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Optic Nerve Head Characteristics in Chronic Angle Closure Glaucoma Detected by Swept-Source OCT

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ABSTRACT

Purpose: To compare structural features in prelaminar and laminar tissues of the optic nerve head (ONH) in chronic angle closure glaucoma (CACG), primary open angle glaucoma (POAG), and control subjects.

Materials and Methods: ONH imaging was performed using swept-source optical coherence tomography (SS-OCT) for measurements of minimum rim width at Bruch’s membrane opening (BMO-MRW), horizontal, and vertical lamina cribrosa depth (LCD). Prelaminar defects, categorized as hole and wedge, and lamina cribrosa (LC) defects were identified. Enhanced depth imaging spectral domain OCT (EDI-OCT) customized to perform high-resolution volume scans was used in conjunction to further characterize prelaminar holes. One eye per subject was analyzed.

Results: Eighty subjects (20 CACG, 40 POAG, and 20 controls) were included in the study. CACG and POAG groups had similar mean deviation on Humphrey visual field testing (−6.9 ± 5.1 vs. −6.3 ± 6.0 dB, p > 0.05) and IOP on the day of imaging (14.0 ± 3.1 vs. 13.8 ± 2.7 mmHg, p > 0.05). Thinnest and global BMO-MRW in CACG (120.3 ± 44.8, 225.5 ± 53.9 μm) and POAG (109.7 ± 56.3, 213.8 ± 59.7 μm) groups were lower than controls (200.1 ± 40.8, 308.3 ± 70.8 μm; p < 0.001 for both). Prelaminar holes were most frequent in CACG (65.0%) than POAG (25.0%; p = 0.008) or control groups (20.0%; p = 0.01). After adjusting for demographic and ophthalmic covariates, CACG was associated with increased odds of having prelaminar holes compared to POAG (odds ratio, 9.79; 95% CI, 2.12–45.19; p = 0.003). Hole volume was similar between CACG and POAG (p > 0.05), but the CACG group had more holes per scan than POAG (maximum 2.5 ± 1.9 vs. 1.2 ± 0.4, p = 0.02). Prelaminar wedge defects were less common in the CACG than the POAG group (5.0% vs. 37.5%, p = 0.02). The CACG group did not differ from controls in laminar characteristics, such as LCD and LC defects.

Conclusions: SS-OCT evaluation of the ONH revealed more frequent prelaminar holes in CACG compared to POAG and control patients.

Introduction

Chronic angle-closure glaucoma (CAGC) differs from primary open angle glaucoma (POAG) in angle anatomy, mechanisms of aqueous outflow obstruction, extent of intraocular pressure (IOP) elevation, risk profile, and epidemiology. Although both conditions manifest in optic nerve damage and visual field (VF) loss, recent studies showed differences in patterns of structural damage. Compared to optic nerves of POAG eyes, CAGC eyes with similar severity of VF loss had smaller cup volume and cup depth on Heidelberg Retina Tomography and less frequent focal damage. While these findings suggest possible differences in disease pathogenesis, the imaging tool utilized did not allow for more detailed visualization of the optic nerve head (ONH).

Newer imaging technologies emerged with spectral-domain OCT (SD-OCT), which can image the ONH in three dimensions with axial and transverse resolutions of 7 μm and 14 μm, respectively. The addition of the enhanced depth imaging mode to SD-OCT (EDI-OCT) enabled visualization of deeper layers of the ONH, such as the lamina cribrosa (LC). More recently, swept-source OCT (SS-OCT) achieved high-resolution imaging of both the shallow, i.e. prelaminar, and deep, i.e. laminar, tissues of the ONH at comparable resolutions to SD-OCT (axial 8 μm and transverse 20 μm). In addition, SS-OCT also reduces shadowing artifacts of the overlying blood vessels, which are abundant in the ONH region. This technology may serve as a useful tool to study the differences in optic nerve structures of CAGC and POAG.

With better resolution of ONH imaging, new quantitative and qualitative parameters have been introduced to describe the optic nerve. Minimum rim width at Bruch’s membrane opening (BMO-MRW) is defined as the minimal distance from the internal limiting membrane to the termination of Bruch’s membrane in the optic canal.
parameter was demonstrated to correlate with disease severity in POAG and performed better than peripapillary retinal nerve fiber layer (RNFL) thickness in the diagnosis of perimetric glaucoma.\textsuperscript{14,15} Lamina cribrosa depth (LCD), which measures the average distance from anterior LC surface to Bruch’s membrane opening plane, has been reported to be higher in eyes with POAG than normal eyes\textsuperscript{16} and may change based on intraocular pressure.\textsuperscript{17} For qualitative parameters, defects of the LC have been identified with EDI-OCT and SS-OCT, particularly in patients with POAG and optic disc pits.\textsuperscript{18,19}

Although previous studies have provided detailed characterizations of the ONH in POAG patients, very few reports described ONH changes in CACG. The purpose of this study is to describe the morphology of the ONH, both quantitatively and qualitatively, in CACG using SS-OCT and to improve disease characterization by exploring the potential differences between CACG and POAG.

**Materials and methods**

This is a prospective cross-sectional study approved by the Institutional Review Board of the Massachusetts Eye and Ear (MEE, Boston, Massachusetts, USA) and adheres to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

**Study population**

Age-matched adult patients with CACG, POAG and control subjects were recruited from the Glaucoma Consultation Service and Comprehensive Ophthalmology Service of MEE between September 2013 and March 2016. The study subjects included Caucasians, African Americans and Asians, between the ages of 30 and 80, with best corrected visual acuity of 20/50 or better in each eye, and phakic refractive error between +5.0D and −5.0D. Patients with significant retinal pathology, such as age-related macular degeneration or diabetic retinopathy, were excluded. All POAG and control subjects were part of a prior study comparing quantitative OCT parameters measured by SS-OCT and EDI-OCT.\textsuperscript{20}

Inclusion criteria for CACG and POAG patients were: (1) glaucomatous visual field (VF) loss on at least two consecutive reliable Humphrey VFs (fixation loss ≤ 33%; false positive and false negative rates ≤ 20%, SITA standard 24-2 algorithm); (2) corresponding glaucomatous optic nerve damage determined by glaucoma specialists (DL and LQS) based on disc photography and/or abnormal RNFL profile obtained by SD-OCT. CACG patients had occludable angles with or without peripheral anterior synechia (PAS) on gonioscopy prior to laser peripheral iridotomy or cataract extraction. In addition, there was a history of IOP > 21 mmHg or requirement for chronic ocular hypertensive treatment.\textsuperscript{5} POAG patients had open angles on gonioscopy. There was no IOP criterion for POAG patients.

Exclusion criteria for both glaucoma groups were: (1) history of previous penetrating glaucoma surgery (trabeculectomy and/or glaucoma drainage device placement), (2) optic disc torsion > 15 degrees or optic disc tilt ratio (maximum to minimum disc diameter) > 1.3 as identified by disc photography.\textsuperscript{21,22}

Inclusion criteria for controls were: (1) intraocular pressure (IOP) < 22 mmHg in each eye, (2) cup-to-disc ratio (CDR) ≤ 0.6 in each eye, with CDR asymmetry ≤ 0.2 between eyes. Exclusion criteria were: (1) glaucoma suspect status including family history of glaucoma, (2) RNFL sectoral thickness outside normal limits (either yellow or red sectors) by SD-OCT.

One eye per subject was included for the analysis. The right eye was used in subjects with both eyes eligible and OCT images of adequate quality.

**Study protocol**

After a complete ophthalmic examination, all subjects underwent SS-OCT and EDI-OCT imaging of both eyes by trained technicians in a single visit. RNFL thickness by SD-OCT and optic disc photographs of both eyes were also obtained if they were not available from the previous year.

Each subject was imaged first with SS-OCT and then by EDI-OCT with a previously described imaging protocol.\textsuperscript{20} In brief, SS-OCT device (deep range imaging, DRI-OCT, Topcon Inc., Tokyo, Japan) uses a center wavelength of 1050 nm width and a scanning speed of 100,000 A-scans per second.\textsuperscript{11} A radial B-scan pattern composed of 12 sequential images and a 5-line cross B-scan pattern composed of five horizontal and five vertical lines spaced 250 μm apart were performed for each eye. Both scanning patterns were centered on the ONH, and 32 image frames were averaged for each B-scan image.

The EDI-OCT device (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) has an average wavelength of 840 nm and a scanning speed of 40,000 A-scans per second.\textsuperscript{8} In contrast to SS-OCT, which has relatively fixed scanning patterns, EDI-OCT allowed for customization of high-resolution scans. Hence, in addition to a radial scanning pattern similar to SS-OCT with 12 sequential images, EDI-OCT was also used to scan the ONH with a 15x10-degree rectangle of 97 horizontal scans spaced 30 μm apart. Each image had 36 OCT frames averaged. RNFL thickness measurement was obtained with the same SD-OCT machine without EDI mode.

Quantitative parameters, such as horizontal lamina cribrosa depth (LCD), vertical LCD, global and thinnest minimal rim width at Bruch’s membrane opening (BMO-MRW), were derived from SS-OCT images, after excluding images with substandard visualization of the prelaminar or laminar tissues due to poor image quality or motion artifacts. Two glaucoma specialists (EVT and DL) masked to the subject’s clinical diagnosis performed measurements independently using customized ImageJ (ImageJ, U.S. National Institutes of Health, Bethesda, Maryland, USA) plugins and the mean value between the two readers was reported. The inter-reader agreement ranged from 0.983 to 0.990 based on intraclass correlation coefficients.\textsuperscript{20} In cases of ambiguity due to difficulty locating Bruch’s membrane opening or the anterior LC surface, a third glaucoma specialist (LQS) repeated the measurements. Horizontal LCD was determined on the horizontal scan with the best centration and visualization of the anterior laminar surface. A line connecting two termination points of Bruch’s membrane and the anterior LC surface were manually delineated. Horizontal LCD was automatically calculated as the mean of the perpendicular distances every 100 μm.
between the Bruch’s membrane opening reference line and anterior LC surface. Vertical LCD was measured in a similar manner. The global BMO-MRW was based on the average of 24 measurements, each representing the shortest distance between the automatically delineated internal limiting membrane, which was inspected and manually adjusted if necessary, and a manually delineated Bruch’s membrane opening on each side of the 12 radial scans. The global BMO-MRW was also normalized with the circumference of Bruch’s membrane opening.23 For the thinnest BMO-MRW, the radial scan with the thinnest visualized neuroretinal rim was identified and measured; radial scans with blood vessels or associated shadowing artifacts in contact with Bruch’s membrane opening were excluded for thinnest BMO-MRW measurements, but not for global BMO-MRW measurements, to be consistent with published protocols.20,24

For qualitative characterization of the ONH, two glaucoma specialists (LQS, DL) masked to the diagnosis reviewed all SS-OCT images and identified defects in the prelaminar tissue, including triangular shaped defects on the prelaminar surface (wedge) or hyporeflective lesions with irregular borders within the prelaminar tissue (holes), as well as laminar defects, defined as discontinuities of the anterior laminar surface, which may extend to the posterior laminar surface (Figure 1). Optic disc photos were used to confirm that the defects were not from blood vessels traversing the prelaminar tissue or LC.

Additional analysis for prelaminar holes required densely spaced high-resolution scans over the entire ONH. SS-OCT did not allow such customization of scanning patterns; therefore, volume scans from EDI-OCT were used. To calculate the volume of prelaminar holes, the margin of each hole was marked manually on each scan (Figure 2A, B). Prelaminar defects from blood vessels indicated by associated shadowing artifacts were excluded. Three-dimensional reconstruction was then performed with Amira (Amira 6.1, FEI, Hillsboro, Oregon, USA) and the volume of all prelaminar holes within the same ONH was calculated (Figure 2D). The inter-reader agreement was found to be excellent (intraclass correlation coefficient = 0.999) on 9 sets (33.3%) of images. Similarly, the largest diameter of prelaminar hole was obtained from 3-D reconstruction. The maximum number of prelaminar holes per scan was manually counted from an SS-OCT image per eye (Figure 2C).

**Statistical analysis**

Statistical analysis was performed using R statistical software version 3.3.1.25 The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. The differences of quantitative parameters among the three groups were compared using one-way Analysis of Variance (ANOVA). The frequency of structural defects from each group was compared by Fisher’s exact test. Statistical significance was
considered at $p < 0.05$; Bonferroni correction was applied for multiple comparisons. A multivariate logistic regression model was created to assess the difference in prelaminar hole frequency between CACG and POAG groups, while adjusting for the effect of age, gender, ethnicity, maximum IOP, pseudophakia and visual field mean deviation.

**Results**

Eighty subjects (20 controls, 40 POAG, and 20 CACG) were included. Overall, the mean age was 66.3 ± 9.4 years with 42.5% male and 86.3% Caucasian; there was no significant difference among the groups (Table 1). POAG patients had better LogMAR visual acuity than controls (0.04 ± 0.09, vs. 0.13 ± 0.11, $p = 0.02$). POAG and CACG groups were similar in mean deviation ($-6.3 ± 6.0$ vs. $-6.9 ± 5.1$ dB, $p = 0.69$) and pattern standard deviation ($5.8 ± 4.1$ vs. $5.5 ± 3.6$ dB, $p = 0.77$) on Humphrey visual field testing, and in IOP on the day of imaging ($13.8 ± 2.7$ vs. $14.0 ± 3.1$ mmHg, $p > 0.99$). The CACG group has the highest maximum IOP ($28.3 ± 13.1$ mmHg), which was significantly higher than controls ($15.2 ± 1.9$ mmHg, $p < 0.001$, Table 1). The CACG group also had highest percentage of pseudophakic eyes (45.0%), which differed from POAG group (12.5%, $p = 0.02$).

For quantitative ONH parameters, the three groups were similar in horizontal LCD ($p = 0.10$) and vertical LCD ($p = 0.06$).

**Table 1.** Baseline characteristics of study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>POAG</th>
<th>CACG</th>
<th>Control - POAG p-Value</th>
<th>Control-CACG p-Value</th>
<th>POAG-CACG p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>20</td>
<td>40</td>
<td>20</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Gender, Male (%)</td>
<td>35.0</td>
<td>47.5</td>
<td>40.0</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.0 ± 7.9</td>
<td>66.5 ± 9.1</td>
<td>65.2 ± 11.6</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>95.0</td>
<td>82.5</td>
<td>85.0</td>
<td>0.54</td>
<td>0.88</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>0.0</td>
<td>0.0</td>
<td>10.0</td>
<td>N/A</td>
<td>0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>African American (%)</td>
<td>5.0</td>
<td>17.5</td>
<td>5.0</td>
<td>0.54</td>
<td>&gt;0.99</td>
<td>0.54</td>
</tr>
<tr>
<td>BCVA (LogMAR)</td>
<td>0.13 ± 0.11</td>
<td>0.04 ± 0.09</td>
<td>0.07 ± 0.08</td>
<td>0.02*</td>
<td>0.13</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Visual Field MD (dB)</td>
<td></td>
<td>−6.3 ± 6.0</td>
<td>−6.9 ± 5.1</td>
<td></td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Visual Field PSD (dB)</td>
<td></td>
<td>5.8 ± 4.1</td>
<td>5.5 ± 3.6</td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>IOP, Current (mmHg)</td>
<td>14.4 ± 2.1</td>
<td>13.8 ± 2.7</td>
<td>14.0 ± 3.1</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>IOP, Maximum (mmHg)</td>
<td>15.2 ± 1.9</td>
<td>20.7 ± 4.5</td>
<td>28.3 ± 13.1</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.06</td>
</tr>
<tr>
<td>Pseudophakia (%)</td>
<td>15.0</td>
<td>12.5</td>
<td>45.0</td>
<td>&gt;0.99</td>
<td>0.12</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation unless described otherwise.

*Statistically significant difference between the two groups, $p < 0.05$.

POAG, primary open angle glaucoma; CACG, chronic angle closure glaucoma, N/A, not available; BCVA, best corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; MD, mean deviation; PSD, pattern standard deviation; IOP, intraocular pressure.
hole volume (3.2 ± 4.8 ×10⁶ (Table 3). Despite of this variability, CACG group had larger standard deviation values in hole volumes and hole diameters that the size of the holes was highly variable, as shown in high control eyes (20.0%, found in CACG (65.0%) than POAG (25.0%, p < 0.05). Additional analysis revealed that the size of the holes was highly variable, as shown in high standard deviation values in hole volumes and hole diameters (Table 3). Despite of this variability. CACG group had larger hole volume (3.2 ± 4.8 ×10⁶ μm³) than controls (0.3 ± 0.4 ×10⁶ μm³, p = 0.05). Also, CACG had more holes per scan (maximum 2.5 ± 1.9) than the POAG group (maximum 1.2 ± 0.4, p = 0.02), while POAG had fewer holes per scan than controls (maximum 1.7 ± 0.6, p = 0.007). Prelaminar wedge defects (Figure 1C) were most common in POAG (37.5%) compared CACG (5.0%, p = 0.02) or control eyes (5.0%, p = 0.02). LC defect (Figure 1D) was found in all three groups: POAG had the highest frequency (30.0%) but the frequency did not differ significantly from controls (5.0%, p = 0.08) or CACG (15.0%, p = 0.62).

To further assess the association between CACG and the presence of prelaminar holes, we performed multivariate logistic regression in the glaucoma groups. Compared to POAG eyes, CACG eyes had nearly 10-fold increased odds of having prelaminar holes in the optic nerve head (odds ratio = 9.79; 95% confidence interval: 2.12–45.19; p = 0.003), after adjusting for age (p = 0.06), gender (p = 0.68), ethnicity (p = 0.20), visual field MD (p = 0.05), maximum IOP (p = 0.92) and pseudophakic status (p = 0.42, Table 4).

### Discussion

In this study, we performed detailed characterization of glaucomatous optic nerve damage in CACG patients using swept-source OCT and compared the results with POAG patients and control subjects. We used SS-OCT to perform the study, as SS-OCT is able to image both shallow and deep ONH structures in high resolution. SS-OCT imaging was performed with 32 image frames averaged per B-scan to optimize image quality, while the fast scanning speed of the device limits motion artifacts. We also used the volume scans from EDI-OCT complementarily for three-dimensional reconstruction of prelaminar holes, because these EDI-OCT scans could be customized to image the entire ONH in a densely-spaced pattern at high resolution. In a previous study, we found good reliability of both SS-OCT and EDI-OCT, and good agreement between SS-OCT and EDI-OCT in quantitative measurements of ONH. In the current study, we measured quantitative parameters with SS-OCT and found that both glaucoma groups had lower BMO-MRW and RNFL thickness compared to controls but did not differ from each other. We also found that the three groups did not differ in LCD, although the CACG group had the highest values of horizontal and vertical LCD. In terms of

### Table 2. Comparison of optic nerve head quantitative parameters.

<table>
<thead>
<tr>
<th>ONH Parameters (μm)</th>
<th>Controls</th>
<th>POAG</th>
<th>CACG</th>
<th>Control - POAG p-Value</th>
<th>Control-CACG p-Value</th>
<th>POAG-CACG p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizontal LCD</td>
<td>433.3 ± 96.3</td>
<td>440.4 ± 98.4</td>
<td>501.5 ± 149.7</td>
<td>&gt;0.99</td>
<td>0.29</td>
<td>0.33</td>
</tr>
<tr>
<td>Vertical LCD</td>
<td>450.7 ± 102.5</td>
<td>457.0 ± 95.0</td>
<td>513.2 ± 142.7</td>
<td>&gt;0.99</td>
<td>0.36</td>
<td>0.37</td>
</tr>
<tr>
<td>Global BMO-MRW</td>
<td>322.7 ± 62.2</td>
<td>213.1 ± 52.2</td>
<td>219.3 ± 42.5</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Scaled Global BMO-MRW</td>
<td>308.3 ± 70.8</td>
<td>213.8 ± 59.7</td>
<td>225.5 ± 53.9</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Thinnest BMO-MRW</td>
<td>200.1 ± 40.8</td>
<td>109.7 ± 56.3</td>
<td>120.3 ± 44.8</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Average RNFL</td>
<td>96.3 ± 9.9</td>
<td>76.5 ± 14.9</td>
<td>73.8 ± 15.0</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Thinnest RNFL</td>
<td>66.3 ± 9.8</td>
<td>54.2 ± 13.2</td>
<td>54.3 ± 14.0</td>
<td>&lt;0.001*</td>
<td>0.01*</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation unless described otherwise.

*Statistically significant difference between the two groups, p < 0.05.

ONH, optic nerve head; POAG, primary open angle glaucoma; CACG, chronic angle closure glaucoma.

### Table 3. Comparison of optic nerve head defects.

<table>
<thead>
<tr>
<th>ONH Defects</th>
<th>Controls</th>
<th>POAG</th>
<th>CACG</th>
<th>Control - POAG p-Value</th>
<th>Control-CACG p-Value</th>
<th>POAG-CACG p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prelaminar Holes (%)</td>
<td>20.0</td>
<td>25.0</td>
<td>65.0</td>
<td>&gt;0.99</td>
<td>0.01*</td>
<td>0.008*</td>
</tr>
<tr>
<td>3-D hole volume (×10⁶ μm³)</td>
<td>0.3 ± 0.4</td>
<td>2.0 ± 5.1</td>
<td>3.2 ± 4.8</td>
<td>0.14</td>
<td>0.05*</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Largest hole diameter (μm)</td>
<td>166.5 ± 102.1</td>
<td>226.1 ± 214.8</td>
<td>305.1 ± 254.0</td>
<td>0.43</td>
<td>0.09</td>
<td>0.72</td>
</tr>
<tr>
<td>Max hole number per scan</td>
<td>1.7 ± 0.6</td>
<td>1.2 ± 0.4</td>
<td>2.5 ± 1.9</td>
<td>0.007*</td>
<td>0.26</td>
<td>0.02*</td>
</tr>
<tr>
<td>Prelaminar Wedge (%)</td>
<td>5.00</td>
<td>37.5</td>
<td>5.00</td>
<td>0.02*</td>
<td>&gt;0.99</td>
<td>0.02*</td>
</tr>
<tr>
<td>Lamina Defect (%)</td>
<td>5.00</td>
<td>30.0</td>
<td>15.0</td>
<td>0.08</td>
<td>0.86</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation unless described otherwise.

*Statistically significant difference between the two groups, p < 0.05.

ONH, optic nerve head; POAG, primary open angle glaucoma; CACG, chronic angle closure glaucoma.
quality parameters, we identified more eyes with prelaminar holes in the CACG group compared to POAG or control groups. The association between CACG and the presence of prelaminar holes was confirmed in multivariate analysis after adjusting for demographic and ophthalmic covariates. On further analysis, the prelaminar holes in CACG eyes are larger than in control eyes and more numerous than in POAG eyes as captured on a cross-sectional scan. It is likely that multiple holes in the prelaminar tissue represent a distinguishing feature of damage pattern in the ONH of CACG eyes.

Cavitary lesions have been previously reported in OCT studies, although not specifically for CACG patients. Hyporeflective lesions have been associated with ONH drusen, but they differ from those we observed as they are usually surrounded by clusters of short, hyper-reflective bands. Holes have been observed in the peripapillary RNFL in patients with POAG and glaucoma suspects, but those tend to be adjacent to blood vessels and may be associated with epiretinal membranes. The prelaminar holes we observed in CACG patients resemble those reported in a histology study by Knox and colleagues in eyes with elevated IOP. In vivo (Figures 1A and 2C) are similar to the histological images of hydropic axonal degeneration which may be associated with empty axonal channels. It is possible that the connective tissue separating axonal channels resulted in the appearance of multiple prelaminar holes per cross-sectional scan on SS-OCT. Knox and colleagues argued that hydropic axonal degeneration in the ONH is not caused by ischemia alone as it differs from the lesions in ischemic optic neuropathy. Similarly, we have noted that the patients with POAG, a disease associated with vascular dysfunction, did not show high frequency of prelaminar holes. Instead, this group showed more prelaminar wedge-shaped lesions in the ONH (Table 3). Hence, it is likely that in CACG patients, the acute elevation of IOP causes direct damage to the axonal bundles of the ONH by impairing axonal transport and leads to axonal degeneration as evidenced by the presence of prelaminar holes in the ONH. This is also supported by animal studies which showed changes in cytoskeleton proteins of retinal ganglion cells and reduced axonal transport in eyes with acute IOP rise lasting up to 12 hours.

In our study, the CACG group had the highest maximum IOP among the three groups, however, the multivariate model failed to confirm the effect of maximum IOP on prelaminar holes. This may reflect inaccuracy in data collection, as maximum IOP was recorded in clinic notes and the actual IOP elevation during acute and/ or sub-acute pressure spikes which led to optic nerve damage may not have been captured. It is also possible that non-IOP factors, such as genetics and anatomy of the choroid, contribute to the differences in optic nerve damage between CACG and POAG. Although the exact etiology of the prelaminar holes is unclear, our study provides evidence for optic nerve structural differences between CACG and POAG, which may be used as an adjunct biomarker.

In contrast to qualitative parameters, quantitative parameters measured by SS-OCT did not differentiate the CACG group from the POAG group in this study. Although all BMO-MRW parameters (global, scaled global and thinnest) were significantly lower in both glaucoma groups compared to controls, they did not differ between POAG and CACG (Table 2). Our results differed from a previous report, which did not find any difference in another neuroretinal rim parameter (rim area) between eyes following acute primary angle closure and the fellow unaffected eyes, which were treated with laser peripheral iridotomy prophylactically. Some of our CACG patients may not have had an acute attack and our control group did not have occludable angles. Another report using Heidelberg Retina Tomography showed difference in rim area between POAG to CACG eyes, whereas our study did not. It is likely that SS-OCT and Heidelberg Retina Tomography are not measuring the same structural parameters as they are different imaging technologies with different reference planes. Furthermore, BMO-MRW has been shown to correlate with VF sensitivities; this may explain the similarity in BMO-MRW values between POAG and CACG groups, which are matched in HVF mean deviation and pattern standard deviation values. Likewise, the matching of HVF parameters between the POAG and CACG groups may explain the results for RNFL parameters. It is also possible that the comparison of these structural parameters between the glaucoma groups is limited by the relatively small sample size in the CACG group.

Characteristics associated with the LC, i.e. LCD (both horizontal and vertical) and the frequency of LC defects, did not show a significant difference between the glaucoma groups or between glaucoma patients and controls. Prior studies have shown that LCD may be affected by IOP, especially after trabeculectomy surgery. In this study, we excluded patients who underwent penetrating glaucoma surgeries and included glaucoma patients receiving IOP lowering treatments, in order to minimize the effect on structural parameters from IOP alone. Hence, the glaucoma patients had similar IOP on the day of imaging to those of control subjects. This may explain the lack of difference in LCD among the groups, although our findings still differed from a previous report, which had 248 subjects and showed higher LCD in treated glaucoma patients even with similar

### Table 4. Multivariable logistic regression analysis for the presence of prelaminar holes in the optic nerve head comparing CACG to POAG.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.17</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender</td>
<td>0.76</td>
<td>0.76</td>
<td>1.74</td>
</tr>
<tr>
<td>Race</td>
<td>0.31</td>
<td>0.05</td>
<td>1.89</td>
</tr>
<tr>
<td>Visual Field MD</td>
<td>0.05</td>
<td>0.73</td>
<td>1.00</td>
</tr>
<tr>
<td>Maximum IOP</td>
<td>1.00</td>
<td>0.91</td>
<td>1.09</td>
</tr>
<tr>
<td>Pseudohakia</td>
<td>0.47</td>
<td>0.08</td>
<td>2.88</td>
</tr>
<tr>
<td>(phakic status = reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CACG (POAG = reference)</td>
<td>9.79</td>
<td>2.12</td>
<td>45.19</td>
</tr>
</tbody>
</table>

*Statistically significant effect on the presence of prelaminar holes, p < 0.05. CACG, chronic angle closure glaucoma; POAG, primary open angle glaucoma; MD, mean deviation; IOP, intraocular pressure.
IOP as the control group. Our detection rate of LC defects was similar to previously reported in the literature for both control subjects and glaucoma patients. It is possible that a larger sample size would be needed to detect a difference among the groups.

This study has several limitations. First, the sample size is relatively small for both control subjects and patients with CACG, potentially limiting the power to detect differences between the groups. Many of the CACG patients required penetrating glaucoma surgery to achieve adequate IOP control and hence were disqualified from the study. Despite this limitation, we were able to find distinguishing features of the ONH in the CACG group. Second, the control group may not represent normal subjects, as their visual acuity was worse than POAG patients. We only recruited returning patients from the comprehensive ophthalmology service, and it is likely that these patients returned because of borderline visually significant cataracts. We tried to address this by the inclusion criterion of best corrected visual acuity of 20/50 or better. Third, OCT imaging does not clearly differentiate neuronal tissue from gliosis. As suggested by Knox and colleagues, proliferation of glial cells may take place in the areas of axonal degeneration. It is possible that gliosis filled in potential cavities in the prelaminar region, making these areas undetectable on OCT. A longitudinal study of CACG patients may better address this limitation. Fourth, the assessment of qualitative parameters was subjective and relied on the expertise of the graders. We minimized any discrepancies by having two graders and by masking them to the diagnosis. Furthermore, the evaluation of prelaminal holes was confirmed by three-dimensional reconstruction of these lesions from a different OCT device (EDI-OCT) with a different imaging protocol. Finally, shadowing artifacts from overlying blood vessels may limit the detection of LC defects on the anterior surface and affect visualization of posterior LC surface. Hence, LC thickness was not examined as we could not visualize the posterior LC surface reliably with SS-OCT or EDI-OCT. This issue has been reported previously by Girard and colleagues.

In conclusion, using swept-source OCT, we identified holes in the prelaminal tissue of the ONH as a distinguishing feature for CACG. These lesions appear to be quite different from prelaminal wedge defects, which were more common in POAG patients. This difference may represent a distinct pathogenic process of glaucomatous damage from chronic angle closure glaucoma and a potential structural biomarker for this disease.

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Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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