Short-Term Changes in the Photopic Negative Response Following Intraocular Pressure Lowering in Glaucoma

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Purpose. To evaluate the short-term changes in inner retinal function using the photopic negative response (PhNR) after intraocular pressure (IOP) reduction in glaucoma.

Methods. Forty-seven participants with glaucoma who were commencing a new or additional IOP-lowering therapy (treatment group) and 39 participants with stable glaucoma (control group) were recruited. IOP, visual field, retinal nerve fiber layer thickness, and electroretinograms (ERGs) were recorded at baseline and at a follow-up visit (3 ± 2 months). An optimized protocol developed for a portable ERG device was used to record the PhNR. The PhNR saturated amplitude (V_{max}), V_{max} ratio, semi-saturation constant (K), and slope of the Naka–Rushton function were analyzed.

Results. A significant percentage reduction in IOP was observed in the treatment group (28 ± 3%) compared to the control group (2 ± 3%; $P < 0.0001$). For PhNR V_{max}, there was no significant interaction ($F_{1,83} = 2.099$, $P = 0.15$), but there was a significant difference between the two time points ($F_{1,83} = 5.689$, $P = 0.019$). Post hoc analysis showed a significant difference between baseline and 3 months in the treatment group (mean difference, 1.23 µV; 95% confidence interval [CI], 0.24–2.22) but not in the control group (0.30 µV; 95% CI, 0.78–1.38). K and slope were not significantly different in either group. Improvement beyond test–retest variability was seen in 17% of participants in the treatment group compared to 3% in the control group ($P = 0.007$, χ^2 test).

Conclusions. The optimized protocol for measuring the PhNR detected short-term improvements in a proportion of participants following IOP reduction, although the majority showed no change.

Keywords: electroretinography, glaucoma, pressure lowering, photopic negative response

There is a growing body of evidence suggesting that, prior to irreversible cell death, compromised retinal ganglion cells (RGCs) enter a dysfunctional state that may partially recover under certain conditions.[1,2] This concept of RGC recovery is not new. In 1985, Spaeth[3] argued that the adequacy of intraocular pressure (IOP) therapy in glaucoma could not be certain unless there were accompanying improvements in the visual field or optic disc.

Although it is well established that lowering IOP can delay visual field progression in the long term,[4,5] there is conflicting evidence regarding visual field recovery in glaucoma. Both Paterson et al.[6] and Flammer et al.[7] separately showed increases in visual sensitivity following acetazolamide administration in a subset of glaucoma patients. Prata and colleagues[8] observed improvements in visual field mean deviation as well as contrast sensitivity 4 weeks after lowering IOP with topical medications. Others have demonstrated visual field improvement following laser trabeculoplasty[9] and surgical IOP reduction.[8,10–12]

However, a similar number of studies have found no visual field improvement after IOP lowering.[13–17] A recent analysis of short-term visual field changes in 255 individuals enrolled in the Early Manifest Glaucoma Trial found that small improvements in sensitivity were just as common as small deteriorations in both the untreated and treated groups.[17] These apparently contradictory findings may be explained by the inherent variability[18] and perimetric learning[19] that confounds visual field interpretation; thus, it remains to be determined if short-term functional improvement can be detected with perimetry.

On the other hand, experimental and clinical studies using electrophysiological tests have provided more compelling evidence for RGC recovery associated with IOP reduction. Experimental models of glaucoma have demonstrated partial reversal of functional loss following IOP lowering measured using the pattern electroretinogram (PERG),[20,21] scotopic threshold response (STR),[22–24] and photopic negative response (PhNR).[25] This improvement in

function may be enhanced with diet restriction,[26] exercise,[27] and nicotinamide (vitamin B_3).[28]

In humans, several studies have observed PERG recovery in a subpopulation of glaucoma patients after IOP lowering with topical medication and surgery,[29–31] with one study finding greater improvement in those with early disease.[29] The PhNR may similarly improve after IOP treatment in glaucoma patients. In their pilot study, Niyadurupola et al.[32] reported short-term PhNR recovery in a small cohort of patients after a significant pressure reduction (greater than 25% of baseline), which was not evident in patients with stable IOP.

The practical advantages of the PhNR over the PERG (e.g., not requiring refractive correction or clear optics[33]), together with the accessibility of recording using a portable electroretinogram (ERG) device (RETeval; LKC Technologies, Gaithersburg, MD, USA),[34–36] make the PhNR an attractive alternative to monitor RGC function in the clinic. We have recently made a number of modifications to the ERG recording and test protocols with the RETeval to reduce intertest variability.[34–36] In this study, we sought to determine whether the optimized protocol can reliably detect changes in the PhNR shortly after IOP lowering in glaucoma and to compare corresponding changes on standard automated perimetry (SAP).

Methods

The research followed the tenets of the Declaration of Helsinki and was approved by the Human Research Ethics Committee at the Royal Victorian Eye and Ear Hospital, Melbourne, Australia (13/1121H). Participants were recruited from two sites: public outpatient clinics at the Royal Victorian Eye and Ear Hospital or a private ophthalmology clinic (Melbourne Eye Specialists). Informed consent was obtained from all participants prior to examination.

The treatment group was comprised of glaucoma suspects or manifest glaucoma patients deemed by the treating glaucoma specialist to require new or additional IOP-lowering treatment due to high IOP or evidence of progression on visual field; they were recruited and baseline tested prior to initiating therapy. Glaucoma patients who were deemed stable by the treating specialist and not requiring a change in treatment at the time of study recruitment were prospectively recruited into the control group. Any control participant who required additional treatment at the 3-month follow-up was excluded from the analysis.

All glaucoma subtypes and treatment modalities were included. The new therapy—ocular hypotensive drops, selective laser trabeculoplasty (SLT), or surgical filtration by trabeculectomy or Xen implant (Allergan, Dublin, Ireland)—was determined by the treating ophthalmologist before recruitment. Ocular hypotensive drops included any or a combination of the following: prostaglandin analogs, beta blockers, alpha-2 selective agonists, and carbonic anhydrase inhibitors.

Exclusion criteria for all participants included visual acuity worse than 6/12, insufficient ERG quality at baseline, diabetes, and other eye conditions (except visually insignificant cataracts). Only one eye was included in the study. In the treatment group, where both eyes were eligible, the eye with the higher IOP was chosen. In the control group, the eye with the better SAP mean deviation was included. Complete ophthalmic examinations, including visual acuity, tonometry, SAP, optical coherence tomography, and ERG recordings, were performed at baseline and follow-up at 3 months (±2-month window period) in both groups.

Full-Field ERG Recording

The ERG setup, recording, and analysis have been described previously.[34–36] Following pupil dilation using 0.5% tropicamide (Mydriacyl; Alcon Laboratories, Macquarie Park, NSW, Australia), a DTL-like electrode (22/1 dtex; Shieldex Trading, Palmyra, NY, USA) was placed along the lower lid margin, with reference and ground Grass gold cup skin electrodes (AstroNova, West Warwick, RI, USA) placed on the temple and forehead, respectively.

Participants were adapted to background light before the stimuli were delivered with the RETeval device. Stimuli consisted of brief, red flashes (13 stimulus strengths from 0.07 to 4.5 cd·s/m^2 in 0.15-log unit increments) on a steady blue background (peak wavelength, 470 nm; photopic luminance, 10 cd/m^2). Fifty flashes per stimulus strength were delivered at 2 Hz. All raw ERG traces were extracted and processed offline using MATLAB (MathWorks, Natick, MA, USA). Baseline detrending using a third-order polynomial was performed as previously described.[35]

The amplitudes of the following parameters were extracted from the average trace: a-wave, defined as the trough in the time window 0 to 30 ms and measured from baseline; b-wave, defined as the maximum after the a-wave and measured from the a-wave trough to peak; and the PhNR, defined as the trough after the b-wave in the time window 55 to 90 ms from flash onset and measured from the baseline. Where two or more troughs were seen, the most negative trough was chosen as the PhNR, which is in line with International Society for Clinical Electrophysiology of Vision recommendations.[37]

The PhNR and b-wave amplitude were plotted as a function of log stimulus strength (Fig. 1). The Naka–Rushton equation, defined as $V = V_{max} \times I^n/(I^n + K^n)$, where V is the amplitude, I is the stimulus strength, V_{max} is the maximum saturating amplitude, n is the slope, and K is the semi-saturation constant, was fitted to the data in MATLAB using a robust, nonlinear, least-squares method with a bi-square weight to reduce the influence of outlier data points. V_{max}, K, slope, and V_{max} ratio, defined as PhNR V_{max} over b-wave V_{max}, were analyzed.

Standard Automated Perimetry

SAP was performed on the Humphrey Field Analyzer (Carl Zeiss Meditec, Jena, Germany) using the 24-2 Swedish interactive thresholding algorithm (SITA) threshold. Mean deviation (MD) values were analyzed by converting the parameter from decibel (dB) to 1/lambert to evaluate change in linear units.[38]

Optical Coherence Tomography

Cross-sectional imaging of the peripapillary retinal nerve fiber layer thickness (RNFLT) was obtained in all participants at each visit with spectral domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany; RS-3000 Advance, NIDEK, Aichi, Japan). Although two different SD-OCT devices were used, each participant was tested with the same instrument at each visit. The average RNFLT (µm) was analyzed.

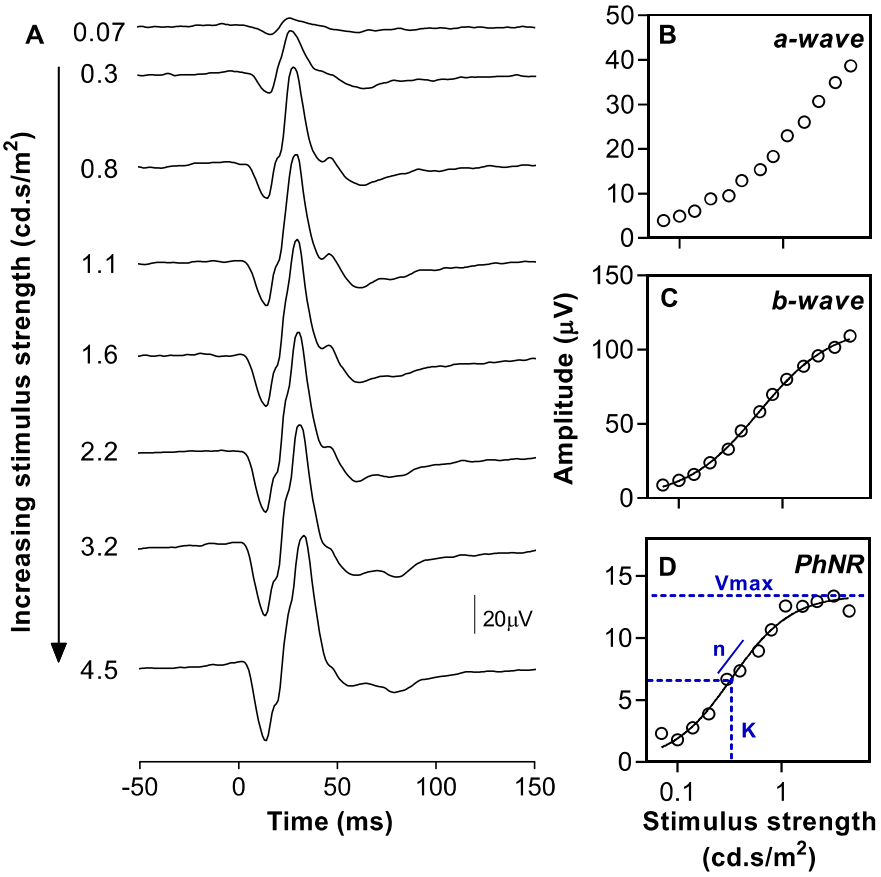

Figure 1. (**A**) Representative ERG waveforms for select stimulus strengths with the corresponding stimulus response function for (**B**) a-wave, (**C**) b-wave, and (**D**) PhNR. The b-wave and PhNR amplitudes were fitted with the Naka–Rushton function, where V_{max} is the maximum amplitude, K is the semi-saturation constant, and n is the slope.

Statistical Analysis

Two-way repeated measures ANOVA was used to compare changes in PhNR parameters between groups. Where significant, Sidak's multiple comparisons tests were used. Significant individual improvement or deterioration from baseline was defined as a change greater than the coefficient of repeatability (COR%), which was calculated using an independent group of healthy individuals who attended two testing sessions 4 weeks apart, with the slope of the Naka–Rushton fixed. The COR% was calculated as ±1.96 SD of the differences between test–retest measurements, expressed as a percentage of the mean value.[39,40] The χ^2 test was used to compare the proportion of change in the treatment and control group. Pearson's correlation was used to evaluate the association between parameters. Values are mean ± SD unless otherwise specified.

Results

Thirty-nine stable glaucoma participants were recruited into the control group and 54 participants were recruited into the treatment group. Data from seven participants in the treatment group were excluded due to significant muscle twitch or blinking artifacts at baseline which interfered with the analysis of the b-wave and PhNR. These artifacts could be neither suppressed with repeat measurements nor ameliorated with post hoc processing; thus, 47 out of the 54 treatment participants were included in the analysis.

Baseline characteristics of the two groups were similar (Table 1), with the exception that the treatment group had significantly higher baseline IOP (22 ± 7 mmHg vs. 14 ± 3 mmHg; $P < 0.0001$) and were followed over a shorter period of time (3.4 ± 1.1 months vs. 3.9 ± 0.8 months; $P < 0.02$). The methods for IOP reduction in the treatment group are shown in Table 2. Representative ERG waveforms with the corresponding stimulus response function for the a-wave, b-wave, and PhNR are shown in Figure 1.

Significant IOP Reduction in the Treatment Group

Figure 2 shows the percentage of IOP change from baseline at follow-up in the two groups. A significant reduction in IOP was observed in the treatment group compared to the control group (28 ± 3% vs. 2 ± 3%; $P < 0.0001$). In the treatment group, 24 participants had an IOP reduction of ≥30%, and nine had an IOP reduction of ≥50%. One participant did not respond to treatment, which led to an increase in IOP following SLT, and the participant was excluded from the analysis.

Table 1. Baseline Clinical and Demographic Characteristics of IOP-Controlled and IOP-Lowering Glaucoma Participants Included in the Study

	Control Group (n = 39)	Treatment Group (n = 47)	P
Age (y), mean ± SD	68 ± 9	65 ± 13	0.2
Female/male (n)	14/25	17/30	1.00
Glaucoma subtype (n)			
Glaucoma suspect	12	10	0.3
POAG	24	29	0.3
PACG	1	1	0.8
PXFG	2	4	0.5
PDG	0	3	NA
Baseline IOP (mm Hg), mean ± SD	14 ± 3	22 ± 7	< 0.0001
Central cornea thickness (µm), mean ± SD	532 ± 34	540 ± 35	0.3
Baseline mean deviation (dB), mean ± SD	–4.6 ± 4.2	–5.0 ± 5.0	0.7
Baseline RNFLT (µm), mean ± SD	72 ± 18	70 ± 17	0.6
Mean follow-up duration (mo), mean ± SD	3.9 ± 0.8	3.4 ± 1.1	0.02

Unpaired Student's t-test and χ^2 test for proportions were performed; where proportions were 0, the χ^2 test could not be performed. POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; PXFG, pseudo-exfoliation glaucoma; PDG, pigment dispersion glaucoma; NA, not available.

Table 2. Method of IOP Reduction and Mean IOP Reduction for Each Method in the IOP-Lowering Group

Method of IOP Reduction	Number of Participants	Mean IOP Reduction (%), Mean ± SD
Addition of topical medication*	25	30 ± 20
Selective laser trabeculoplasty	15	16 ± 27
Trabeculectomy	4	53 ± 16
Xen implant	3	34 ± 19

* Topical medication included prostaglandin analogs, beta blockers, alpha-2 selective agonists, and carbonic anhydrase inhibitors alone or in combination.

Significant Increase in V_{max} in the Treatment Group

Figure 3 compares the baseline and 3-month values of V_{max}, K, and slope in the treatment and control groups. For PhNR V_{max}, there was no significant interaction ($F_{1,83}$ = 2.099, P = 0.15); however, there was a significant difference between the two time points ($F_{1,83}$ = 5.689, P = 0.019). Post hoc analysis using Sidak's multiple comparisons test showed a significant difference between baseline and 3 months in the treatment group (mean difference, 1.23 µV; 95% CI, 0.24–2.22) but not in the controls (mean difference, 0.30 µV; 95% CI, 0.78–1.38) (Fig. 3A). K and slope of the Naka–Rushton function were not significantly different in either group (K: $F_{1,81}$ = 3.363, P = 0.07; slope: $F_{1,81}$ = 0.00, P = 1.00) (Figs. 3B, 3C), and they were not analyzed further.

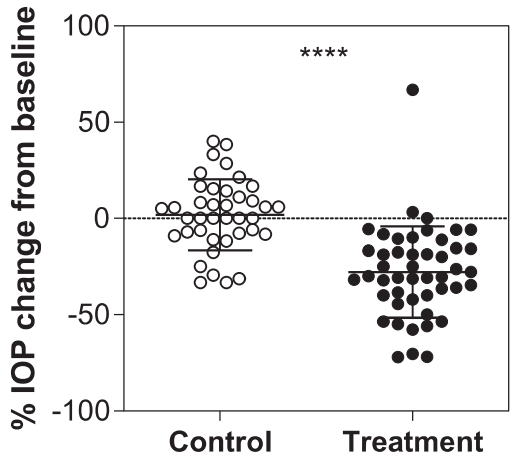

Figure 2. Percentage change in IOP in the control and treatment groups. Values are mean ± SD. One participant had an IOP increase following treatment and was excluded from further analysis. Unpaired Student's t-test was performed; $^{****}P < 0.0001$.

Figure 4 compares the group percentage change from baseline for the ERG parameters. Compared to the control group, there was a significant increase from baseline in the treatment group for PhNR V_{max} (control vs. treatment: –3.5 ± 18% vs. 12.7 ± 30.4%; P = 0.005) (Fig. 4A) and V_{max} ratio (control vs. treatment: –4.8 ± 13.6% vs. 7.5 ± 26%; P = 0.01) (Fig. 4B). There was no group difference in the b-wave V_{max} (control vs. treatment: 2.8 ± 18.2% vs. 5.3 ± 15.1%; P = 0.49) (Fig. 4C). In addition, there was no significant group change for MD (control vs. treatment: 3.1 ± 31.8% vs. 20.1 ± 52.2%; P = 0.08) and RNFLT (control vs. treatment: 0.2 ± 4.1% vs. 0.2 ± 5.9%; P = 0.96).

Individual Improvement Detected in a Proportion in the Treatment Group

Eight participants (17%) in the treatment group improved beyond the 95% confidence intervals of test–retest variability for the PhNR V_{max} or V_{max} ratio, compared to one participant (3%) in the control group (P = 0.007, χ^2 test). However, the majority of participants did not show significant change. Further, there was no correlation between the change in PhNR V_{max} with baseline IOP or the magnitude of IOP change (Fig. 5).

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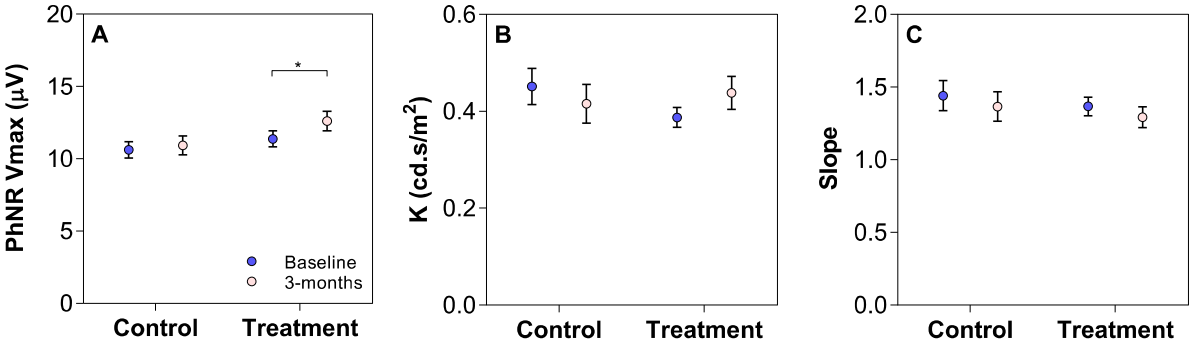

Figure 3. Group comparison at baseline and 3 months for (**A**) PhNR V_{max}, (**B**) K, and (**C**) slope (n). Values are mean ± SD. Two-way repeated-measures ANOVA and Sidak's multiple comparison test were performed; $^{*}P = 0.019$.

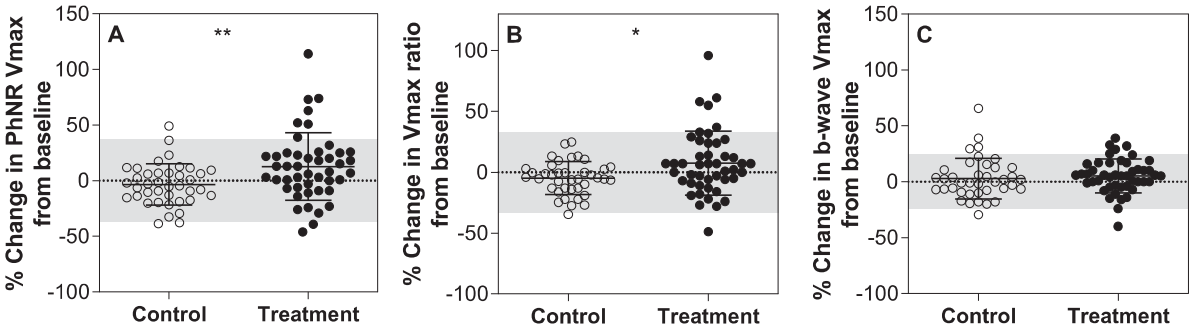

Figure 4. Percentage change from baseline for the control and treatment group for (**A**) PhNR V_{max}, (**B**) V_{max} ratio, and (**C**) b-wave V_{max}. The *gray area* represents the coefficient of repeatability determined in an independent sample of healthy participants (unpublished data). Values are mean ± SD. Unpaired Student's t-test was performed; $^{**}P < 0.01$, $^{*}P < 0.05$.

Discussion

Current clinical tools lack sufficient sensitivity to detect treatment response in the short term in glaucoma and represent a barrier to the development of novel therapies. This study identified improvement in the PhNR in a small proportion of glaucoma participants 3 months after additional IOP-lowering treatment, although the majority of participants did not show significant change.

The average increase in PhNR V_{max} from baseline across the treatment group was 12.7 ± 30.4% (Fig. 4), and there was considerable variability compared to the controls (–3.5 ± 18%). One explanation for this may be the sample heterogeneity, as it included a range of glaucoma subtypes, levels of severity, and treatment modalities. However, this sample was also representative of a typical patient sample in glaucoma clinics, and no significant difference was observed in the demographics of the treatment and control groups. Despite the heterogeneity, a significant group improvement was found in the treatment group. A larger effect may potentially have been observed if more stringent criteria were set

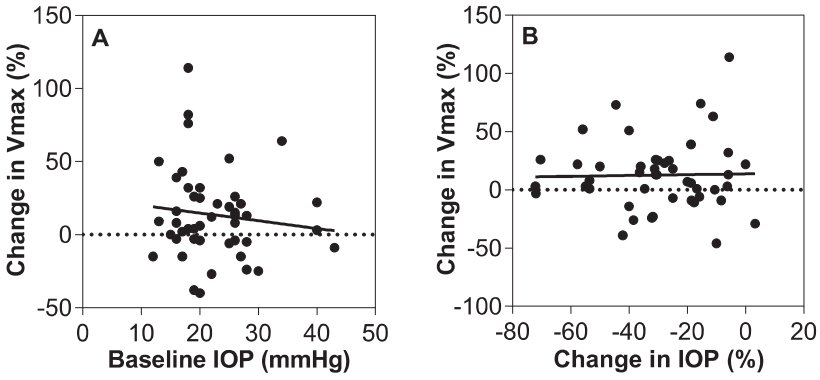

Figure 5. Correlation of PhNR V_{max} with (**A**) baseline IOP and (**B**) percent change in IOP.

regarding disease severity or baseline IOP, although such a correlation was not evident in our cohort (Fig. 5).

Although 17% of the cohort showed a functional improvement with our optimized PhNR protocol, the majority of participants did not show significant changes. Large changes in PhNR or visual fields at 3 months were not expected, as a significant proportion of those in the treatment group were already undergoing glaucoma therapy at commencement of the study. There is potential that a treatment-naïve group could show a greater change in retinal function; however, including such a group was beyond the scope of this study. Further, we cannot exclude the possibility that the current technology is not yet sensitive enough to detect more subtle changes in retinal function, although it is also possible that a 3-month time point was insufficient to capture a detectable change in some people. Future longitudinal studies with closely titrated follow-ups could potentially elucidate the range in time at which short-term changes may be detected, and studies with a longer follow-up may determine whether these short-term effects are sustained and are predictive of treatment efficacy and future disease progression.

In line with previous electrophysiological studies, not all participants showed improved retinal function after treatment. In a retrospective pilot study, Ventura and Porciatti[29] reported a significant improvement in the PERG amplitude or phase in 56% (12 of 24) of right eyes and 21% (5 of 24) of left eyes following medical therapy. Kараskiewicz et al.[31] observed an increase in PERG in 71% of eyes after trabeculectomy; however, they defined improvement (amplitude increase of 20%) based only on published PERG variability rather than laboratory-specific normative values. Surgical reduction of IOP has also been found to improve amplitudes using PERG optimized for glaucoma screening,[30] although the magnitude of amplitude change fell within the variability of the instrument.

Glaucoma progression is also influenced by factors aside from IOP, and the relationship between functional recovery and IOP lowering, at least in our cohort, was not direct. Aside from one study,[32] no correlation has been observed between the magnitude of IOP lowering and the increase in electrophysiological measure in other studies.[29,30] Similarly, a study reporting improvement in visual field sensitivity also found no association with IOP reduction.[12] Indeed, a recent preclinical study demonstrated RGC and functional preservation using treatments that were independent of IOP lowering.[28]

Fitting the Naka–Rushton function to the PhNR stimulus response data has been proposed to reduce intersession variability and provide additional information about the mechanisms and dynamics of RGC dysfunction in glaucoma.[41] To date, only two studies have examined the PhNR stimulus response relationship in inner retinal disease. In eyes of patients with multiple sclerosis, Wang et al.[42] observed a reduction in PhNR maximum amplitude without a change in the other parameters of the Naka–Rushton function. Kremers and colleagues[43] showed that only the maximum PhNR was reduced in glaucoma. Similarly, our study did not observe a change in K or slope following IOP treatment, suggesting that the stimulus response function may not provide additional information; however, as saturating stimulus strengths vary among individuals, it is necessary to record over a range of stimulus strengths rather than at an arbitrary "maximum." Further, we have observed greater test–retest repeatability using V_{max} compared to a single stimulus strength, as well as with the slope fixed (unpublished results). However, to reduce testing time in clinical settings, the protocol may be refined to use fewer stimulus strengths to fit the Naka–Rushton function.

Finally, because we investigated a range of treatment modalities, we were unable to determine if change in RGC function was influenced by a particular treatment type. In addition, the sensitivity of the detection of PhNR improvement was limited by the test–retest variability in an independent sample of healthy participants. Although assessing individual variability with repeat measurements at baseline as an internal control may improve the sensitivity in detecting change, delaying treatment to establish variability is impractical in the real-word setting. However, this could be addressed if the PhNR became a routine clinical measure.

Conclusions

In summary, our optimized protocol for measuring the PhNR using the RETeval device was able to detect short-term improvements in inner retinal function in a proportion of participants following IOP reduction. Although only a small proportion improved, such short-term changes in PhNR may provide a means for detecting improvement or deterioration in RGC function, and this approach merits further investigation for its utility in longitudinal glaucoma monitoring and the assessment of new treatments.

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