ORIGINAL RESEARCH

Retinal Ganglion Cell Functional Recovery after Intraocular Pressure Lowering Treatment Using Prostaglandin Analogs in Glaucoma Suspects: A Prospective Pilot Study

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Abstract

Aim and background: To evaluate the ability of pattern electroretinogram (PERG) to detect improvement of retinal ganglion cell (RGC) function in glaucoma suspects (GS) after medically reducing intraocular pressure (IOP) using prostaglandin analog drops.

Materials and methods: Six subjects (eight eyes) received topical IOP lowering treatment based on their clinical examination and were observed at Manhattan Eye, Ear & Throat Hospital over an average of 3.1 ± 2.2 months. During this time, participants underwent a full ophthalmologic exam and were evaluated with a Humphrey visual field analyzer (HFA) 24–2 [24–2 mean deviation (MD), 24–2 pattern standard deviation (PSD), and 24–2 visual field indices (VFI)], Diopsys NOVA PERG optimized for glaucoma [magnitude (Mag), magnitudeD (MagD), and magnitudeD/magnitude ratio (MagD/Mag ratio)] and optical coherence tomography (OCT)-derived average retinal nerve fiber layer thickness (avRNFLT) and average ganglion cell layer + inner plexiform layer (avGCL + IPL) thicknesses at baseline visit (pretreatment) and 3 months later (posttreatment). Goldman applanation tonometry was used to measure IOP at each visit. Paired sample *t*-tests were conducted to determine the statistical significance of the change in IOP, HFA indices, PERG parameters, and OCT thickness measurements between the two visits.

Results: Lowering IOP by 22.29% resulted in a significant increase (32.98 and 15.49%) in MagD [t (7) = −3.174, 95% confidence interval (CI) = −0.53, −0.08, p = 0.016] and MagD/Mag ratio [t (7) = −3.233, 95% CI = −0.20, −0.03, p = 0.014], respectively. There was a positive percentage change for all variables of interest, however, 24–2 MD, Mag, avRNFLT, and GCL+ IPLT did not reach statistical significance.

Conclusion: After reducing IOP by 22.29% for a duration of 3.1 months, the PERG parameters, MagD and MagD/Mag ratio, significantly improved by 32.98 and 15.49%, respectively.

Clinical significance: Pattern electroretinogram (PERG) may be a crucial tool for clinicians to locate a window of opportunity in which degenerating yet viable RGCs could be rescued from irreversible damage. We suggest consideration of PERG as a tool in early retinal ganglion cell (RGC) dysfunction detection as well as for monitoring IOP lowering treatment.

Keywords: Ganglion cell layer + inner plexiform layer, Glaucoma suspects, Intraocular pressure treatment, Pattern electroretinogram, Retinal ganglion cells, Retinal nerve fiber layer thickness.

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Introduction

Glaucoma is a leading cause of vision loss worldwide. Although there is no current cure for glaucoma, there are many ways to detect it early on and possibly slow its progression.[1] Glaucoma is a disease of progressive optic neuropathy characterized by the degeneration of retinal ganglion cells (RGCs).[2] The primary targets in the pathophysiology of glaucoma are RGCs and their axons.[3] The optic nerve is composed of RGC axons, and any damage may result in changes to the ganglion cell layer and the retinal nerve fiber layer (RNFL) thickness.[4] Glaucoma can cause progressive loss of vision over many years, although it typically begins as subclinical with a prolonged occult period without any noticeable visual symptoms.[5]

Glaucoma is currently viewed as an insidious deterioration of the optic nerve head (ONH) with changes in the RNFL preceding visual field (VF) changes, as assessed by means of standard automated perimetry (SAP).[6] It has been estimated that at least 25% of RGC must have died before the change is detectable by SAP.[7–9] VF test may still be full, without visual disturbances, while the RGCs, are in fact, deteriorating.[10] Meaning by the time VF detection is possible, the patient may have significant damage and may be progressing toward overt glaucoma with significant visual impairment.[11]

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There are several functional and structural tests that can be performed on a patient to determine preglaucomatous damage despite normal visual field tests. It has been shown in studies that optical coherence tomography (OCT) may be used to detect RNFL loss up to 4 years before the development of VF loss.[12] A new functional technology, pattern electroretinogram (PERG), measures retinal response to a contrast reversing pattern, providing information about central RGC function.[8] PERG has been shown to have the ability to detect early RGC dysfunction up to eight years before OCT can detect a structural change in the RNFL.[13]

A user-friendly paradigm for PERG was optimized for glaucoma screening (PERGLA),[14] and the tool has been found to reliably assess RGC function in glaucoma.[1] It has been demonstrated that the steady-state PERG (ss-PERG) may be used to detect early functional abnormalities in glaucoma suspects (GS) preceding abnormalities in SAP.[15] Furthermore, it has been demonstrated that PERG was successfully used to assess RGC function in primate and rodent models of glaucoma.[1] PERG has also been shown to be dominated by inner retina activity with minimization of outer retina activity. Several pharmacological studies have demonstrated that interfering in various ways with the activity of inner retina neurons reduces PERG as well as inner-retina-sensitive ERG components in cats, rodents, and primates.[16–19] Additionally, PERG has been shown to improve after pharmacologic reduction of IOP in patients with ocular hypertension.[20–24] In this patient population, PERG may also show exacerbated losses after transient increases of intraocular pressure (IOP) with a suction cup.[25,26]

For many decades, damage to the optic nerve caused by glaucoma was thought to be irreversible, but recent literature has demonstrated that timely IOP-lowering therapy can improve both the VF and the function of RGC.[11] IOP-lowering therapy has been shown to be effective in slowing the progression and reversing the damage caused to RGC under certain circumstances.[27] Functional improvement achieved through IOP-lowering therapy has been measured by means of VF and PERG testing, however, it was not clear how much of the IOP should be decreased in order to improve RGC function.[28] "Target IOP" is the highest IOP expected to prevent further glaucomatous damage, and yet, there is no safe agreed-upon IOP level to be used in practice.[28] Many researchers have tried to determine the "target IOP'' by evaluating the percentage of IOP reduction after intervention. In a study by Dietlein et al., they recommended an IOP reduction of 20–50% depending on the type of intervention (monotherapy or surgical), the degree of existing glaucomatous damage, the rate of progression, and the patient's age.[29] However, they concluded that they still did not know how much IOP should be achieved to reverse the RGC function.[29] In a study by Sehi et al., an IOP reduction of about 47% was achieved through surgery in glaucoma patients, and the authors were able to demonstrate the reversal of RGC dysfunction with the functional recovery quantified using PERGLA.[15] In another study in which IOP was reduced by about 20% with prostaglandin analogs (latanoprost), PERGLA was used in GS and glaucomatous eyes to evaluate the impact of the IOP reductions on RGC function. They concluded that this IOP reduction was insufficient to improve the PERGLA signal generated by RGC.[30]

The goal of current glaucoma management is early detection of glaucomatous damage and prevention of visual disability through slowed progression and possible reversal.[31] The early detection of RGC structural damage is essential to allow for early intervention and treatment by modifying the only risk factor, an elevated IOP. Lowering this crucial factor will slowdown progressive damage, and hopefully, reverse RGC dysfunction and prevent their programmed apoptosis.

Therefore, the purpose of this study was to identify RGC dysfunction by means of PERG and to evaluate RGC function after lowering IOP in newly diagnosed, nontreated GS subjects after 3 months. A third purpose of this study was to determine the optimal percentage change in IOP that would elicit a significant RGC functional recovery, as reflected by PERG tests. Finally, we will offer a new approach to the clinical management of GS subjects using PERG technology.

Materials and Methods

All eligible subjects were recruited from the ophthalmology practice of Manhattan Eye Ear & Throat Hospital. Six consecutive GS (eight eyes) were included in this prospective pilot study, as part of a large longitudinal study on RGC function. In that longitudinal study, 46 GS were followed up for a duration of 3 years to detect early converters to overt glaucoma. The conversion of GS was assessed based on their risk profile, family history of glaucoma, Humphrey visual field deterioration by >1.1 dB/year, as well as average RNFL thickness thinning by −0.82 µm/year. All participants underwent a complete ophthalmologic examination, which included a full eye exam, a Humphrey visual field test and an ss-PERG examination by means of Diopsys NOVA PERG. This study was approved by the Institutional Review Board.

Inclusion Criteria

Participants were recruited at the practice as part of their regular routine eye exams. Patients were defined as GS according to the following criteria—the presence of suspicious glaucomatous activity and a normal Humphrey visual field analyzer (HFA) 24–2 Swedish Interactive Thresholding Algorithm (SITA)—standard test at the baseline visit. Participants 40–70 years of age, with best corrected visual acuity better than or equal to 20/40 (Snellen), any IOP level, and any type of angle were enrolled in this study. Any newly diagnosed subject with no prior IOP lowering treatment with signs of disease progression based on their eye examination, VF, and IOP levels were offered to participate in this study prior to beginning their treatment with prostaglandin analog eye drops.

Exclusion Criteria

Participants with prior intraocular or posterior segment intraocular surgery, ocular trauma, ocular or systemic conditions that may affect the ONH, retinal structure or function (e.g., ischemic optic neuropathy, optic neuritis, papilledema, and corneal and retinal diseases), were not included in this study. Other exclusion criteria were individuals with prior intraocular surgery in the study eye, except for uncomplicated cataract extraction with posterior chamber intraocular lens (IOL) implant, with no escape of the vitreous, as well as if cataract extraction was performed <1 year prior to enrollment. Individuals with unreliable HFA visual field results, with fixation losses, false positive and false negative rates, each >20%, were excluded from the study.

Tests Performed

Visual Field Testing

All participants in this study had prior experience with this examination, using a Humphrey perimeter (Humphrey Field Analyzer II, Carl Zeiss Meditec, Inc, Dublin, California), which has been described elsewhere.[32] The SITA 24–2 standard strategies and global indices, including mean deviation (MD), pattern standard deviation (PSD), and visual field indices (VFI), were used in the analysis. Using HFA SITA 24–2 results, only participants with visual fields corresponding to stage 0 (no visual field losses) following the glaucoma staging system (GSS) 2 were included.[1] Only four eyes completed both HFA 24–2 tests at the baseline and follow-up visits.

Steady-state Pattern Electroretinogram Measurements

The ss-PERG in this study follows the PERGLA protocol developed by Porciatti, which was developed for glaucoma screening.[14] The PERGLA protocol adds filters and amplifiers to ss-PERG recordings to achieve an amplitude and signal-to-noise ratio adherent to the International Society for Clinical Electrophysiology of Vision standards.[10]

The ss-PERG was recorded using a commercially available system, Diopsys® NOVA-PERG (Diopsys, Inc. Pine Brook, New Jersey, United States of America). The subjects' preparation and testing procedures were described elsewhere.[8,33–35]

For each eye, three ss-PERG measurements [Magnitude (Mag), MagnitudeD (MagD), and MagD/Mag ratio) were displayed in the results section of the printout. Mag (μV) represents the amplitude of the signal strength at the specific reversal rate of 15 Hz in the frequency domain, while MagD (μV) represents an adjusted amplitude of the ss-PERG signal impacted by phase variability throughout the waveform recording. MagD is equal to the Mag that was altered by phase change, and therefore, it may also reflect phase consistency. A recording where the phase of the response is consistent will produce a MagD value close to that of Mag, whereas a recording where the phase of the response varies will produce a MagD value lower than that of Mag (Figs 1 and 2). This is because averaging responses that are out-of-phase with each other will cause some degree of cancellation and yield a lower MagD value. MagD/Mag ratio is a ratio that is a within-subject representation of the phase consistency of ss-PERG. These ss-PERG parameters are repeatable, reproducible, and sufficiently reliable in clinical practice.[10] Results were also presented in a color-coded system, like a "traffic light system," with green showing results within the reference range, yellow, values within the borderline reference range, and red, results outside of the reference range.[8]

Statistical Analysis

Shapiro–Wilk test was used to determine the normality of the distribution for all important variables. Descriptive statistics were used to evaluate continuous and demographic data. Data is presented as (mean ± standard deviation). To assess the change in IOP, HFA, OCT, and PERG parameters between the pre- and posttreatment visits, a paired sample *t*-test was used. Statistical Package for the Social Sciences Statistics version 28 was used to conduct this analysis.

Results

Six middle-aged subjects (eight eyes), with a mean age of 61 years, were included in the analysis (Table 1). All subjects had at least one first-degree relative affected with glaucoma. A paired sample *t*-test was conducted to evaluate the impact of lowering IOP (Table 2). The results showed a significant decrease in IOP from 22.43 ± 2.573 to 17.43 ± 1.272 [t (6) = 6.908, 95% confidence interval (CI) = 3.23, 6.77, $p < 0.001$] and large effect size (Cohen's d coefficient = 2.611). We report a percentage change in IOP reduction of 22.29%, which

Table 1: Study characteristics

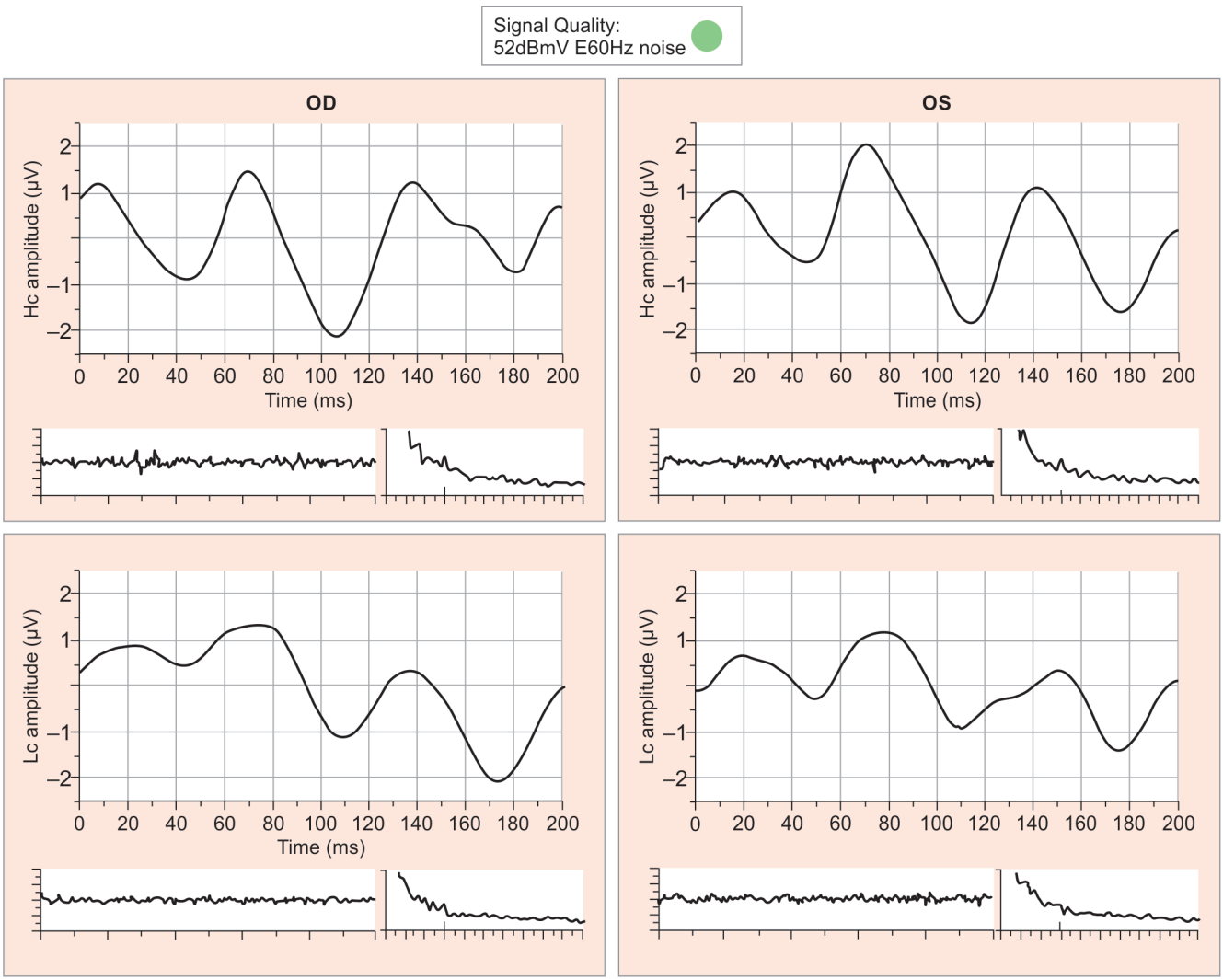
N = eight eyes (six subjects)	*Mean ± SD*
Age (years)	61.00 ± 11.80
Sex (% females)	Four females (67.00%)
IOP (mm Hg)	22.43 ± 2.57
Humphrey visual field	
24–2 MD (dB)	−0.96 ± 0.90
24–2 PSD (dB)	1.71 ± 0.34
24–2 VFI (%)	98.43 ± 0.54
SD-OCT	
avRNFLT (μm)	84.67 ± 12.86
avGCL + IPLT (μm)	77.00 ± 8.03
ss-PERG	
Mag (μV)	1.29 ± 0.40
MagD (μV)	0.94 ± 0.44
MagD/Mag ratio	0.71 ± 0.15

All visual field, OCT and PERG variables listed are from timepoint 1. avGCL + IPLT, average ganglion cell layer+inner plexiform layer thickness; avRNFLT, average RNFL thickness; IOP, intraocular pressure; MD, mean deviation; PSD, pattern standard deviation; SD-OCT, spectral domain-optical coherence tomography; ss-PERG, steady-state pattern electroretinogram; VFI, visual field index

Table 2: IOP, VF, PERG, and OCT measurements at baseline and 3 months after treatment

	Effect size	*Percent change*	*p-value*	*t-value*
IOP (mm Hg)	2.611	22.29	<0.001	6.908
24–2 MD (dB)	−4.714	219.62	0.095	−6.667
Mag (μV)	−0.779	17.05	0.063	−2.204
Mag D (μV)	−1.122	32.98	0.016	−3.174
MagD/Mag ratio	−1.143	15.49	0.014	−3.233
avRNFLT (μm)	−0.354	1.09	0.705	−0.500
avGCL + IPLT (μm)	0.577	0.62	0.182	−1.732

avGCL + IPLT, average ganglion cell layer + inner plexiform layer thickness; avRNFLT, average retinal nerve fiber layer thickness; IOP, intraocular pressure; MD, mean deviation; MagD/Mag ratio MagnitudeD/Magnitude ratio; OCT, optical coherence tomography; PERG, pattern electroretinogram; VF, visual field



Parameter	OD Hc	OD Lc	OS Hc	OS Lc
Magnitude (uV)	1.77	1.37	1.70	1.26
Magnitude	1.38	0.96	1.46	0.78
MagD/Mag Ratio	0.78	0.70	0.66	0.62
SNR (dB)	3.6	3.8	3.7	2.0
Artifacts	0	0	0	0

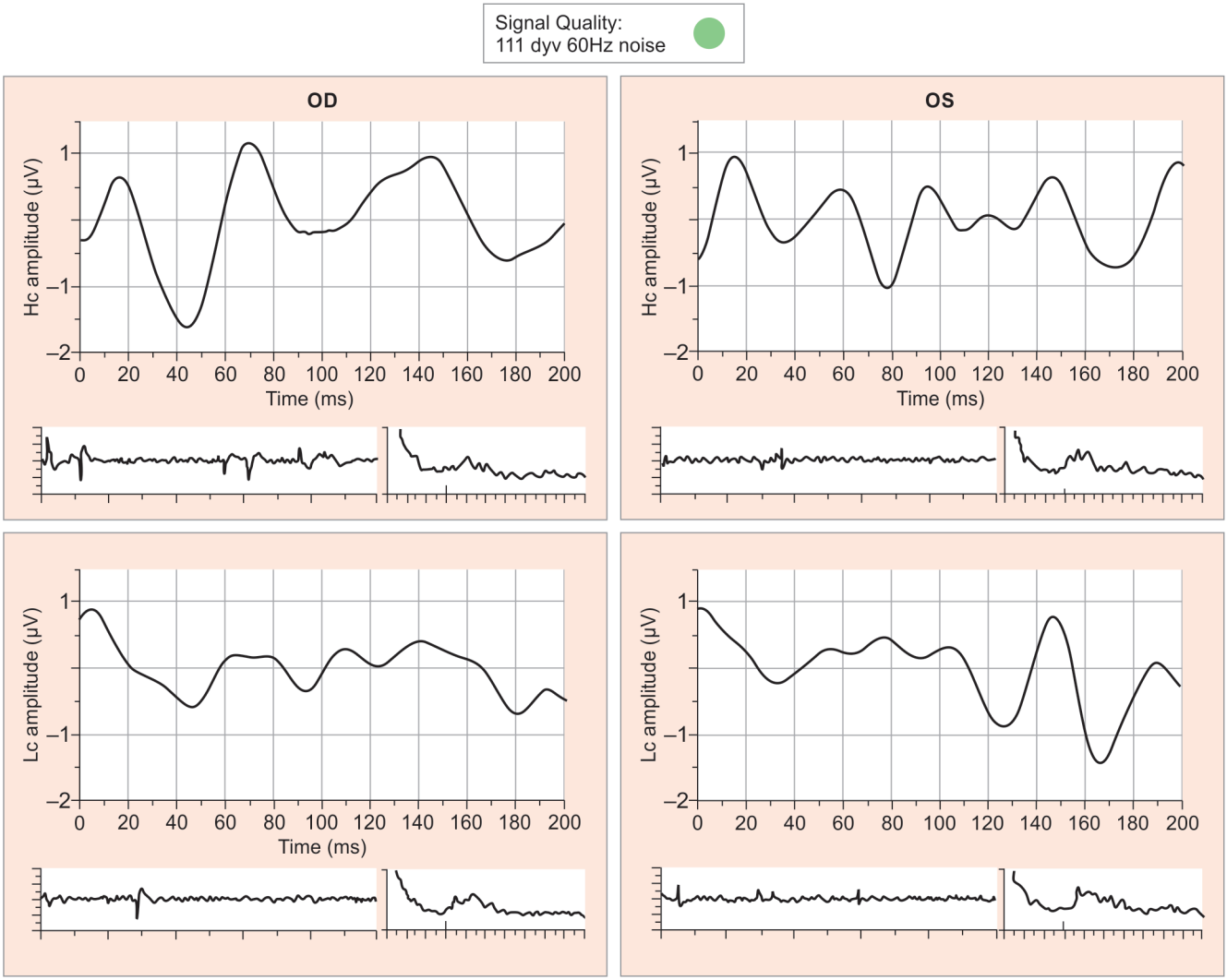
Fig. 1: Steady-state PERG results of a healthy subject. Results are presented in numeric values as well as color coded (green means within reference range, yellow within borderline reference range, and red outside reference range). Hc, high contrast; Lc, low contrast; OD, right eye; OS, left eye; Mag, Magnitude; MagD, MagnitudeD; PERG, pattern electroretinogram; SNR, signal-to-noise ratio

resulted in an improvement of the ss-PERG parameters, MagD, and MagD/Mag ratio. Mag improved by 17.05% but did not reach statistical significance ($p = 0.063$) (Table 2).

A paired sample *t*-test was conducted to evaluate the impact of lowering IOP on ss-PERG parameters (Table 2). The results showed an increase in Mag from 1.29 ± 0.398 to 1.51 ± 0.374, but it did not reach statistical significance [t (7) = −2.204, 95% CI = −0.45, 0.16, p = 0.063]. The Cohen's d coefficient for Mag was −0.779. However, there was a significant increase in MagD from 0.94 ± 0.443 to 1.25 ± 0.356 [t (7) = −3.174, 95% CI = −0.53, −0.08, p = 0.016] and in MagD/Mag ratio from 0.71 ± 0.153 to 0.82 ± 0.085 [t (7) = −3.233, 95% CI = −0.20, −0.03, p = 0.014]. The Cohen's d coefficients for MagD and MagD/Mag ratio were −1.122 and −1.143, respectively (Table 2 and Figs 3A and B).

A paired sample *t*-test was conducted to evaluate the impact of lowering IOP on MD 24–2 (n = four eyes) (Table 2). The results showed an increase in MD 24–2 from −0.26 ± 0.311 to 0.14 ± 0.226 [t (1) = −6.667, 95% CI = −1.16, 0.36, p = 0.095], but they did not reach any statistical significance. Cohen's d coefficient was −4.714.

A paired sample *t*-test was conducted (n = six eyes) to evaluate the impact of lowering IOP on average retinal nerve fiber layer thickness (avRNFLT) and average ganglion cell layer + inner plexiform layer thickness (avGCL + IPLT) (Table 2). The results showed that both variables improved after lowering IOP but did



Parameter	OD Hc	OD Lc	OS Hc	OS Lc
Magnitude (uV)	1.26	1.15	1.19	1.03
Magnitude	0.82	0.36	0.23	0.43
MagD/Mag Ratio	0.66	0.31	0.19	0.42
SNR (dB)	1.5	1.5	0.0	0.0
Artifacts	0	0	0	0

Fig. 2: Steady-state PERG results of a glaucoma suspect study subject with abnormal RGC function. Results are presented in numeric values as well as color coded (green means within reference range, yellow within borderline reference range, and red outside reference range). OD exhibits borderline RGC function, while OS demonstrates values outside the reference range, suggesting a severe RGC dysfunction. Hc, high contrast; Lc, low contrast; OD, right eye; OS, left eye; Mag, Magnitude; MagD, MagnitudeD; PERG, pattern electroretinogram; SNR, signal-to-noise ratio

not reach any statistical significance. Average RNFLT improved from 92.00 ± 2.00 to 93.00 ± 4.00 [t (1) = −0.500, 95% CI = −26.41, 24.41, $p = 0.705$], while avGCL + IPLT improved from 80.50 ± 2.081 to 81.00 ± 2.449 [t (3) = −1.732, 95% CI = −1.42, 0.42, $p = 0.182$].

Discussion

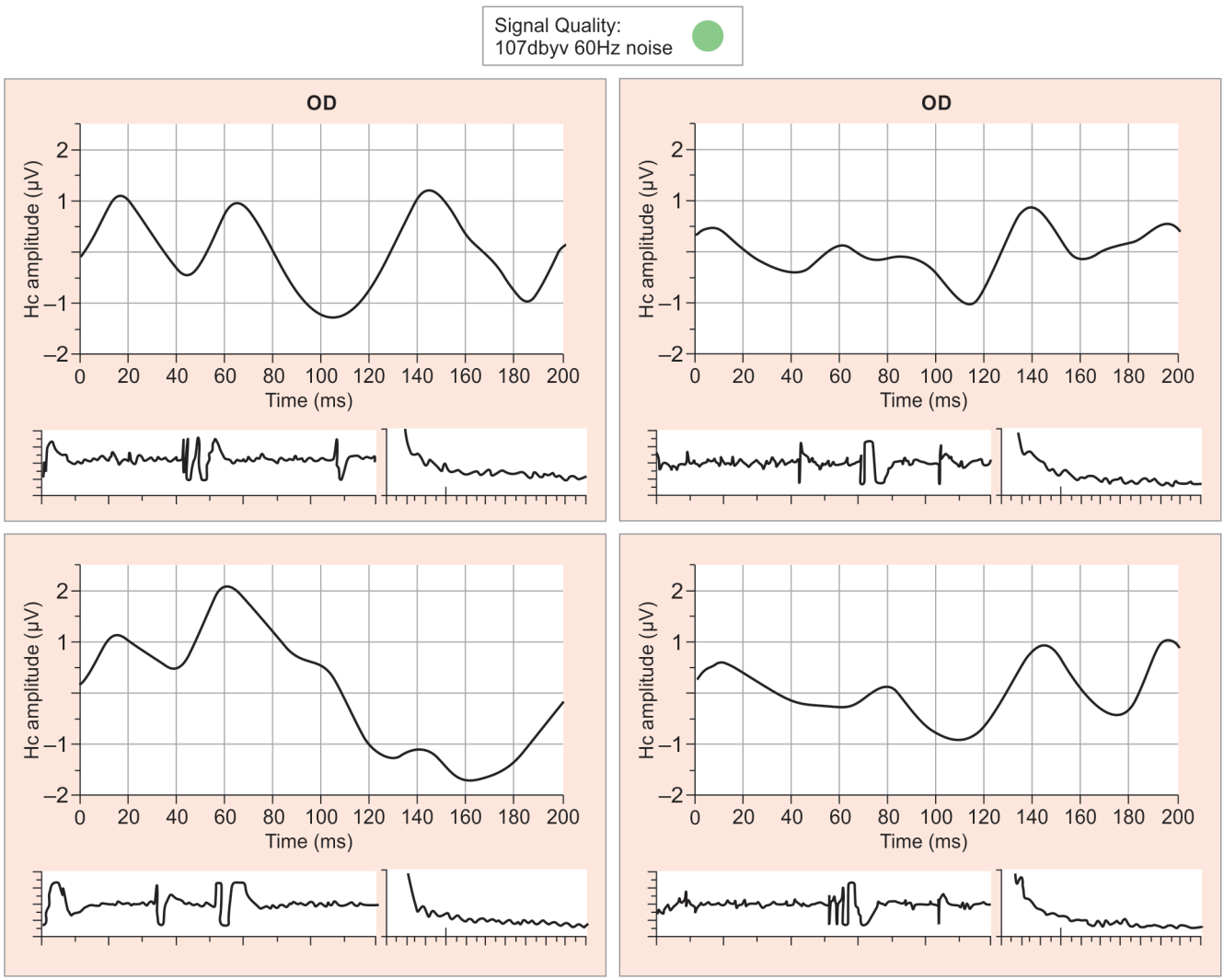
In this study, the results suggested that reducing IOP by approximately 22.29% for a duration of 3.1 months in newly diagnosed GS subjects with signs of RGC dysfunction significantly improved RGC function, as assessed by ss-PERG. Study subjects had no history of prior IOP-lowering treatment. Glaucomatous damage is generally believed to be irreversible, but recent cross-sectional studies have reported improvements in psychophysical visual sensitivity,[36] as well as ss-PERG amplitude.[6,13,15] These studies have demonstrated that a population of initially dysfunctional but living RGCs could restore function after IOP lowering therapies. Because IOP-lowering treatment may restore at least partial function of RGCs, IOP was considered to be the direct or indirect cause of RGC dysfunction.[13]

We have demonstrated that GS subjects presented at the baseline visit with mostly viable RGCs and signs of RGC dysfunction (decreased MagD and MagD/Mag ratio), in part because of an

increased IOP, which is the only modifiable risk factor. We reported that RGC dysfunction could be reversed by reducing IOP to an optimal percentage change of 22.29%. Mag, which is a measure of RGC loss, was found to decrease but still within the normal range (>1.0 μV). Similarly, MagD and MagD/Mag ratio were significantly decreased (normal range for MagD and MagD/Mag ratio >0.752), indicating that the study subjects were GS with significant RGC dysfunction and no electrophysiological evidence of major RGC loss (Table 1). In this study, we also reported improved HFA global indices, as well as increased avRNFLT and avGCL-IPLT, but the changes were not statistically significant ($n = 6$).

Quantification of RGC functional status was always of considerable interest to scientists, as well as to clinicians seeking new biomarkers for early diagnosis of glaucoma and monitoring the progression of the disease. However, the most crucial question is when to start treatment and how efficient the response to therapy (IOP-lowering and potentially non-IOP-lowering therapies) is for each patient case.[37]

In this study, ss-PERG optimized for glaucoma screening (PERGLA) was used because it is a noninvasive and objective functional test with high test-retest repeatability.[14,38,39] Furthermore, PERGLA relies on its incorporated normative data and uses Fourier transformation for noise reduction.[14,40] The glaucoma-specific PERGLA has been shown to be useful not only in detecting early glaucomatous RGC dysfunction but in assessing treatment efficacy as well.[37]



Parameter	OD Hc	OD Lc	OS Hc	OS Lc
Magnitude (uV)	1.32	1.16	0.96	0.97
Magnitude	0.87	0.38	0.48	0.62
MagD/Mag Ratio	0.66	0.33	0.50	0.64
SNR (dB)	2.9	2.0	0.0	0.5
Artifacts	2	3	3	3

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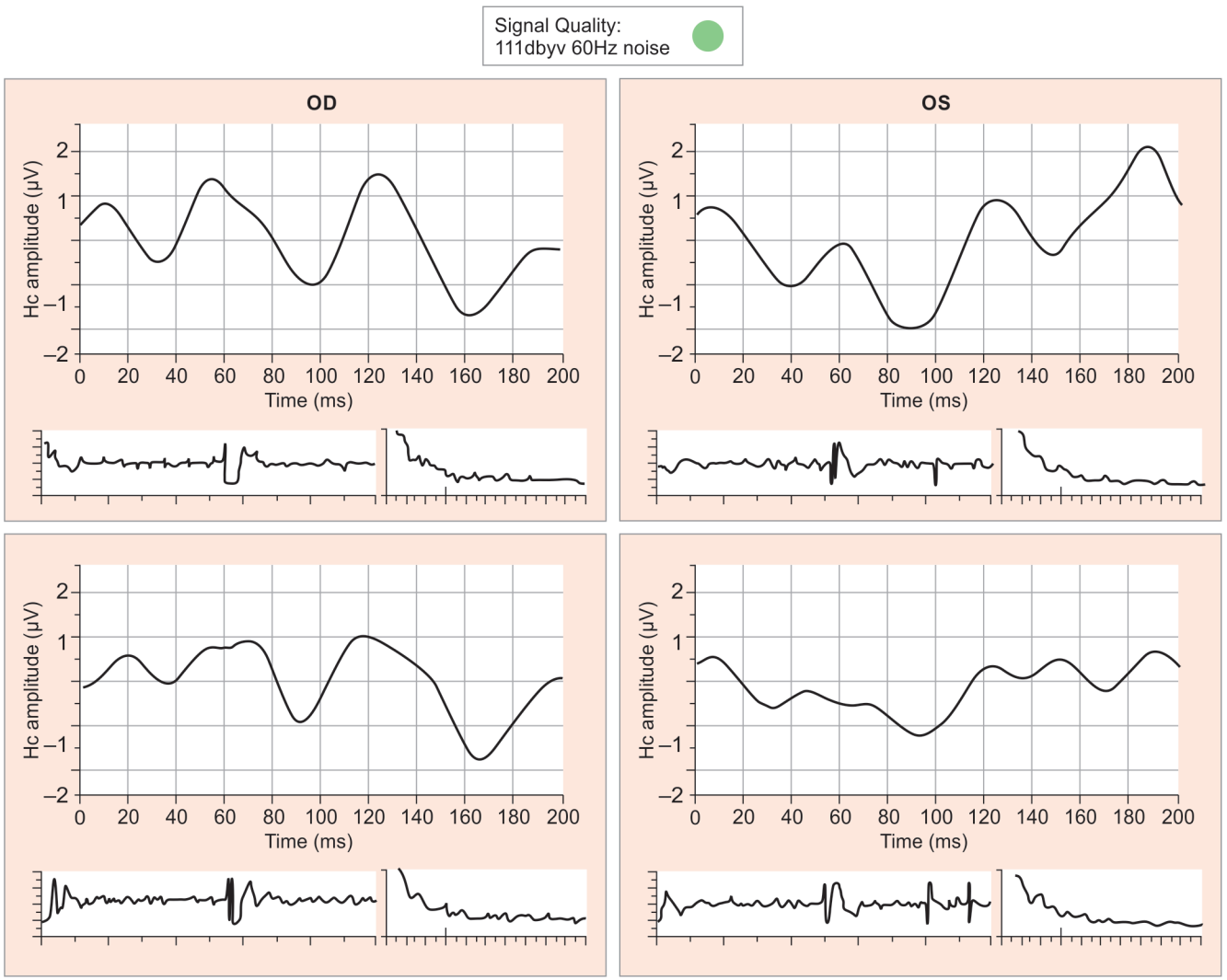


Parameter	OD Hc	OD Lc	OS Hc	OS Lc
Magnitude (uV)	1.89	1.25	1.42	0.99
Magnitude	1.36	0.56	0.12	0.44
MagD/Mag Ratio	0.57	0.56	0.69	0.45
SNR (dB)	1.6	2.0	1.0	0.0
Artifacts	2	1	0	2

Figs 3A and B: (A) Steady-state PERG results of glaucoma suspect study subject showing borderline RGC dysfunction OD and severe RGC dysfunction OS before treatment. Results are presented in numeric values as well as color coded (green means within reference range, yellow within borderline reference range, and red outside reference range). OD exhibits borderline RGC function, while OS demonstrates values outside the reference range. Hc, high contrast; Lc, low contrast; OD, right eye; OS, left eye; Mag, Magnitude; MagD, MagnitudeD; PERG, pattern electroretinogram; SNR, signal-to-noise ratio; (B) PERG test results showing significant RGC functional recovery in both eyes, when compared to figure 3A. MagD/Mag ratio of OS remained borderline. Results are presented in numeric values as well as color coded (green means within reference range, yellow within borderline reference range, and red outside reference range). Hc, high contrast; Lc, low contrast; OD, right eye; OS, left eye; Mag, Magnitude; MagD, MagnitudeD; PERG, pattern electroretinogram; SNR, signal-to-noise ratio

When healthy RGC are subjected to insults such as increased IOP or microvascular disturbances, they undergo morphological changes and become dysfunctional.[41] RGC soma and dendritic tree reduces in size, as well as their axons,[42] and these changes are believed to be reversible if the cells remain alive.[6]

In this study, we reported that average RNFL thickness measurements improved by 1.09%. Even though this positive percentage change was not statistically significant, its clinical significance is worth mentioning. A study by Knight et al. reported that the mean average RNFL thickness of normal subjects in the same type of spectral domain (SD)—OCT used in this study was 92.0 ± 10.8 μm.[43] We reported the mean RNFL thickness to be 84.67 ± 12.86 μm, which was very close to values reported in the same study in GS (88.1 ± 13.5 μm) and in mild glaucoma

(73.3 ± 11.8 μm).[43] We concluded that these study subjects were exhibiting some structural damage, mostly associated with the morphological RGC change, such as axonal reductions in diameter, as well as functional damage. Considering the age-related change in RNFL thickness per year in healthy subjects with an overall decrease of about 0.365 μm for every 1-year increase in age (<0.3%), we hypothesized that this change was less likely to occur since the study duration was only for 3 months.[44] Another factor to consider is the test-retest variability of RNFL thickness measurements using the identical SD-OCT device. Wadhwani et al. reported a variability up to 0.3 μm (coefficient of variation of 0.19%) in RNFL thickness measurements during three sessions in healthy subjects.[45] These findings suggest that the RNFL thickness improvements were in the right direction, especially considering that the reversal of structural abnormalities would possibly need >3 months to fully recover.

Similarly, we reported that avGCL + IPL thickness measurements improved by 0.62%. We reported that the mean avGCL + IPL in this study was 77.00 ± 8.03 μm while studies using the exact same type of SD-OCT in healthy subjects reported normal values between 80.4 ± 6.4 and 82.1 ± 6.2 μm, but the authors acknowledged that their reported values were higher than the ones reported in earlier studies.[46] Since age is not a factor in these results, the test-retest variability of GCL+IPL thickness was found to have a coefficient of variation of 0.09%. Based on this report, it would be safe to conclude that, even though the findings were not statistically significant, there was evidence of the reversal of morphological and structural changes occurring inside the RGCs as they were recovering their function.

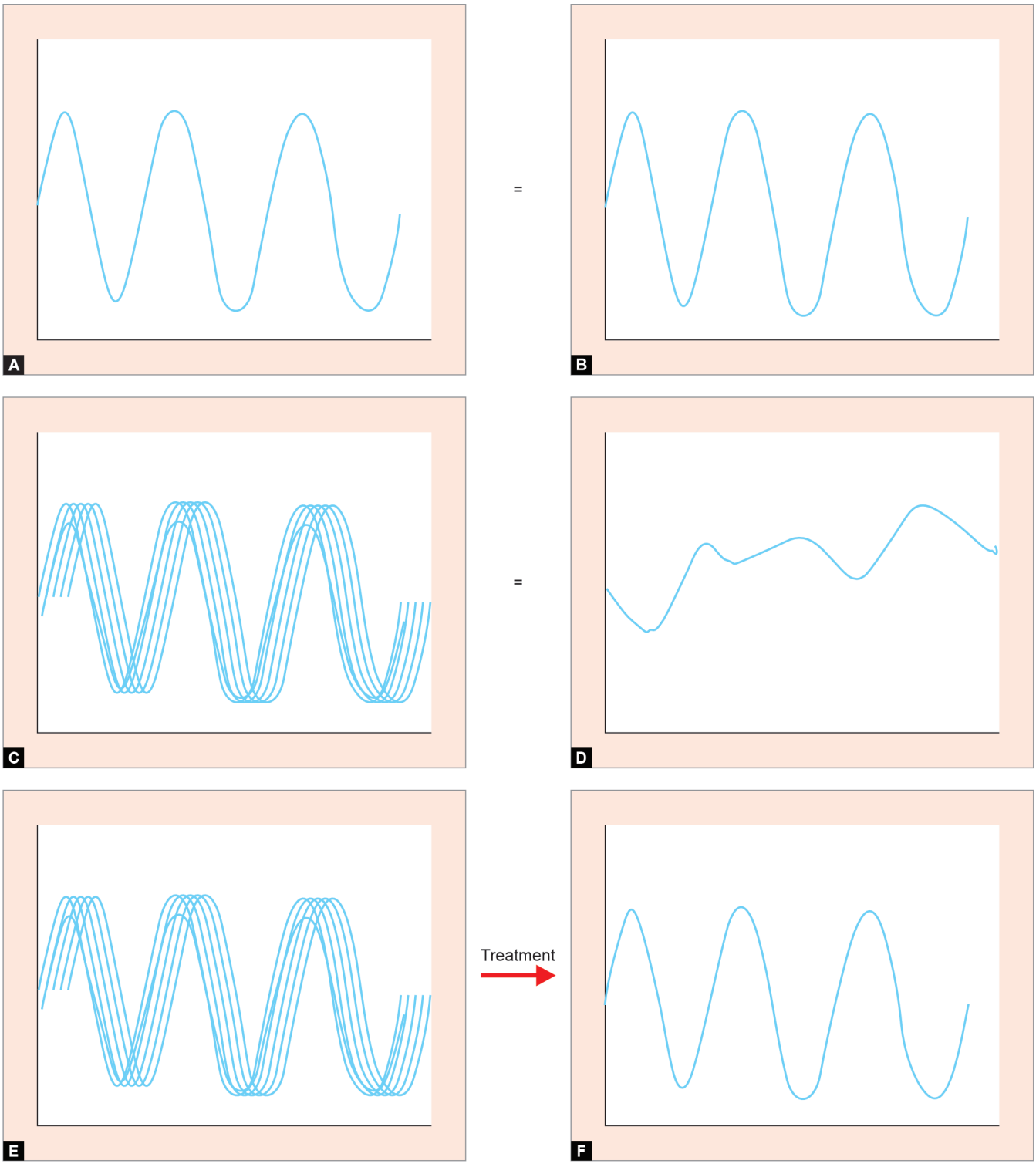
Appreciation of the cellular and axonal RGC dysfunction that precedes cell death in glaucoma highlights the need for early development of effective treatment and monitoring strategies during the window of opportunity. During this time, degenerating but still viable cells may be rescued from irreversible damage and possibly have RGC function restored.[47] As a first step in identifying that window of opportunity, this study has demonstrated the presence of RGC dysfunction by means of ss-PERG prior to treatment in newly diagnosed GS patients with signs of progression. The understanding that ss-PERG and 24–2 VF probe different visual functions and regions of the retina highlights that ss-PERG's global response of central RGCs allows for possible early detection of dysfunction of still viable RGCs while 24–2 VF is relatively insensitive to such central retinal activity.[6] Using ss-PERG, this study further demonstrated the improvement in RGC function after lowering IOP in these newly diagnosed, nontreated GS patients after 3 months of treatment. We found significant changes in ss-PERG parameters, particularly based on MagD, which have been shown to be useful for monitoring RGC function over.[10,25,48] Finally, this study used ss-PERG tests to determine the optimal percentage change in IOP that elicited a significant RGC functional recovery.

Retinal ganglion cell (RGC) dysfunction, based on damage or ultimate death of the RGCs, is a critical pathologic occurrence event in glaucoma that stresses the posterior structures of the eye and results in compression and deformation-related mechanical damage to the axons of RGCs, as well as interruption of axonal transport.[49] RGCs are central nervous system neurons with cell bodies in the inner retina and axons located in the optic nerve. Due to the optic nerve's composition of RGC axons, any damage to the optic nerve results in changes to the ganglion cell layer, RNFL, intrapapillary region of the ONH, and ONH morphology.[8] The correlation between RNFL thickness and SAP test sensitivity has shown approximately 40% loss of the functional RNFL in preperimetric glaucoma patients.[50] The damaged RGCs are also responsible for the secondary degeneration of adjacent neuronal cells.[32] RGC apoptosis is an early manifestation of cell death in glaucoma, and a number of studies have found that over 25% of RGCs may be lost before normal field tests are able to discriminate VF deficiencies.[32,51]

In glaucoma practice, the current opinion is that structural change found on OCT and ONH, such as RNFL thinning, precede functional tests as measured by VF testing.[6] Meanwhile, studies have shown that there is a time lag between PERG amplitude and RNFL thickness to lose 10% of their initial values, on the order of 8 years.[12,13] Our results using ss-PERG underlie this new concept—in GS, reversible RGC dysfunction, measured by means of PERG, may precede RGC death and subsequent structural damage.

The PERG can be used to objectively evaluate RGC function since RGC death and dysfunction can alter the waveform of the ss-PERG.[34] The ss-PERG allows for the assessment of RGC function in the retina, providing objective measurements that are repeatable and noninvasive.[52] There are two distinct aspects to the PERGLA paradigm—amplitude and phase.[51] The PERG amplitude (Mag) is proportional to the number of contributing RGC at a retina location.[47] That is, the response amplitude is related to the number and vitality of the RGCs contributing to the electrical signal.[53] A reduced signal may result from lost or dying and dysfunctional RGC in relation to remaining healthy cells in unknown relative proportion.[46] PERG phase or latency (MagD) is temporal phase lag, which indicates the vitality of the activated neurons, with a larger lag representing a slower generation of the electrical signal by the activated cells.[53] A delayed PERG latency may show viable but distressed RGCs that are responding in a desynchronized manner.[3] Figure 1 is demonstrates a PERG report from a control subject with normal RGC function, while Figure 2 shows a GS subject with different aspects of RGC dysfunction. Figure 4 illustrates MagD signal generation in subjects with normal RGC function (A-B) and in GS subjects with RGC dysfunction (C-D), demonstrating a flattened sinusoidal curve with a decreased Mag after accounting for the latency. In early stages of glaucoma, the total RGC population consists of RGCs with normal function, dysfunctional RGCs, and nonviable cells undergoing different stages of degeneration.[15] In this study, as expected, we reported that Mag (the denominator in the MagD/Mag ratio) did not improve after the treatment, since it is a marker for RGC death. This result highlighted the fact that if there were nonviable RGCs, they did not come back to life to improve the Mag parameter dramatically. On the contrary, MagD (the numerator) improved significantly, and now the population of viable but dysfunctional RGCs with delayed responses recovered their functionality to fire in synchronicity (Fig. 4). The ratio only reflects these changes and confirms the relationships between different RGC populations.

A number of studies have shown that RGC dysfunction may be reversed, at least partially, by reducing IOP.[6,33,47] In a study of glaucoma patients with surgical IOP reduction of approximately 47% on average, reversal of RGC dysfunction was shown and was quantifiable using PERG.[15] In a more recent study, preperimetric glaucoma patients were given daily IOP-lowering therapy for a period of 1 month that significantly decreased IOP by an average of 31%, and based on PERG measurement before and after the treatment period, improved RGC function was shown.[28] However, in another study, patients who achieved a mean reduction in IOP of 20% based on treatment with latanoprost did not show significant changes in PERG amplitude, meaning the treatment was insufficient to improve the signal generated by RGC.[30] From a review of these research projects, there still remains a need to identify a target IOP for



Figs 4A to F: (A) MagnitudeD generation in healthy (A-B) and in glaucoma subjects (CD). RGC functional restoration following IOP lowering treatment (E-F). Normal function of multiple RGCs responding to a pattern stimulus, resulting in a response in phase with no delays and no latencies; (B) The result is one unique sinusoidal curve with overlying identical synchronized responses (normal latency); (C) Multiple dysfunctional RGCs responding to a pattern stimulus resulting in out of phase response (increased latency) demonstrating a desynchronized response; (D) The result is an abnormal sinusoidal curve with a tendency to flatten and with a decreased amplitude; (E) Dysfunctional multiple desynchronized RGCs in GS (increased latency); (F) The result following treatment demonstrating a return to normal latency, depicted by one unique sinusoidal curve with overlying identical synchronized responses

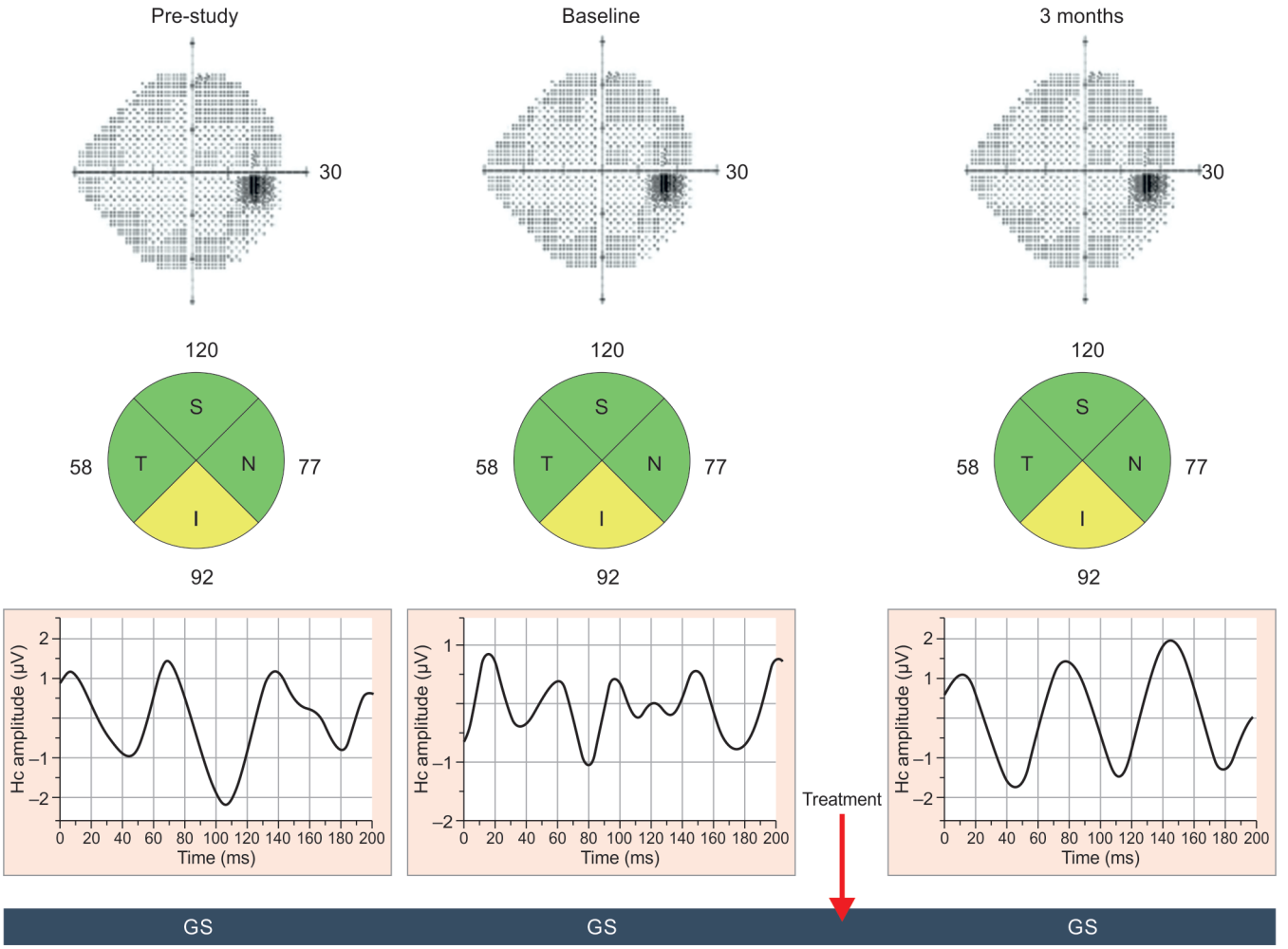


Fig. 5: Summary of the study—model of RGC functional deterioration in glaucoma suspect subjects during a two-visit course with subsequent treatment over a 3-month period. PERG showing complete RGC functional recovery

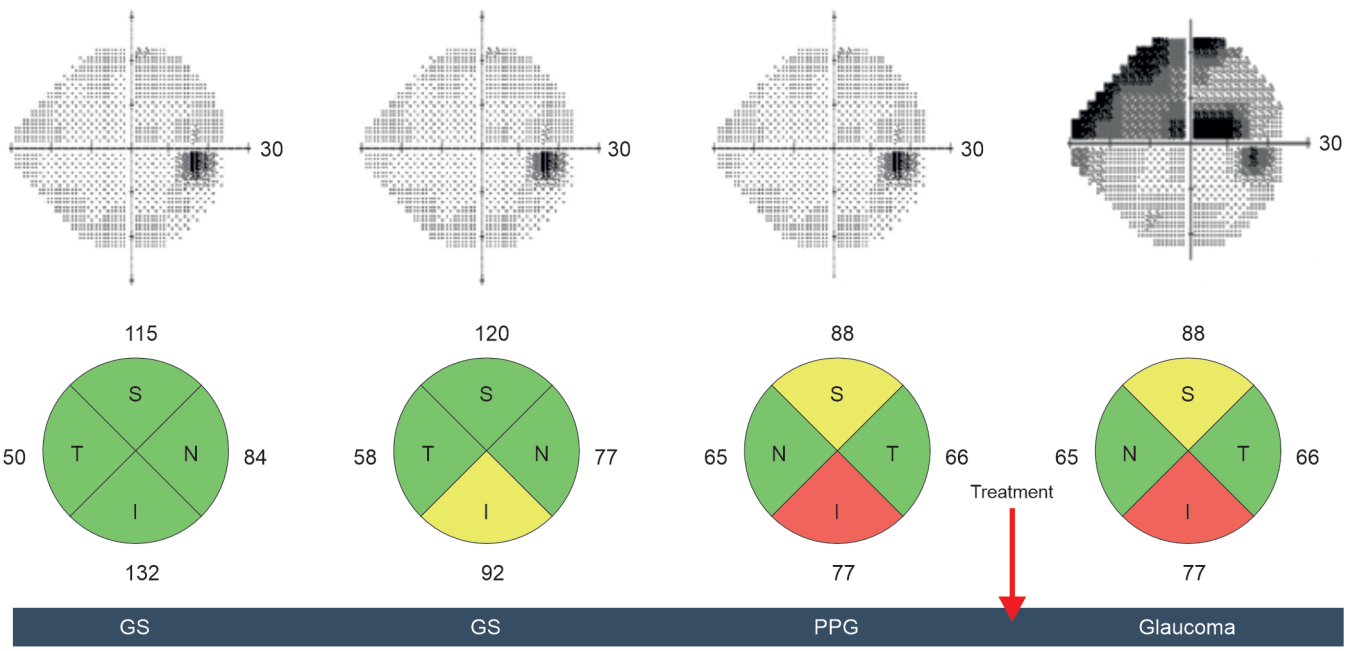


Fig. 6: Current assessment and management of glaucoma suspect

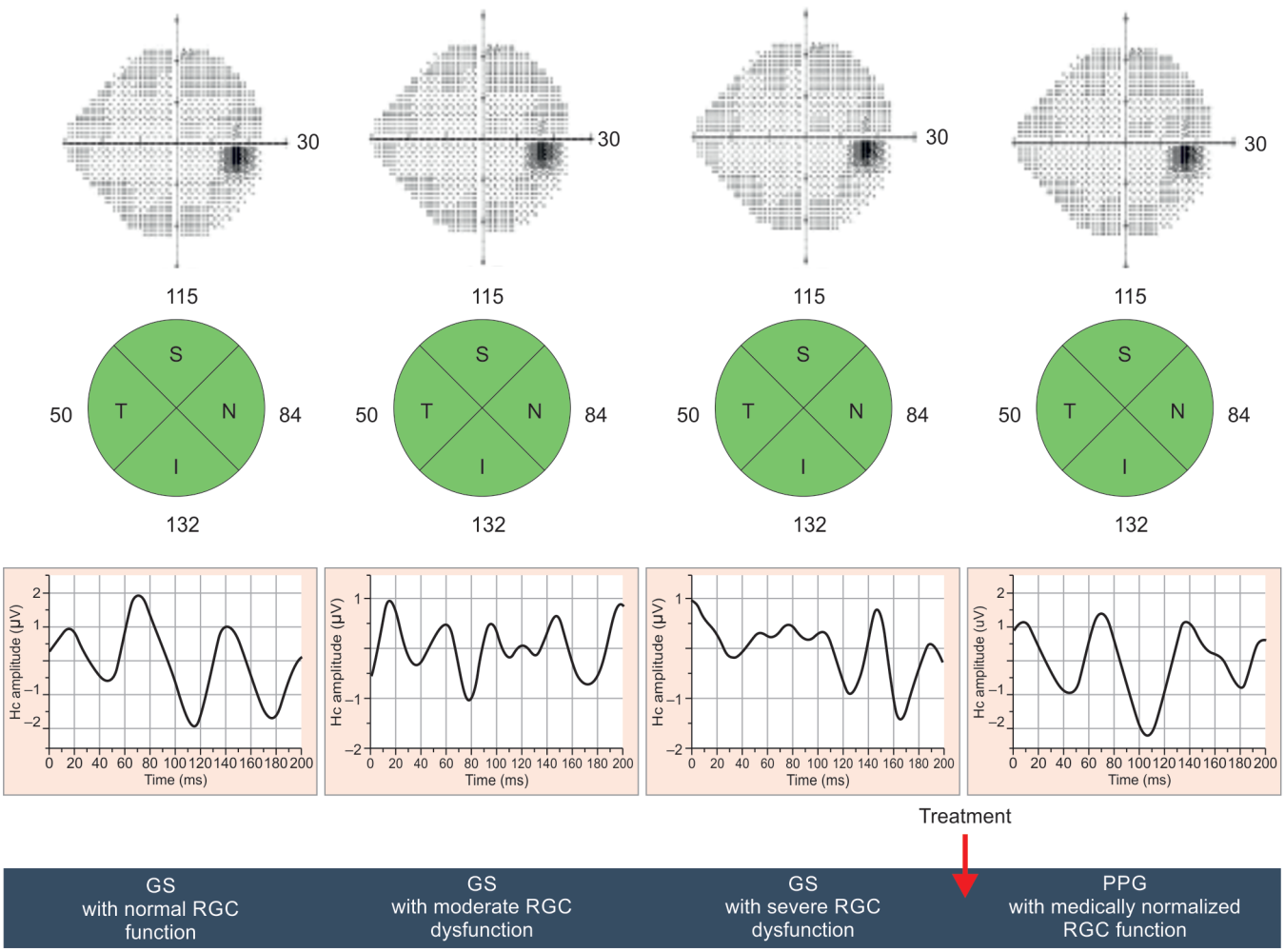


Fig. 7: Suggested assessment and management of glaucoma suspect

a treatment program—that is, the lowest achievable IOP reduction expected to prevent further glaucomatous damage or at least to slowdown the disease progression. In this study, we proposed IOP reduction of at least 20% in order to achieve dysfunction reversal.

The IOP elevation affects not only the visual field but also mechanics of the eye and its nerves. Toward the back of the eye, in front of the optic nerve, lies the lamina cribrosa. The lamina cribrosa is the main structural element of the ONH that forms the bottom of the optic cup on the inner surface of the ONH.[54] The lamina cribrosa allows the RGC axons and the central retinal vein to leave the eye, the central retinal artery to enter the intraocular space, and stabilizes the IOP by forming a barrier between the intraocular space and the extraocular space.[54] Because of this, when there is an IOP elevation, the lamina cribrosa is affected. The lamina cribrosa has micropores in it, which allow the RGC axons to pass through and connect into the brain. If IOP is elevated, the once horizontally located lamina cribrosa will become more of a "U shape," deflecting posteriorly without affecting its thickness.[54] Because of this, the web of nerves in the lamina cribrosa will become compressed and the axonal transport and blood supply will get compromised.

It has been shown that reducing IOP in patients with ocular hypertension or glaucoma may result in significant improvement of PERG amplitude and/or phase, which is indicative of cell function restoration since ss-PERG reflects both RGC death and dysfunction of viable RGC.[6,28] For some RGC, there may be an IOP-dependent dysfunction causing ss-PERG reduction that is reversible with IOP-reducing treatment, showing that in early stages of glaucoma, reversible dysfunction may precede cell death.[6] It has been demonstrated that neuronal activity can eliminate apoptosis, meaning early detection of functional deficits prior to death allows for the possibility of synaptic function enhancement in sick RGCs to attempt to avoid vision loss in glaucoma.[3] Reduction of IOP, with a return to more normal pressure levels, has been shown to stop deformation of the tissues building ONH and can facilitate axonal flow to allow for the transport of intracellular nutrients, protein biosynthesis, and glycolysis.[28] Early detection and treatments are crucial because it has been shown that greater PERG improvement is associated with normal or early altered VFs as opposed to eyes with more severe VF defects.[6] Because of this relationship between PERG improvements and the extent of VF loss, eyes with preserved VF would have a larger population of viable RGCs when compared with advanced glaucoma stages with severe VF defects and severely decreased populations of viable RGC.

In evaluating the RGC activity before and after treatment using ss-PERG, we undertook the task of measuring reversal of RGC dysfunction in GS patients who have undergone IOP reduction therapy. We report that these RGCs in GS have an IOP-dependent dysfunction causing ss-PERG parameters to be reduced, and we have shown that RGCs dysfunction was reversible with an IOP-lowering treatment.

As mentioned previously, our study is not the first to explore the reversal of RGC dysfunction, with lowering of IOP,[6,15,28,47,54] with some studies even noting improvement in psychophysical visual sensitivity.[36] However, this is the first study to report a target percentage change in IOP that would elicit a significant functional recovery, as reflected by ss-PERG testing. Furthermore, this study is also the first to report a quantified measure of RGC functional recovery, up to 32.29% after 3 months of treatment. It is worth highlighting the much-improved MagD, which underlies the reversal of RGC dysfunction. A summary of the study and the current assessment and management of GS is shown in Figures 5 and 6. Based on the study findings, we propose a novel approach for GS assessment and management using ss-PERG technologies (Fig. 7). Figure 7 demonstrates different severity stages of glaucoma and corresponding diagnostic tests, as well as a model of RGC loss relative to time. These figures will illustrate the importance of early glaucoma diagnosis and its improved management using ss-PERG.

This pilot study had limitations. The sample size was small, and some VF and OCT data on follow-up visits were not available. Therefore, we cannot recommend a change to current clinical practice at this time. Additionally, the period of this study was not long enough to capture the long-term validity of PERG as a screening tool. Furthermore, different glaucoma stages would have been helpful to compare the percent recovery for each stage of the disease, and we cannot account for the slow conversion rate of glaucoma. ss-PERG has also been shown to be prone to significant variability due to noise, adaptation, and fluctuation.[55] It should be acknowledged that electroretinography is a costly investment for both patients and institutions, which greatly limits accessibility. As our study is not conclusive on the reliability of ss-PERG as a screening tool in clinical practice, caution and thought should be taken before commitment to evaluation with this device. Future prospective studies with larger sample sizes are needed to better understand the relationship between ss-PERG improvement and IOP reductions, as well as their relationships with other structural and functional measures such as OCTA, including a varied spectrum of disease severity.

Conclusion

After reducing IOP by 22.29% after a duration of 3.1 months posttreatment, ss-PERG parameters, MagD, and MagD/Mag ratio improved, with the most improved variable being MagD. Lowering IOP additionally yielded improvement in VF test variables. Although OCT variables had an increased percentage change after treatment, this was not statistically significant. These results highlight the reversibility of RGC dysfunction in GS. Considering the cellular and axonal processes that are involved in the pathogenesis of glaucoma, we appreciate the possibility of ss-PERG as a tool to elucidate a window of opportunity in which degenerating yet viable RGCs may be rescued from irreversible damage.

Clinical Significance

Although our study has a short period and few participants, we hope to highlight the potential of ss-PERG as a screening tool in monitoring the effectiveness of IOP-lowering treatment with the goal of improving glaucoma management. Additionally, we propose a target IOP reduction of 22.29% for the improvement of the RGC function in GS.

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References

1. Porciatti V. Electrophysiological assessment of retinal ganglion cell function. Exp Eye Res 2015;141:164–170. DOI: 10.1016/j.exer.2015.05.008
2. Križaj D. Webvision: The Organization of the Retina and Visual System. 2019.
3. Jafarzadehpour E, Radinmehr F, Pakravan M, et al. Pattern electroretinography in glaucoma suspects and early primary open angle glaucoma. J Ophthalmic Vis Res 2013;8(3):199–206. PMID: 24349662.
4. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:701–713. DOI: 10.1001/archopht.120.6.701
5. Tan JC, Kaufman PL. Primary open angle glaucoma. In: Yanoff M, Duker JS (Eds). Ophthalmology, 5th edition. Philadelphia, Pennsylvania, United States: Saunders, Elsevier; 2019. pp. 1057–1060.
6. Ventura LM, Porciatti V. Restoration of retinal ganglion cell function in early glaucoma after intraocular pressure reduction: a pilot study. Ophthalmology 2005;112(1):20–27. DOI: 10.1016/j.ophtha.2004.09.002
7. Kerrigan-Baumrind L, Quigley H, Pease M, et al. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. Invest Ophthalmol Vis Sci 2000;41(3):741–748. PMID: 10711689.
8. Tirsi A, Gliagias V, Moehringer J, et al. Pattern electroretinogram parameters are associated with optic nerve head morphology abnormalities in pre-perimetric glaucoma after controlling for disc area. J Ophthalmol 2021;2021:8025337. DOI: 10.1155/2021/8025337
9. Medeiros FA, Zangwill LM, Bowd C, et al. The structure and function relationship in glaucoma: implications for detection of progression and measurement of rates of change. Invest Ophthalmol Vis Sci 2012;53(11):6939–6946. DOI: 10.1167/iovs.12-10345
10. Gillmann K, Mansouri K, Rao HL, et al. A prospective evaluation of the repeatability and reliability of new steady-state pattern electroretinogram parameters. J Glaucoma 2018;27(12):1079–1085. DOI: 10.1097/IJG.0000000000001103
11. Kreft D, Doblhammer G, Guthoff RF, et al. Prevalence, incidence, and risk factors of primary open-angle glaucoma - a cohort study based on longitudinal data from a German public health insurance. BMC Public Health 2019;19(1):851. DOI: 10.1186/s12889-019-6935-6
12. Kuang TM, Zhang C, Zangwill LM, et al. Estimating lead time gained by optical coherence tomography in detecting glaucoma before development of visual field defects. Ophthalmology 2015;122(10):2002–2009. DOI: 10.1016/j.ophtha.2015.06.015
13. Banitt MR, Ventura LM, Feuer WJ, et al. Progressive loss of retinal ganglion cell function precedes structural loss by several years in glaucoma suspects. Invest Ophthalmol Vis Sci 2013;54(3):2346–2352. DOI: 10.1167/iovs.12-11026
14. Porciatti V, Ventura LM. Normative data for a user-friendly paradigm for pattern electroretinogram recording. Ophthalmology 2004;111(1):161–168. DOI: 10.1016/j.ophtha.2003.04.007
15. Sehi M, Grewal DS, Goodkin ML, et al. Reversal of retinal ganglion cell dysfunction after surgical reduction of intraocular pressure. Ophthalmology 2010;117(12):2329–2336. DOI: 10.1016/j.ophtha.2010.08.049
16. Fortune B, Bui BV, Morrison JC, et al. Selective ganglion cell functional loss in rats with experimental glaucoma. Invest Ophthalmol Vis Sci 2004;45(6):1854–1862. DOI: 10.1167/iovs.03-1411
17. Hare WA, Hau T. Effects of APB, PDA, and TTX on ERG responses recorded using both multifocal and conventional methods in monkey. Effects ofAPB, PDA, and TTX on monkey ERG responses. Doc Ophthalmol 2002;105(2): 189–222. DOI: 10.1023/a:1020553020264
18. Hood DC, Frishman LJ, Viswanathan S, et al. Evidence for a ganglion cell contribution to the primate electroretinogram (ERG): effects of TTX on the multifocal ERG in macaque. Vis Neurosci 1999;16(3):411–416. DOI: 10.1017/s0952523899163028

19. Viswanathan S, Frishman L, Robson J. The uniform field and pattern erg in macaques with experimental glaucoma: removal of spiking activity. Invest Ophthalmol Vis Sci 2000;41:2797–2810. PMID: 10937600.
20. Papst N, Bopp M, Schnaudigel OE. The pattern evoked electroretinogram associated with elevated intraocular pressure. Graefes Arch Clin Exp Ophthalmol 1984;222(1):34–37. DOI: 10.1007/BF02133775
21. Arden GB, O' Sullivan F. Longitudinal follow up of glaucoma suspects tested with pattern electroretinogram. Bull Soc Belge Ophtalmol 1992;244:147–154. PMID: 1363653.
22. Nesher R, Trick GL, Kass MA, et al. Steady-state pattern electroretinogram following long term unilateral administration of timolol to ocular hypertensive subjects. Doc Ophthalmol 1990;75(2):101–109. DOI: 10.1007/BF00146546
23. Falsini B, Colotto A, Porciatti V, et al. Follow-up study with pattern ERG in ocular hypertension and glaucoma patients under timolol maleate treatment. Clin Vision Sci 1992;7:341–347.
24. Colotto A, Salgarello T, Giudiceandrea A, et al. Pattern electroretinogram in treated ocular hypertension: a cross-sectional study after timolol maleate therapy. Ophthalmic Res 1995;27(3):168–177. DOI: 10.1159/000267663
25. Kremmer S, Tolksdorf-Kremmer A, Stodtmeister R. Simultane ableitung von VECP und muster-ERG bei küunstlicher erhöhung des augeninnendrucks. Ophthalmologica 1995;209:233–241. DOI: 10.1159/000310622
26. Colotto A, Falsini B, Salgarello T, et al. Transiently raised intraocular pressure reveals pattern electroretinogram losses in ocular hypertension. Invest Ophthalmol Vis Sci 1996;37(13):2663–2670. PMID: 8977480.
27. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Ophthalmol 2002;120(10):1268–1279. DOI: 10.1001/archopht.120.10.1268
28. Karaśkiewicz J, Penkala K, Mularczyk M, et al. Evaluation of retinal ganglion cell function after intraocular pressure reduction measured by pattern electroretinogram in patients with primary open-angle glaucoma. Doc Ophthalmol 2017;134(2):89–97. DOI: 10.1007/s10633-017-9575-0
29. Dietlein TS, Hermann MM, Jordan JF. The medical and surgical treatment of glaucoma. Dtsch Arztebl Int 2009;106(37):597–605. DOI: 10.3238/arztebl.2009.0597
30. Sehi M, Grewal DS, Feuer WJ, et al. The impact of intraocular pressure reduction on retinal ganglion cell function measured using pattern electroretinogram in eyes receiving latanoprost 0.005% versus placebo. Vision Res 2011;51(2):235–242. DOI: 10.1016/j.visres.2010.08.036
31. Al-Nosairy KO, Hoffmann MB, Bach M. Non-invasive electrophysiology in glaucoma, structure and function—a review. Eye (Lond) 2021;35(9):2374–2385. DOI: 10.1038/s41433-021-01603-0
32. Wen JC, Lee CS, Keane PA, et al. Forecasting future humphrey visual fields using deep learning. PLOS One 2019;14(4):e0214875. DOI: 10.1371/journal.pone.0214875
33. Tirsi A, Orshan D, Wong B, et al. Associations between steady-state pattern electroretinography and estimated retinal ganglion cell count in glaucoma suspects. Doc Ophthalmol 2022;145(1):11–25. DOI: 10.1007/s10633-022-09869-9
34. Orshan D, Tirsi A, Sheha H, et al. Structure-function models for estimating retinal ganglion cell count using steady-state pattern electroretinography and optical coherence tomography in glaucoma suspects and preperimetric glaucoma: an electrophysiological pilot study. Doc Ophthalmol 2022;145(3):221–235. DOI: 10.1007/s10633-022-09900-z
35. Tirsi A, Wong A, Zhu D, et al. Pattern electroretinogram parameters and their associations with optical coherence tomography in glaucoma suspects. J Curr Glaucoma Pract 2022;16(2):96–104. DOI: 10.5005/jp-journals-10078-1365
36. Gandolfi SA, Cimino L, Sangermani C, et al. Improvement of spatial contrast sensitivity threshold after surgical reduction of intraocular pressure in unilateral high-tension glaucoma. Invest Ophthalmol Vis Sci 2005;46(1):197–201. DOI: 10.1167/iovs.04-0199
37. Sehi M, Pinzon-Plazas M, Feuer WJ, et al. Relationship between pattern electroretinogram, standard automated perimetry, and optic nerve structural assessments. J Glaucoma 2009;18(8):608–617. DOI: 10.1097/IJG.0b013e31819afb5c
38. Bowd C, Vizzeri G, Tafreshi A, et al. Diagnostic accuracy of pattern electroretinogram optimized for glaucoma detection. Ophthalmology 2009;116(3):437–443. DOI: 10.1016/j.ophtha.2008.10.026
39. Fredette MJ, Anderson DR, Porciatti V, et al. Reproducibility of pattern electroretinogram in glaucoma patients with a range of severity of disease with the new glaucoma paradigm. Ophthalmology 2008;115(6):957–963. DOI: 10.1016/j.ophtha.2007.08.023
40. Holder GE, Brigell MG, Hawlina M, et al. ISCEV standard for clinical pattern electroretinography–2007 update. Doc Ophthalmol 2007;114(3):111–116. DOI: 10.1007/s10633-007-9053-1
41. Jeon SJ, Park HL, Jung KI, et al. Relationship between pattern electroretinogram and optic disc morphology in glaucoma. PLoS One 2019;14(11):e0220992. DOI: 10.1371/journal.pone.0220992
42. Liu M, Duggan J, Salt TE, et al. Dendritic changes in visual pathways in glaucoma and other neurodegenerative conditions. Exp Eye Res 2011;92(4):244–250. DOI: 10.1016/j.exer.2011.01.014
43. Knight OJ, Chang RT, Feuer WJ, et al. Comparison of retinal nerve fiber layer measurements using time domain and spectral domain optical coherent tomography. Ophthalmology 2009;116(7):1271–1277. DOI: 10.1016/j.ophtha.2008.12.032
44. Celebi AR, Mirza GE. Age-related change in retinal nerve fiber layer thickness measured with spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 2013;54(13):8095–8103. DOI: 10.1167/iovs.13-12634
45. Wadhwani M, Bali SJ, Satyapal R, et al. Test-retest variability of retinal nerve fiber layer thickness and macular ganglion cell-inner plexiform layer thickness measurements using spectral-domain optical coherence tomography. J Glaucoma 2015;24(5):e109–115. DOI: 10.1097/IJG.0000000000000203
46. Mwanza JC, Durbin MK, Budenz DL, et al. Profile and predictors of normal ganglion cell–inner plexiform layer thickness measured with frequency-domain optical coherence tomography. Invest Ophthalmol Vis Sci 2011;52(11):7872–7879. DOI: 10.1167/iovs.11-7896
47. Porciatti V, Chou TH. Modeling retinal ganglion cell dysfunction in optic neuropathies. Cells 2021;10(6):1398. DOI: 10.3390/cells10061398
48. Ahmad, SS. Glaucoma suspects: a practical approach. Taiwan J Ophthalmol 2018;8(2):74–81. DOI: 10.4103/tjo.tjo_106_17
49. Shiga Y, Aizawa N, Tsuda S, et al. Preperimetric glaucoma prospective study (PPGPS): predicting visual field progression with basal optic nerve head blood flow in normotensive PPG eyes. Transl Vis Sci Technol 2018;7(1):11. DOI: 10.1167/tvst.7.1.11
50. Kim SH, Jeoung JW, Park KH, et al. Correlation between retinal nerve fiber layer thickness and visual field sensitivity: diffuse atrophy imaging study. Ophthalmic Surg Lasers Imaging 2012;43(6 Suppl):S75–S82. DOI: 10.3928/15428877-20121001-01
51. Kudrna JJ, Ferguson TJ, Swan RJ, et al. Short-term steady-state pattern electroretinography changes using a multi-pressure dial in ocular hypertensive, glaucoma suspect, and mild open-angle glaucoma patients: a randomized, controlled, prospective, pilot study. Ophthalmol Ther 2020;9(4):981–992. DOI: 10.1007/s40123-020-00302-5
52. Ventura LM, Porciatti V, Ishida K, et al. Pattern electroretinogram abnormality and glaucoma. Ophthalmology 2005;112(1):10–19. DOI: 10.1016/j.ophtha.2004.07.018
53. Porciatti V, Ventura LM. Physiologic significance of steady-state pattern electroretinogram losses in glaucoma: clues from simulation of abnormalities in normal subjects. J Glaucoma 2009;18(7):535–542. DOI: 10.1097/IJG.0b013e318193c2e1
54. Gordon PS, Kostic M, Monsalve PF, et al. Long-term PERG monitoring of untreated and treated glaucoma suspects. Doc Ophthalmol 2020;141(2):149–156. DOI: 10.1007/s10633-020-09760-5
55. Triolo G, Toft-Nielsen J, Monsalve P, et al. Physiological and noise components of the PERG intrinsic variability. Invest Ophthalmol Vis Sci 2015;56(7):467.