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Relationship between Pattern Electretinogram, Standard Automated Perimetry, and Optic Nerve Structural Assessments

Mitra Sehi, PhD, Mariana Pinzon-Plazas, MD, William J. Feuer, MS, and David S. Greenfield, MD

From the Department of Ophthalmology, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, Palm Beach Gardens, FL

Abstract

Purpose—To examine the relationship between retinal ganglion cell function measured using pattern electretinogram optimized for glaucoma screening (PERGLA), retinal nerve fiber layer (RNFL) thickness and optic nerve head topography.

Methods—Twenty-nine normal, 28 glaucoma and 37 glaucoma suspect volunteers were enrolled. All participants were age-similar. One randomly selected eye underwent complete eye examination, standard automated perimetry (SAP), scanning laser polarimetry with enhanced corneal compensation (GDxECC), optical coherence tomography (OCT), Heidelberg retina tomograph (HRT) and PERGLA measurements. PERGLA amplitude (microvolt) was converted to decibel for comparison with SAP mean deviation (MD) and pattern standard deviation. The correlation between PERGLA amplitude in dB and the average of sensitivity values for 16 central test locations of SAP were calculated. Analysis of variance, Pearson and Spearman rank correlations, coefficient of variation (CoV) and intraclass correlation coefficients (ICC) were calculated.

Results—PERGLA amplitude in glaucomatous eyes was significantly lower than normal eyes (0.47 ± 0.20 vs. $0.70 \pm 0.28 \mu\text{v}$, $p < 0.001$) but not glaucoma suspects ($0.54 \pm 0.21 \mu\text{v}$, $p = 0.84$). PERGLA amplitude was inversely correlated with age ($r = -0.31$, $p = 0.002$). PERGLA amplitude (in dB) was associated with the sensitivity values of the SAP central 16 test locations ($r = 0.40$, $p < 0.001$) across the entire cohort, GDxECC superior RNFL thickness ($r = 0.38$, $p < 0.001$) and HRT Moorfields regression analysis classification ($\rho = -0.34$, $p = 0.001$). The CoV and ICC were 14.5% and 0.89 for PERGLA amplitude, 2.4% and 0.98 for OCT average RNFL, 2.2% and 0.97 for GDxECC TSNIT average and 6.3% and 0.94 for HRT rim area.

Conclusion—Retinal ganglion cell function measured using PERGLA is reduced in glaucoma and demonstrates modest correlations with central SAP sensitivity values, and structural measures of optic nerve topography and RNFL thickness.

Keywords

glaucoma; pattern electretinogram; retinal ganglion cells; nerve fiber layer; optic nerve

Inquiries to: Mitra Sehi, PhD; Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 7101 Fairway Drive, Palm Beach Gardens, FL 33418, USA. Phone: (561) 515-1500; Email: msehi@med.miami.edu.

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Introduction

Glaucoma is a multifactorial optic neuropathy known to cause progressive loss of retinal ganglion cells and their axons. Imaging technologies such as confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph, HRT, Heidelberg Engineering, Germany), scanning laser polarimetry (GDxVCC, Carl Zeiss Meditec, Dublin, CA), and optical coherence tomography, (OCT, Carl Zeiss Meditec, Dublin, CA) provide objective and quantitative measurements that are highly reproducible and show good agreement with clinical estimates of optic nerve head structure and visual function.^{1–6} Modern imaging devices are associated with high levels of reproducibility^{7–11} incorporate age-matched normative data, and allow non-invasive assessment of optic nerve topography and peripapillary retinal nerve fiber layer (RNFL) thickness^{12–16} through an undilated pupil. Recent advances in imaging technology have included a GDx enhancement module for corneal compensation (enhanced corneal compensation, GDxECC) which reduces atypical birefringence patterns that may confound glaucoma detection^{17–20} and expansion of the HRT normative database with optic nerve classifications (glaucoma probability score, GPS) that employ a contour line independent neural network analysis.^{21–23} Pattern electroretinogram optimized for glaucoma screening (PERGLA) is an objective technique for assessment of retinal ganglion cell (RGC) activity and has been reported to have high test-retest repeatability.²⁴ In contrast with conventional PERG, PERGLA employs cutaneous electrodes instead of corneal electrodes,²⁵ 26 has an incorporated normative database, and employs Fourier transformation for noise reduction. PERGLA measures retinal biopotentials that are evoked when a steady-state patterned stimulus with alternating black and white grating at 16.28 reversals/second (8.14 Hz) is viewed.²⁴ 27 In experimental models of glaucoma, using a suprathreshold stimulus, it has been demonstrated that changes in PERG are associated with reduced RGC activity.²⁸ Preliminary data suggest that PERGLA abnormalities exist early in glaucoma²⁵ 29 and may be capable of measuring reversal of RGC dysfunction in glaucomatous eyes that undergo pharmacologic reduction in IOP.³⁰

Limited studies have explored the relationship between PERG, optic nerve structure, and visual function.³¹ 32 Garway-Heath and colleagues³¹ found a significant correlation between reduced neuroretinal rim area measured with HRT and PERG amplitude measured using corneal electrodes among persons with glaucoma. Ventura and colleagues²⁷ found a significant correlation between modified PERGLA amplitude and visual field mean deviation (MD) among a population of glaucoma suspects and persons with early glaucoma. Others³³ have reported a correlation between RNFL thickness measured using OCT and PERG amplitude in persons with ocular hypertension (OHT) and primary open-angle glaucoma. Few studies have broadly examined the relationship between RGC function using PERGLA and comprehensive measures of optic nerve topography and RNFL thickness among normals, glaucoma suspects, and glaucomatous eyes.²⁴ 27 29 30 The purpose of this study was to examine the relationship between retinal ganglion cell function measured using PERGLA, retinal nerve fiber layer (RNFL) thickness and optic nerve head topography.

Patients and Methods

Normal volunteers, glaucoma suspects, and glaucoma patients meeting eligibility criteria were prospectively enrolled in this study. All participants signed a consent form approved by the Institutional Review Board for Human Research at the University of Miami that was in agreement with the provisions of the Declaration of Helsinki. All subjects underwent complete ophthalmic examination including slit lamp biomicroscopy, dilated stereoscopic examination, gonioscopy, Goldmann applanation tonometry, ultrasound pachymetry and photography of the optic disc. Two standard automated perimetry (SAP) examinations were obtained using the Humphrey Field Analyzer (Carl-Zeiss Meditec, Dublin, CA; SITA standard strategy, program

24-2). All subjects underwent optical coherence tomography (Stratus™ OCT; software version 4.0.2., Carl Zeiss Meditec, Dublin, CA), scanning laser polarimetry with enhanced corneal compensation (GDxECC; 5.5.0.11., Carl Zeiss Meditec, Dublin, CA) confocal scanning laser ophthalmoscopy using the Heidelberg retina tomograph (HRTII, software version 1.4.1.0., Heidelberg Engineering, GmbH, Heidelberg, Germany) and pattern electroretinogram examination optimized for glaucoma screening (PERGLA, Lace Ellectronica, Glaid Version 1.2, Pisa, Italy). Only one eye per subject was enrolled. If both eyes met eligibility criteria, one eye was randomly selected.

Inclusion criteria common to all groups consisted of spherical equivalent refractive error between -7.00 DS and $+3.00$ DS, best corrected visual acuity equal to or better than 20/25, age range between 40 and 85 years, reliable SAP (less-than-33% rate of fixation losses, false positives and false negatives), no prior history of intraocular surgery except for uncomplicated cataract extraction. All subjects had clear media defined as no or minimal lens changes (grade 1 or less) or absence of posterior capsular opacification based on the Lens Opacification Classification system. Exclusion criteria consisted of ocular disease other than glaucoma, visual acuity worse than 20/25, pupil diameter of <2 mm, or unreliable SAP.

Normal subjects consisted of volunteers such as office employees, and friends or family members of glaucoma patients. Normal subjects had intraocular pressure (IOP) less than or equal to 21 mmHg by Goldmann applanation tonometry, normal optic disc appearance based upon clinical stereoscopic examination and review of stereodisc photography, two normal SAP examinations defined as glaucoma hemifield test within normal limits and mean and pattern standard deviation of probability $> 5\%$. Absence of glaucomatous optic neuropathy was defined as an intact neuroretinal rim without thinning, localized pallor, RNFL defect, or optic disc hemorrhage. Glaucomatous optic neuropathy was defined as narrowing of the neural rim to the optic disc margin, notching, excavation; or RNFL defect. Glaucoma patients had glaucomatous optic nerve damage and abnormal SAP defined as a glaucoma hemifield test (GHT) “outside normal limits” or pattern standard deviation outside 95% normal limits. Patients with SAP abnormalities had at least one confirmatory visual field examination. Glaucoma suspects had normal SAP, ocular hypertension (IOP ≥ 24 mmHg in one eye and IOP ≥ 22 mmHg in the fellow eye) and/or glaucomatous optic nerve damage visible on the fundoscopic examination and stereo optic disc photography.

Pattern Electroretinogram Examination

Pattern electroretinograms were recorded on both eyes simultaneously using the commercially available steady-state PERGLA (Lace Ellectronica, Glaid Version 1.2, Pisa, Italy) with a glaucoma paradigm as described by Porciatti and Ventura²⁴. Pupils were undilated and had a diameter of ≥ 2 mm and the subject's refraction was corrected for 30 cm.²⁴ The skin was cleansed and prepared using electrode prep pads. Five gold-plated electrode cups with 9mm diameter filled with conductive gel (Parker Laboratories, Inc.; Fairfield, NJ) were taped on the central forehead, temples and lower eyelids. A pre-adaptation period of 3 minutes was allowed prior to recording PERGLA. The PERGLA system evaluates the electrodes' impedance automatically. The impedance is considered acceptable when it is lower than 5000 Ohm, and an LED provides feedback to the operator regarding each electrode. There is also an oscilloscope in live mode that provides feedback about the background noise. Black and white horizontal bars subtending a visual angle of 25° were presented in counter-phase on a video monitor placed at 30 cm. Spatial frequency was 1.64 c/d and temporal frequency was 8.14 Hz (c/s). The target luminance was 40 cd/m² and the background luminance was 4 cd/m² using a 98% contrast. Each presentation consisted of 300 registered sweeps after exclusion of the first 30 sweeps to allow a steady-state recording. There is no video monitor, gaze tracking or similar system provided in this device. However, there is a mechanism incorporated in this technology

that automatically rejects unacceptable signals originating from blinking or eye movements over a threshold voltage of ± 25 microvolts. The acquisition time for each sweep was 122.8 milliseconds. Digital Fourier transformation was utilized to exclude noise and improve the signal to noise ratio. For each patient an average of three measurements was used. Each measurement consisted of two separate sequential series, each of which was composed of 300 artifact-free signal registrations. Outcome measures consisted of PERGLA amplitude (μV) and phase (pi-radian). PERGLA amplitude was converted to a logarithmic scale (dB) to evaluate its association with visual field MD, PSD and sensitivity values. The PERGLA stimulus subtends a 25-degree visual angle, which compares to the central 16 locations on a 24-2 SITA SAP visual field. Hence, for each patient the sensitivity values of the central 16 test locations (in dB) were collected and converted to 1/lambert. The average of these sensitivity values were calculated for each patient and converted back to dB in order to investigate the association between similar size PERG and SAP in logarithmic dB.

Optic nerve and RNFL imaging

GDxECC imaging (software version 5.5.0.11, Carl Zeiss Meditec, Dublin, CA) was performed through undilated pupils. Two consecutive scans were obtained on the same day by the same examiner. The average of two measurements was used for the analysis. A primary scan was obtained prior to each measurement to compensate for the corneal birefringence. Images that were obtained during eye movement were excluded, as well as unfocused, poorly centered images, or images with a quality scan score of less than 8. A fixed concentric measurement band centered on the optic disc with a 3.2 mm outer and a 2.4 mm inner diameter was used to generate the peripapillary retardation measurements. Parameters used as outcome measures for this investigation included TSNIT (temporal superior nasal inferior temporal) average, superior average and inferior average RNFL thickness (μm).

OCT imaging (Stratus™ OCT, software version 4.0, Carl-Zeiss Meditec, Dublin, CA) was performed through undilated pupils using a fast RNFL thickness acquisition protocol on the same day by the same examiner. Images with failure of the RNFL segmentation algorithm, or that were obtained during eye movement or were unfocused, poorly centered or had a signal strength < 7 were excluded. The average of two high quality images was used for the analysis. OCT parameters used as outcome measures for this investigation included average, superior, and inferior RNFL thickness values (μm).

HRT imaging (HRTII, software version 1.4.1.0., Heidelberg Engineering, GmbH, Heidelberg, Germany) was performed through undilated pupils on the same day by the same examiner. Images that were unfocused, poorly centered, or had a mean pixel standard deviation $> 30 \mu\text{m}$ were excluded. The average of two high quality HRT images was included for the analysis. HRT images were further analyzed using HRT3 software (software version 1.5.1.0.). HRT parameters used as outcome measures for this investigation included rim area (mm^2), linear cup/disc ratio, overall GPS classification (normal, borderline or outside normal limits) and overall Moorfields regression analysis (MRA) classification (normal, borderline, outside normal limits). The GPS classification categorizes the nerve head as “within normal limits” ($\text{GPS} \leq 24\%$), “outside normal limits” ($\text{GPS} \geq 64\%$) and “borderline” ($24\% < \text{GPS} < 64\%$).

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL) and STATISTICA version 8.0 (StatSoft Inc., Tulsa, OK). Analysis of variance with Bonferroni pairwise comparisons and the Chi-square test were used to compare different measures between groups. Pearson correlation coefficient was applied to evaluate the association between optic

nerve head and RNFL parameters and PERGLA amplitude. Spearman rank correlation coefficient was performed to calculate the association between GPS and MRA categorical classifications and PERGLA amplitude. The relative measure of test-retest dispersion was examined using the coefficient of variation (CoV) and was calculated as the square root of the pooled within person test-retest variance divided by the group mean. The intraclass correlation coefficient (ICC) was calculated as a measure of agreement of values within cases based on the variance between and within subjects.

Results

Twenty-eight glaucoma patients (mean age 67.9 ± 7.3 years, including 22 patients with primary open angle glaucoma, 3 patients with pigmentary glaucoma, 2 patients with chronic angle-closure glaucoma and 1 patient with low-tension glaucoma), 37 glaucoma suspects (mean age 62.9 ± 10.2 years) and 29 normal volunteers (mean age 62.7 ± 10.6 years) were enrolled. Table 1 demonstrates the clinical characteristics of the study population. Compared to normal volunteers and glaucoma suspects, glaucomatous eyes had significantly ($p < 0.001$ for all values) worse visual field MD and PSD; average, superior and inferior RNFL thickness measurements using OCT and GDxECC, and HRT rim area and linear cup/disc ratio. Visual field MD and PSD, average, superior and inferior RNFL thickness measurements using OCT and GDxECC and HRT rim area were similar in normal eyes and glaucoma suspects, however linear cup/disc ratio was significantly greater in glaucoma suspects ($p < 0.001$). RGC responses were recorded using a commercially available PERGLA. PERGLA amplitude in glaucomatous eyes ($0.47 \pm 0.20 \mu\text{v}$, $p = 0.001$) was significantly lower than normal eyes ($0.70 \pm 0.28 \mu\text{v}$). PERGLA amplitude in glaucomatous eyes was not significantly different from glaucoma suspect eyes ($0.54 \pm 0.21 \mu\text{v}$, $p = 0.84$).

Figure 1 illustrates the relationship between PERGLA and assessments of optic nerve structure and function in a patient with glaucomatous optic neuropathy. Advanced glaucomatous optic disc damage is present (top right) with corresponding SAP visual field loss (top middle), diffuse RNFL atrophy measured using GDxECC (bottom left) and OCT (bottom middle), and abnormal Moorfields regression analysis using HRT (bottom right). The PERGLA box plot analysis (top left) represents ± 2 standard deviations from age-predicted normals for amplitude (y-axis) and phase (x-axis); the center of the box represents zero deviation from age-predicted normals. Note that the depression in the PERGLA waveform for this patient falls more than 4 standard deviations below the age-predicted normal value.

Table 2 illustrates the distribution of eyes in each diagnostic category with PERGLA amplitude and phase deviation within or outside 95% normal tolerance limits ($\pm 2\text{SD}$) compared with the machine's normative database. Twenty-one percent of normal eyes (6 eyes), 46% (17 eyes) of glaucoma suspects, and 57% (16 eyes) of glaucoma patients had amplitude below -2SD . Seventy-nine percent of normal eyes (23 eyes), 51% (19 eyes) of glaucoma suspects, and 43% (12 eyes) of glaucoma patients had amplitude within 95% normal tolerance limits.

We examined the association between the mean sensitivity values of the central 16 SAP test locations (dB) and the PERG amplitude (dB). The best correlations were identified in the glaucoma group ($r = 0.53$, $p = 0.0038$), and across the entire cohort ($r = 0.40$, $p < 0.001$). Table 3 demonstrates the association between PERGLA amplitude (μv), visual field indices, and structural assessments obtained using OCT, GDxECC, and HRT for each group and across the entire cohort ($n = 94$). PERGLA amplitude (μv) and phase (π radian) had an inverse correlation with age across the entire cohort ($r = -0.32$, $p = 0.002$; $r = -0.43$, $p < 0.001$ respectively). PERGLA amplitude was most strongly correlated with the sensitivity values of SAP central 16 test locations ($r = 0.40$, $p < 0.001$), GDx TSNIT superior average ($r = 0.38$, $p < 0.001$) and HRT MRA classification ($r = -0.34$, $p = 0.001$) across the whole group. Weaker but statistically

significant correlations were also found with PERGLA and MD, PSD, OCT average, GDx TSNIT average and inferior average, HRT rim area and linear C/D ratio. When the effect of age on PERGLA was accounted for, correlations remaining statistically significant included those with MD, OCT inferior RNFL thickness, GDx TSNIT average, GDx superior average, GDx inferior average and HRT rim area. All the correlations that we found were accounted for 15% or less of the variability of the PERGLA measurements.

PERGLA amplitude was measured in μV (linear scale) for assessment of correlations with OCT, GDx and HRT measures but was converted to dB (logarithmic scale) to evaluate its association with visual field MD, PSD and the sensitivity values of SAP central 16 test locations. The relationship between PERGLA amplitude and mean sensitivity values of the central 16 SAP test locations (dB) were plotted for each group (Figure 2). The correlation between PERGLA phase and all SAP measures (1/lambert) were non-significant. No relationship was found between PERGLA phase and SAP MD ($r = 0.25$, $p = 0.19$ in glaucoma patients; $r = 0.17$, $p = 0.09$ for all subjects), SAP PSD ($r = -0.03$, $p = 0.86$ in glaucoma patients; $r = 0.02$, $p = 0.86$ for all subjects), and the central 16 SAP test locations ($r = 0.32$, $p = 0.10$ in glaucoma patients; $r = 0.05$, $p = 0.64$ for all subjects).

Table 4 demonstrates the root mean square (RMS) test-retest standard deviations and CoV and ICC values. RMS test-retest SDs were not different between study groups for any of the parameters studied. The power of this study to demonstrate differences was small; however, since groups did not display differences we calculated coefficients of variation over the entire study group for each parameter. CoV were similar for OCT average RNFLT and GDxECC TSNIT values, but the PERG amplitude COV was larger by a factor of more than 5 times. Intraclass correlation coefficients were excellent (>0.75) for all parameters; however, the ICC values for OCT average RNFLT and GDxECC TSNIT were higher than PERG.

Discussion

Experimental models have demonstrated that PERG amplitude diminishes in early glaucoma prior to clinically significant optic nerve head cupping, and it is associated with the magnitude of cupping and IOP elevation.³⁴ Similar results have been reported in humans^{35–38} and preliminary data suggest that PERG may be capable of measuring reversal of RGC dysfunction in glaucomatous eyes that undergo pharmacologic reduction in IOP.³⁰ A reduction in PERG amplitude has also been reported to precede abnormalities in SAP in eyes with progression of OHT to glaucoma.^{29, 39, 40}

In the present study we examined the relationship between RGC function measured with PERGLA, SAP, and structural measures of optic nerve topography and RNFL thickness. Our results demonstrate that PERGLA was mild to moderately associated with SAP and structural measures obtained using various imaging technologies, and the highest correlations were observed with the central 16 SAP test locations. Few studies have explored this relationship.^{29, 32, 39} We also found an inverse correlation between age and PERGLA amplitude in agreement with previous studies.²⁷ When we accounted for the effect of age on PERGLA amplitude, correlations were weakened but many retained statistical significance. The processing of visual signals may be impacted both by age-related changes within the brain and central visual pathway structures⁴¹, in addition to the reduction of retinal illumination due to cataract and small pupils in older persons. Further, normal individuals have been shown to lose 5,000 to 10,000 retinal ganglion cells per-year^{42, 43} which may also contribute to the reduction in PERGLA amplitude observed in older persons. In the present study, all subjects had corrected visual acuity of at least 20/25, and eyes with significant cataract were excluded. Our results emphasize the importance of age-stratification of normative PERG data.

We investigated the ability of PERGLA to differentiate normal eyes, eyes with OHT or suspected to have glaucoma, and eyes with varying degrees of glaucomatous damage. Several interesting results were observed. Indeed, our study demonstrates that glaucomatous eyes have significantly reduced PERG amplitudes compared with normal subjects and corroborates the results of others.^{33, 40, 44, 45} Glaucomatous eyes also have RNFL thickness reduced from normal; however, PERGLA functional measurements versus OCT or GDx structural measurements give different results for glaucoma suspects. Glaucoma suspect eyes have significantly reduced PERGLA amplitudes but not significantly reduced RNFL thickness. The mean PERGLA amplitude in normal ($0.70 \pm 0.28 \mu\text{V}$) and glaucomatous eyes ($0.47 \pm 0.20 \mu\text{V}$, $p < 0.001$) was similar to other published reports^{24, 29, 46} However, wide variability in PERGLA responses was observed amongst all groups of patients in our study with large measurement standard deviations.

We calculated the CoV and ICC and found that CoV values were lower and ICC values were higher for OCT and GDx than PERG over the entire range of measurements in this study. However, this does not address PERGLA's usefulness for discriminating glaucoma suspects and early glaucoma patients from normal subjects. To assess this question, the test-retest variability must be compared against the dynamic range of each instrument that would be useful in identifying such cases. Dividing the test-retest SD of PERGLA by the difference between the normal and glaucoma suspect group averages and multiplying by 100 gives a CoV of 59.3%. For OCT and GDx ECC TSNIT, the respective percentages are 48.7% and 119%. Thus, our data suggests the test-retest standard deviation of PERGLA amplitude measurements is large enough to compromise its efficacy, even when examining patients for which PERGLA is most likely to be useful. One solution could be to take the mean of several PERGLA measurements per patient, which reduces the effect of test-retest variability by the square-root of N. Taking the average of three measurements, as was done in this study, effectively reduces the CoV from 59.3% to 34.3%; if one averages five measurements the CoV would be further reduced to 26.5%.

Although the PERGLA instrument has an automated analysis²⁴ to compare individuals with age-corrected normals, we found that 21% of normal subjects had abnormal PERGLA amplitudes as compared to the machine's normative database (defined as outside 95% normal tolerance limits); 43% of glaucomatous eyes had normal PERGLA amplitudes. Similar overlap has been demonstrated with other assessments of structure and function which may limit the sensitivity and specificity of this technology for glaucoma detection.^{47–50} Hood and colleagues⁵¹ have also theorized that some eyes with large baseline PERGLA amplitudes may remain within the normative range despite a significant reduction in RGC function due to glaucomatous damage. In our study, we limited variables that could potentially contribute to measurement artifact including cataract or other media opacity, poor visual acuity, and pupillary miosis, yet patient's fixation loss may represent a confounding variable that cannot be quantified using this technology.

It has been suggested that both PERGLA and SAP are measures of RGC function.^{24, 46, 52–54} We converted PERGLA amplitude values from microvolts to decibels for comparison with SAP central 16 locations and SAP MD and PSD and demonstrated a modest correlation supporting the observations of other investigators.^{31, 35, 37, 51, 55–58} The PERGLA stimulus subtends a 25-degree visual angle, which compares to the central 16 test locations on the SAP visual field. Consistent with previous studies, we found stronger levels of agreement between SAP and PERGLA when sensitivity values were used in conjunction with this methodology.^{31, 37} Figures 2a–2c demonstrate the association between PERGLA amplitude and mean sensitivity of the SAP central 16 test locations in normal (2a), glaucoma suspect (2b) and glaucoma patients (2c) in logarithmic scale with the strongest association in the glaucoma group. Although the correlation between PERGLA amplitude in dB and the central 16 locations

was better than its correlation with the central 24-degree eccentricity, it was not considered a strong correlation. Several factors may explain why the correlations were not stronger. PERGLA amplitudes been shown to be extinguished early in glaucoma. PERGLA may be more sensitive to early glaucomatous loss in the central field compared to SAP that shows lesser loss due to the redundancy in the ganglion cell population. Further, PERGLA and SAP may measure different RGC populations. In contrast to SAP, it has been suggested that PERGLA may target dysfunctional RGCs and detect reversible RGC dysfunction.²⁹

In this study we demonstrate a modest relationship between RGC function using PERGLA and a comprehensive array of structural measures including GDxECC superior RNFL thickness, OCT inferior RNFL thickness, and HRT Moorfields regression analysis classification. Previous studies have confirmed similar associations between PERG and structural measures.^{31, 59–61} The relationship between structure and function in glaucoma is often complex. Although it is logical to expect that loss of RGCs and their axons should correspond to a measurable reduction in visual function, randomized clinical trials suggest that changes in structure and function often disagree. In the Ocular Hypertension Treatment Trial⁶², only 12 of 125 endpoints (9.6%) represented a simultaneous change in structure and function and in the European Glaucoma Prevention Study⁶², there were no patients with overlapping optic disc and visual field endpoints. We speculate that at any given time point, the total RGC population includes a mixed population of normal, dysfunctional, non-viable, and atrophic RGCs in various stages of degeneration. At present, imaging technologies are capable only of quantifying structural changes in RGC axons in the retina or the optic nerve head, and unlike PERG or SAP do not specify the level of RGC dysfunction. This disparity contributes to the complex relationship between measurement of structure and function in glaucoma. It is of interest, however, that Fortune et al.⁶³ have suggested that birefringence changes measured with GDx may reflect axonal microtubule dysfunction and precede RNFL atrophy in experimental primate glaucoma. Also, Falsini and colleagues discuss that RNFL thickness change may not only reflect nerve fiber loss but it may also indicate both neural loss and glial remodeling at very early stages of glaucoma and PERG abnormalities might reflect both the neural dysfunction as well as glial changes.³²

In conclusion, RGC function as measured using PERGLA is reduced in glaucomatous eyes, and demonstrates modest correlations with central SAP sensitivity values, RNFL thickness measured by GDxECC and optic nerve head topography across the entire cohort. Longitudinal studies are warranted in order to better understand the role of PERG as a surrogate measure of RGC dysfunction in glaucoma suspects and patients with glaucomatous optic neuropathy.

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Figure 1.

Figure illustrates the relationship between PERGLA and assessments of optic nerve structure and function in a patient with glaucomatous optic neuropathy. Advanced glaucomatous optic disc damage is present (top right) with corresponding SAP visual field loss (top middle), diffuse RNFL atrophy measured using GDxECC (bottom left) and OCT (bottom middle), and abnormal Moorfields regression analysis using HRT (bottom right). The PERGLA box plot analysis (top left) represents ± 2 standard deviations from age-predicted normals for amplitude (y-axis) and phase (x-axis); the center of the box represents zero deviation from age-predicted normals. Note that the depression in the PERGLA waveform for this patient falls more than 4 standard deviations below the age-predicted normal value.

Figure 2. Relationship between PERGLA amplitude (dB) and the average of the sensitivity values of SAP central 16 test locations (dB) in normal (2a), glaucoma suspect (2b) and glaucoma subjects (2c).

Table 1

Clinical characteristics of the study population (N=94). Values represent mean $\pm$ SD (range).

	Normal (n = 29)	Suspect (n = 37)	Glaucoma (n = 28)	P-value (Suspect vs Normal)	P-value (Suspect vs GL)	P-value (GL vs Normal)
Age (yrs)	62.7 $\pm$ 10.6 (45–82)	62.9 $\pm$ 10.2 (42–79)	67.9 $\pm$ 7.3 (57–79)	1.00	0.12	0.14
Gender						0.91*
Male	12	17	13			
Female	17	20	15			
Race						0.38*
Asian	0	0	1			
Black	0	0	1			
White Non-Hispanic	28	35	23			
Hispanic	1	2	3			
VF MD (dB)	-0.2 $\pm$ 1.1 (-3.0 to 1.5)	-0.3 $\pm$ 1.1 (-3.0 to 1.8)	-5.01 $\pm$ 5.4 (-17.0 to -0.02)	1.00	< 0.001	< 0.001
VF PSD (dB)	1.5 $\pm$ 0.7 (0.0–2.7)	1.6 $\pm$ 0.5 (1.1–3.0)	5.3 $\pm$ 4.7 (1.5–15.6)	1.00	< 0.001	< 0.001
PERGLA amplitude (μ v)	0.70 $\pm$ 0.28 (0.21–1.28)	0.54 $\pm$ 0.21 (0.26–1.30)	0.47 $\pm$ 0.20 (0.17–0.98)	0.02	0.84	< 0.001
PERGLA phase (π radian)	1.67 $\pm$ 0.19 (1.26–1.97)	1.70 $\pm$ 0.15 (1.40–2.01)	1.72 $\pm$ 0.16 (1.27–2.02)	1.00	1.00	0.72
OCT average RNFLT (μ m)	95.88 $\pm$ 13.28 (65.0–132.3)	91.60 $\pm$ 8.95 (72.2–109.7)	73.21 $\pm$ 15.74 (45.7–110.1)	0.55	< 0.001	< 0.001
OCT superior RNFLT (μ m)	115.34 $\pm$ 21.80 (73.0–182.0)	112.72 $\pm$ 17.16 (69.0–152.0)	85.38 $\pm$ 22.86 (45.0–146.5)	1.00	< 0.001	< 0.001
OCT inferior RNFLT (μ m)	123.52 $\pm$ 17.68 (73.0–152.0)	115.85 $\pm$ 15.43 (83.0–153.0)	89.29 $\pm$ 28.82 (46.0–143.5)	0.44	< 0.001	< 0.001
GDxECC TSNIT average (μ m)	51.20 $\pm$ 5.13 (39.1–60.8)	50.16 $\pm$ 4.35 (42.0–59.2)	43.43 $\pm$ 6.85 (30.6–55.3)	1.00	< 0.001	< 0.001
GDxECC superior average (μ m)	61.41 $\pm$ 7.13 (45.2–75.1)	58.53 $\pm$ 6.57 (44.9–74.0)	49.66 $\pm$ 8.65 (32.1–67.2)	0.40	< 0.001	< 0.001
GDxECC inferior average (μ m)	63.47 $\pm$ 8.24 (49.9–79.2)	62.45 $\pm$ 6.88 (49.6–78.5)	52.79 $\pm$ 9.97 (37.6–71.9)	1.00	< 0.001	< 0.001
HRT rim area (mm ²)	1.32 $\pm$ 0.23 (0.91–2.0)	1.26 $\pm$ 0.28 (0.8–2.0)	1.04 $\pm$ 0.32 (0.37–1.68)	1.00	0.008	0.001
HRT linear cup/disc ratio	0.38 $\pm$.16 (0.02–0.7)	0.52 $\pm$ 0.15 (0.1–0.7)	0.68 $\pm$ 0.14 (0.4–0.9)	0.001	< 0.001	< 0.001

GL = glaucoma; PERGLA = pattern electroretinogram optimized for glaucoma screening; OCT = optical coherence tomography; GDxECC = GDx with enhanced corneal compensation; HRT = Heidelberg retina tomograph; MD = mean deviation; PSD = pattern standard deviation; PERG = pattern electroretinogram; RNFLT = retinal nerve fiber layer thickness; GL = glaucoma

* Chi-Square

Table 2

Distribution of eyes in each diagnostic category with PERGLA amplitude and phase deviation within or outside 95% normal tolerance limits ($\pm 2SD$) compared with the normative database.

	Amplitude deviation (SD)			Phase deviation (SD)		
	< -2SD	Within $\pm 2SD$	> +2SD	< -2SD	Within $\pm 2SD$	> +2SD
Normal (n = 29)	6 (21%)	23 (79%)	0 (0%)	11 (38%)	18 (62%)	0 (0%)
Glaucoma suspect (n = 37)	17 (46%)	19 (51%)	1 (3%)	16 (43%)	20 (54%)	1 (3%)
Glaucoma (n = 28)	16 (57%)	12 (43%)	0 (0%)	9 (32%)	19 (68%)	0 (0%)

Table 3

The association between PERGLA amplitude (μV), visual field 16 central test locations, visual field indices; and structural assessments obtained using OCT, GDxECC, and HRT in normal, glaucoma suspect, glaucoma subjects and across the entire cohort. The Bonferroni multiple comparison adjusted critical alpha is $p < 0.001$.

	Normal (n=29)		Suspect (n=37)		Glaucoma (n=28)		All subjects (n=94)	
	r	p	r	p	r	p	r	p
Age (yrs)	-0.45	0.02	-0.11	0.53	-0.28	0.15	-0.32	0.002
SAP central 16 locations (dB) [§]	0.38	0.05	0.05	0.76	0.53	0.004	0.40	<0.001*
MD (dB) [§]	0.22	0.25	0.21	0.22	0.19	0.33	0.31	0.002
PSD (dB) [§]	-0.09	0.65	-0.15	0.38	-0.17	0.39	-0.24	0.02
OCT average RNFLT (μm) [‡]	-0.15	0.45	-0.10	0.57	0.49	0.009	0.24	0.02
OCT superior RNFLT (μm) [‡]	-0.28	0.14	-0.06	0.72	0.37	0.05	0.13	0.17
OCT inferior RNFLT (μm) [‡]	-0.10	0.62	0.05	0.78	0.46	0.01	0.29	0.005
GDxECC TSNT average (μm) [‡]	0.14	0.49	0.006	0.97	0.38	0.04	0.29	0.005
GDxECC superior average (μm) [‡]	0.36	0.05	0.14	0.43	0.32	0.09	0.38	<0.001*
GDxECC inferior average (μm) [‡]	0.09	0.63	0.08	0.65	0.32	0.10	0.26	0.01
HRT rim area (mm^2) [‡]	0.16	0.41	0.22	0.19	0.15	0.45	0.25	0.02
HRT linear cup/disc ratio [‡]	0.02	0.91	-0.10	0.56	-0.02	0.91	-0.24	0.02
HRT GPS classification [‡]	-0.14	0.47	-0.07	0.66	-0.13	0.53	-0.29	0.005
HRT MRA classification [‡]	-0.17	0.39	-0.32	0.05	-0.06	-0.29	-0.34	0.001*

SAP = standard automated perimetry; MD = mean deviation; PSD = pattern standard deviation; OCT = optical coherence tomography; GDxECC = GDx with enhanced corneal compensation; RNFLT = retinal nerve fiber layer thickness; GPS = glaucoma probability score, MRA = Moorfields regression analysis

[§]PERGLA amplitude was converted to a logarithmic scale (dB) to evaluate its association with visual field sensitivities and indices.

[‡] Pearson's Correlation Coefficient

[‡] Spearman Rank Correlation Coefficient

Table 4

The root mean square test-retest standard deviations, coefficient of variation and intraclass correlation coefficient values for the parameters measured in this cohort.

	RMS test-retest SD in Diagnostic categories				P-value Between groups	CoV	ICC
	Normal	Suspect	Glaucoma	Total			
PERGLA amplitude	0.103	0.074	0.068	0.083	0.39	14.5%	0.89
PERGLA phase	0.049	0.054	0.051	0.052	0.98	3.1%	0.91
OCT average RNFL	1.890	1.963	2.430	2.092	0.84	2.4%	0.98
OCT superior RNFL	3.762	5.012	6.172	5.060	0.39	4.8%	0.96
OCT inferior RNFL	3.063	5.100	4.066	4.250	0.24	3.9%	0.97
GDxECC TSNIT average	1.023	0.896	1.310	1.072	0.76	2.2%	0.97
GDxECC superior average	6.072	5.973	5.153	5.773	0.78	10.2%	0.74
GDxECC inferior average	1.694	1.820	1.831	1.785	0.41	3.0%	0.97
HRT rim area	0.064	0.054	0.107	0.076	0.22	6.3%	0.94
HRT linear cup/disc ratio	0.048	0.068	0.115	0.080	0.77	15.3%	0.83

RMS = root mean square; CoV = coefficient of variation; ICC = intraclass correlation coefficient; PERGLA = Pattern electroretinogram optimized for glaucoma screening