Progressive Loss of Retinal Ganglion Cell Function Is Hindered with IOP-Lowering Treatment in Early Glaucoma

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PURPOSE. To investigate progressive changes of retinal ganglion cell (RGC) function in glaucoma suspects before and after IOP-lowering treatment.

METHODS. The authors retrospectively analyzed pattern electroretinograms (PERG) recorded twice a year in 32 glaucoma suspects over at least 6 years. Fifteen patients (28 eyes in the study group) received IOP-lowering treatment at intermediate points during the follow-up, thereby generating a break point between the untreated period and the treated period. Seventeen patients (31 eyes in the control group) were not treated; a break point in the follow-up period was randomly assigned. To assess the effect of treatment, linear regression slopes of PERG amplitude were calculated for periods before and after the break point, and compared both within and between groups. Linear mixed models applied to raw PERG amplitudes recorded over the entire follow-up period were also calculated.

RESULTS. Before the break point, slopes had a similar negative trend in both groups, whereas after the break point the slope became shallower in the treated group ($P = 0.002$). The linear mixed model revealed an interaction between groups, period relative to break point, and segment duration ($P = 0.001$). Both analyses agreed that after the break point, the rate of PERG amplitude decline slowed in treated eyes by $0.013\text{--}0.019\ \mu\text{V}/\text{year}$ compared with the untreated eyes. Mean IOPs measured before and after break point were similar in control eyes (14.8 ± 3.20 vs. 14.8 ± 3.14 mm Hg) but different in treated eyes (16.84 ± 3.96 vs. 14.8 ± 3.24 mm Hg; $P < 0.001$).

CONCLUSIONS. Progressive loss of RGC function in early glaucoma may be alleviated after IOP lowering, as measured by PERG. (*Invest Ophthalmol Vis Sci.* 2012;53:659–663) DOI: 10.1167/iovs.11-8525

The pattern electroretinogram (PERG) has long been considered an important functional marker for retinal ganglion cell (RGC) function,^{1,2} and has been extensively used for detecting dysfunction in ocular hypertension and glaucoma.^{3–7} PERG abnormalities are frequent in glaucoma suspects and in patients with early manifest glaucoma.^{4,7,8} Cross-sectional studies have shown that an abnormal PERG amplitude may increase

after IOP lowering in ocular hypertension^{9–12} and glaucoma.^{13,14} These studies provide proof-of-concept that RGC dysfunction, as measured by PERG, may be at least in part reversed after IOP lowering.

Here we report results obtained from retrospective analysis of a group of glaucoma suspects ($n = 32$, 59 eyes) monitored twice a year for > 6 years with PERG. A subgroup of them ($n = 17$, 31 eyes) was monitored untreated over the entire follow-up period, whereas another subgroup ($n = 15$, 28 eyes) initiated IOP-lowering treatment at intermediate points during the follow-up period. We had therefore the opportunity to compare serial PERG measurements between untreated and treated patients, and asked the question of whether there were differences in the rates of change of the PERG signal between the two groups. Results show that the progressive loss of PERG signal occurring in both groups of patients during the untreated follow-up period was reduced in treated patients compared with the untreated.

METHODS

Subjects

Study subjects were part of a larger longitudinal cohort of patients enrolled as glaucoma suspects at their initial visit based on a detailed medical and ocular history and a comprehensive eye examination as previously described.⁶ Inclusion criteria were: refractive errors within -5 to $+3$ diopters, best corrected visual acuity (BCVA) better than or equal to 20/20 (Snellen), normal standard automated perimetry (SAP) according to the Ocular Hypertension Treatment Study (OHTS) criteria¹⁵ (reliability $< 15\%$ on all indices, normality $> 5\%$ on all global indices in two consecutive sessions 6 months apart), and glaucomatous optic disc appearance (vertical cup/disc ratio [C/D] ≥ 0.5 , C/D asymmetry ≥ 0.2 , localized thinning of the disc, splinter hemorrhage) or increased IOP (> 21 mm Hg). To qualify for the present retrospective study, patients had to be monitored with PERG twice a year over a follow-up period longer than 6 years. We identified in our longitudinal cohort all glaucoma suspects ($n = 15$, 28 eyes) that received treatment at some point during the follow-up and had a sufficient number of observations before and after the break point. From the same cohort, a control group of untreated patients ($n = 17$, 31 eyes) was randomly selected with similar age range and follow-up time as the study group. Initiation of therapy in the study group was weighted in concert with the individual patients taking into account a constellation of risk factors including optic disc cupping, corneal thickness, family history, race, life expectancy, and psychosocial issues.¹⁶ The 5-year risk of developing primary open-angle glaucoma, retrospectively calculated using the OHTS-European Glaucoma Prevention Study (EGPS) point system available online (<http://ohts.wustl.edu/risk/calculator.html>), was higher in the treated group compared with the untreated (9.03 ± 2.36 vs. 7.83 ± 1.71 ; $P = 0.028$). The decision to treat was not based on the OHTS-EGPS calculated risk, as the predictive models are valid for patients that meet the inclusion criteria of OHTS, and could not be generalized to our glaucoma suspect population.¹⁶ The decision to

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treat was also not based on PERG measurements. Treatment consisted of either prostaglandin analogs (22/28 eyes; 79%) or β -blockers (6/28 eyes; 21%), which are known not to cause changes in pupil size (American Academy of Ophthalmology Preferred Practice Pattern, Glaucoma Panel, Hoskins Center for Quality Eye Care; <http://www.aaofppp>).

Patients' characteristics are summarized in Table 1. All eyes included in the analysis contributed data from at least four visits both before and after the break point (time of treatment in the study group, randomly assigned in the control group). The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Miami. Informed written consent was obtained from all subjects after the nature of the test and possible risks were explained in detail.

PERG Recording

We used a recording paradigm optimized for glaucoma detection (PERGLA) whose details have been previously described.¹⁷ The paradigm yields steady state responses reported to have relatively low test-retest and operator-dependent variability.^{7,14,17–20} In brief, retinal signals were simultaneously recorded from both eyes by means of standard 10 mm Grass gold surface electrodes taped on the lower eyelids. Similar electrodes were placed over the ipsilateral temples (reference) and central forehead (common ground). Subjects were fitted with the appropriate lens correction to reach J1+ visual acuity for viewing a pattern stimulus placed at 30 cm distance, and were instructed to fixate on a target at the center of it. Subjects did not receive dilating drops, and were allowed to blink freely. The pattern stimulus consisted of horizontal gratings (1.7 cyc/deg, 25° diameter circular field, 98% contrast, 40 cd/m² mean luminance), reversing 16.28 times per second. Electrical signals were conventionally band-pass filtered (1–30 Hz), amplified (100,000-fold), and averaged in synchrony to the reversal period. During signal acquisition, sweeps contaminated by eye blinks or gross eye movements were automatically rejected over a threshold voltage of 25 μ V. Two successive responses of 300 artifact-free sweeps each were recorded, separated by a brief pause. The first 30 sweeps of each response were rejected to allow steady state conditions. The software allowed visual inspection of the two consecutive responses superimposed to check for consistency, and then computed the final PERG waveform (600 artifact-free sweeps). Because the PERG was recorded in response to relatively fast alternating gratings, the response waveforms were typically sinusoidal-like, with a temporal period corresponding to the reversal rate (see examples in Ref. 6). PERG waveforms were automatically analyzed in the frequency domain by discrete fourier transform (DFT) to isolate the frequency component at the contrast-reversal rate (16.28 Hz), and compute its amplitude in μ V. The stimulus luminance/contrast did not change over the observation period as measured with a photometer (Gamma Scientific DR-2000-1, San Diego, CA). Each subject participating in the study was tested with PERG by different operators ($n = 2$ –4) that alternated/overlapped during the follow-up period. How-

ever, untreated and treated patients were tested by the same operators in a given time window.

Analysis of PERG Changes with Time

To assess the effect of treatment on PERG amplitude in the study group, we compared the data set recorded before treatment with the data set recorded after treatment. The transition between untreated and treated periods (break point) was set as the time of the first recording after initiation of therapy. As the control group did not receive treatment, the break point was randomly assigned in individual eyes at intermediate follow up times, however allowing at least 4 measurements before and after it. We conducted two different data analyses. The first analysis was based on the comparison of rates of amplitude change (linear regression slopes) occurring in individual eyes during the untreated and treated periods. The second analysis was based on the comparison of amplitudes recorded in the entire group of eyes before and after the break point. To do so, follow-up times were normalized by assigning a zero value at the break point time, and then by expressing years preceding and after the break point as negative and positive values, respectively. Linear mixed models applied to raw PERG amplitudes recorded over the entire follow-up period were then used to assess the effect of treatment. Random effects included patient and eye within patient. Fixed effects included group (study vs. control), period (segment 1 vs. segment 2), follow-up (duration of each segment), and group $\times$ period $\times$ follow-up interaction.

RESULTS

An example of how PERG data were analyzed is shown in Figure 1 for a patient who received repeated testing ($n = 16$) over 7.3 years and displayed different rates of PERG amplitude change in the untreated and treated periods. PERG amplitude data were fitted with linear regression lines for both untreated and treated periods, using the time of treatment as known intersection point between untreated and treated periods. Regression slopes for all eyes are reported in Figure 2.

It can be noted in Figure 1A that the PERG amplitude at baseline was within the normal range in both eyes (above the lower 95% confidence interval [CI] of the normal population⁶). Over time, the PERG amplitude progressively decreased in both eyes and became abnormal. After IOP-lowering treatment was initiated (arrowhead on the x-axis), the PERG amplitude did not appear to change substantially over time in both eyes. Mean IOPs and corresponding SDs were calculated for untreated and treated periods and displayed Figure 1B. In this patient the treated IOP decreased in both eyes (OD, 17.7 ± 2.8 to 14.1 ± 2.56 mm Hg; $P = 0.020$; OS, 17.8 ± 2.8 to 15.0 ± 2.36 ; $P = 0.049$).

The scattergrams displayed in Figures 2A and 2B contrast slopes computed with linear regressions of PERG amplitude data recorded before (slope 1) and after (slope 2) the break point in untreated and treated eyes. Open symbols represent individual eyes; black symbols and errors bars represent the bidirectional averages and corresponding 95% CIs of the mean, respectively.

It is apparent in Figures 2A and 2B that in treated eyes, compared with untreated eyes, more data points fell above the line of equivalence. In treated eyes, differently from untreated eyes, the 95% CI of the averages did not overlap with the line of equivalence. In treated eyes, the mean slope 1 was significantly steeper than the mean slope 2 (slope 1, -0.0642 ± 0.0908 μ V/year; slope 2, 0.0121 ± 0.0556 μ V/year; t -test, $P = 0.002$). Slope 1 was significantly different from zero ($P < 0.01$), whereas slope 2 was not significantly different from zero ($P = 0.26$). In the eyes that received medications, the PERG amplitude slope became less steep by 0.019 μ V/year compared with the untreated eyes. In untreated eyes, slope 1 was not signifi-

TABLE 1. Summary of Patients' Characteristics

	Treated Patients ($n = 15$, 28 Eyes) Mean $\pm$ SD	Untreated Patients ($n = 17$, 31 Eyes) Mean $\pm$ SD	t -Test, P
Age, y	54.9 ± 11.8	53.9 ± 8.7	0.785
Baseline SAP-MD, dB	-1.28 ± 2.5	-0.59 ± 1.01	0.162
Baseline C/D, vertical	0.55 ± 0.2	0.50 ± 0.13	0.623
Baseline IOP, mm Hg	15.6 ± 2.7	14.7 ± 2.9	0.224
Follow-up, y	6.44 ± 1.07	6.74 ± 0.92	0.252
PERG tests, n	14.2 ± 2.88	13.7 ± 1.3	0.386

cantly different from slope 2 (slope 1, -0.0418 ± 0.0892 $\mu\text{V}/\text{year}$; slope 2, -0.007 ± 0.052 $\mu\text{V}/\text{year}$; t -test, $P = 0.1$).

IOP measurements obtained before and after break point were averaged and their means considered representative of the IOP in each period. Figure 2C displays the mean IOPs and corresponding SDs for untreated and treated eyes measured before and after the break point. In untreated eyes the mean IOP was virtually identical before and after the break point (14.8 ± 3.20 mm Hg vs. 14.8 ± 3.14 mm Hg). In treated eyes the mean IOP was significantly higher before the break point than after it (16.84 ± 3.96 mm Hg vs. 14.8 ± 3.24 mm Hg; $P < 0.001$), and the corresponding SD tended to be relatively larger. Altogether, results shown in Figure 2 suggest that prolonged exposure to IOP-lowering treatment may alleviate the progressive loss of PERG signal occurring during the untreated follow-up period. However, the correlation between IOP change (differences between mean IOPs calculated before and after the break point in individual eyes) and slope change (difference between slope calculated for the period before and

after the break point in individual eyes) was not significant ($R = 0.298$; $P = 0.124$).

Figure 3 summarizes the results of the linear mixed model in untreated (left panel) and treated eyes (right panel) calculated on raw PERG amplitudes of all eyes before and after the break point. Follow-up times were normalized by assigning a zero value at the break point time and expressing years preceding and after the break point as negative and positive values, respectively. Random effects included patient and eye within patient. Fixed effects included group (study vs. control), period (segment 1 vs. segment 2), follow-up (duration of each segment), and corresponding interactions. There was a highly significant group $\times$ period $\times$ follow-up interaction ($P = 0.001$). For every year of follow-up after the break point, the eyes that received medications had a positive difference of 0.013 μV compared with the untreated eyes.

Altogether, results of the linear mixed model shown in Figure 3 are consistent with the results of regression analysis shown in Figure 2, and further support the hypothesis that

FIGURE 2. Linear regression slopes for untreated control eyes and treated eyes (*open symbols* in A and B) calculated in the period before (*slope 1*) and after (*slope 2*) the transition between untreated and treated periods (break point). In treated eyes, the break point was set as the time of the first recording after initiation of therapy. In untreated eyes, the break point was randomly assigned in individual eyes at intermediate follow-up times, however allowing at least four measurements before and after. The *black symbols* in (A) and (B) represent the bidirectional averages of slope 1 and slope 2 and corresponding 95% confidence intervals of the mean. The bar graph (C) represents the mean IOP and SD calculated by averaging all IOPs recorded in untreated and treated eyes before and after the break point. Asterisks symbolize the significance level ($P < 0.001$).

FIGURE 3. PERG amplitudes recorded in all eyes of untreated (A) and treated patients (B) during the entire follow-up period. Individual time scales have been normalized by assigning a zero value to the break point (time of the first recording after initiation of therapy in treated eyes; randomly assigned at intermediate follow-up times in untreated eyes). The *thick lines* in (A) and (B) represent the linear mixed model that fits the data. Note that before the break point, the PERG amplitude displayed a progressive decline in both control (A) and study (B) eyes. After the break point, the PERG amplitude decline was arrested in the study group (B) but not in the control group (A).

prolonged exposure to IOP-lowering treatment may slow the progressive loss of PERG signal.

DISCUSSION

Glaucomatous damage to visual function is generally considered to be irreversible. This view, however, is challenged by several cross-sectional studies reporting improvement of either psychophysical visual sensitivity (reviewed in Ref. 21) or PERG amplitude (reviewed in Refs. 13, 14) after IOP lowering. Improvement of visual sensitivity and RGC electrical responsiveness implies that a population of living RGCs is initially dysfunctional. IOP may be the direct or indirect cause of dysfunction, because IOP-lowering treatment restores, at least partially, the normal function of RGCs. Here we approached the issue of modifiable RGC dysfunction in a longitudinal study. Compared with cross-sectional studies, longitudinal studies have the advantage of tracking the same subjects with repeated observations over a relatively long period and are less prone to short-term or random effects. The PERGLA protocol we used has been previously shown to have relatively low test-retest/operator-dependent variability and is reported to be suitable for longitudinal studies. We retrospectively analyzed PERG measurements in a group of glaucoma suspects who were monitored untreated for approximately 3 years on average and then received topical treatment for glaucoma for the subsequent 3.5 years on average. We compared longitudinal changes of the PERG signal occurring in study patients during untreated and treated periods with those occurring in a control group of patients that matched the mean age, inclusion criteria, and follow-up period of the treated group but did not receive IOP-lowering treatment. While in treated eyes the transition between untreated and treated period (break point) was obvious, in untreated eyes the break point was randomly assigned at intermediate points during the follow-up period. As the effects were expected to be relatively small and embedded in a substantial variability, we conducted different data analyses to minimize the risk that the results depended on a particular statistic.

The results show that before the break point, the PERG amplitude tended to progressively decrease with time in the eyes of both controls and study patients. After IOP-lowering treatment was initiated, however, the negative PERG trend was hindered or even arrested in study eyes. In contrast, the negative trend of PERG amplitude with time continued in control eyes.

While IOP-lowering therapy slowed the slope of PERG amplitude decline, the magnitude of IOP lowering was not significantly correlated with the magnitude of PERG slope change. Lack of correlation between PERG amplitude change and magnitude of IOP lowering after topical or surgical treatment was previously reported in cross-sectional studies by Ventura and Porciatti¹³ and Sehi et al.¹⁴ A strong correlation between IOP and PERG was not expected, as the mutual relationships between these two variables may be very complex, and involve a host of neuro-vascular-metabolic-biomechanical components eventually impacting RGC electrical activity. It should be considered, however, that while the magnitude of IOP lowering was relatively small (approximately 2 mm Hg on average, -12.2%), it was protracted for several years, thereby resulting in a substantial reduction of IOP exposure compared with the untreated period. Reduction in IOP exposure during the treated period was associated with a reduction in IOP SD of 18.3%. Protracted reduction of IOP associated with reduction in IOP fluctuations²² may have hindered progressive decline of RGC function in treated eyes. Progressive decline of PERG signal in untreated eyes may reflect both the reduced activity of dysfunctional, yet viable, RGCs as well as the lack of activity from lost RGCs. The positive change in slope steepness after IOP lowering may mean that progressive degradation of RGC function has slowed down, that the rate of RGC death has diminished, or a combination of both conditions.

It is unlikely that changes of PERG amplitude over time in control and treated eyes were artifactual. We periodically checked the luminance/contrast of the visual stimulus and the amplifiers' gain to exclude failure of the instrumental setup. Even though different operators changed during the study period, control and study patients were recorded by the same operators during similar time windows. The PERG amplitude is known to physiologically decline with age in normal subjects based on cross-sectional data.^{6,17} In the present study, normalization to age-specific norms was not necessary, as we longitudinally compared untreated controls and treated patients of similar age ranges and conditions. This retrospective study was not designed for randomization to treatment between control and patient groups. We identified in our longitudinal cohort of glaucoma suspects all patients that received treatment at some point during the follow-up and had a sufficient number of observations before and after the break point. In this study group, initiation of treatment was based on a constellation of clinical criteria, and was not based on either OHTS calculated risk or PERG. The untreated control group was randomly

selected from the same cohort with similar age range and follow-up time as the study group.

Several multicenter studies have indicated that IOP reduction delays the onset or the progression of visual field deterioration in ocular hypertension,²³ early manifest glaucoma,²⁴ advanced glaucoma,²⁵ and normal-tension glaucoma.²⁶ Our results are in keeping with these studies. That the progressive decline of PERG signal is hindered or even arrested in treated eyes does not imply that the risk of progression of the disease itself is diminished or prevented with treatment. The disease may progress from risk factors other than, or in addition to, IOP, or may not progress at all. Further investigation is needed to understand the predictive role of PERG changes on glaucoma progression and the role of more aggressive pressure-lowering strategy on restoring RGC function.

Overall, the results of this study indicate that progressive loss of RGC function in early glaucoma may be alleviated after IOP-lowering. This, together with a considerable body of converging evidence on the PERG as a measure of RGC function in human and mouse models of glaucoma, suggest that this electrophysiological measure may represent a useful functional end point to monitor for progression of RGC dysfunction in the early (ideally preperimetric) stages of glaucoma. Furthermore, by monitoring potential recovery of RGC dysfunction after IOP-lowering treatment, PERG may become an effective measure to assess the efficacy of an individual's IOP-lowering regimen.

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