% ± 7%) (P = 0.003) but less than cpVD in the fellow eyes (62.4% ± 5.0%) (P < 0.001). RNFL thickness for the APAC eyes at 1 week (120.6 ± 18.0 μm) was greater than the analogous values for affected eyes (90.1 ± 13.2 μm; P = 0.037) and fellow eyes at 6 weeks (102.5 ± 5.7 μm; P = 0.001).

CONCLUSIONS. Vessel density decreased over 6 weeks after an APAC episode compared with the contralateral unaffected eyes. In contrast, there was an initial increase in RNFL thickness that was followed by a subsequent decrease.

Keywords: optical coherence tomography angiography, glaucoma, vessel density, retinal nerve fiber layer, acute primary angle closure

Primary angle closure glaucoma (PACG) accounts for nearly one-third of all glaucoma cases, and half of glaucoma-related blindness worldwide.1 Although most PACG cases are clinically asymptomatic, a proportion of patients experience acute symptomatic attacks, described as acute primary angle closure (APAC) crises.2 There is recent evidence that retinal vascular insufficiency has a role in the development of PACG.3,4

With optical coherence tomography angiography (OCTA), vessel density can be estimated in each selected region of the optic nerve head (ONH). This new technology has been suggested for the assessment of glaucoma severity and progression.5,6 Studies using OCTA have demonstrated a reduction of vessel density within the ONH, the peripapillary retina, and the macula in primary open-angle glaucoma (POAG) eyes.8 Moreover, decreased vessel density was associated with the severity of visual field damage.8,9 Several studies conducted have suggested that impaired perfusion of the ONH could have a primary role in the progression of glaucomatous optic neuropathy in POAG.7,10 OCTA can also detect retinal microvascular dropout in eyes without detectable visual field damage,11,12 and radial ONH vessel density is strongly correlated with retinal nerve fiber layer (RNFL) thickness.13 OCTA has been mostly used to investigate ONH perfusion in patients with POAG.5,8,9,11–14 However, there are a few studies that have reported decreased vessel density in eyes with PACG.4

Optic nerve damage can occur after the sudden rise in intraocular pressure (IOP) associated with an APAC episode. Perimetric examination during acute episodes is difficult and usually unreliable, and RNFL might be edematous in the first few weeks after an attack.15,16 The pattern of glaucomatous damage has been reported to be different after an acute IOP rise compared to a chronic IOP rise. The progressive thinning of the RNFL in the weeks after the initial insult also may implicate secondary degeneration in the propagation of damage after APAC.17,18 A recent study by Wang et al.19 has shown that the vessel density in APAC eyes was less than that in fellow eyes 2 to 120 days after an APAC episode and was associated with RNFL thickness. However, the sequence of events is very important to understand the significance of vascular factors in the pathogenesis of glaucoma20 and has not been studied before.

The purpose of this study was to determine ONH vessel density changes occurring in APAC eyes after a recent acute episode and to compare them with RNFL changes. Changes in
vessel density and RNFL measurements in APAC eyes were compared with the fellow unaffected eyes to investigate the pattern of vessel density and thickness loss.

**Patients and Methods**

In this prospective study, we enrolled consecutive patients who presented with unilateral APAC to the emergency department of Farabi Eye Hospital (Tehran, Iran). The normal control subjects were recruited from the comprehensive ophthalmology service. The protocol for this prospective, case-control study was approved by the institutional review board of Tehran University of Medical Sciences. Written informed consent was obtained from each subject. Inclusion criteria for cases were (1) unilateral APAC, (2) ability to perform testing at 6 weeks follow-up, (3) a broken attack after medical treatment, and (4) IOP of 21 mm Hg or less in both eyes for up to 6 weeks after an APAC episode. Patients were excluded if there was (1) preexisting glaucoma (or previous APAC); (2) history of trauma, uveitis, or surgery; or (3) history of any laser or intraocular surgery (e.g., laser peripheral iridotomy [LPI]) in either affected or contralateral eyes.

An APAC was defined by the presence of the following: (1) at least two of the symptoms of an acute episode of IOP rise, which are nausea and/or vomiting, decreased vision, ocular pain or headache, and rainbow-colored halos around lights; (2) IOP at presentation of 30 mm Hg or more by Goldmann applanation tonometry; (3) signs such as corneal epithelial edema, conjunctival injection, shallow anterior chamber, and a fixed matted pupil; (4) closed angles in at least three quadrants on gonioscopic examination (defined as invisible trabecular meshwork in at least 270 degrees); and (5) narrow angle in the fellow eye.

The control subjects were included if they did not have any ocular pathology, such as glaucoma, retinal disease, corneal opacity, or high myopia. They were required to have healthy optic nerves, normal visual fields, and an IOP of 21 mm Hg or less.

After the acute attack had been fully resolved, all subjects underwent a complete ophthalmic examination, which included a review of their medical history, slit-lamp biomicroscopy, IOP measurement (Goldmann applanation tonometry), and gonioscopy. All patients underwent LPI as standard medical care. The patients were scheduled for a visit at 6 weeks after the APAC episode, during which spectral-domain optical coherence tomography (SDOCT) and OCTA examination were performed. Axial length was measured by the partial coherence interferometer method by using IOL Master (Carl Zeiss Meditec Ltd, Jena, Germany). Vessel density and structural measurements of APAC eye were performed for the patients who had a visit at 1 week and at 6 weeks after APAC remission. Those who underwent cataract surgery or trabeculectomy during follow-up were excluded from the analysis. The Spectralis SDOCT (Spectralis HRA+OCT; Heidelberg Engineering Inc., Heidelberg, Germany) was used for RNFL measurements (software version 5.4.7.0).

**Optical Coherence Tomography Angiography**

The ONH vessel density was evaluated at baseline by using the OCT AngioVue system (Optovue, Inc., Fremont, CA, USA, software version 5.6.3.0). This system has been described previously. In brief, it uses an 840-nm light source and has an A-scan rate of 70,000 scans/s. Each volume contains 304 × 304 A-scans with two consecutive B-scans captured at each fixed position. The split-spectrum amplitude-decorrelation angiography (SSADA) method was used to capture the dynamic motion of the red blood cells and provide a high-resolution three-dimensional visualization of perfused retinal vasculature. Vessel density was automatically calculated as the proportion of measured area occupied by flowing blood vessels defined as pixels having decorrelation values acquired by the SSADA algorithm above the threshold level. Vessel density in the peripapillary RNFL was assessed within a 4.5 × 4.5-mm field of view centered on the ONH. Circumpapillary vessel density (cpVD) was calculated in the region defined as a 750-μm-wide elliptical annulus extending from the optic disc boundary.

Trained graders reviewed scans and excluded poor-quality images, defined as images with (1) a signal strength index of less than 48, (2) poor clarity, (3) residual motion artifacts visible as irregular vessel pattern or disc boundary on the enface angiogram, (4) local weak signal, or (5) segmentation errors.

**Statistical Analysis**

Linear mixed effects modeling was used to compare vessel density and structure measurements among groups to account for correlations between the two eyes of an individual and confounders (age, and sex). Percentage loss for each variable (var) (i.e., RNFL thickness or vessel density) was calculated globally and sectorally with following formula and depicted using a heatmap plot:

\[
\text{Percentage Var Loss} = \frac{\text{Var}_{\text{APAC}} - \text{Var}_{\text{fellow}}}{\text{Var}_{\text{fellow}}} \times 100%
\]

Receiver operating characteristic (ROC) curves and sensitivities at 80% specificities were used to explore the ability of OCTA and RNFL parameters to discriminate APAC eyes from fellow eyes. A bootstrap resampling procedure was used (\(n = 1000\) resamples) to obtain confidence intervals (CIs) for area under the ROC curves (AUC) and sensitivities. Comparison of mean values at 1 week and 6 week after remission was performed using Wilcoxon signed rank for nonparametric data. Spearman correlation was used to describe the association of global RNFL thickness and cpVD. All statistical analyses were performed with commercial software (Stata V.14.0; StataCorp, College Station, TX, USA). A \(P\) value of less than 0.05 was considered statistically significant.

**Results**

The final sample included 28 patients (28 pairs of eyes) with unilateral APAC and 39 normal subjects (64 eyes). Sixteen eyes of 8 patients (6 APAC patients; 2 normal subjects) had been excluded because of poor OCTA quality or SDOCT at 6-weeks follow-up. Two APAC patients underwent phacoemulsification in their affected eye during follow up and were not included for the final analysis.

The demographic and ocular characteristics of study groups are summarized in Table 1. Presenting IOP for APAC eyes was 44.3 ± 4.7 mm Hg (range, 38–65 mm Hg). There were no significant differences in age, sex, or IOP among the groups at 6 weeks (all \(P > 0.05\)). Statistically significant differences were found among groups in terms of the number of glaucoma medications (\(P < 0.001\)) and axial length (\(P < 0.001\)).

At the 6-week follow-up, cpVD was significantly lower in APAC eyes (57.3% ± 6.8%) than in fellow eyes (63.1% ± 3.5%) and control eyes (65.6% ± 3.4%) (\(P < 0.001\)). Similar results were found for all peripapillary sector vessel density measurements (\(P < 0.05\) for all). Likewise, APAC eyes had thinner RNFL globally and in each sector (except temporal and nasal sectors) than in fellow and normal eyes at 6 weeks (Table 1).

Figure 1 depicts the percentage of vessel density and RNFL thickness loss at 6 weeks when compared to the fellow eyes.
Although all the sectors showed a loss in vessel density, the superonasal sector had the greatest and the temporal sector had the least percentage loss of vessel density compared to fellow eyes. The RNFL maps showed a more localized percentage loss, sparing the temporal and nasal sectors and affecting mostly the superotemporal and inferotemporal regions.

The AUCs and sensitivities at fixed specificities of the cpVD and RNFL parameters for discriminating APAC from fellow eyes at 6 weeks of remission are shown in Table 2. AUCs of the OCTA parameters were comparable (P > 0.05 for all parameters) between cpVD and RNFL thickness, both sectorally and globally. Overall, superonasal and superotemporal sector measurements showed the best AUCs and sensitivity at 80% specificity for vessel density and RNFL thickness, respectively. The AUC of all the OCTA measurements (except for the temporal sector) were greater than 0.70. However, the only RNFL thickness parameter that had an AUC greater than 0.70 was the superotemporal sector.

In 18 APAC eyes, good quality OCTA images were available within 1 week after remission of the attack (Table 3). A comparison of global and sectoral cpVD in the affected eyes over time showed significantly greater values at 1 week than values at 6 weeks after the APAC episode (P = 0.003), but cpVD

### TABLE 1. Comparison of Clinical and Ocular Characteristics of Eyes With APAC, Their Fellow Eyes, and Normal Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>APAC</th>
<th>Fellow</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Number of eyes</td>
<td>28</td>
<td>28</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.3 ± 9.3</td>
<td>58.3 ± 9.3</td>
<td>59.6 ± 11.4</td>
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<tr>
<td>Sex, F/M</td>
<td>19/9</td>
<td>19/9</td>
<td>43/21</td>
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</tr>
<tr>
<td>IOP, mm Hg</td>
<td>14.6 ± 4.2</td>
<td>14.8 ± 3.4</td>
<td>13.7 ± 1.8</td>
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</tr>
<tr>
<td>Number of glaucoma medications</td>
<td>1.9 ± 0.4</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>21.9 ± 0.6</td>
<td>22.0 ± 0.8</td>
<td>23.8 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RNFL thickness, μm</td>
<td>Global 87.5 ± 16.0</td>
<td>100.0 ± 8.6</td>
<td>99.6 ± 7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Nasal sector 70.7 ± 20.2</td>
<td>75.8 ± 13.4</td>
<td>70.4 ± 11.1</td>
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</tr>
<tr>
<td></td>
<td>Inferonasal sector 105.2 ± 26.3</td>
<td>121.4 ± 20.5</td>
<td>116.0 ± 16.8</td>
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</tr>
<tr>
<td></td>
<td>Inferotemporal sector 119.0 ± 55.1</td>
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<td>139.9 ± 13.5</td>
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<tr>
<td></td>
<td>Superotemporal sector 113.8 ± 27.2</td>
<td>143.0 ± 19.8</td>
<td>145.0 ± 13.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Superonasal sector 99.7 ± 19.5</td>
<td>112.8 ± 17.0</td>
<td>112.2 ± 18.0</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Temporal sector 64.6 ± 15.6</td>
<td>66.6 ± 10.7</td>
<td>71.8 ± 8.6</td>
<td>0.087</td>
</tr>
<tr>
<td>cpVD, %</td>
<td>Global 57.3 ± 6.8</td>
<td>65.1 ± 5.5</td>
<td>63.6 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Nasal sector 55.9 ± 7.7</td>
<td>60.3 ± 4.3</td>
<td>61.5 ± 4.6</td>
<td>&lt;0.001</td>
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<td>Inferonasal sector 58.7 ± 7.7</td>
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<td>64.7 ± 5.4</td>
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</tr>
<tr>
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<td>Inferotemporal sector 61.5 ± 8.9</td>
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<td>66.7 ± 4.0</td>
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<td>Superotemporal sector 58.9 ± 9.1</td>
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<td>66.0 ± 3.7</td>
<td>&lt;0.001</td>
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<td>62.1 ± 5.0</td>
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<td>Temporal sector 59.0 ± 7.7</td>
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<td>63.7 ± 5.1</td>
<td>0.012</td>
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<td></td>
<td>Global 57.3 ± 6.8</td>
<td>65.1 ± 5.5</td>
<td>63.6 ± 3.4</td>
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<td>0.012</td>
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</table>

Continues data are shown in mean ± standard deviation. Categorical variables were compared using the chi-square test. Continues parameters were compared with linear mixed model and post hoc Tukey’s honest significant difference test. Values with statistical significance are shown in bold.

**Figure 1.** Pattern of vessel density (A) and RNFL (B) loss after 6 weeks of APAC episode compared to unaffected fellow eye.
in affected eyes was less than in fellow eyes (P < 0.001), demonstrating that the cpVD decreases progressively for at least 6 weeks after the attack is broken. However, RNFL thickness for the APAC eyes at 1 week was greater than the analogous values for affected eyes (P = 0.037) and fellow eyes at 6 weeks (P = 0.001), indicating an initial increase in RNFL thickness after APAC episode, followed by a subsequent decrease (Fig. 2). cpVD in the APAC eyes was correlated with global RNFL thickness at 6 weeks (Spearman’s rho = 0.61, P = 0.027) but not at 1 week (Spearman’s rho = -0.27, P = 0.347).

Figure 3 as an example depicts a patient with APAC in his left eye who showed a decrease in vessel density over 6 weeks compared to the contralateral unaffected eye. The RNFL was thicker than the fellow eye at the first week, which became thinner after 6 weeks.

**DISCUSSION**

In the present study, we demonstrated that cpVD decreased diffusely 6 weeks after an APAC episode compared to fellow eyes. To the best of our knowledge, this is the first report to investigate changes in vessel density after an episode of APAC. Vessel density decreased over 6 weeks after an APAC episode compared with the contralateral unaffected eyes. In contrast, RNFL thickness initially increased after an APAC episode, followed by a subsequent decrease.

Studies using OCTA have shown that there is reduced perfusion in the ONH and the central retina with glaucoma.5,8,9,11–14 Most of these studies included patients with POAG, which is associated with insidious damage to the optic nerve.5,8,9,11–14 Rao et al.3 observed ONH vessel density in PACG by using OCTA and compared that with POAG and normal eyes. PACG eyes had comparable vessel density with POAG eyes. However, when they accounted for the effect of glaucoma severity on their analysis, the sensitivity of the ONH vessel density appeared to be better in POAG compared with PACG with increasing severity of the disease, and they suggested that the ocular perfusion abnormality in PACG had a lower prevalence than that in POAG.

APAC eyes are commonly associated with previous anterior segment ischemia, such as iris stromal atrophy or glaukom-flecken.21 In a longitudinal study by Aung et al.,15 RNFL thickness was found to decrease significantly from 2 to 16 weeks after APAC, with the greatest change in the inferior thickness. Investigators17,18 have suggested a mechanism, called secondary degeneration, in which glaucomatous neuropathy continues to progress, even after the reduction of the high IOP. This mechanism involves a propagative effect on apparently healthy neurons that escaped the primary insult but that are subjected to degenerative factors due to their proximity to injured neurons.

Our results showed that vessel density dropout is evident even at 1 week after an APAC episode, and the vessel density continues to decrease in APAC eyes for 6 weeks. The loss of vessel density in APAC eyes reflects the loss of capillaries with active flow and may be a measure of reduced perfusion. Although iris stroma is the most susceptible ocular tissue to raised IOP during APAC, retinal perfusion can also be severely affected by IOP elevation to between 40 to 50 mm Hg.22 Brubaker23 reported a series of patients in whom the glaucoma continued to progress after therapeutic normalization of their
FIGURE 2. Changes in vessel density (A) and RNFL (B) over time after APAC episode. Dash line depicts the average values for the unaffected fellow eyes at 6 weeks.

FIGURE 3. OCTA images and retinal RNFL thickness of a patient with APAC (top two rows) and his fellow eye (bottom two rows) at the first week and 6 weeks after the attack. A-ONH OCTA macula scan showing (A1) cpVD and (A2) corresponding color-coded flow density map of the ONH flow (the warmer the color, the greater the flow). (B) Circumpapillary RNFL thickness. In the APAC eye, vessel density decreased over 6 weeks compared to contralateral unaffected eye. Note that the RNFL was thicker than contralateral eye at the first week, which become thinner after 6 weeks.
increased IOP and proposed that one possible mechanism might be that the retinal ganglion cells (RGCs) have been rendered hypersensitive to IOP by irreversible damaging effects of previously increased IOP. We hypothesized that the change in microcirculation after an APAC episode may have a role in the secondary degeneration of the RGCs. A recent study by Moghimi et al.14 on eyes with POAG showed that reduced vessel density is associated with a faster rate of glaucoma progression. Although vascular factors may play an important role in a subgroup of patients with POAG and normal-tension glaucoma in series of studies,28 it may have a synergistic effect with mechanical factors for RNFL loss after APAC.

In the present study, vessel density decreased earlier than RNFL loss. This is in agreement with a previous study that used OCT for detecting changes in RNFL after APAC eyes. Tsi et al.16 compared the affected eyes with their fellow eyes after an attack and observed a thicker RNFL at 1 week and attributed that to the persistence of mild edema, possibly after onset. The OCT measurement of RNFL thickness is influenced by optic disc edema from optic neuropathy, retinal vein occlusion, or mild papilledema; greater RNFL thickness was evident relative to control subjects.25 OCTA has been shown to be a useful method in differentiating etiologies of optic disc swelling. Fard et al.26 observed that vessel density after ischemic processes, such as nonarteritic anterior ischemic optic neuropathy, was significantly lower than in papilledema eyes and control eyes. Similar to our results, Wang et al.19 detected a significant reduction in ONH vessel density in APAC eyes 2 to 120 days after the attack by using OCTA, even when the structural measurements were not significantly changed. In their study, a close correlation was found between peripapillary retinal vessel density and visual functions but not between RNFL and visual function. In another study on PACG eyes with a history of acute angle-closure glaucoma: an update.

In the current study, all the sectors showed a loss in vessel density compared to the fellow eyes, with the greatest decrease occurring in the supranasal region and the smallest decrease in the temporal region. Although RNFL thinning was diffuse, the temporal and nasal regions did not experience significant RNFL loss. One reason for this discrepancy could be that the built-in software we used did not remove large vessels for vessel density measurements and might not represent actual microvascularization over time. Finally, the OCTA algorithm that we used included large vessels along with capillaries in its estimation of vessel density and might not represent actual microvascular drop-out in particular regions.

In summary, there was a progressive loss of peripapillary vessel density in APAC eyes in the early follow-up period after an acute attack. Vessel density was lower in APAC eyes than in their fellow eyes at 6 weeks after an APAC episode in all sectors. RNFL showed an initial thickening after week 1, followed by a subsequent thinning.

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