Foveal Dysfunction and Central Visual Field Loss in Glaucoma

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Objective: To determine whether foveal function distal to the ganglion cell layer is an independent predictor of central visual field function in glaucoma.

Setting: University affiliated hospital and private practice.

Participants: Twenty-seven eyes (27 patients) with normal-pressure glaucoma, 10 eyes (10 patients) with primary open-angle glaucoma, and 47 eyes of 47 matched normal volunteers.

Intervention and Main Outcome Measures: Foveal cone electroretinogram (ERG) amplitude, relative optic cup to disc area and their relations to Humphrey full-threshold 30-2 visual field central 4-point mean total deviation (C4MTD) and pattern deviation (C4MPD).

Results: Foveal cone ERG amplitude was subnormal in 14 (37.8%) of the 37 glaucomatous eyes and lower in the glaucoma group compared with normal eyes (P < .01). The C4MTD and C4MPD were lower in glaucomatous eyes with subnormal amplitudes compared with those with normal amplitudes (P < .01 and P < .05, respectively). Amplitude was directly correlated with C4MTD (P < .01) and C4MPD (P < .01). Relative optic cup to disc area was inversely correlated with C4MTD (P < .001) and C4MPD (P < .001). Partial correlation analysis revealed that amplitude and relative optic cup to disc area were independent predictors of C4MTD and C4MPD.

Conclusion: Foveal function distal to the ganglion cell layer and optic disc cupping independently predict central visual field function in glaucoma.

OPTIC NEUROPATHY and nerve fiber layer loss have historically been considered the main if not the sole mechanism of visual field loss in glaucoma. Retinal dysfunction distal to the ganglion cell layer (GCL) has also been documented in glaucoma, but no information is available to help determine whether this dysfunction is also an underlying mechanism of visual field loss in glaucoma. That mechanisms other than optic neuropathy alone may lead to visual field loss in this disease was supported by the demonstration that total visual field loss may not be directly correlated with optic disc changes in normal pressure glaucoma (NPG). This technique has also been determined to be the most reliable tool for evaluating macular function not only in eyes with overt maculopathy but also in those with an entirely normal macular appearance on ophthalmoscopic examination, as is the case in many eyes with glaucoma. Furthermore, while the recorded foveal ERG amplitudes are reduced in many types of maculopathy, they are normal in optic neuropathy and amblyopia. We present foveal cone ERG recording data and their relation to central visual field function in eyes with NPG and POAG.

Central visual field loss is not rare among patients with NPG or primary open-angle glaucoma (POAG). In the present study, we investigated whether foveal dysfunction distal to the GCL could be an underlying mechanism of central visual field loss in glaucoma in addition to optic neuropathy. To that end we used stimulator-ophthalmoscope foveal cone electroretinography (ERG) that allows for accurate control of the retinal area tested. This technique has also been determined to be the most reliable tool for evaluating macular function not only in eyes with overt maculopathy but also in those with an entirely normal macular appearance on ophthalmoscopic examination, as is the case in many eyes with glaucoma. Furthermore, while the recorded foveal ERG amplitudes are reduced in many types of maculopathy, they are normal in optic neuropathy and amblyopia. We present foveal cone ERG recording data and their relation to central visual field function in eyes with NPG and POAG.

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We found foveal function to differ significantly between eyes of matched normal volunteers and eyes with glaucoma.
PATIENTS AND METHODS

Twenty-seven eyes of 27 patients with NPG and 10 eyes of 10 patients with POAG (age range, 39-80 [mean ± SD, 66.8 ± 8.5] years) were tested. Eyes with NPG were from patients extracted from our database and who were available for testing. Eyes with POAG were preselected based on past Humphrey visual field examinations showing reduced total or pattern deviation in one or more of the central 4 points. Inclusion criteria included the diagnosis of NPG or POAG based on the characteristic combination of optic disc cupping, progressive visual field loss, and intracocular pressure (IOP). Exclusion criteria were any of the following: media opacities or insufficient pupillary dilation precluding reliable observation of the ERG test target on the fovea by the tester throughout recording; best-corrected visual acuity less than 20/50 impeding fixation; any maculopathy or other retinopathy on ophthalmoscopic examination; previous ocular surgery; any general medical condition such as diabetes mellitus that may affect retinal function \(^2\), and family history positive for retinal or macular dystrophies.

PATIENT EVALUATION AND CLINICAL FINDINGS

Associated conditions included systemic hypertension, ischemic heart disease, and hypothyroidism in 4 patients each (10.8%), and treated pulmonary tuberculosis in 1 patient (2.7%). Ocular medications included 0.5% timolol maleate in 12 eyes (32.4%), 0.5% betaxolol hydrochloride in 11 eyes (29.7%), 0.005% latanoprost in 6 eyes (16.2%), 2% pilocarpine hydrochloride in 4 eyes (10.8%), methazolamide tablets orally and 2% dorzolamide hydrochloride drops in 3 eyes each (8.1%), 0.2% brimonidine tartrate and 1% carteolol hydrochloride in 2 eyes each (5.4%), and 0.1% dipivefrin hydrochloride in 1 eye (2.7%). Family history was positive for glaucoma in 5 patients (13.3%).

Best-corrected Snellen visual acuity was 20/20-20/50 (mean ± SD, 0.79 ± 0.20, approximately 20/25). Refractive error spherical equivalent ranged from −4.50 to +5.00 diopters (D) (mean ± SD, +0.08 ± 2.34 D). Intraocular pressure measured 10 to 27 mm Hg (mean ± SD, 14.9 ± 4.2 mm Hg). Results of detailed ophthalmoscopic examination in all 37 eyes tested revealed no notable media opacities and normal fundus appearance except for nerve fiber layer loss and abnormal optic disc cupping.

Among the 47 normal eyes, the foveal ERG mean (±SD) amplitude was 0.310 ± 0.098 µV. This is consistent with the previously published value of 0.18 µV as the lower normal limit for amplitude.9 Based on this value we determined the previously published value of 0.18 µV as the lower normal limit for amplitude.9,23 Based on this value we determined the interpretation of the ERG test target on the fovea by the tester throughout recording; best-corrected visual acuity less than 20/50 impeding fixation; any maculopathy or other retinopathy on ophthalmoscopic examination; previous ocular surgery; any general medical condition such as diabetes mellitus that may affect retinal function \(^2\), and family history positive for retinal or macular dystrophies.

RELATIVE CUP TO DISC AREA (RCDA)

Optic disc area can be calculated reliably by slitlamp biomicroscopy.22 We defined RCDA as the product of horizontal cup-disc ratio × vertical cup-disc ratio, also determined on slitlamp biomicroscopy. The RCDA is thus a relative number, not expressed in area units, and was found in our pilot studies to be better correlated with central visual field indices than either horizontal or vertical cup-disc ratio alone. In our study RCDA ranged from 0.12 to 0.81 (mean ± SD, 0.46 ± 0.20).

CENTRAL VISUAL FIELD INDICES

We performed Humphrey full-threshold 30-2 visual fields following pupillary dilation if pupillary diameter was 3 mm or less. Appropriate near correction was used in all cases. Data were collected only from visual fields that demonstrated no significant fixation losses, false negatives, or false positives. Since foveal ERG tests only the retinal central 4°, we used only the central 4 points of the visual field that are aligned on the central 3° isopter. Averaging these 4 points, we calculated central 4-point mean total deviation (C4MTD) and central 4-point mean pattern deviation (C4MPD). Based on the Humphrey field analyzer database, C4MTD represents the age-corrected total deviation from normal of data collected from the central 4 points of the visual field, and C4MPD represents the age-corrected local (inter-point) deviation from normal of data collected from these 4 points.

FOVEAL CONE ERG RECORDING

All ERG testing was done by one of us (A.W.) following visual field testing. Recordings were obtained with a handheld, dual-beam stimulator-ophthalmoscope (Maculoscope Spectrum, Doran Instruments, Littleton, Mass), similar to instrumentation and techniques described previously.2,21 Briefly, foveal responses were elicited through dilated pupils in a dark room with a 4° white stimulus of 4.8-log trolands (td) retinal illuminance, flickering at 42 Hz with a 50% duty-cycle resulting in 4.5-log td mean retinal illuminance. The stimulus was positioned on the fovea and centered within a 12° white, steady surround of 5.5 log td. Responses were monitored with a bipolar amplitude that was directly correlated with C4MTD (P = .004, r\text{30}= 0.464, Figure 2) and C4MPD (P = .006, r\text{30}= 0.445, Figure 3).

Furthermore, when we compared central visual field indices in glaucomatous eyes with subnormal amplitudes with those with normal amplitudes, C4MTD (mean ± SD, −11.2 ± 10.4 vs −3.6 ± 6.0, respectively, P = .008, \(t_{35}= -2.808\), and C4MPD (mean ± SD, −8.8 ± 7.9 vs −3.7 ± 4.3, respectively, P = .013, \(t_{35}= -2.608\)) were significantly lower in the former group.

We found RCDA to be correlated with central visual field indices among the glaucomatous eyes as well. It was inversely correlated with C4MTD (P = .0001, \(r_{30}= 0.616\)) and C4MPD (P = .0001, \(r_{30}= 0.613\)). However, multiple regression analysis indicated that both foveal ERG amplitude and RCDA were independently correlated with C4MTD (P = .0004 and P = .0001, Figure 3).
contact lens electrode (GoldLens, Doran Instruments). Using the stimulator-ophthalmoscope, factory default software signals were differentially amplified, smoothed by a narrow bandpass filter tuned to 42 Hz, and summed by a signal-averaging computer containing an artifact reject buffer that eliminated voltage deflections of more than 3 µV due to eye or eyelid movements. Testing involved consecutive recording periods lasting 60 to 120 seconds each depending on response phase reliability and separated from each other by 5 to 10 seconds in the dark. Responses were quantified with respect to stabilized amplitude and implicit time. In all cases, 3 or more recordings were performed until responses had stabilized to ensure response reproducibility and reliability. The published lower limit of normal for amplitude is 0.18 µV and the upper limit of normal for implicit time is 38 milliseconds.\(^3\,^2,^3\)

**CONTROL METHODS**

The RCDA was determined for each eye by two of us (A.W. and D.J.R.) separately. Their results did not differ significantly but when 2 determinations for an eye differed the average was used.

The ERG tester and the visual field technicians were masked to each other’s data. However, the ERG tester could not be masked to optic disc cupping data since we record foveal cone ERGs under direct observation of the fovea and the tester cannot avoid observing the optic disc. Nevertheless, we believe that the objective nature of foveal cone ERG recording is a safeguard against biased recording data.

Immediately prior to each ERG testing we routinely performed a photocell light-response calibration of the stimulator-ophthalmoscope, in addition to the instrument internal calibration, to verify system integrity and stability.

Foveal cone ERG testing results were compared with those obtained from 47 eyes of 47 normal volunteers and we determined the false-positive rate among these normal eyes. The volunteers were not related to the patients with glaucoma and were matched for age, sex, refractive error, and ethnic origin. Inclusion criteria included volunteers with no ocular history except for refractive error. Exclusion criteria included those described above for patients with glaucoma as well as visual complaints, a best-corrected visual acuity less than 20/25, an IOP greater than 21 mm Hg, any abnormal finding on dilated ocular examination, and vertical or horizontal cup-disc ratio of 0.4 or greater on slit-lamp biomicroscopy. Among these 47 normal volunteers, mean (±SD) age was 63.1 ± 12.3 years, and mean refractive spherical equivalent was -0.32 ± 1.65 D.

We found that a 2.5- to 5.0-week (mean ± SD, 3.5 ± 0.6 weeks) IOP-lowering medication washout period did not help demonstrate an overt medication-induced depression of foveal function. When we retested 6 eyes with NPG following this washout period, foveal ERG amplitude, C4MTD, and C4MPD did not rise in any of these eyes. This also helped to verify a low intertest variability for C4MTD and C4MPD.

To determine the degree of foveal cone ERG recording variability and false-negative rate, we tested a separate group of 12 eyes (7 patients) with known maculopathy twice within 1 to 3 months and compared the recording data between the 2 testing sessions. This study followed the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board. Prior to testing, all subjects gave informed consent after the nature, possible consequences, and the possible complications of the tests used were explained.

Foveal ERG amplitude false-positive rate was determined based on data collected from the 47 normal eyes. Among these eyes, amplitude was less than 0.18 µV in 2 eyes (4.3%), constituting a specificity rate of 95.7%, similar to previously published rates of 92% to 95%.\(^6,^11\) The amplitude false-negative rate was determined based on test vs retest data collected from 12 eyes with known maculopathy. Among these eyes we found no significant difference in amplitude between the 2 recording sessions, suggesting low intertest recording variability. However, amplitudes were subnormal in the first testing session and normal in the second in 2 of these 12 eyes, and vice versa in 2 other eyes, suggesting a 16.7% false-negative rate (sensitivity rate, 83.3%) for each of the recording sessions. This rate is in agreement with published rates of 66% to 91% depending on visual acuity levels.\(^7\) Our speci-
The results of our study suggest that foveal dysfunction distal to the GCL can be found in a significant number of eyes with NPG and POAG, and that glaucomatous eyes have significantly lower foveal cone ERG amplitudes compared with eyes of matched normal volunteers. Thus, our findings are in agreement with results of other studies that demonstrated retinal dysfunction distal to the GCL in glaucomatous eyes based on abnormal flash full-field and focal ERG data. Furthermore, among the glaucomatous eyes in our study, foveal function was directly correlated with central visual field indices, and glaucomatous eyes with subnormal ERG amplitudes had significantly lower central visual field indices compared with glaucomatous eyes with normal amplitudes. While RCDA, a measure of optic disc cupping, was also correlated with central visual field indices, we found that ERG amplitude and RCDA were independent predictors of these indices; amplitude explained 28.1% to 31.4% and RCDA explained 44.9% of their variance. Since foveal cone ERG amplitudes are well correlated with visual function in various retinal conditions, our findings suggest that at least some degree of central visual field loss in glaucoma can be explained by foveal dysfunction distal to the GCL in addition to loss explained by optic nerve axonal damage. To the best of our knowledge, this is also the first report of a significant direct correlation between foveal cone ERG amplitude and central visual field indices in any patient group.

We found foveal dysfunction in 14 (37.8%) of the 37 eyes tested. Our foveal cone ERG sensitivity rate (83.3%) and specificity rate (95.7%) are comparable to those previously published from other laboratories. Taking these rates into account, the number of glaucomatous eyes with foveal dysfunction distal to the GCL among the glaucomatous eyes we studied is in the range of 13.4 to 17.8 (36.2%-48.1%).
ing and since eyes with POAG were preselected based on their past visual fields. Nevertheless, our results suggest that foveal dysfunction distal to the GCL is not rare among eyes with glucomatous and could be a significant mechanism of visual loss in this disease.

The origin of this foveal dysfunction is not clear. Glaucomatous optic neuropathy itself cannot be regarded as the underlying cause since studies demonstrated normal retinal function distal to the GCL, as measured by flash ERG recording, in eyes with optic atrophy11,20 and even months after optic nerve resection.24

Retinal dystrophy or macular degeneration associated with glucomata are not likely causative factors as well. We have excluded from our study all eyes with any retinal or macular changes on ophthalmoscopic examination. Furthermore, results from previous histopathological studies of eyes with POAG23 and NPG26 have shown that photoreceptors and other outer retinal elements are of normal appearance even at an advanced stage of glucoma. In addition, our results cannot substantiate foveal dysfunction as an adverse effect or an artifact of IOP-lowering medications, at least not a dysfunction that can be reversed within weeks of medication washout.

One possible cause of foveal dysfunction distal to the GCL in glucomata is vascular insufficiency. On one hand, several studies demonstrated abnormal flash fullfield and foveal ERGs in various retinal vasculopathies21,27,28 and choroidal perfusion abnormalities.29 On the other hand, a previous finding of reduced oscillatory potentials in eyes with glucoma,3 similar to reductions found in diabetic vasculopathy30 and central retinal vein occlusion31 can be consistent with underlying vascular insufficiency in some eyes with glucoma. Indeed, evidence supporting abnormal ocular blood flow in some eyes with NPG and POAG is mounting.32-34 That these abnormalities may be related to visual loss was demonstrated by a study that correlated Humphrey visual field mean deviation to the ophthalmic artery Prouclet resistivity index in eyes with NPG.35 These ocular blood flow abnormalities should not be interpreted as a potential cause of optic neuropathy alone. Rather, other ocular structures including the choroid and the retina may be affected by vascular insufficiency. This is particularly suggested by the blood flow abnormalities found in the short posterior ciliary arteries34 supplying the choroid underlying the macular area, and by abnormal ocular blood flow measurements reflecting abnormal choroidal blood flow in eyes with NPG.36 Since the outer 130 μm of the retina, including the photoreceptors and other retinal elements to the level of the outer part of the inner nuclear layer are dependent on the choroidal vascular bed,37 abnormal choroidal blood flow could result in outer retinal dysfunction in glucomatous eyes. Furthermore, abnormalities in the vascular supply of the optic nerve head and the fovea may be interrelated since both the prelaminar optic disc and the foveal outer retina are nourished by the choroidal circulation.38,39 Other hypothetical causes of foveal dysfunction distal to the GCL in glucomatous eyes could be neurotoxic effects of compounds, such as glutamate that was found in excessive concentrations in glucomatous eyes,38 or the negative feedback of dying ganglion cells on more distal retinal elements.

Our results may also have some future therapeutic implications. Studies have shown that central visual loss in eyes with NPG may be potentially reversible with vasodilators.39-42 Since our study suggests that foveal dysfunction contributes significantly to central visual loss in some glucomatous eyes, at least some of the therapeutic effect of vasodilators on central visual function may have occurred through improved choroidal perfusion pressure in the macular area rather than improved optic disc vascular supply. Therefore, foveal cone ERG, being a sensitive and an objective measure of foveal function distal to the GCL,21,27,28 could be considered as a monitoring tool to determine the therapeutic effect of various agents on foveal function in glucoma.

Accepted for publication June 9, 1998.


We thank Michael A. Sandberg, PhD, Massachusetts Eye and Ear Infirmary, Boston, for his advice in statistical analysis and the staff of Northeast Ohio Eye Surgeons, Kent, for their technical assistance.

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leukodystrophy patients from the Optic Neuritis Treatment Trial (ONTT) regarding sex (P =.36), age (P =.08), and with ONTT patients (29 [7%] of 409 patients; P <.002) and at follow-up examination of at least 1 year, Emory African American patients had more frequent severe visual loss (visual acuity ≤20/200) at presentation (18 [90%] of 20 patients vs 161 [36%] of 448 patients; P <.001) and at follow-up examination of at least 1 year (6 [18%] of 33 patients vs 12 [3%] of 409 patients; P =.002). Seven (58%) of 12 African American patients with multiple sclerosis had a “neuromyelitis optica” presentation defined by the presence of neurological deficits limited to the optic nerves and spinal cord.

Conclusions: The African American study patients with a single episode of demyelinating optic neuritis had visual acuities more severely affected at onset and after 1 year of follow-up compared with the white study patients and with patients in the ONTT. In the African American patients, multiple sclerosis occurred most frequently in a “neuromyelitis optica” form. (1998;55:186-192)

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