Central Visual Fields For Short Wavelength Sensitive Pathways in Glaucoma and Ocular Hypertension

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While conventional clinical visual acuity and kinetic visual fields may be essentially normal in ocular hypertension and early stages of glaucoma, other foveal aspects of vision (eg color, spatial and temporal contrast sensitivity) may be quite abnormal. Specifically, a selective vulnerability of the short wavelength sensitive (SWS) visual pathways in these conditions has previously been noted. Here we studied the central visual fields of 33 primary open angle glaucoma (POAG) patients, 32 ocular hypertensives (OHT), and 24 age-matched normal controls using blue and yellow test flashes on bright yellow backgrounds. SWS cone and MWS and/or LWS cone pathway sensitivities were measured at the fovea and at 2.5°, 5°, 10° and 15° eccentricities, in either the inferior temporal (for OHT) or horizontal nasal retina (for POAG). As expected, all groups had normal sensitivity to yellow flashes—detected by LWS and/or MWS cones—in these meridians. By comparison, for the blue flashes—detected by the SWS cones—the POAG and OHT groups had sensitivity deficits, uniformly across the central visual field, of about 6X and 1.8X, respectively, compared to normals. While six of 31 (19%) OHT subjects had localized glaucomatous field defects (>0.4 log units) in the non-foveal inferior temporal retina, none of the 12 OHT subjects who were also tested in the horizontal nasal retina showed loss in this meridian. Finally, while no POAG subjects had localized sensitivity loss for yellow flashes in the horizontal nasal retina, four did show local field defects with blue test flashes. These results are consistent with significant local and diffuse ganglion cell loss involving the blue-sensitive visual pathways in both OHT and POAG patients. Invest Ophthalmol Vis Sci 29:64–72, 1988

The loss of nerve fibers in glaucoma is thought to occur in two ways. A localized loss of axons, usually occurring at the poles of the optic nerve head,1 produces the familiar changes of asymmetric cupping of the disk and notching of the neuroretinal rim. This loss may be evident as a defect of the retinal nerve fiber layer2–4 and give rise to the typical nerve fiber bundle defects found in the Bjerrum areas of the visual fields. The second type of axon loss produces a generalized reduction in retinal sensitivity, and may be observed at the nerve head as an overall enlargement of the optic cup with a reduction in the neuroretinal rim area.4,6

Traditionally, greater emphasis has been placed on evaluating the localized loss of nerve fibers, using visual field evaluation. The earliest localized visual field loss typically occurs outside of the central macular area and, in recent times, much work has been carried out on improving methods of visual field examination to provide increasingly more sensitive tests of the earliest signs of functional loss. Whether the localized loss of nerve fibers can first be detected functionally by the visual fields, or structurally by examination of the optic nerve head and retinal nerve fiber layer, is currently a matter of some debate.7,8 The recent reports by Quigley1,8–10 which suggest that patients with mild or moderate visual field defects may have lost as many as 50% of their axons at the optic nerve head have stimulated interest in identifying the earliest possible changes in glaucoma. More provocative is the evidence from Quigley's studies suggesting that even ocular hypertensive eyes, with no clinically manifested visual field loss or change in the appearance of the nerve head, may have as many as 35% of the axons of the nerve head missing.

A generalized reduction of retinal sensitivity from the diffuse loss of axons, although present, is difficult to demonstrate by visual field examination.4,5 How-
ever, a number of changes of visual function at the fovea have been reported and are usually cited as evidence of diffuse loss. Much of this evidence comes from color vision studies, although studies of spatial and temporal contrast sensitivity in the central macula also contribute to this conclusion. In fact, even though visual acuity is normally thought to be unaffected in the earlier stages of glaucoma, careful assessment often shows that it may be mildly reduced. A number of studies of foveal color vision can now be cited as showing that, in glaucoma, hue discrimination is reduced selectively in the blue-yellow axis of color discrimination. More specifically, both achromatic and chromatic sensitivity is reduced, with the greatest sensitivity loss occurring in the blue end of the spectrum. Surprisingly, similar results have been reported among many ocular hypertensive patients where no localized loss of axons has been presumed. Now there is evidence linking foveal color vision loss to diffuse retinal nerve fiber loss. Such findings, along with reports of loss of other central vision function in many ocular hypertensives, raises the possibility that diffuse loss may precede localized loss in the evolution of glaucomatous field loss. Of course such a conclusion must always be tempered by the fact that the relative sensitivity of a particular test paradigm can confound any conclusions about whether central diffuse loss of vision precedes or follows localized field defects in glaucoma.

Against bright yellow backgrounds, which depress the sensitivity of MWS and LWS cones, SWS cones are responsible for the detection of deep blue flashes of light in the normal eye. We have shown previously that the actual conditions we used in this study isolate short wavelength sensitive (SWS) cones in just this way. SWS cones play no role in detection of yellow flashes superimposed on a bright yellow background; this is done by MWS and/or LWS cones. In this study we use the test of SWS cone thresholds to examine the foveal and central visual field sensitivity in groups of glaucoma, ocular hypertension and age-matched normal subjects. We were particularly interested in identifying both local and diffuse sensitivity loss. In the glaucoma patients sensitivity profiles were determined primarily along the nasal retina horizontal raphe with about 30% of the subjects also being tested along the temporal meridian in the inferior retina with about 30% of them also tested along the nasal horizontal retina. Here we were interested in revealing diffuse or localized field loss that clearly had not been identified by conventional clinical field testing. (The 40° meridian in the temporal inferior retina is thought to represent one of the earliest locations for localized loss in the development of glaucoma.) A similar sized group of age-matched control subjects was used for measurements in both meridians.

### Materials and Methods

Glucoma and ocular hypertensive patients were recruited for this study from the Eye Clinic of the Silas Hayes Hospital at Fort Ord, California. Glaucoma patients (n = 33) were of the primary open angle type (POAG), had visual acuities of 20/40 or better in the tested eye (all except two had 20/30 or better), were under reasonable control and had not undergone any laser or filtration surgery. Seventeen of the POAG patients had small paracentral or arcuate scotomas only or an isolated nasal step, five had large paracentral or arcuate scotomas including nasal steps, six had marked nasal or temporal depression with large paracentral or arcuate scotomas, and five were categorized as endstage with small temporal or central islands of vision. All subjects consented to participation after details of the study and its procedures were explained.

The ocular hypertensives (OHT, n = 32) were defined as having IOP (by applanation) of greater than 22 mm Hg on two or more occasions, no visual field defects (Humphrey Instruments, San Leandro, CA; Central Threshold Test: Stimulus III white and background 31.5 apostilbs), normal appearance of the optic nerve head, and acuity better than 20/30 in the tested eye.

The age-matched normal control group (n = 24) had acuity better than 20/30, pressures less than 21 mm Hg, no glaucomatous visual field defects, no field loss, and no pathological cupping, pallor, or edema of the disk. All of the subjects in the study had only minor cortical and nuclear lens changes, and were free of retinal disease by fundus examination and fundus photography.

SWS cone thresholds were determined using an 11° yellow (Schott, Jena, East Germany; filter OG530) background onto which a 1° blue (Kodak, Rochester, NY; Wratten filter 47B) test spot was projected. For comparison, a threshold was obtained using a 1° yellow spot projected onto the same background. (This spot is detected by MWS and/or LWS, but not SWS cones.) A viewing distance of 33 cm was used and a suitable optical correction worn when ap-
Fig. 1. Log sensitivity to 1° yellow test flashes (300 msec) on an 11° yellow background at the fovea and at 2.5°, 5°, 10° and 15° eccentricity. Normal and ocular hypertensive groups measured along the inferior temporal retina, glaucoma group measured along the nasal retina to 10° eccentricity. Sensitivities determined by method of limits. Mean ages, numbers of subjects, test and background dimensions, and light levels as in Table 1. ± One standard deviation is indicated for the normal group.

Fig. 2. Log sensitivity to 1° blue test flashes (300 msec) on an 11° yellow background at the fovea and at 2.5°, 5°, 10° and 15° eccentricity. Normal and ocular hypertensive groups measured along the inferior temporal retina, glaucoma group measured along the nasal retina to 10° eccentricity. Sensitivities determined by method of limits. Mean ages, numbers of subjects, test and background dimensions, and light levels as in Table 1. ± One standard deviation is indicated for the normal group.

Results

Yellow on Yellow Test Sensitivities

The sensitivity to yellow test flashes is highest at the fovea and gradually drops off out to 15 degrees eccentricity in the normal eye (Fig. 1). This is consistent with the profile of the "hill of vision" for white photopic backgrounds normally encountered in clinical perimetry. Furthermore, the sensitivity falls at essentially the same rate in the inferior temporal retina as it does in the nasal retina. It can be seen from Figure 1 that the sensitivity profiles for the glaucoma and ocular hypertension groups do not differ from that of the normal group either in shape or absolute sensitivity. In fact there is no statistically significant difference between the three groups for any of the eccentricities measured. This result is not surprising since ocular hypertensives were included in this study because of their normal fields, and most glaucoma patients would not be expected to have sensitivity loss in the horizontal nasal retina unless their visual field defects could be described as severe.

Blue on Yellow Test Sensitivities

Quite a different result is seen for sensitivity profiles determined with blue test flashes where the SWS cone mechanisms are responsible for detection. Figure 2 shows that, in the normal eye, the sensitivity to blue test flashes is greatest at about 2° retinal eccentricity and falls off gradually towards the fovea and towards greater eccentricities. This result could have been anticipated from the known distribution of SWS receptors and the presence of the yellow macular pigment in the central 2° - 4°. The ocular hypertensive and glaucoma patients are significantly less sensitive to the 1° blue test flashes compared to the normal group.
Log sensitivities ±1 sd for central visual field

<table>
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<tr>
<th>Retinal location</th>
<th>n</th>
<th>Mean age (years)</th>
<th>B test flash</th>
<th>Y test flash</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2.5°</td>
<td>5°</td>
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<td>Glaucoma</td>
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<td>nasal</td>
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<td>± 7.2</td>
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<tr>
<td>mean age</td>
<td></td>
<td>59.8</td>
<td>± 15.6</td>
<td>± 0.42</td>
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Log sensitivities ±1 standard deviation for glaucoma, ocular hypertension, and normals for the central 15° of retina (method of limits). Inferior temporal retina = 40° below horizontal meridian. Nasal retina = horizontal meridian. Y = yellow test flash, B = blue test flash. All thresholds measured for a 1° spot (300 mcd) against an 11° yellow background (Schott OG530) set at 500 cd/m². See text for details.

alized loss of sensitivity is between 0.2 and 0.3 log units. Even this clinically small difference between the ocular hypertensive group and the normal group is statistically significant \((P < 0.05)\) at each eccentricity. The generalized sensitivity loss for the glaucoma group is more marked, being about six times less sensitive (0.8 log units) than the normal control group and four times less sensitive (0.6 log units) than the ocular hypertensive group. The results for both yellow and blue test flash threshold measures in the various retinal locations for all three groups are shown in Table 1.

Age-Matched Comparisons

It can be seen from Table 1 that the mean age for each of the three groups is very similar. However, since we know that the ocular media becomes more yellow with age and could be expected to influence the detection of blue flashes, it is important to establish that the differences we see between the three groups cannot be attributed to age. Two comments bear directly on this issue. First, in a separate study (Adams, unpublished) using the same instrument, one of the authors has shown that there is no significant change in sensitivity to yellow spots on a yellow background with age for normal eyes, but an approximately 0.2 log unit decline per decade for the detection of blue spots by the same eyes. Since the difference in mean age for the three groups is less than 1 decade, we would anticipate that normal aging effects would account for less than 0.2 log units; this is far less than the 0.8 log unit difference seen between normals and glaucoma patients. Second, in an attempt to analyze our data with a tighter control on age matching, we paired 21 glaucoma patients individually age-matched to 21 normals. Here the mean age differed by less than 1 year with the normals being slightly older. The difference in SWS cone thresholds for the two groups was 0.7 log units and was statistically significant \((P < 0.001)\), two-tailed t test. Clearly age effects cannot account for the differences seen in our results between normals and the other two study groups.

Pupil Size

Pupil size differences between the two groups could also conceivably influence the test results. Theoretically, a small pupil could lower the test sensitivity by creating an effectively longer path length through the thicker portion of the crystalline lens, or it might reduce the effective background to bring the patient off the Weber portion of the threshold versus intensity curve. In normals, we had previously established that at the background light levels used for this test even relatively large changes in effective background intensity—due to ocular media attenuation of pupil size—should not significantly influence test scores.33 Nevertheless, in an attempt to directly test the possible influence of pupil size on test results for our glaucoma patients we compared the sensitivities of those glaucoma patients whose pupil diameter was less than 3 mm \((n = 12)\) to those whose pupil diameter...
Visual Fields For SWS Cones

In addition to noting overall losses in sensitivity for both the glaucoma and ocular hypertensive groups we were interested to see if for the ocular hypertensive group, where clinical visual fields were normal, there was a selective "glaucomatous" field defect for the SWS cone pathways. Thus, we compared ocular hypertensive results to those for normals at each of the four retinal eccentricities out to 15° in the inferior temporal retina. By normalizing each individual's results at the fovea and looking only for deviations greater than 0.4 log units from the normal profile of sensitivity across the retina, we found that six of 31 ocular hypertensives had field defects for at least one retinal eccentricity. While only 12 of the ocular hypertensive patients were tested in the nasal retina, none of those showed comparable loss at any of the eccentricities tested in that retinal meridian. We were also interested in whether or not glaucomatous field defects in glaucoma patients were either more extensive or of greater magnitude for the blue test flash condition than for the detection of yellow flashes. None of the 33 glaucoma patients had localized sensitivity loss (greater than 0.4 log units) for yellow flashes in the nasal retina. Four of these patients had loss for the blue flashes with an additional two patients having 0.4 log unit loss. This included one of three patients who showed a sensitivity loss at only a single location on the clinical central field measures. Unfortunately, interpretation of sensitivity measures for the inferior temporal retina is limited by the fact that only 11 patients were tested. Both the clinical field measures and the blue flash measures identified four individuals with greater than 0.4 log unit loss for at least one location within 15 degrees of the fovea; two of these were common failures. Three of the patients had greater loss for the SWS cone pathways than for yellow flashes along this inferior temporal meridian. The results for one such glaucoma patient is shown for both the blue and the yellow test stimulus conditions in Figure 3.

Discussion

Two important conclusions may be drawn from the results of these studies. First, compared to an age-matched normal control group, both glaucoma and ocular hypertension patient groups show a significant loss of sensitivity for the SWS cone pathways throughout the central visual field. This loss is uniform across the central field up to the 15° eccentricity that we measured, and is considerably greater for the glaucoma patients than for the other two study groups. The result cannot be accounted for on the basis of age or pupil size differences between the study groups. Second, our results provide some evidence for glaucomatous-like field defects in about 16% of ocular hypertensive patients when tested with blue flashes detected by SWS cone pathways. Similarly, there is some evidence that glaucoma patients may have exaggerated local field loss for these same blue targets when compared to more conventional yellow test targets. Together these findings suggest that color perimetry with blue test targets, designed to
be detected selectively by the SWS cones, may be a sensitive perimetric test for functional loss in glaucoma and ocular hypertension.

We have already noted that a number of studies suggest that foveal color discrimination losses, particularly in the blue-yellow axis, are frequently reported for patients with glaucoma. Some have suggested that the acquired dyschromatopsia is related to the severity of the visual field defect.\textsuperscript{18,20,27,28} Drance et al\textsuperscript{21} suggested that error scores on the FM 100-Hue test or abnormalities in the yellow-blue or green-blue spectrum on the anomaloscope were predictive of subsequent development of localized nerve fiber bundle field defects in suspected glaucoma. However, in spite of this a significant number (about 25\%) of eyes with advanced glaucomatous visual field defects show no abnormality in color discrimination.\textsuperscript{32} This lack of a "clear-cut relationship" between the color discrimination and the severity of the glaucomatous visual field defect suggested to Airaksinen et al\textsuperscript{32} that a separate mechanism may be responsible for the color vision and visual field deficits. They found that color vision losses on the anomaloscope could significantly predict diffuse loss, but not localized loss, in the retinal nerve fiber layer. This result lends further support to the suggestion by Flammer\textsuperscript{33} that the diffuse loss and the localized loss may have separate, but not mutually exclusive, origins. He suggests that the diffuse loss occurs as a result of direct mechanical damage related to raised intraocular pressure and is revealed functionally, for example, by abnormal color vision and depressed contrast sensitivity. On the other hand, he proposes that localized loss occurs primarily as a vascular disorder and may, for example, result from a microinfarction at the optic nerve head producing the familiar nerve fiber bundle defect. This loss may be much less directly related to intraocular pressure. In his scheme raised intraocular pressure can also be a cause of localized loss, especially in cases where there are other vascular risk factors. Consequently, in individual cases, axon loss may result from more than one cause. Unfortunately, our results do not provide any evidence, one way or another, for separate mechanisms involved in the diffuse and localized axon loss. They do show that loss of foveal sensitivity for the SWS cone pathways is associated with a generalized loss of sensitivity across the entire central field, consistent with the proposition that color discrimination losses at the fovea are related to diffuse retinal nerve fiber loss.\textsuperscript{32}

Our results also show that localized glaucomatous-like field defects may be present for blue test targets which are detected by the SWS cone mechanisms, when the same defect is not apparent with more standard yellow or white test targets. These results point to the use of color perimetry for blue targets on a bright yellow background. The usefulness of color perimetry has been questioned in the past; despite the interest it generated in the 1920s,\textsuperscript{36,37} it was largely discredited by the publication of DuBois-Poulsen's book in 1952.\textsuperscript{38} Many of the problems of color perimetry appear to have been related to the reliable isolation and control of chromatic and luminance parameters of the presenting stimuli. The biggest problem, however, may have been the lack of a clear and common purpose for the use of color to define the visual field. In many cases the color target acted only as a reduced luminance test target; in other instances patients were required to name the color as it moved through the visual field. Beginning in the mid-1970s color has been used for a quite different purpose in perimetry. Modern color perimetry manipulates color in an attempt to isolate detection by different underlying vision mechanisms.\textsuperscript{39-46} Most of these approaches have attempted to isolate each of the three cone mechanisms in the visual field measurement. It is along these lines that we suggest that perimetry for the SWS cone mechanism may be most useful in early glaucoma detection. The conditions we use, a deep blue test target against a bright yellow background, were specifically designed to isolate visual detection by the SWS cones.

There have been at least four recent studies that have used colored test lights in testing the visual fields of glaucoma patients, including the use of blue test spots.\textsuperscript{47-50} Two reports\textsuperscript{47,48} provide preliminary evidence for blue test stimuli being more useful than white stimuli in glaucoma visual field testing. In particular, a case report for a woman with chronic open angle glaucoma shows that, with white stimuli, the abnormality is of the order of 0.4 log units while with a blue stimulus the abnormality is of the order of 1.0 log units. In a more extensive study, Logan and Anderson\textsuperscript{49} tested 60 eyes and concluded that the blue stimulus was not more sensitive in detecting glaucomatous defects than the white stimulus. However, the white background light levels that they used were too low to isolate SWS cones with the blue test stimulus. Consequently, the test target was probably detected by other cone types (LWS and/or MWS) which, from our results, would not be expected to show any selective sensitivity loss when compared to white or yellow test stimuli. In the fourth study of early glaucomatous cases, using a color campimeter, Abe et al\textsuperscript{50} found greater reduction in sensitivity in the Bjerrum area for the "blue-sensitive" mechanism than for the "red- or green-sensitive" mechanisms or for a white stimulus.

The selective vulnerability of the SWS cone pathways in glaucoma has been suggested by four pre-
vius studies and a similar loss has been reported for some ocular hypertensives in two of these studies. These latter studies also revealed loss of sensitivity to fast-flickering stimuli at the fovea for both glaucoma and ocular hypertensive patients. A growing body of physiological evidence from both human and primate studies may help explain this selective loss of the SWS pathways and pathways which carry high temporal and low spatial frequency signals.

Color signals appear to be carried in two separate parallel pathways with origins in the retina of the primate visual system; one carries signals relaying blue and yellow and the other relays signals for red and green. The red-green cells may also carry achromatic information, multiplexed with the red-green color information. The axons of the ganglion cells of both these pathways, which project to the parvocellular layers of the lateral geniculate nucleus, are smaller than those carrying the signals to the magnocellular layers. The SWS cones appear to send signals only to the chromatic pathways and provide little or no basis for everyday vision of high resolution objects (visual acuity) or brightness contrast detection. Instead, they appear to provide important signals to the blue-yellow color pathway. There is some evidence, based on relative somata size, conduction latencies and receptive field sizes for macaque monkey retinal ganglion cells at comparable retinal eccentricities, that SWS cones send signals to larger axons than those processing red-green information. These observations and the more recent observations by Quigley et al that there is a sequential loss of large, medium and then small axons, when glaucoma was experimentally induced in the monkey retina by chronically raised intraocular pressure, may help explain our results and those of earlier studies. (It has been known for some time that large nerve fibers are more susceptible than small fibers to increased pressure, and this has recently been used to selectively block the larger Y optic nerve fibers in the cat. The loss of sensitivity to high frequency flicker (thought to be mediated by the largest ganglion cell axons to the magnocellular layers) and the selective loss of sensitivity to blue light for the chromatic pathways (carried by the larger of the axons to the parvocellular layers), with relative sparing of the chromatic pathways for red and green light (carried by the smallest axons to the parvocellular layers), is consistent with the sequential loss of large to small axons in the monkey retina.

Studies of other vision functions in glaucoma patients are also consistent with the sequential loss of the larger axons. For example, studies in which grating test targets were used to measure visual fields have shown that this approach reveals defects not apparent from conventional field and acuity testing. These visual field defects were revealed using low spatial frequency targets which were flickered at moderate flicker rates. Such test conditions are ideally suited for "isolating" pathways involving larger axons to the magnocellular layers of the lateral geniculate nucleus. Also related is the growing body of evidence that the pattern ERG is reduced in ocular hypertension and glaucoma while the flash ERG is unaffected. This result has been confirmed recently in a study of experimental glaucoma in monkeys. Of significance is the fact that the pattern ERG amplitude was particularly reduced for low spatial frequency patterns; Marx et al suggest that this dysfunction may be associated with Y ganglion cells whose larger fibers terminate in the magnocellular layers of the lateral geniculate nucleus. Finally, Drum et al have shown relative elevation of diffuse scotopic perimetric thresholds, compared to photopic thresholds, in both glaucoma and ocular hypertensive patients and they cite evidence that this is consistent with selective vulnerability of large ganglion cells.

Together, the studies of color, scotopic perimetric thresholds, contrast sensitivity for low spatial frequencies, and fast flicker detection are consistent with the selective and progressive loss of the larger to smaller axons of retinal ganglion cells. Whether this results from direct pressure at the optic nerve head and/or the retina, or from a pressure-related ischemia at the optic nerve head producing axon death, is unclear.

Key words: glaucoma, ocular hypertension, visual fields, SWS cone sensitivity

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References


