Article

Goldmann V Standard Automated Perimetry Underestimates Central Visual Sensitivity in Glaucomatous Eyes with Increased Axial Length

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Purpose: To investigate the effect of axial length (AL) on the structure–function relationship between retinal nerve fiber layer (RNFL) thickness measurements and visual field (VF) sensitivity measured with Goldmann III and V.

Method: There were 85 eyes of 85 patients with primary open angle glaucoma included in the current study. Optical coherence tomography and VF (Humphrey Field Analyzer 24-2 or 30-2) measurements with Goldmann III and V targets were carried out in all patients. The optic disc and the VF were divided into six clusters and the relationship between circumpapillary RNFL (cpRNFL) thickness and VF sensitivity (with Goldmann III or V), age, and AL were investigated in each cluster.

Result: Visual sensitivity with Goldmann III (19.3 ± 11.7 dB, mean ± standard deviation) was significantly lower than that with Goldmann V (24.6 ± 11.0 dB, P = 0.001, linear mixed model). Visual sensitivities with both Goldmann III and V were significantly correlated with cpRNFL thickness in all clusters. Visual sensitivity decreased with increasing AL in the nasal retinal area for both targets, however, this phenomenon was only observed with the Goldmann V target in the temporal area.

Conclusion: Visual sensitivity measured with the size V target decreases with increasing AL in the temporal area, which corresponds to the papillomacular bundle. In the nasal retinal area, visual sensitivity decreases with the increase of AL for both Goldmann III and Goldmann V.

Translational Relevance: Careful consideration is needed when measuring visual sensitivity using Goldmann V target in glaucomatous eyes with increased AL.

Introduction

Standard automated perimetry (SAP) with a Goldmann III target (4 mm² or 0.43°) is the gold standard to assess the visual field (VF) in glaucoma; however, previous studies have suggested that SAP measurements with a larger target size, such as Goldmann V (64 mm² or 1.72°), are associated with better reproducibility.1–3 Furthermore, a recent study suggested that SAP sensitivity measurements with Goldmann III are particularly unreliable when VF sensitivity falls below 20 dB.4 In contrast, previous research suggests that SAP measurements with a smaller target size are beneficial for the early detection of glaucoma.5–7 Studies have investigated the usefulness of SAP with different target sizes in glaucoma,5–8 however, these studies were performed in patients without myopia; a limited number of reports have investigated the usefulness of SAP with different target sizes in eyes with increased axial length (AL). Myopia is a risk factor for the development and progression of glaucoma, because a tilted optic disc, parapapillary atrophy, and thinning of the lamina cribrosa and parapapillary sclera alter glaucoma susceptibility.9–15 It has been reported that the prevalence of myopia in the United Kingdom is approximately 50%,16 and the prevalence of myopia in East Asia is expected to be even higher.17–19
It is possible to measure glaucomatous structural damage using optical coherence tomography (OCT). Investigation of the structure–function relationship is very important, because structural alterations at the optic nerve head or in the circum-papillary retinal nerve fiber layer (cpRNFL) can precede measurable VF damage. Many previous studies have investigated the glaucoma structure–function relationship using OCT and VF tests, but most of these studies investigated the relationship using SAP with the Goldmann III target, usually excluding eyes with high myopia. No study has investigated the structure–function relationship in myopic eyes, using Goldmann III and V targets. Thus, the purpose of the current study was to investigate the influence of the increase of the axial length on the structure–function relationship between OCT-measured retinal nerve fiber thickness and SAP thresholds measured with target sizes III and V.

Methods

This cross-sectional study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at the University of Tokyo. Written consent was given by the patients for their information to be stored in the hospital database and used for research. This study was performed according to the tenets of the Declaration of Helsinki.

Subjects

There were 85 eyes of 85 subjects with open angle glaucoma (OAG) included in this investigation. All patients were under treatment in the University of Tokyo Hospital, Tokyo, Japan. Criteria for inclusion were visual acuity better than 0.5 logMAR following our previous study, an AL longer than 22 mm and shorter than 30 mm, and no other anterior or posterior segment eye disease, including clinically significant cataract. Aberrant disc morphology and/or with pathological myopic findings on fundus were carefully examined and these eyes were not included in the current study. The patients satisfying the criteria were consecutively recruited and one eye was randomly chosen if both eyes met the inclusion criteria.

VF Testing

VF testing was performed, within 3 months of the spectral-domain (SD)-OCT examination, using the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA) with Goldmann III and V targets and a stimulus duration equal to 200 ms. The order of the Goldmann III and Goldmann V VF measurement was decided in a random manner and a sufficient break was given between tests. The same test grid pattern (24-2 or 30-2 test program) was used for both sets of measurements. The Goldmann III measurement was performed using the SITA standard strategy and the full-threshold strategy was used for the Goldmann V measurement, following previous studies. Near-refractive correction was used as necessary. All of the participants had previous experience in VF testing. VFs with fixation losses greater than 20%, or false–positive responses greater than 15% were excluded, as recommended by the manufacturer.

SD-OCT Measurement

SD-OCT data were obtained using the three-dimensional OCT-2000 (Topcon Corp., Tokyo, Japan), along with the AL measurement. SD-OCT measurements were carried out after pupil dilation with 1% tropicamide and imaging was performed using the raster-scan protocol. cpRNFL thickness was measured as the RNFL thickness along a 3.4-mm diameter circle around the disc, but the radius of the circle was adjusted for AL. The temporal horizontal line (9-o’clock position, right eye) was designated 0°, and angles were counted in a clockwise direction. Left eyes were mirror imaged to a right eye configuration. The optic disc was divided into 12, 30° sectors and the angle was calculated: the angles between –15° and 15° in the temporal area (T), 15° and 30° in the temporo-superior area (TS), 45° and 75° in the supero-temporal area (ST), 75° and 105° in the superior area (S), 105° and 135° in the supero-nasal area (SN), 135° and 165° in the nasal-superior area (NS), 165° and 195° in the nasal area (N), 195° and 225° in the nasal-inferior area (NI), 225° and 255° in the inferior-nasal area (IN), 255° and 285° in the inferior area (I), 285° and 315° in the infero-temporal area (IT), and 315° and 345° in the nasal-inferior area (NI).
Data with apparent eye movements and involuntary blinking or saccade during the measurement were carefully excluded. Following the manufacturer's recommendation, imaging data with quality factor less than 30% were also excluded.

Statistical Analysis

Following Garway-Heath's structure–function map (fig. 4 in Ref. 44), we first identified the angle on the optic disc corresponding to each test point. Then, the whole field was divided into 12, 30° sectors, matching the 12 sectors in OCT (see Fig. 1). Because of the approximately horizontally symmetrical structure of the retina, TS and TI, S and I, ST and IT, SN and NS were analyzed together. Also, because of the small number of test points, the sectors of N, NS, and NI were combined (cluster NS/N/NI) and analyzed altogether.

Data with apparent eye movements and involuntary blinking or saccade during the measurement were carefully excluded. Following the manufacturer's recommendation, imaging data with quality factor less than 30% were also excluded.

Table 1. Subject Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD [range]</td>
<td>59.4 ± 11.6 [30–84]</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>42:43</td>
</tr>
<tr>
<td>Eye, right:left</td>
<td>39:46</td>
</tr>
<tr>
<td>AL, μm, mean ± SD [range]</td>
<td>25.5 ± 1.5 [22.7–29.95]</td>
</tr>
<tr>
<td>Refractive error, diopter, mean ± SD [range]</td>
<td>−3.5 ± 3.0 [−11.0–1.75]</td>
</tr>
<tr>
<td>MD, dB, mean ± SD [range]</td>
<td>−10.8 ± 5.8 [−32.0–0.74]</td>
</tr>
</tbody>
</table>

MD: mean deviation.

Results

Subject characteristics are given in Table 1. Among the 85 eyes, 12 eyes were pseudophakic. Figure 2 shows the histogram of AL. There was a significant relationship between refractive error and AL (r = −0.74, P < 0.001, Pearson's correlation).

Visual sensitivity with Goldmann III (19.3 ± 11.7 [0–36] dB, mean ± standard deviation [SD] [range]) was significantly lower than that with Goldmann V (24.6 ± 11.0 [0–40] dB, P < 0.001, linear mixed thickness, age, and AL was also investigated using a linear mixed model. Lens status (phakic/pseudophakic) was included as a fixed effect, because lens status can interfere with VF test results.

All statistical analyses were carried out using the statistical programming language R (ver. 3.1.3; The R Foundation for Statistical Computing, Vienna, Austria).

Figure 1. Test points corresponding to five optic disc clusters (left eye). VF test points corresponding to each of the 12, 30° sector were identified following Garway-Heath's structure–function map. TS and TI, ST and IT, SN and NS were analyzed together. Also, because of the small number of test points, the sectors of N, NS, and NI were combined (cluster NS/N/NI) and analyzed altogether.

Figure 2. Histograms of AL. AL was 25.5 ± 1.5 (mean ± SD) (range: 22.7–29.95 μm).
As shown in Figure 3, there was a significant relationship between visual sensitivity measured with Goldmann III and Goldmann V ($R^2 = 0.74, P < 0.001$). This significant relationship was observed in all clusters ($R^2$ between 0.53 and 0.74, all of the $P$ values were $< 0.001$, linear mixed model).

Table 2 shows the visual sensitivity with Goldmann III and V targets in each cluster. In all clusters, visual sensitivity with Goldmann V target was significantly higher than that with target Goldmann III ($P < 0.05$, linear mixed model). Table 3 shows the RNFL thickness in each cluster.

Figure 4 shows the relationship between visual sensitivity measured with Goldmann III and V, and AL in clusters T, TS/TI, S/I, ST/IT, SN/SI, and NS/N/NI. As shown in Table 4, in the linear mixed models using multiple variables (age, AL, and RNFL thickness), there was a significant relationship between visual sensitivity both with Goldmann III and Goldmann V, and cpRNFL thickness in all sectors ($P < 0.01$), except one: NS/N/NI ($P = 0.16$ for Goldmann III and 0.39 for Goldmann V). In cluster T, increase of AL was significantly related to visual sensitivity measured with the Goldmann V target ($P = 0.010$, linear mixed model), but not with the Goldmann III target ($P = 0.11$). In cluster NS/N/NI, increased AL was significantly related to visual sensitivity measured with target sizes; Goldmann V target ($P = 0.012$) and Goldmann III ($P = 0.019$). Age was not significantly related to visual sensitivity in all clusters ($P > 0.05$).

**Discussion**

In the current study, VF measurements were carried out using Goldmann III and Goldmann V SAP, and compared with cpRNFL measurements from SD-OCT. As expected, there was a significant correlation between visual sensitivity measured with Goldmann III and Goldmann V SAP, however visual sensitivity measured with Goldmann V SAP was significantly higher compared with Goldmann III SAP. Visual sensitivities with both Goldmann III and Goldmann V targets were significantly correlated with cpRNFL thickness in all clusters around the optic disc. Visual sensitivity significantly decreased

<table>
<thead>
<tr>
<th>Cluster</th>
<th>cpRNFL Thickness in Each Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>62.1 ± 17.5 [28.2–112.00]</td>
</tr>
<tr>
<td>TS/TI</td>
<td>64.3 ± 21.6 [23.0–153.1]</td>
</tr>
<tr>
<td>ST/IT</td>
<td>66.6 ± 27.9 [23.3–189.6]</td>
</tr>
<tr>
<td>S/I</td>
<td>78.5 ± 24.5 [30.7–164.7]</td>
</tr>
<tr>
<td>SN/IN</td>
<td>81.2 ± 23.5 [34.3–130.3]</td>
</tr>
<tr>
<td>N3</td>
<td>63.3 ± 16.7 [33.3–112.8]</td>
</tr>
</tbody>
</table>

**Table 2.** Average Visual Sensitivity in Each Cluster

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Size III</th>
<th>Size V</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T, dB</td>
<td>28.4 ± 7.0 [0–35]</td>
<td>32.4 ± 5.3 [9–40]</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>TS/TI, dB</td>
<td>22.2 ± 12.2 [0–36]</td>
<td>27.7 ± 10.5 [0–40]</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>ST/IT, dB</td>
<td>15.5 ± 12 [0–35]</td>
<td>20.8 ± 11.8 [0–39]</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>S/I, dB</td>
<td>18.6 ± 12 [0–34]</td>
<td>24.1 ± 11.2 [0–38]</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>SN/IN, dB</td>
<td>22.1 ± 9.1 [0–34]</td>
<td>27.5 ± 8.3 [0–38]</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>NS/N/NI, dB</td>
<td>26.1 ± 6.4 [0–34]</td>
<td>30.5 ± 6.4 [0–37]</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>
Figure 4. Relationship between visual sensitivity measured with Goldmann III and Goldmann V targets, and AL. (a) Cluster T, (b) cluster TS/TI, (c) cluster ST/IT, (d) cluster S/I, (e) cluster SN/IN, (f) cluster NS/N/NI. Significant relationship was observed between visual sensitivity measured with Goldmann V target and AL in cluster T (coefficient = 0.72, P = 0.038).
with increasing AL with both Goldmann III and Goldmann V targets in the nasal retinal area, whereas this phenomenon was only observed with the Goldmann V target in the temporal retinal area. SAP with the Goldmann III target is frequently used in the evaluation of glaucomatous VF damage worldwide. However, it has been reported that SAP measurements with a larger target size, such as Goldmann V, are associated with better reproducibility, and indeed a recent study suggested SAP sensitivity measured with Goldmann III is not reliable below 20 dB. In the current study, a significant structure–function relationship was observed in all clusters around the optic disc, both with Goldmann III and V targets. However, this structure–function relationship was altered by increasing AL, when visual sensitivity was measured with the Goldmann V target in cluster T. The retinal nerve fiber in cluster T runs along the papillomacular bundle, which corresponds to VF test points located at the center of VF. In this central area, the density of retinal ganglion cell is high. According to Ricco’s law, when a small stimulus is projected on the retina, the stimulus’s total energy is constant at threshold (complete spatial summation), both in normative and glaucomatous eyes, but in contrast, when larger stimuli, such as the Goldmann III and V targets, are projected, only partial, instead of complete summation occurs, and the threshold is determined probabilistically. Tolhurst et al. have reported that the psychometric function or multiplicative neural probability summation is the result of pooling over multiple receptive fields. The reason why structure–function relationship was altered by in-
creasing AL, when visual sensitivity was measured with the Goldmann V target in cluster T is not entirely clear, but this may be because the stretching effect caused by the increase of the eye ball is most obvious in this area, as is seen in the development of peripapillary atrophy. This stretching effect may cause accelerated partial summation, which is sufficient to decrease visual sensitivity measured with Goldmann V, but not that with smaller target size, such as Goldmann III.

Araie et al. investigated the relationship between myopia and the location of VF damage in 217 primary OAG eyes and suggested that the strength of myopia is significantly correlated with VF damage in the lower cecocentral subfield. Similar results were found in another study, which may be related to the torsion of the optic disc. It is important to note that the lower cecocentral subfield corresponds to cluster T in the current study, where visual sensitivity measured with the Goldmann V target decreased with increasing AL. This implies careful consideration is needed when assessing glaucomatous damage in myopic eyes in this area, using the Goldmann V target.

In cluster NS/N/NI, visual sensitivity decreased with increasing AL, not only with the Goldmann III target, but also with the Goldmann V target. The reason for this is not entirely clear, but structural changes, such as a hump of retinal nerve fibers (nasal hump or peripapillary nerve fiber elevation [pNFE]) has been reported in the nasal retina area in eyes with long AL, probably because the retina is dragged posteriorly as the AL increases, even if the fundus lacks pathological myopic findings. These structural changes are more prominent with the increase of the eye ball, and this may be the reason why visual sensitivity, measured with both Goldmann III and V targets, is decreased with the increase of AL. In the current 24-2 HFA, only three test points are allocated in the area corresponding to cluster NS/N/NI. In addition, some of the 0-dB test points may be a consequence of an overlapping blind spot. Further investigation should be carried out increasing the number of test points in this area.

In eyes with the nasal hump or pNFE due to increase of AL, a conus was usually present on the side opposite the elevation. As the target is much larger with Goldmann V (64 mm²), compared with Goldmann III (4 mm²), the possibility that the projected light overlaps with the conus is much higher with the larger size target (e.g., due to small eye movements). This may be another reason why visual sensitivity measured with Goldmann V target in cluster T decreased with increasing AL, whereas that phenomenon was not observed with the Goldmann III target.

There are a number of limitations with the current study. First, the SITA standard algorithm was used in the Goldmann III measurement while the full-threshold algorithm was adopted in the Goldmann V measurement. It would be of interest to see whether a different result would be observed if the same

| Table 4. Relationship between Visual Sensitivity and Age, AL and cpRNFL Thickness |
|---------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Cluster                  | Age Coefficient | SE      | P Value | AL Coefficient | SE      | P Value | RNFL Thickness Coefficient | SE      | P Value |
| Size III                 |          |         |         |          |         |         |                      |         |         |
| T                        | -0.028   | 0.068   | 0.68    | -0.76    | 0.49    | 0.12    | 0.10                | 0.039    | 0.0072 |
| TS/TI                    | -0.10    | 0.088   | 0.25    | -0.34    | 0.67    | 0.61    | 0.23                | 0.035    | <0.001 |
| ST/IT                    | 0.17     | 0.087   | 0.058   | 0.22     | 0.65    | 0.74    | 0.21                | 0.030    | <0.001 |
| S/I                      | 0.017    | 0.065   | 0.80    | -0.16    | 0.48    | 0.73    | 0.19                | 0.012    | <0.001 |
| SN/IN                    | 0.093    | 0.068   | 0.18    | 0.19     | 0.50    | 0.71    | 0.047               | 0.019    | 0.012  |
| NS/N/NI                  | -0.019   | 0.056   | 0.74    | -0.96    | 0.41    | 0.021   | 0.033               | 0.022    | 0.14   |
| Size V                   |          |         |         |          |         |         |                      |         |         |
| T                        | -0.025   | 0.049   | 0.61    | -0.92    | 0.36    | 0.013   | 0.089               | 0.029    | 0.0028 |
| TS/TI                    | -0.11    | 0.071   | 0.14    | -0.67    | 0.54    | 0.22    | 0.17                | 0.030    | <0.001 |
| ST/IT                    | 0.13     | 0.089   | 0.15    | 0.037    | 0.67    | 0.96    | 0.18                | 0.030    | <0.001 |
| S/I                      | 0.0029   | 0.064   | 0.96    | -0.54    | 0.47    | 0.26    | 0.19                | 0.011    | <0.001 |
| SN/IN                    | 0.014    | 0.064   | 0.83    | -0.65    | 0.47    | 0.17    | 0.050               | 0.017    | 0.0031 |
| NS/N/NI                  | -0.032   | 0.059   | 0.59    | -0.99    | 0.44    | 0.025   | 0.020               | 0.022    | 0.36   |

SE: standard error.
strategy was used for both measurements. Also, as discussed above, the Goldmann V stimulus evokes only partial spatial summation, and the threshold is determined probabilistically. A further study is needed to understand if evoking complete summation, by changing stimulus duration, gives different results. Although the purpose of the current study was to investigate the structure–function relationship using Goldmann size III and V in a wide range of glaucoma severity patients, it would be of interest to investigate the usefulness of Goldmann V in severe glaucoma cases.

In conclusion, visual sensitivity measured with the Goldmann V target decreases with increasing AL in the area corresponding to the papillomacular bundle, whereas this was not the case with the Goldmann III measurement. Also, visual sensitivity decreases with the increase of AL in the area corresponding to the nasal retina, and this phenomenon was observed with both Goldmann III and V targets.

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