The Stiles-Crawford effect in retinitis pigmentosa

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Stiles-Crawford functions were obtained from the maculas of 22 patients with different genetic types of retinitis pigmentosa and visual acuity of 20/40 or better. Reduced cone directional sensitivity was seen in the fovea with both focal cone electroretinographic testing and psychophysical testing. Functions from the parafovea determined with psychophysical testing showed either significant flattening or displaced peak locations. Results are discussed in terms of factors known to affect photoreceptor orientation and histologic findings in retinitis pigmentosa. (Invest Ophthalmol Vis Sci 22:157-164, 1982.)

Key words: retinitis pigmentosa, Stiles-Crawford, electroretinography, retina, macula, photoreceptor orientation, retinal degeneration, cone, fovea

In all vertebrate species that have been studied to date, photoreceptors exhibit a graded change in alignment across the retina such that light entering the center of the pupil is approximately co-axial with the inner and outer segments. In addition, individual photoreceptors act as light guides or fiber optic elements and are selective for incoming light from a narrow range of angles of incidence. This anterior pointing in conjunction with the limiting apertures of individual receptors results in maximal sensitivity to light entering the center of the pupil and reduced sensitivity to eccentric pupil entry positions. The relative insensitivity to obliquely incident light serves to minimize the effects of spherical and chromatic aberrations of the eye and to maximize image contrast and visual resolution.

The alignment of photoreceptors with the pupil center and the optical properties of individual photoreceptors in the human retina can be inferred from measurements of the Stiles-Crawford effect. Recent studies of the Stiles-Crawford effect in disease have shown a general correspondence between the degree of directional sensitivity and the quality of visual resolution. For example, serous elevations and detachments of the neurosensory retina, which disrupt normal alignment and structure of photoreceptors in the macula, lead to reductions in both directional sensitivity and visual acuity. Furthermore, improvements in both directional sensitivity and acuity follow a similar time course after surgical reattachment of the retina and after laser treatment or spontaneous remission of serous leaks in central serous chorioidopathy.

The Stiles-Crawford effect in patients with hereditary retinitis pigmentosa has not previously been reported. However, the associ-
ation between reduced directional sensitivity and decreased visual acuity in other diseases raises the possibility that reduced directional sensitivity occurs in conjunction with decreased acuity in patients with retinitis pigmentosa. Furthermore, limited ultrastructural studies of donor eyes from patients with reduced visual acuity have shown that the remaining photoreceptors in the macula are cones with widened and shortened inner and outer segments. In the present study, Stiles-Crawford functions were obtained as measures of foveal and parafoveal cone directional sensitivity in patients with acuity of 20/40 or better.

Methods

Cone directional sensitivity in the macula was assessed with the Stiles-Crawford technique by means of a two-channel Maxwellian-view optical system. One channel was used to present a test stimulus flickering (10% duty cycle) at 30 Hz (i.e., above the rod fusion frequency) and contained a long wavelength pass filter (cut-on = 620 nm) and a cross-rotating balanced Inconel-coated neutral density wedge. Stimulus diameter was determined by a field stop that could be varied in position to minimize blur at the retina (Badal optometer). The final objective lens produced a 0.6 mm image of the aperture stop in the plane of the pupil. The second channel was used to present a fixation target. In addition, an auxiliary optical channel with an infrared image intensifier was used for continuous observation of the position of the entrance pupil (dilated with 1% cyclopentolate hydrochloride and 10% phenylephrine hydrochloride) relative to a calibrated reticle. The patient's head was held firmly in place on a moveable bite bar/headrest assembly. The entry position of the test beam in the pupil was varied in the horizontal midline by translating the head horizontally in 1 mm steps (± 0.1 mm).

Stiles-Crawford functions were derived from electoretinograph (ERG) responses from the fovea. Responses were monitored with a bipolar contact-lens electrode placed on the topically anesthetized cornea, differentially amplified, band-passed, and summed with a signal averaging computer. The computer contained an artifact reject buffer to eliminate deflections greater than 5 μV (presumably caused by eye movements). The responses were elicited by a 3.2 log troland stimulus. Pilot studies with this retinal illuminance in normal observers showed that there was little if any stray light contribution to the response. For example, amplitudes in the fovea were about 1.0 μV and decreased with increasing eccentricity to less than 0.1 μV at 5° from the fovea. Responses were nondetectable when the stimulus was placed on the optic disc. Pilot studies also showed that a 4° stimulus diameter was the smallest diameter that produced reliable focal ERG responses. Responses were obtained from seven to nine pupil entry positions in the horizontal meridian. Repeated measurements were obtained at the central entry position. Amplitudes were converted into equivalent sensitivity values through a retinal illuminance vs. amplitude function obtained for the central entry position.

Stiles-Crawford functions were also obtained with a psychophysical procedure in the fovea and parafovea (5° eccentricity) to investigate possible regional differences in directional sensitivity in retinitis pigmentosa. A test stimulus diameter of 4° was used for these measurements to facilitate direct comparisons to the foveal ERG results. Functions were also obtained with a smaller (2°) stimulus in five patients. A flicker-threshold technique was used, whereby the patient increased the retinal illuminance of the stimulus from a level at which it appeared steady to a level of just-detectable flicker. Several settings were determined at each pupil entry position to obtain a mean value, with repeated checks for stability of criteria at the central entry position.

For both ERG and psychophysical determinations, sensitivity (1/threshold) was plotted for each pupil entry position. A parabola was fitted (least-squares criterion) to sensitivity values for pupil entry positions within 3 mm from peak sensitivity by the formula

$$\eta = \eta_{\text{max}} 10^{-pr^2}$$

where $\eta$ is sensitivity in trolands$^{-1}$, $\eta_{\text{max}}$ is peak sensitivity, $r$ is displacement in millimeters of the beam from the pupil position giving peak sensitivity, and $\rho$ (rho) is a scalar denoting the steepness of the curve. Since a shift of 1 mm in the entrance pupil corresponds approximately to a change of 2.5° in angle of incidence on the retina, $\rho$ is then an index of directional sensitivity and the higher the value, the greater the directionality. For data from patients with peak sensitivity displaced more than 1 mm from the pupil center, parabolas were not fitted because the functions were asymmetrical.
The Stiles-Crawford effect was measured in 22 patients (ages 14 to 34 years) with different genetic types of retinitis pigmentosa, best-corrected visual acuity of 20/40 or better, and stable central fixation. All patients had clear media on slit-lamp examination. None had scotomas in the region of testing as determined on the Goldmann perimeter (V-4e white test light). Some patients had a granular appearance to the macula and/or a high macular reflex, but none had cystoid macula edema on ophthalmoscopic examination. All patients had spherical equivalents of less than 5.5 diopters of myopia. None of the patients had a hereditary protan deficiency (Farnsworth D-15 panel). Seven observers (age range 20 to 35) with at least 20/20 acuity (O.U.), normal color vision, clear media, normal fundi, and 5 or less diopters of myopia served as controls.

**Results**

Representative results from ERG testing in a normal observer are shown in Fig. 1. Focal cone ERG amplitudes were greatest in response to light entering near the center of the entrance pupil and were reduced by a factor of approximately 4 to light entering near the edge of the pupil. Fig. 1 also shows the retinal illuminance vs. amplitude function obtained for light entering the center of the pupil. The best-fit equation was determined by a least-squared error criterion.
Fig. 2. Mean Stiles-Crawford functions from the fovea in seven normal observers and from the parafovea in five normal observers. Vertical bars represent ± 1 S.E.M.

From this equation, amplitudes obtained at each pupil entry position were converted into equivalent log troland values and plotted as sensitivity (1/log trolands) vs. pupil entry position. For comparison, the psychophysical determination of the Stiles-Crawford function is also included. The particular criterion used to derive the ERG sensitivity values in normals led to peak sensitivity values that were, on the average, 0.9 log unit below the sensitivity values derived from psychophysical determinations. To facilitate comparisons between the two techniques, the ERG sensitivity values have been shifted 0.9 log unit vertically in this and all succeeding figures.

Mean cone directional sensitivity ($\tilde{p}$) functions for normal observers in the fovea and parafovea (5° temporal retina) are shown in Fig. 2. Psychophysical and ERG testing gave similar results in the fovea, with $\tilde{p}$ equaling 0.050 and 0.051, respectively. In the parafovea $\tilde{p}$ was 0.059, and this value was significantly greater than the foveal values ($p \leq 0.05$).

Results from ERG testing in a patient with retinitis pigmentosa are shown in Fig. 3. In comparison to those of a normal observer, ERG amplitudes from this patient showed less variation with pupil entry position. Amplitudes and implicit times were within the normal range for light entering the center of the pupil but amplitudes decreased only slightly to light entering near the edge of the pupil. Fig. 3 also contains the retinal illumination vs. amplitude function for this patient and the derived log sensitivity values for each pupil entry position. The psychophysical determination of the Stiles-Crawford function is also included.

The results of Stiles-Crawford testing in the foveas of all patients with retinitis pigmentosa are listed in Table I. Five patients were tested on more than one occasion, and seven patients were tested with both psychophysical and ERG procedures. Rho values determined from psychophysical (2° or 4° stimulus) and ERG (4° stimulus) functions were in close agreement, with a mean difference of less than 0.01. Table I also includes Snellen acuity measures obtained on the same day for the eye that was tested and log sensitivity values (relative to the mean normal sensitivity [see Fig. 2]) at the peak of the foveal Stiles-Crawford function. Snellen acu-
Stiles-Crawford effect in RP

Fig. 3. Stiles-Crawford effect in the focal cone ERG of a patient with dominant retinitis pigmentosa. Top, Computer-averaged responses obtained from the fovea with eight pupil entry positions. Bottom left, Retinal illuminance vs. amplitude function for central entry. Bottom right, Derived ERG Stiles-Crawford function (solid circles) and psychophysical Stiles-Crawford function (solid curve). ERG sensitivity values have been raised 0.9 log unit vertically.

ity is correlated with directional sensitivity (\(\rho\)) in the fovea (Spearman’s rank correlation coefficient = 0.60, \(p \leq 0.005\)) and with peak sensitivity (Spearman’s rank correlation coefficient = 0.42, \(p \leq 0.025\)). However, no significant correlation exists between directional sensitivity and peak sensitivity (Spearman’s rank correlation coefficient = 0.02, not significant). There was no obvious relationship between rho and the appearance of the macula.

Representative foveal Stiles-Crawford functions from patients are shown in Fig. 4. For purposes of comparisons, the normal directional sensitivity function (\(\rho = 0.05\)) is also included. Peak sensitivity values for the patient data lying below the vertical bar at the peak of the normal function have a probability of less than 5% of being normal. Some patients showed normal directional sensitivity with either normal or reduced peak sensitivity (Fig. 4, A). Other patients showed reduced directional sensitivity, again with either normal or reduced peak sensitivity (Fig. 4, B). Normal directional with reduced peak sensitivity (e.g., Patient 2401) and reduced directional with normal peak sen-
sitivity (e.g., Patient 1588) were found with both psychophysical and ERG testing. All patients with measurable directionality were most sensitive to light entering within 1 mm of the pupil center.

Thirteen patients were also tested in the parafovea. Four patients showed a large displacement (>1.0 mm) in the peak of the Stiles-Crawford function. The remaining patients showed no evidence of directional sensitivity. Representative functions are shown in Fig. 5. Abnormal directional sensitivity in the parafovea was observed with or without losses in peak sensitivity.

Discussion

The results of this study indicate that most patients with different genetic types of retinitis pigmentosa and slightly reduced visual acuity have reduced directional sensitivity and/or reduced peak sensitivity in the fovea. The ERG is a summed response from cones within the test area, and the responses demonstrate that both reduced directional sensitivity and reduced peak sensitivity in these patients are caused by abnormal function in the distal retina. Furthermore, a close correspondence was found between ERG and psychophysical measurements of the Stiles-Crawford effect in normal observers (see also refs. 14 and 15) and in patients. This correspondence would not have been found in patients if the psychophysical threshold response were mediated by a small subset of highly directional cones. Thus the agreement between the results obtained with the two procedures suggests that each samples the average directional sensitivity of cones within the test area.

Despite the use of a relatively large (4°) test stimulus, significant correlations were found between visual acuity and directional sen-
Table I. Ocular findings in patients with retinitis pigmentosa

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Snellen acuity</th>
<th>Genetic type</th>
<th>Rho&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Peak cone sensitivity&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Macular appearance</th>
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<td>0.1&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Normal</td>
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<td>0.5</td>
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<td>0.000&lt;sup&gt;0&lt;/sup&gt;</td>
<td>0.1&lt;sup&gt;0&lt;/sup&gt;</td>
<td>High reflex</td>
</tr>
<tr>
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<td>20/25</td>
<td>X-linked</td>
<td>0.027</td>
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<td>Normal</td>
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<tr>
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<tr>
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<td>X-linked</td>
<td>0.000</td>
<td>2.4</td>
<td>Granular</td>
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</tbody>
</table>

<sup>a</sup>Patient identification in the data bank of the Berman-Gund Laboratory.

<sup>b</sup>Values of directional sensitivity from foveal Stiles-Crawford functions.

<sup>c</sup>Log unit decreases from normal mean peak sensitivity in the fovea.

<sup>d</sup>Test stimulus diameter 2° (all other measurements were obtained with a 4° stimulus).

Sensitivity and between visual acuity and peak sensitivity. These correlations are consistent with previous suggestions that acuity losses may be associated with increases in absorbance of stray light and/or light leakage between adjacent cones and with losses of cones and/or shortened cone outer segments. However, these associations should be viewed with caution, since the Stiles-Crawford testing involved a larger retinal area than that generally needed to make a resolution judgment; that is, a subset of sensitive and highly directional cones could mediate fine resolution judgments. Additional testing with small (minutes of arc) test stimuli could help to determine whether local variations in directional sensitivity exist within the fovea in patients with retinitis pigmentosa.

Some patients with retinitis pigmentosa retained normal directional sensitivity despite greater than 10-fold reductions in peak sensitivity. Reduced peak sensitivity presumably reflects a decrease in the amount of cone photopigment in the macula due either to reduced numbers of cones or to reduced cone outer segment length—structural changes that have been reported in moderately advanced retinitis pigmentosa. Other patients with retinitis pigmentosa showed reduced directional sensitivity. Normal peak sensitivity precludes substantial reductions in the amount of cone photopigment in the macula. These results suggest that reduced directional sensitivity is not simply caused by a decrease in the amount of cone photopigment in these patients. Furthermore, previous results from normal observers have shown that directional sensitivity is actually increased slightly by a reduction in the amount of unbleached photopigment during the initial stages of dark adaptation or by intense background illumination.

All patients tested in both locations had higher directional sensitivity in the fovea than that in the parafovea, a variation opposite to that seen in normal observers. This result makes it unlikely that reduced directional sensitivity in these patients is caused by changes in the properties of the ocular media that were not visible on a rou-
tine ocular examination; if changes in the media were significant, all areas should have been comparably affected. The most likely explanations for reduced directional sensitivity in these patients involve changes in the alignment of macular cones and/or changes in the structure of individual cones. Further research will be necessary to evaluate these two alternatives and to determine whether these reductions in directional sensitivity reflect primary changes within macular cones or secondary changes in the shape and/or alignment of macular cones after rod photoreceptor death.

REFERENCES