The Ability of 10-2 Short-Wavelength Perimetry in Detecting Functional Loss of the Macular Area in Preperimetric Glaucoma Patients

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Submitted: August 2, 2015
Accepted: November 2, 2015
Citation: Jung Y, Park H-YL, Jeong HJ, Choi SY, Park CK. The ability of 10-2 short-wavelength perimetry in detecting functional loss of the macular area in preperimetric glaucoma patients. Invest Ophthal Vis Sci. 2015;56:7708–7714. DOI:10.1167/iovs.15-17819

PURPOSE. To better understand functional loss in the macular area of preperimetric glaucoma patients exhibiting structural loss by exploring correlations between parameters of the ganglion cell–inner plexiform layer (GCIPLT) and 10-2 short-wavelength perimetry (SWAP).

METHODS. One hundred thirty-four patients underwent 10-2 SWAP and conventional 24-2 visual field (VF) testing using a Humphrey field analyzer and macular scanning via Cirrus optical coherence tomography (OCT). Correlations between GCIPLT thickness (GCIPLT) and the mean sensitivity (MS) of topographically corresponding areas explored in various VF tests were calculated. Correlations between GCIPLT parameters and MS of the VF, in terms of the asymmetries of various VF sectors, were also determined.

RESULTS. Glaucoma patients, preperimetric by standard 24-2 VF analysis but exhibiting GCIPLT thinning, had lower MS in 10-2 SWAP and central 24-2 VF analyses. The correlations between average GCIPLT thickness and the corresponding MS were significant for both 10-2 SWAP (r = 0.291, P = 0.018) and 24-2 standard automated perimetry (r = 0.235, P = 0.029). The associations between sectoral GCIPLT and the corresponding 10-2 SWAP MS were significant for all sectors, with the highest correlation evident in the inferotemporal (r = 0.324, P = 0.009) and the lowest in the superonasal GCIPLT sectors (r = 0.214, P = 0.043). Asymmetric relationships between GCIPLT and 10-2 SWAP MS exhibited similar yet stronger correlations.

CONCLUSIONS. Preperimetric glaucoma patients exhibiting structural loss in the macula also had functional loss revealed by 10-2 SWAP, which was less prominent in conventional 24-2 VF. Therefore, if structural abnormality is evident in the macular area, the central VF areas should be further examined even if the standard 24-2 data appear to be normal.

Keywords: preperimetric glaucoma, ganglion cell analysis, short wavelength perimetry

In early-stage glaucoma, structural loss is traditionally considered to be greater than functional loss. Many studies have suggested that 25% to 35% of all retinal ganglion cells (RGCs) may be lost before any abnormality is evident via standard automated perimetry.1–4 Even when functional loss is detected, glaucomatous visual field (VF) damage usually commences in the Bjerrum area (thus, the midperipheral VF); the central VF tends to be preserved until glaucoma is advanced.5 However, growing evidence suggests that structural damage to the macula occurs even in the early stages of glaucoma.6–10 The macula is especially important; VF damage to this area renders patients unable to perform various tasks of daily living.11 Because glaucoma is irreversible, detecting functional damage to the central VF as early as possible is crucial to preserve vision.

When structural damage to the macular area is to be evaluated, the Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) ganglion cell analysis algorithm, which measures the thickness of the ganglion cell–inner plexiform layer (GCIPLT), has been shown to successfully assess GCIPLT thickness (GCIPLT). Reproducibility is excellent, and the technique can be used to detect early-stage glaucoma.12,13 Glaucoma-associated functional loss is often assessed by 30-2 or 24-2 standard automated perimetry (SAP) using the Swedish Interactive Threshold Algorithm (SITA) running on a Humphrey field analyzer (Carl Zeiss Meditec, Inc.). Many such studies have suggested that structural loss precedes functional loss, and that conventional perimetry does not detect VF damage until large numbers of optic nerve fibers are lost.1–4 However, although approximately 50% of all RGCs are located within 4.5 mm of the fovea, and although cell density decreases as a function of eccentricity,14 30-2 and 24-2 SITA do not have the same proportion of points representing the central retina as the peripheral retina. Jung et al.15 found that glaucoma patients with parafoveal VF defects had narrower neural rims and larger cups than those with similar extents of paranasal field defects; the authors speculated that detection of central VF defects required damage to greater numbers of RGCs compared to those of peripheral regions.

10-2 short-wavelength automated perimetry (SWAP) affords several advantages over conventional 24-2 SAP/SITA for evaluation of central VF function. First, the former test analyzes 68 data points located within a central arc of 10° (the points lie 2° apart); test points of a 24-2 SITA lie 6° apart. Other studies...
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have shown that 10-2 VF detects macular defects missed by 24-2 VF in early-stage glaucoma patients. Second, SWAP strategy may detect glaucomatous damage earlier than SAP. There are conflicting studies on whether SWAP detects glaucomatous damage earlier than SAP. In a study comparing 24-2 SWAP and 24-2 SAP for their ability to predict conversion to glaucoma, 24-2 SAP predicted glaucoma conversion earlier than 24-2 SWAP in more cases than vice versa, and the authors concluded that SAP seems to be at least as sensitive in detecting conversion to glaucoma as SWAP. In addition, Bengtsson and Heijl compared the ability of 24-2 SWAP (using both SITA and full-threshold algorithms) and 24-2 SAP (using SITA Fast algorithm) in detecting early glaucoma and concluded that SAP with SITA Fast algorithm was not less sensitive than SWAP. Yet more studies support that SWAP may be more sensitive than SAP in detecting early glaucoma. Johnson et al. reported that 30-2 SWAP detects functional loss in glaucoma patients up to 5 years earlier than does 30-2 SAP. Polo et al. also reported that 30-2 SWAP predicts the onset of VF defect earlier than 30-2 SAP.

The aim of the present study was to evaluate macular function via 10-2 SWAP full-threshold analysis in preperimetric glaucoma patients exhibiting structural loss as shown by GCIPL measurement, but no functional loss upon conventional 24-2 SAP/SITA testing.

METHODS

This prospective study included 134 preperimetric glaucoma patients selected using the clinical database of the glaucoma clinic of Seoul St. Mary’s Hospital College of Medicine, the Catholic University of Korea, between September 2014 and November 2014. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and with the approval of the Institutional Review Board of Seoul St. Mary’s Hospital College of Medicine.

Initially, each patient underwent a comprehensive ophthalmic examination, including measurement of best-corrected visual acuity, Goldmann applanation tonometry, slit-lamp gonioscopic and dilated fundoscopic examinations, red-free retinal nerve fiber layer (RNFL) photography, achromatic SAP using the 24-2 SITA standard program (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Inc.), 10-2 full-threshold SWAP, and spectral-domain optical coherence tomography (SD-OCT) scanning (Cirrus HD-OCT; Carl Zeiss Meditec, Inc.). All patients underwent SAP at least twice prior to study commencement.

Inclusion criteria included a best-corrected visual acuity of 20/40 or better, a spherical error of +4.0 to −6.0 diopters, a cylinder error within ±2 diopters, an open angle on gonioscopic examination, and reliable VF test results with false-positive and -negative error rates < 15% and a fixation loss < 20% for 24-2 SAP/SITA, and < 33% false-negative and -positive rates and a fixation loss < 20% for 10-2 SWAP. A VF evaluated by 24-2 SAP/SITA was considered normal if the pattern standard deviation had a P value > 5% and the glaucoma hemifield test results were within normal limits.

Exclusion criteria included a history of any form of retinal pathology, neurological disease, or ocular trauma or surgery, except for uncomplicated cataract surgery. Any patient with a history of systemic medication use or of a cerebrovascular event that could affect the VF was also excluded. One eye of each subject was chosen at random for inclusion.

Preperimetric glaucoma was defined as any glaucomatous optic neuropathy (neuroretinal rim thinning, notching, and/or an RNFL defect) detected by two glaucoma specialists masked to patient data (YJ and CKP), accompanied by normal 24-2 SAP/SITA results.

Visual Field Examination

Structure-function relationships were analyzed by comparing GCIPL parameters and the corresponding mean sensitivity (MS) measured using 24-2 SAP/SITA and full-threshold 10-2 SWAP. Visual field sensitivity was recorded using a logarithmic decibel scale and a nonlogarithmic 1/L scale. Each nonlogarithmic 1/L value was calculated as decibel = 10 log10 (1/L).

The 24-2 SAP/SITA central MS, which were assumed to correspond topographically to the area scanned upon GCA, were defined as the averages of data from 12 central points. Similarly, SWAP 10-2 central MS were defined as the averages of data from 36 central points. Figure 1 shows the 10-2 SAP data points corresponding topographically to each GCIPL sector, after taking RGC displacement in the foveal area into account as suggested by Sato et al. Asymmetry in VF sensitivity was calculated as the sum of VF sensitivities of inferior sectors divided by those of the superior sectors for the inferonasal, inferior, and inferotemporal VF sectors; and vice versa for the superior sectors (Fig. 1).

Statistical Analyses

Differences between patients with preperimetric glaucoma, with and without GCIPL thinning, were assessed using an independent Student’s t-test for continuous parameters and the χ² test for categorical parameters. To assess structure–function relationships via regression analysis, global/regional GCIPLTs were treated as independent and the corresponding VF sensitivities as dependent variables. To measure associations between GCIPLTs and the MS of the corresponding VFs, Pearson’s correlation coefficients (r values) were calculated both globally and regionally.

Each of the following comparisons was made for SWAP 10-2: average GCIPLT versus central MS, GCIPLT of each sector versus the MS of the corresponding test points, and GCIPLT asymmetry versus MS asymmetry. All values are presented as means ± standard deviations, and P < 0.05 was considered to reflect statistical significance. The Statistical Package for the Social Sciences version 18.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Of 134 patients diagnosed with preperimetric glaucoma, 90 exhibited GCIPL thinning and 44 did not. Patient demograph-
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Figure 1. Ganglion cell-inner plexiform layer (GCIP) thickness measurement by Cirrus HD-OCT (A), and the corresponding central visual field sectors examined using 10-2 short-wavelength perimetry (B) or the conventional 24-2 paradigm (C). Asymmetry in the GCIP superior sector (D) was assessed by dividing the superior sector GCIP thickness by the inferior sector GCIP thickness (E). Associated asymmetry testing of visual field mean sensitivity was performed by dividing the inferior sector mean sensitivity by the superior sector mean sensitivity (10-2 SWAP data) (F).

Ganglion cell–IPLTs and 24-2 SITA MS (expressed in dB) exhibited a linear relationship, whereas GCIP thickness measurement by Cirrus HD-OCT (GCIP) and 10-2 SWAP MS (expressed in decibels) exhibited a quadratic relationship. Figure 3 shows data from a representative case, in which the GCIP was thinner, in both the inferior and inferonasal sectors.

Discussion

We explored the relationships between global and regional GCIPTs and central VF MS as measured by 10-2 SWAP in patients with preperimetric glaucoma. Our purpose was to determine if reduced macular function accompanied structural reduction in such patients. To the best of our knowledge, this is the first study to explore structure-function relationships in the macular area using 10-2 SWAP.

We found that GCIP LT correlated significantly with both 10-2 SWAP and 24-2 SITA data from central points. Correlations between GCIP LTs and the corresponding MS (in dB) were all significant, ranging from 0.534 (P = 0.009) in the superotemporal to 0.324 (P = 0.009) in the inferotemporal GCIP LT sectors. For 24-2 SAP/SITA, the correlation between MS and the corresponding GCIP LT was significant for the inferior GCIP LT sector only (r = 0.249, P = 0.010). Table 4 shows the correlations between regional GCIP LT asymmetries and the topographically corresponding VF asymmetries. The correlations between GCIP LTs and 10-2 MS asymmetries were all significant (ranging from 0.628 in the inferotemporal GCIP LT to r = 0.416 in the superonasal GCIP LT) evaluated. Of the six sectors, the inferotemporal GCIP LT and superonasal 10-2 SWAP points exhibited the highest correlations.

There may be several possible explanations for this. First, 10-2 SWAP has more testing points in the macular area than 24-2 SAP. Previous studies have shown that glaucomatous change in the macular area may be better detected by 10-2 VF testing than 24-2.

Hangai et al.27 studied three patients with glaucomatous structural changes in their maculae; paracentral scotomata were detected by 10-2 SAP but not 24-2 SAP. In addition, Asaoaoka5 showed that glaucomatous functional loss was detected by 10-2 VF, but not 30-2 SAP, and speculated that this was attributable to poor spatial sampling. The importance of rigorous estimations in the central macula was emphasized.

Second, SWAP testing targets the small bistratified RGCs, and this strategy may detect early glaucomatous field loss more sensitively.16-21 Johnson et al.16 showed that SWAP predicts conversion to glaucoma 3 to 5 years earlier than SAP. Sit et al.28 described a case in which SWAP detected glaucomatous VF defect 10 years earlier than SAP. Moreover, Sample and Weinreb29 compared SAP and SWAP results in glaucoma patients and concluded that SWAP may show significant...
Table 1. Patient Demographics and Ocular Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preperimetric Glaucoma Patients With GCIPL</th>
<th>Preperimetric Glaucoma Patients Without GCIPL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thinning, n = 90</td>
<td>Thinning, n = 44</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>44.60 ± 11.13</td>
<td>47.82 ± 11.90</td>
<td>0.166</td>
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<tr>
<td>Sex, male:female</td>
<td>40:50</td>
<td>20:24</td>
<td>0.912</td>
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<tr>
<td>Laterality, right:left</td>
<td>48:42</td>
<td>25:19</td>
<td>0.705</td>
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<tr>
<td>Intraocular pressure, mm Hg</td>
<td>14.53 ± 3.92</td>
<td>14.03 ± 3.27</td>
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</tr>
<tr>
<td>Spherical equivalent, D</td>
<td>−4.06 ± 3.97</td>
<td>−3.78 ± 2.79</td>
<td>0.385</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>23.61 ± 1.05</td>
<td>23.18 ± 1.47</td>
<td>0.475</td>
</tr>
<tr>
<td>Macular GCIPLT, μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>72.03 ± 6.60</td>
<td>84.85 ± 4.88</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>65.10 ± 7.88</td>
<td>82.18 ± 4.79</td>
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<tr>
<td>Superior</td>
<td>76.36 ± 6.80</td>
<td>87.27 ± 5.40</td>
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<tr>
<td>Superotemporal</td>
<td>73.85 ± 6.14</td>
<td>85.45 ± 6.00</td>
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<tr>
<td>Inferonasal</td>
<td>72.60 ± 5.34</td>
<td>83.61 ± 4.05</td>
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</tr>
<tr>
<td>Inferior</td>
<td>68.48 ± 5.04</td>
<td>83.18 ± 3.83</td>
<td></td>
</tr>
<tr>
<td>Inferotemporal</td>
<td>69.65 ± 5.65</td>
<td>83.85 ± 5.46</td>
<td></td>
</tr>
<tr>
<td>Visual field parameters</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>24-2 mean deviation, dB</td>
<td>−1.18 ± 1.70</td>
<td>−0.66 ± 1.39</td>
<td>0.092</td>
</tr>
<tr>
<td>24-2 pattern standard deviation, dB</td>
<td>1.97 ± 1.23</td>
<td>1.76 ± 1.02</td>
<td>0.441</td>
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<tr>
<td>Visual field index, %</td>
<td>97.96 ± 3.51</td>
<td>98.55 ± 2.60</td>
<td>0.498</td>
</tr>
<tr>
<td>24-2 central MS, dB</td>
<td>31.49 ± 1.65</td>
<td>32.24 ± 1.52</td>
<td>0.036*</td>
</tr>
<tr>
<td>24-2 superior central hemifield MS, dB</td>
<td>31.12 ± 1.93</td>
<td>32.06 ± 1.74</td>
<td>0.026*</td>
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<tr>
<td>24-2 inferior central hemifield MS, dB</td>
<td>31.85 ± 1.55</td>
<td>32.42 ± 1.43</td>
<td>0.091</td>
</tr>
<tr>
<td>10-2 SWAP central MS, dB</td>
<td>23.67 ± 3.21</td>
<td>25.33 ± 4.08</td>
<td>0.006*</td>
</tr>
<tr>
<td>10-2 SWAP inferotemporal sector, dB</td>
<td>24.46 ± 3.81</td>
<td>26.60 ± 3.28</td>
<td>0.021*</td>
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<tr>
<td>10-2 SWAP inferior sector, dB</td>
<td>24.40 ± 3.65</td>
<td>26.60 ± 3.28</td>
<td>0.002*</td>
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<tr>
<td>10-2 SWAP inferonasal sector, dB</td>
<td>24.25 ± 3.61</td>
<td>26.22 ± 3.46</td>
<td>0.008*</td>
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<tr>
<td>10-2 SWAP superotemporal sector, dB</td>
<td>23.66 ± 3.89</td>
<td>25.33 ± 4.08</td>
<td>0.048*</td>
</tr>
<tr>
<td>10-2 SWAP superior sector, dB</td>
<td>22.36 ± 4.04</td>
<td>25.33 ± 4.08</td>
<td>0.004*</td>
</tr>
<tr>
<td>10-2 SWAP inferotemporal sector, dB</td>
<td>22.89 ± 4.02</td>
<td>25.43 ± 4.12</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

Independent t test for continuous variables; χ² test for categorical variables. D, diopters.

* P < 0.05.

change in visual function before SAP. However, van der Schoot et al.26 found that SWAP did not reveal conversion to glaucoma earlier than SAP in over 90% of study patients. In addition, Bengtsson and Heijl17 compared the ability of 24-2 SWAP using both SITA and full-threshold algorithms and 24-2 SAP using SITA Fast algorithm in detecting early glaucoma, and concluded that SAP with SITA Fast algorithm was not less sensitive than SWAP. Although the reason for this difference remains unclear, we speculate that SWAP sensitivity is affected by the location of SAP. Although the reason for this difference remains unclear, we speculate that SWAP sensitivity is affected by the location of SAP.

In terms of sectoral correlations, the inferotemporal GCIPLT sector exhibited the highest correlation with the corresponding MS. Our results are consistent with those of Sato et al.26 The cited authors found that structure-function relationships were more evident in the inferior and temporal sectors than the superior and nasal sectors. This may be explained by sectoral differences in GCIPLT. Histological studies in humans,14 as well as our work, show that the temporal and inferior sectors have fewer ganglion cells than do the superior and nasal sectors.

In addition, we found that the relationship between GCIPLT and VF MS (in decibels) was linear, and that between GCIPLT and unlogged MS (in 1/L) was quadratic. Structure-function relationships vary across the spectrum of glaucomatous neuropathy, and we included only preperimetric glaucoma patients in our present work. Leung et al.31 reported similar results; the relationship between RNFL thickness (measured using a glaucoma-detecting retinal scanner) and MS (in decibels) was logarithmic in nature, and that between RNFL thickness and unlogged MS (in 1/L) quadratic, in both glaucoma-suspect and glaucoma patients. It was concluded that structure-function relationships varied over the disease spectrum, with the extent of visual sensitivity, and with the imaging modality used.

A limitation of our current study is that 10-2 SWAP may offer several advantages over 24-2 SAP in detecting visual function in the macular area, a denser testing pattern, and SWAP strategy. It is unclear whether the fine testing pattern, SWAP strategy, or both account for the better correlation between 10-2 SWAP and GCIPLT than that of 24-2 SITA and GCIPLT. Therefore
further research with 10-2 SAP is warranted to determine the role of each potential advantage. In addition, SWAP exhibited greater between- and within-subject variability than did SAP.32 We sought to reduce between-subject variability by comparing VF asymmetries. Horizontal hemifield asymmetry has been shown to be valuable in assessment of early glaucomatous changes.24,33,34 Similarly, in our study, the relationships between GCIPL and MS asymmetries exhibited higher correlations than did direct comparisons between GCIPLT and MS.

In summary, 10-2 SWAP revealed functional defects in preperimetric glaucoma patients with macular damage evident by GCA in corresponding areas. Therefore, if structural abnormalities are evident in the macula, the central VF regions...
Figure 3. A representative 59-year-old male with preperimetric glaucoma. The inferonasal and inferior sectors exhibit thinning of the ganglion cell–inner plexiform layer.
should be carefully examined further even if the standard 24-2 data appear to be normal.

Acknowledgments
Disclosure: Y. Jung, None; H.-Y.L. Park, None; H.J. Jeong, None; S.Y. Choi, None; C.K. Park, None

References