Electrophysiological and Psychophysical Flicker Sensitivity in Patients with Primary Open-Angle Glaucoma and Ocular Hypertension

Karen Holopigian, William Seiple, Charles Mayron, Richard Kory, and Monica Lorenzo

Temporal sensitivity was assessed in patients with primary open-angle glaucoma (POAG) and ocular hypertension (OHT). Three measures of flicker sensitivity were obtained: psychophysical modulation thresholds, visual-evoked potentials (VEPs), and focal electroretinograms (FERGs). We found elevated psychophysical thresholds at higher temporal frequencies (30–50 Hz) in patients with POAG, relative to thresholds for age-matched controls. The OHT patients had elevated psychophysical thresholds only at 50 Hz. On the other hand, VEP amplitudes in POAG patients were reduced at all temporal frequencies, with the magnitude of the loss increasing with temporal frequency. The OHT patients, however, showed no reductions in VEP amplitude at any temporal frequency. Finally, POAG patients’ FERG amplitudes were reduced at 30–50 Hz; whereas FERG amplitudes in the OHT patients were normal at all temporal frequencies. These results indicate that OHT patients can exhibit psychophysical threshold losses at high temporal frequencies which are not observed in the suprathreshold electrophysiological amplitude measures. On the other hand, patients with POAG show both psychophysical and VEP losses across a range of temporal frequencies. In addition, the decreases in FERG amplitudes in POAG patients suggest changes in the functioning of the outer retina in this disease. Invest Ophthalmol Vis Sci 31:1863–1868, 1990

Patients with primary open-angle glaucoma (POAG) have characteristic visual abnormalities. Along with elevated intraocular pressures, POAG is typically accompanied by optic disc cupping and visual field losses. These visual losses have been traditionally thought to be caused by damage to the optic nerve fibers from elevated intraocular pressure. However, these standard measures of visual loss in glaucoma may not be very sensitive; that is, by the time visual field and optic disc cupping are clinically detectable in a patient, a significant percentage of the optic nerve fibers may already be damaged. As a result, researchers are searching for more sensitive measures of optic nerve damage in POAG and also for reliable predictors of progression in patients with ocular hypertension (OHT) (patients with elevated intraocular pressures but no signs of glaucomatous damage). One sensitive measure to detect changes in both glaucoma and OHT patients is psychophysically determined pattern contrast sensitivity. Contrast sensitivity losses have been shown for both stationary and flickering targets, although these losses are more pronounced for flickering targets. In general, the magnitude of these deficits increases with increasing temporal frequency. These temporal frequency-dependent losses have been attributed to a selective loss of large ganglion cell fibers, as shown histologically in POAG by Quigley et al. These large ganglion cell fibers are believed to be important for the detection of rapidly flickering patterns.

We attempted to localize the site(s) of these temporal frequency losses further using psychophysical and electrophysiological measures. Psychophysical modulation thresholds and visual-evoked potential (VEP) amplitudes were examined to determine the amount of loss attributable to optic nerve deficits. Focal electroretinographic (FERG) amplitudes were examined to determine the status of the outer retina in patients with OHT and POAG. It was expected that FERG amplitudes would be normal since the outer retina was thought to be unaffected by these diseases.

Materials and Methods

Subjects

Thirteen patients with POAG, 11 patients with OHT, and 10 control patients with normal intraocular...
The mean age of this patient group was 66.8 ± 10.1 yr. The POAG patients had characteristic visual field

tuations, participated in this experiment. All patients
gave their informed consent to participate.

The POAG patients had characteristic visual field
losses, cup:disc ratios greater than 0.5, asymmetric
cupping, or some combination of these. The mean
age of this patient group was 66.8 ± 10.1 yr.

The OHT patients' intraocular pressures were > 22
mm Hg on two separate ophthalmologic examina-
tions. However, these patients had normal visual
fields (Goldmann perimetry), symmetric discs, nor-
al retinal nerve fiber layers, and cup:disc ratios
≤ 0.5. Their average age was 63.7 ± 9.7 yr.

The control subjects had intraocular pressures < 22
mm Hg, normal Snellen acuity, normal visual fields,
and no ocular or neurologic problems. They were
age-matched to the OHT and POAG patients (mean
age of controls, 61.6 ± 13.8).

Table 1. Observer characteristics—POAGs

<table>
<thead>
<tr>
<th>Obs</th>
<th>Eye</th>
<th>Sex</th>
<th>Age</th>
<th>T_a</th>
<th>C/D</th>
<th>VA</th>
<th>%CFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>JB</td>
<td>OD</td>
<td>M</td>
<td>68</td>
<td>21.12</td>
<td>0.90</td>
<td>20/50</td>
<td>Superior arcuate and parafoveolar scot* 75%</td>
</tr>
<tr>
<td>JD</td>
<td>OD</td>
<td>M</td>
<td>88</td>
<td>22.15</td>
<td>0.40</td>
<td>20/50</td>
<td>Altitudinal defect*</td>
</tr>
<tr>
<td>JK</td>
<td>OD</td>
<td>M</td>
<td>68</td>
<td>19.16</td>
<td>0.75/0.80</td>
<td>20/20</td>
<td>Full</td>
</tr>
<tr>
<td>WL</td>
<td>OD</td>
<td>M</td>
<td>69</td>
<td>22.26</td>
<td>0.50</td>
<td>20/15</td>
<td>Arcuate and parafoveolar scot*</td>
</tr>
<tr>
<td>FM</td>
<td>OD</td>
<td>M</td>
<td>60</td>
<td>15.18</td>
<td>0.50/0.40</td>
<td>20/70</td>
<td>General constriction* 33%</td>
</tr>
<tr>
<td>JN</td>
<td>OS</td>
<td>M</td>
<td>63</td>
<td>20.16</td>
<td>0.60/0.70</td>
<td>20/25</td>
<td>Superior nasal step</td>
</tr>
<tr>
<td>JR</td>
<td>OD</td>
<td>M</td>
<td>62</td>
<td>15.16</td>
<td>0.60/0.50</td>
<td>20/20</td>
<td>Inferior nasal arcuate scot* 50%</td>
</tr>
<tr>
<td>AE</td>
<td>OS</td>
<td>M</td>
<td>69</td>
<td>16.24</td>
<td>0.90/0.75</td>
<td>20/30</td>
<td>Nasal step parafoveolar scot 75%</td>
</tr>
<tr>
<td>GC</td>
<td>OD</td>
<td>M</td>
<td>62</td>
<td>17.23</td>
<td>0.40</td>
<td>20/20</td>
<td>Paracentral and nasal step 50%</td>
</tr>
<tr>
<td>AB</td>
<td>OD</td>
<td>M</td>
<td>68</td>
<td>16.20</td>
<td>0.90/0.85</td>
<td>20/50</td>
<td>Paracentral &amp; arc blind spot baring 33%</td>
</tr>
<tr>
<td>WH</td>
<td>OD</td>
<td>M</td>
<td>78</td>
<td>17.20</td>
<td>0.70/0.50</td>
<td>20/25</td>
<td>Paracentral scot 25%</td>
</tr>
<tr>
<td>JS</td>
<td>OS</td>
<td>F</td>
<td>44</td>
<td>16.26</td>
<td>0.50/0.40</td>
<td>20/20</td>
<td>Nasal step</td>
</tr>
<tr>
<td>JT</td>
<td>OD</td>
<td>M</td>
<td>70</td>
<td>12.24</td>
<td>0.80/0.70</td>
<td>20/25</td>
<td>Nasal step arcuate defect</td>
</tr>
</tbody>
</table>

Mean age = 66.8. SD = 10.1.

Abbreviations: T_a = intraocular pressure in mmHg (on two separate visits); C/D = cup to disc ratio (vertical or vertical/horizontal); VA = best corrected Snellen acuity; VF = Goldmann visual field (H4 unless otherwise indicated); %CFL = percent of the central 9° affected.

* Goldmann IV4c.
† Goldmann IV4c.
‡ Goldmann IV4c.

All subjects in this study were referred by an oph-
thalmologist after a complete ocular examination.
Their visual characteristics are given in Tables 1–3.

Apparatus

The stimulus in these experiments was a circular
display of 96 tightly clustered red light-emitting
diodes (LEDs: average luminance, 40 cd/m²) sur-
rounded by an illuminated ganzfeld background of
90 cd/m². A ground glass placed in front of the LEDs
diffused the light so that it appeared as a uniform
circle of red light subtending 9° at the eye. The LED
stimulus was sinusoidally modulated at temporal fre-
frequencies between 10 and 50 Hz. For the psychophys-
ical threshold experiments, modulation depth of the
LEDs was independently manipulated using a hand-
held potentiometer. For the electrophysiological ex-
periments, modulation depth was constant at 100%.

Table 2. Observer characteristics—OHTs

<table>
<thead>
<tr>
<th>Obs</th>
<th>Eye</th>
<th>Sex</th>
<th>Age</th>
<th>T_a</th>
<th>C/D</th>
<th>VA</th>
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<tr>
<td>MS</td>
<td>OD</td>
<td>M</td>
<td>71</td>
<td>22.24</td>
<td>0.20</td>
<td>20/25</td>
</tr>
<tr>
<td>MV</td>
<td>OD</td>
<td>F</td>
<td>58</td>
<td>20.26</td>
<td>0.25</td>
<td>20/25</td>
</tr>
<tr>
<td>GW</td>
<td>OD</td>
<td>F</td>
<td>49</td>
<td>26.22</td>
<td>0.30/0.20</td>
<td>20/30</td>
</tr>
<tr>
<td>FR</td>
<td>OD</td>
<td>M</td>
<td>55</td>
<td>16.25</td>
<td>0.30</td>
<td>20/25</td>
</tr>
<tr>
<td>CM</td>
<td>OD</td>
<td>M</td>
<td>67</td>
<td>30.22</td>
<td>0.40</td>
<td>20/20</td>
</tr>
<tr>
<td>MG</td>
<td>OS</td>
<td>M</td>
<td>73</td>
<td>20.30</td>
<td>0.30</td>
<td>20/30</td>
</tr>
<tr>
<td>MP</td>
<td>OD</td>
<td>F</td>
<td>79</td>
<td>19.22</td>
<td>0.20</td>
<td>20/30</td>
</tr>
<tr>
<td>JM</td>
<td>OD</td>
<td>M</td>
<td>58</td>
<td>18.26</td>
<td>0.30</td>
<td>20/25</td>
</tr>
<tr>
<td>CO</td>
<td>OS</td>
<td>M</td>
<td>59</td>
<td>26.22</td>
<td>0.30/0.35</td>
<td>20/25</td>
</tr>
<tr>
<td>JC</td>
<td>OD</td>
<td>M</td>
<td>75</td>
<td>18.26</td>
<td>0.50</td>
<td>20/20</td>
</tr>
<tr>
<td>PPF</td>
<td>OD</td>
<td>F</td>
<td>57</td>
<td>22.22</td>
<td>0.25</td>
<td>20/20</td>
</tr>
</tbody>
</table>

Mean age = 63.7. SD = 9.7.

Abbreviations: T_a = intraocular pressure in mmHg (on two separate visits); C/D = cup to disc ratio (vertical or vertical/horizontal); VA = best corrected Snellen acuity.

Table 3. Observer characteristics—controls

<table>
<thead>
<tr>
<th>Obs</th>
<th>Eye</th>
<th>Sex</th>
<th>Age</th>
<th>T_a</th>
<th>C/D</th>
<th>VA</th>
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</thead>
<tbody>
<tr>
<td>AB</td>
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<td>M</td>
<td>74</td>
<td>16</td>
<td>0.30</td>
<td>20/20</td>
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<tr>
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<td>OD</td>
<td>F</td>
<td>39</td>
<td>10</td>
<td>0.30</td>
<td>20/20</td>
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<tr>
<td>CC</td>
<td>OD</td>
<td>F</td>
<td>41</td>
<td>12</td>
<td>0.20</td>
<td>20/20</td>
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<tr>
<td>MC</td>
<td>OS</td>
<td>F</td>
<td>73</td>
<td>18</td>
<td>0.40</td>
<td>20/20</td>
</tr>
<tr>
<td>AR</td>
<td>OD</td>
<td>F</td>
<td>60</td>
<td>17</td>
<td>0.20</td>
<td>20/25</td>
</tr>
<tr>
<td>MG</td>
<td>OD</td>
<td>F</td>
<td>49</td>
<td>18</td>
<td>0.30</td>
<td>20/20</td>
</tr>
<tr>
<td>LM</td>
<td>OS</td>
<td>F</td>
<td>74</td>
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<td>0.30</td>
<td>20/30</td>
</tr>
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<td>OD</td>
<td>F</td>
<td>65</td>
<td>16</td>
<td>0.30</td>
<td>20/25</td>
</tr>
<tr>
<td>MB</td>
<td>OD</td>
<td>M</td>
<td>71</td>
<td>16</td>
<td>0.30</td>
<td>20/20</td>
</tr>
<tr>
<td>MP</td>
<td>OD</td>
<td>F</td>
<td>70</td>
<td>16</td>
<td>0.30</td>
<td>20/25</td>
</tr>
</tbody>
</table>

Mean age = 61.6. SD = 13.8.

Abbreviations: T_a = intraocular pressure in mmHg; C/D = cup to disc ratio (vertical or vertical/horizontal); VA = best corrected Snellen acuity.
Procedure

Before visual testing, the subject's pupils were dilated with 1% tropicamide and 2.5% phenylephrine. Any patient with a pupil diameter smaller than 5 mm after dilation was excluded from the study. The POAG patients who were receiving pilocarpine hydrochloride on a daily basis were requested to discontinue the drug for 2 days before the study and to resume it immediately after participation. All measurements were made monocularly, with the contralateral eye patched. The stimulus was centrally fixated for all experiments.

Psychophysical flicker thresholds for sinusoidally modulated stimuli as a function of temporal frequency were measured first. The threshold for flicker was measured by manually adjusting the modulation voltage from below threshold to a level where the observer could just detect the flicker. Four threshold estimates were averaged for each temporal frequency.

After this, FERGs and VEPs were measured simultaneously with the LEDs modulated at 100%. The FERGs were recorded with a gold-foil electrode placed over the canthus of the tested eye. The ipsilateral ear served as a reference and the contralateral ear as a ground. The VEPs were recorded using a gold-cup electrode (Grass, Quincy, MA) placed 2.5 cm above the inion at the center of the midline. Each electrophysiological measure was amplified 10,000× and bandpass filtered (Grass preamplifier, Model P511J) so that no amplitude attenuation occurred at the frequency of stimulation. These measures were independently averaged (n = 128) with artifact reject on a Nicolet 1130B (Madison, WI).

Results

Figure 1 shows the mean (±one standard error) of psychophysical flicker modulation sensitivities (/threshold) for each group as a function of temporal frequency. The normal subjects showed a characteristic temporal modulation transfer function (MTF). The greatest sensitivity for normals occurred at 10 Hz with a sharp high frequency fall-off. The shape of the MTF for the OHT and POAG patients was similar to that of the controls, except for a steeper fall-off at the higher temporal frequencies. An analysis of variance on these psychophysical data indicated a significant effect for temporal frequency (F(3,107) = 99.2, P < 0.001). There were no significant effects for group nor was the group by temporal-frequency interaction significant.

Figure 2 shows the mean (± one standard error) VEP amplitudes as a function of temporal frequency for the three groups of subjects. For all groups, the amplitude versus temporal-frequency response functions were broadly low-pass tuned, with amplitude decreasing as a function of temporal frequency. The amplitudes for the OHT patients were comparable to the amplitudes for the controls, but the POAG patients showed reductions in amplitude, especially at the higher temporal frequencies. An analysis of variance indicated a significant main effect for group (F(2,87) = 6.8, P < 0.005) and for temporal frequency (F(3,87) = 11.4, P < 0.001). The interaction of group and temporal frequency was not statistically significant.

Figure 3 shows the mean (± one standard error) of FERG amplitude data as a function of temporal frequency. The response functions for the control subjects are narrowly bandpass in shape, with the largest
amplitudes at 30 Hz. The shapes of these functions are consistent with the FERG amplitude functions previously collected in our laboratory for normal observers.\(^{14}\) The shape of the OHT patients' averaged response function was similar to the controls, but the amplitudes were slightly reduced. The data for the POAG patients showed increasing losses at the higher temporal frequencies. An analysis of variance indicated significant main effects for group (F(2,105) = 10.7, \(P < 0.001\)) and for temporal frequency (F(3,105) = 6.6, \(P < 0.001\)). There was no statistically significant interaction.

To present the data more clearly, the results from Figures 1–3 were converted into percent change values and plotted as visuograms. In Figures 4–6 the 0% change line represents the mean data for the controls for each temporal frequency. Patient data equal to that of the controls is plotted as a 0% loss. Patient data which deviates from the control data is plotted as either a negative (reductions in amplitude or sensitivity) or positive (increases in amplitude or sensitivity) percent change.

Figure 4 shows the psychophysical percent change data for the OHT and POAG patients. The OHT patients' sensitivities were normal at all temporal frequencies except 50 Hz, where a large loss in modulation thresholds was observed. The averaged data for
the POAG patients shows losses in sensitivity at all temporal frequencies above 10 Hz.

Figure 5 shows the percent change data for VEP amplitudes. The results for the OHT patients are somewhat reduced but not significantly different from normal. The POAG patients amplitudes were significantly reduced. This deficit increased with temporal frequency.

Figure 6 shows the FERG percent change data. The OHT patients showed no losses in FERG amplitude, relative to the control data. The POAG patients showed large amplitude losses, increasing at the higher temporal frequencies.

We were also interested in determining if factors such as the patients’ cup:disc ratios or Snellen acuities were correlated with their psychophysical and electrophysiological results. To determine this, a cross-correlational matrix analysis was done on the data for each patient group. This analysis provided Pearson product moment correlations (r values) for all factors entered into the matrix. The factors included were several patient characteristics (patients’ ages, intraocular pressures, cup:disc ratios, and Snellen acuities) along with the psychophysical, VEP, and FERG results at each temporal frequency (10, 30, 40 and 50 Hz).

The results indicated that there were significant correlations among the different measures of flicker sensitivity, as expected. For example, FERG amplitudes at 30 Hz were significantly correlated with FERG amplitudes at 40 Hz. The observer characteristics such as cup:disc ratios, however, did not correlate highly with the experimental data. For the patients, none of the four observer characteristics (patients’ ages, intraocular pressures, cup:disc ratios, and Snellen acuities) were significantly correlated with any psychophysical or electrophysiological measure of flicker sensitivity.

Discussion

The pattern contrast sensitivity of glaucoma and OHT patients has been examined by numerous investigators.2,3 Psychophysically measured contrast threshold deficits for stationary gratings were reported primarily for intermediate spatial frequencies in OAG and OHT patients.6,15 Later findings demonstrated that these losses were more pronounced for flickering pattern targets.4,16 Morency et al7 have recently shown that as the temporal frequency of the stimulus was increased, contrast threshold impairment also increased in both OAG and OHT patients. These authors found that the highest temporal frequency they tested (25 Hz) was the most sensitive for assaying contrast sensitivity loss. This pattern of contrast sensitivity loss implies that the visual subsystem which subserves sensitivity to higher temporal and lower spatial frequency stimuli9,17 may be preferentially affected. This hypothesis is further supported by the findings of a relatively greater loss of large retinal ganglion cells in OAG.8

We examined temporal-frequency sensitivity with a uniform (nonpatterned) stimulus. We found that both POAG and OHT patients had psychophysically measured flicker threshold losses. These deficits were more pronounced and involved lower temporal frequencies in the POAG patients. Our findings are consistent with a previous report by Tyler,2 who showed psychophysically measured high-frequency losses in POAG patients using a uniform flickering field. Tyler also reported threshold losses in OHT patients similar in magnitude to our results.

We also demonstrated electrophysiological amplitude losses at high temporal frequencies in POAG patients. The VEP amplitude losses were greatest at intermediate and high temporal frequencies. There have been previous reports of VEP amplitude losses in OAG patients for both patterned18 and unpatterned stimuli.19 These losses were always greatest at the highest temporal rate tested (eg, >13 Hz19). Using a uniform field we also found VEP amplitude deficits only at higher flicker rates (>10 Hz). These findings are similar to the high-frequency specific losses observed psychophysically.

To our knowledge, no one has examined VEP amplitude changes as a function of temporal frequency in OHT patients. Our results indicate that the averaged VEP amplitudes for the OHT patients are not significantly reduced. These patients did, however, have psychophysical threshold losses. This apparent discrepancy in results may be due to the supathreshold nature of our VEP paradigm.

We also measured FERG amplitudes to assess the integrity of the outer retina. The OHT patients showed normal FERG amplitudes at all temporal frequencies. The POAG patients, however, had reduced FERG amplitudes, especially for higher temporal-frequency stimuli. These results indicate changes in the outer retina occur in POAG. Previous studies report equivocal results concerning damage to the outer retina in glaucoma. For example, there have been reports of normal ERGs in glaucoma patients. Wagner and Persson20 compared ERG amplitudes between the two eyes in patients with unilateral glaucoma and found no ERG changes. However, this comparison may not have been valid since some of the contralateral eyes had elevated intraocular pressures. Fiorentini et al21 also found normal ERGs in OAG, but an age-matched control group was not used for comparison in this study. Johnson et al22
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reported normal ERG parameters in monkeys with laser-induced glaucoma, but it may not be appropriate to compare these results to data from humans. On the other hand, abnormal ERGs have also been reported. Henkes23 found that 40% of the ERGs in POAG patients were subnormal, and Alvis24 found that all 17 of his glaucoma patients had abnormal ERGs. Fazio et al.25 likewise, reported numerous ERG abnormalities in POAG patients. Also in support of outer retinal involvement, Mehaffey et al.26 also reported abnormal electro-oculography ratios in POAG and OHT patients. Our results support the hypothesis of outer retinal damage in glaucoma.

Although increases in intracocular pressure and cup:disc ratios have been classically used to diagnose glaucoma, none of these characteristics are significantly correlated with psychophysical or electrophysiological temporal frequency sensitivity. In addition, neither the age of the patients nor their Snellen acuities were significantly correlated with temporal responsiveness.

In summary, both the psychophysically measured flicker threshold losses and the VEP amplitude losses in both OHT and POAG patients suggest selective loss of those optic nerve fibers which mediate high temporal frequencies. Additionally, we found that FERG amplitudes are reduced at high temporal frequencies in POAG patients, suggesting involvement of the receptor layer as well.

Key words: temporal modulation, psychophysics, visual-evoked potential, focal electroretinogram, glaucoma, ocular hypertension

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References