

Assessing Residual Cone Function in Retinitis Pigmentosa Patients

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Purpose: The purpose of this study was to investigate cone function deterioration in patients with retinitis pigmentosa (RP) using full field electroretinogram (ffERG), pattern electroretinogram (pERG), and optical coherence tomography (OCT) and their correlation with visual acuity (VA).

Methods: Clinical records (2008–2018) of patients with RP undergoing repeat electrophysiology were reviewed. Results of ffERG (30 Hz flicker and fused flicker amplitude [FFAmp]), pERG [p50 and n95], and macular OCT (ellipsoid zone [EZ] and outer segment thickness) were collected.

Results: One hundred twenty-six eyes from 63 patients (33 women, mean age 35 years) were included. The mean decline in VA was 0.11 ± 0.14 logarithm of minimum angle of resolution (logMAR). The FFAmp decreased by $3.01 \pm 5.9 \mu\text{V}$ with global cone function deteriorating by 18.7% annually. The percentage change in FFAmp (RE [$r = 0.553$], LE [$r = 0.531$]), and 30 Hz flicker amplitude (RE [$r = 0.615$], LE [$r = 0.529$]) strongly correlated with VA ($P < 0.00001$). The pERG p50 (15 and 30 degrees) change analyzed in 34 patients showed reduction by 23% and 23.4%, respectively. The percentage change in p50 30 degrees ($r = 0.397$) correlated with VA and EZ layer ($P < 0.05$). The EZ layer change was calculated in 45 patients and the shortening and thinning rate was 4.3% and 4.4% annually, respectively. The EZ length percentage change correlated with VA (RE [$r = 0.34$] and LE [$r = 0.466$]; $P < 0.05$).

Conclusions: We quantified the decline in cone function in patients with RP utilizing ffERG and FFAmp measures of residual cone function. These parameters correlated with VA and OCT when measurable. These objective measures may assist in monitoring disease progression.

Translational Relevance: Residual cone function provides an objective estimate of residual visual function, which aids in counselling patients regarding prognosis.

Introduction

Retinitis pigmentosa (RP) is a heterogeneous group of inherited retinal diseases characterized primarily by progressive degeneration of rod photoreceptor cells and secondary degeneration of cone photoreceptor cells.¹ Recent studies suggest the prevalence is

approximately 1:1000² and is now the major cause of blind registrations in developing countries.^{3,4} RP symptoms present with nyctalopia, constriction of peripheral visual fields, and, eventually, reduction in central vision.^{5,6} In RP, along with photoreceptor degeneration, there is also associated degeneration of the retinal pigment epithelium (RPE), and attenuation of the retinal vessels and choriocapillaris.⁷

Visual electrophysiology provides an objective measure of retinal function. The full-field electroretinogram (ffERG) is important for diagnosis, staging of disease,^{8–11} assessing long-term visual prognosis,^{12,13} and monitoring photoreceptor function changes over time.^{13–18}

In RP, secondary cone degeneration follows rod degeneration centripetally and is slowest at the macular where cone density is greatest.¹⁹ This correlates with the clinical finding of central visual acuity preservation until advanced stages.²⁰ Measuring the rate of cone degeneration with the ffERG, provides one measure of RP progression. Berson et al. found that the global electroretinogram (ERG) deteriorated by 17% per year, and cone ERG by 5% per year.²¹ The longer follow-up studies showed a slightly lower decay rate of 7% to 13% in global ERG^{22,23} and higher central cone decay rate of 10%.¹⁸ The differences in the global and central rates of change may be attributed to heterogeneity in patient characteristics, genetic factors, and study types.

Optical coherence tomography (OCT) is another valuable tool in assessing residual macular function. Few studies have described the changes in the retinal layers and their correlation with best corrected visual acuity (BCVA).^{24–27} In particular, in RP the ellipsoid zone (EZ) length has been observed to have good correlation with central vision.^{3,28}

Aim

To measure the residual cone-function by evaluating changes in structural and functional biomarkers utilizing ffERG and OCT parameters. The biomarkers included ffERG parameters (light adapted [LA] 3.0 wave, 30 Hz flicker amplitude, photopic fused flicker amplitude [FFamp]), pattern ERG (pERG), OCT (EZ layer length and outer segment thickness), and BCVA.

Methods

Patient Characteristics

This retrospective review included 63 patients from a tertiary referral center (the Save Sight Institute, Sydney Eye Hospital campus, Sydney, NSW, Australia) between 2008 and 2018, who were diagnosed with RP and had undergone electrophysiology testing, including the fused flicker response at least twice with a minimum of 1 year apart. The study was approved by the Local Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

The primary diagnosis was made by visual symptoms of deteriorating night vision, restricted visual fields, typical fundus findings, and a diminished scotopic ffERG response more than photopic response (rod-cone dystrophy). Patients who had a diagnosis other than typical RP or did not have adequate ERG testing performed (minimum of 2 fused flicker readings) were excluded from this study. Demographic details, such as age, gender, date of first and last visit, the time interval between tests, and change in test results were calculated. Any associated systemic or ocular findings present were also noted. Genotyping was not included as a variable in this study.

Visual Function

Vision was tested using the Early Treatment Diabetic Retinopathy Study (ETDRS) Chart (unaided and best corrected) at both the first and last visits. The findings were converted to logarithm of minimum angle of resolution (logMAR) equivalent, for statistical purposes. For children under 5 years of age, Kay's picture test was performed. The refractive error was recorded for all patients using an autorefractor and the error was classified as myopic, hyperopic, emmetropic, or a mixed astigmatism.

Electroretinogram

All ffERG were recorded according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards using the Espion Diagnosys (Lowell, MA). In each patient, both eyes were separately recorded and plotted. The change in the amplitude and latency with time was calculated. The ffERG was recorded using gold foil electrodes. The photopic parameters, light adapted 3.0 b wave (amplitude = μV and latency = ms), 30 Hz flicker (amplitude = μV and latency = ms) were studied.

The 30 Hz flicker is a quick method of objectively assessing the cone system sensitivity and is reliable even in children.¹³ It becomes undetectable from background noise when the amplitude falls below 10 μV . This may be improved with narrow bandpass filtering and computer averaging, the range of detection increases at 100-fold.

The fused flicker is a non-ISCEV standard waveform that enables assessment of residual cone function, as described by Berson et al.¹³ The machine records at the frequency of 30 Hz \pm 1 Hz and improves the signal-to-noise ratio by electronically filtering the bandpasses. The narrow bandpasses are then averaged to record amplitudes as low as 0.05 μV . The importance of recording FFamp is that useful vision is

retained even when the cone function drops below $10 \mu\text{V}$ and is maintained until $0.05 \mu\text{V}$.¹³ Below this critical level, virtual blindness ensues. Responses were recorded in the following manner. Stimulus: flash mode – pulse, flash cycles – continuous, frequency Hz (pulse frequency) – 30.30, on time milliseconds (pulse period) – 1, intensity cd.s/m^2 (pulse intensity) – 0.2 (P), and color (pulse color) – white – 6500 K. Background: intensity cd.s/m^2 – 25.5, and color – white – 6500 K. Fixation: LED – center, intensity – 1.27%, and trigger mode – internal. General: results per run – 1, and time between results – 0. Acquisition: sample frequency (Hz) – 1000, sweep pre-trigger time (ms) – 20, sweep post-trigger (ms) – 200, sweeps per results – 200, first sweep delay (ms) – 2000, filter low frequency cutoff – 28, and filter high frequency cutoff – 32. As the FFamp is sensitive to low cone responses, we defined global cone function change as FFamp change per year.

Pattern Electretinogram

Thirty-four patients from the total of 63 underwent pERG recordings to assess macular status (P50 and N95 amplitudes) to 15 degrees and 30 degrees fields. The readings from the first and last visits were divided by the time interval between the visits and averaged. This provided the change in amplitude of the pERG waves with time. The pERG was recorded according to ISCEV standards, including undilated pupils to preserve retinal image quality. The stimulus was a checkerboard pattern with each square subtending 15 degrees and using 1:1 ratio at the viewing distance of 56 cm. The check size was 0.65 degrees and the mean of the width and the height of the first stimulus field was 15 degrees and for the second stimulus field 30 degrees. The mean luminance of the pattern was 50 cd/m^2 . Each tracing was the average of 150 sweeps.

Optical Coherence Tomography

Horizontal linear macular scans and macular OCT volume scans were generated by spectral domain OCT (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany and Cirrus OCT / Zeiss Humphrey, Sun Leandro, CA) with horizontal and vertical 3 mm scans through the fovea. The EZ length was measured from grey-scale OCT images.

Macular scans were assessed for the presence of cystoid macular edema (CME). Macular thickness was recorded using the ETDRS maps as generated by the macular OCT volumes. This study analyzed the central zone of the ETDRS map. The EZ layer length was

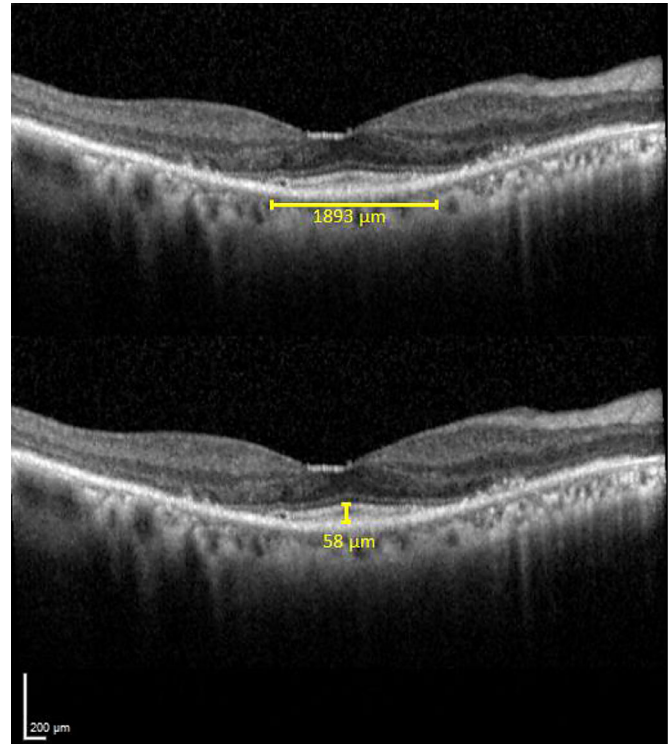


Figure 1. Macular OCT image showing measurement of the EZ layer (a) length of the foveal island remaining (b) thickness measurement at the foveal center.

measured using the caliper tool embedded into the spectral domain-optical coherence tomography (SD-OCT) software (Fig. 1). The length was measured thrice and averaged by the same user. The EZ layer was identified and the thickness of the outer segments (from the top of the EZ line to the top of the RPE line encompassing the hyporeflexive space in between) was measured at the foveal center (see Fig. 1). This was done to improve measurability as the hyporeflexive space in between is too small to measure effectively. Macular scans with absent EZ layer at baseline visit or disrupted EZ layer beneath the fovea were recorded as a null value. The EZ length of macular scans with an undisrupted EZ layer was recorded as the length of the scan. A residual foveal island was seen in many patients, wherein the EZ was present only at the fovea and disrupted at the parafoveal region. The change in the EZ layer length and outer segment thickness was determined by calculating the difference in the two readings between the first and last visit and dividing it by the time interval. Cirrus SD-OCT volume values were corrected using conversion tables and made comparable to the scans acquired by Spectralis OCT to minimize the thickness differences existing between the two instruments.^{29,30}

Statistical Methods

Descriptive statistics included the mean and standard deviation. Correlations among fERG recordings, change in OCT EZ line length, and macular thickness and change in pERG readings with change in BCVA was calculated using Pearson's correlation coefficient. All analyses were conducted using R version 3.5.1. A *P* value of 0.05 was considered statistically significant.

Relationship between the percentage change in P50 amplitude per year (15 degrees and 30 degrees) and the percentage change in EZ length per year was analyzed using generalized estimating equations to account for intracorrelation of measurements of eyes from the same patient. We report the model coefficient, β , and the R^2 value.

Results

One hundred twenty-six eyes of 63 patients were included in the study (33 women and 30 men) with a mean age of 35 ± 20 years. The average age at first symptom was 23 ± 20 years (ranging from birth to 63 years). The mean age at the first visit was 35 ± 21 years and the last visit was 39 ± 21 years. The duration between the first and last visits was 3 ± 2 years (from 1–9 years).

The mean BCVA at the first and last visits was 0.29 ± 0.37 logMAR and 0.49 ± 0.52 logMAR, respectively, with the mean decline per year in BCVA in the right eye (RE) being 0.09 ± 0.12 logMAR and in the left eye (LE) 0.13 ± 0.16 logMAR.

Twenty patients (31.75%) were hypermetropic, 27 patients (42.86%) had myopia, 14 patients (22.22%) had mixed astigmatism, and only 2 patients (3.17%) were emmetropic.

CME was present in 15.8% of the eyes. The mean central macular thickness calculated in 56 patients on the first and last visits was 273.7 ± 55.3 μ m and 279.9 ± 51.6 μ m, respectively. Thirty-seven patients had macular volume scans done on both the visits and the average change in macular thickness was 6.18 μ m.

In our cohort, 14 patients (22.22%) had autosomal recessive inheritance, 1 patient (1.59%) was autosomal dominant, 5 cases (7.94%) were X-linked RP, 9 patients (14.29%) had syndromic RP, out of which 7 patients (11.11%) had Usher's syndrome. The remaining 33 patients (52.38%) had no family history of RP and their inheritance was unknown. The changes in different ISCEV standard waveforms and FFamp is

described in Table 1 and the changes in different OCT parameters is described in Table 2.

Fused Flicker Amplitude

The mean decline in FFamp was 2.63 ± 4.75 μ m in the RE and 3.39 ± 7.05 μ m in the LE, which represents an average amplitude decrease of 18.7% per year. The percentage change in FFamp in the RE ($r = 0.553$, $P < 0.00001$) and the LE ($r = 0.531$, $P < 0.00001$) strongly correlated with BCVA at $P < 0.01$ (Fig. 2).

30 Hz Flicker Amplitude

The percentage change in 30 Hz flicker amplitude in the RE ($r = 0.615$, $P < 0.00001$) and the LE ($r = 0.529$, $P < 0.00001$) and change in latency in the RE ($r = 0.561$, $P < 0.00001$) and the LE ($r = 0.433$, $P = 0.003$) strongly correlated with BCVA at $P < 0.01$ after removing an outlier (Figs. 3 and 4, respectively). The outlier was removed as it was artificially induced while converting data into the percentage change. Decrease in 30 Hz flicker amplitude was 14.6% per year and latency changed by 9.3% every year.

Pattern Electroretinogram

The pERG was recorded in 34 patients. We found that the pERG P50 (15 and 30 degrees) reduced by 23% and 23.4%, respectively, and N95 (15 and 30 degrees) reduced by 16.9% and 17.8%, respectively. The percentage change in pERG P50 amplitude at 15 degrees ($r = 0.198$, $P = 0.261$) did not correlate with vision at $P < 0.05$. Change in pERG N95 amplitude at 15 degrees did not show correlation with vision change at $P < 0.05$ ($r = 0.124$, $P = 0.484$). The P50 amplitude at 30 degrees correlated with vision at $P < 0.05$ ($r = 0.397$, $P = 0.02$). However, N95 30 degrees ($r = 0.144$, $P = 0.416$) did not correlate with vision at $P < 0.05$.

Optical Coherence Tomography

The change in OCT parameters was calculated in 45 patients as 18 patients did not have a detectable EZ line at the first visit. The rate of shortening and thinning was 4.3% and 4.2% per year, respectively. The length of EZ layer showed a correlation with vision in the RE ($r = 0.34$, $P = 0.022$) and the LE ($r = 0.466$, $P = 0.001$) at $P < 0.05$ (Fig. 5). In addition, 28.57% of patients had no detectable EZ layer on OCT, 26.98% had a normal EZ layer at the start of their follow-up, and 44.44% had an attenuated EZ layer (< 1 mm).

A subgroup analysis in patients with no detectable EZ line showed a similar rate of decline in FFamp of 18%.

Table 1. Changes in Different fERG and pERG Waveforms

Parameter	Mean Value at First Visit	Mean Value at Last Visit	Mean Change Per Year	Percentage Change Per Year	Correlation With Vision
ERG recordings					
ISCEV standard waveforms					
LA 3.0 a wave amplitude	RE 16.61 ± 13.82 µV LE 16.63 ± 14.29 µV	9.70 ± 11.28 µV 10.31 ± 10.86 µV	2.76 ± 3.73 µV 3.27 ± 4.67 µV	19.37% 19.43%	NC NC
LA 3.0 a wave latency	RE 14.76 ± 3.77 µV LE 14.92 ± 3.75 µV	19.98 ± 6.74 µV 19.83 ± 6.20 µV	1.93 ± 2.64 µV 1.83 ± 2.57 µV	16.99% 17.10%	NC NC
LA 3.0 b wave amplitude	RE 46.93 ± 46.88 µV LE 52.43 ± 54.64 µV	34.68 ± 36.04 µV 39.22 ± 41.78 µV	5.01 ± 8.56 µV 5.82 ± 13.27 µV	11.67% 11.05%	NC NC
LA 3.0 b wave latency	RE 31.65 ± 6.88 µV LE 30.76 ± 8.64 µV	36.40 ± 5.80 µV 35.70 ± 6.27 µV	1.99 ± 3.80 µV 2.01 ± 3.73 µV	8.29% 10.74%	NC NC
30 Hz flicker amplitude	RE 35.99 ± 34.12 µV LE 38.28 ± 38.74 µV	24.09 ± 25.57 µV 27.39 ± 29.96 µV	4.94 ± 8.79 µV 5.25 ± 10.40 µV	14.80% 14.37%	Yes Yes
30 Hz flicker latency	RE 29.86 ± 6.53 µV LE 30.92 ± 6.13 µV	36.03 ± 7.64 µV 36.75 ± 7.22 µV	2.21 ± 2.90 µV 2.26 ± 2.79 µV	9.93% 8.71%	Yes Yes
pERG P50 amplitude ^a (15 degrees)	RE 1.97 ± 1.60 µV LE 2.01 ± 1.44 µV	1.25 ± 0.92 µV 1.37 ± 1.76 µV	0.44 ± 0.41 µV 0.49 ± 0.49 µV	22% 24%	No No
pERG P50 amplitude ^a (30 degrees)	RE 2.57 ± 1.97 µV LE 2.89 ± 3.10 µV	1.69 ± 1.80 µV 1.70 ± 1.97 µV	0.55 ± 0.54 µV 0.63 ± 0.54 µV	23.51% 23.37%	Yes Yes
pERG N95 amplitude ^a (15 degrees)	RE 3.12 ± 2.15 µV LE 3.17 ± 2.12 µV	2.03 ± 1.43 µV 2.14 ± 2.07 µV	0.50 ± 0.52 µV 0.68 ± 0.96 µV	14.84% 18.91%	No No
pERG N95 amplitude ^a (30 degrees)	RE 3.92 ± 2.89 µV LE 3.93 ± 3.66 µV	2.53 ± 2.48 µV 2.72 ± 2.93 µV	0.60 ± 0.62 µV 0.61 ± 0.43 µV	16.86% 18.81%	No No
Non ISCEV standard waveforms					
Fused flicker amplitude	RE 11.40 ± 15.33 µV LE 13.75 ± 17.86 µV	5.12 ± 7.32 6.33 ± 10.34 µV	2.63 ± 4.75 µV 3.39 ± 7.05 µV	18.78% 18.62%	Yes Yes

NC, not calculated.

^apERG recorded in 34 patients.

Table 2. Changes in Different OCT Parameters

Parameter	Mean Value at First Visit	Mean Value at Last Visit	Mean Change Per Year	Percentage Change Per Year	Correlation With Vision
OCT parameters ^a					
EZ layer length	RE 3658.98 ± 1569.65 μm LE 3741.64 ± 1611.86 μm	3463.71 ± 1571.02 μm 3545.76 ± 1625.47 μm	161.22 ± 326.66 μm 156.43 ± 292.44 μm	4.3% 4.34%	Yes Yes
Outer segment thickness	RE 51.52 ± 10.76 μm LE 51.45 ± 10.99 μm	47.31 ± 11.65 μm 47.80 ± 10.91 μm	1.93 ± 1.93 μm 2.26 ± 2.98 μm	4.05% 4.28%	NC NC

NC, not calculated.

^aOCT change measured in 45 patients.

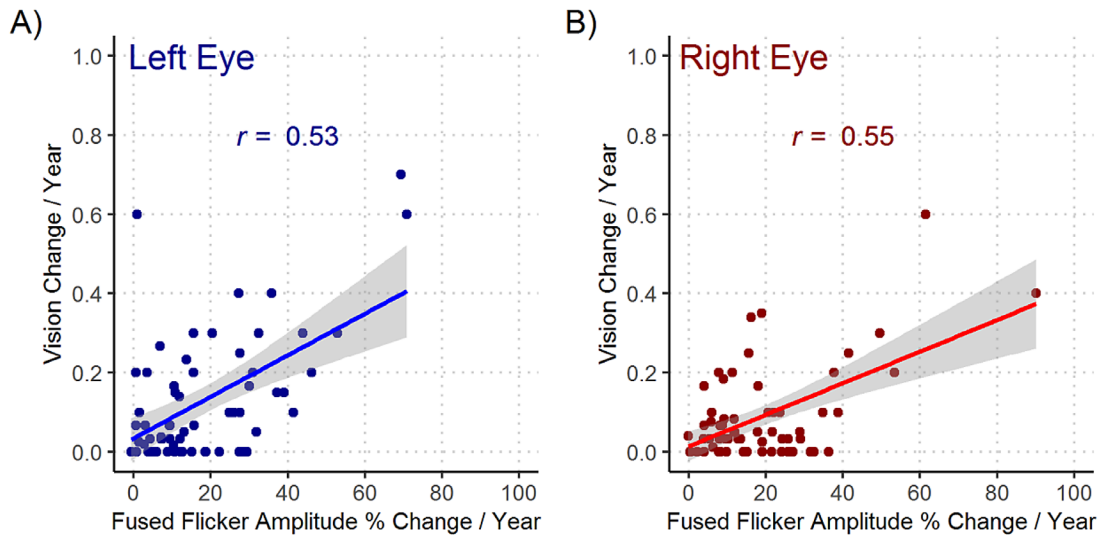


Figure 2. Scatterplot of the percentage change in fused flicker amplitude and the percentage change in vision showing positive correlation between them.

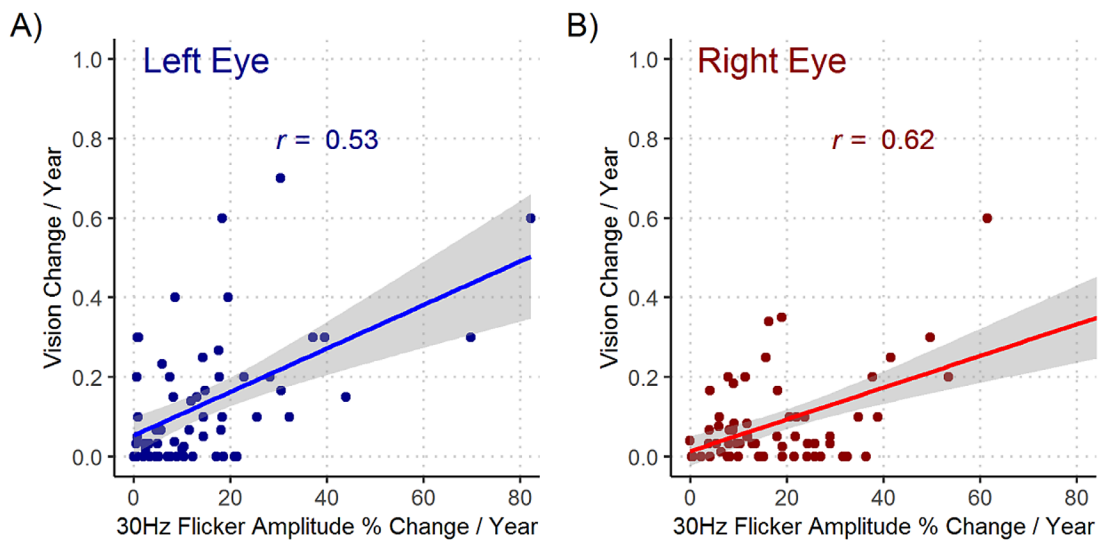


Figure 3. Scatterplot of the percentage change in 30 Hz flicker amplitude and the percentage change in vision showing positive correlation between them.

pERG and EZ Length

The relationship between EZ length and P50 15 degrees amplitude was not significant ($\beta = 0.123$, $R^2 = 0.13$, $P = 0.068$), but the relationship of EZ length and P50 30 degrees amplitude was significant ($\beta = 0.183$, $R^2 = 0.24$, $P = 0.017$; Fig. 6 and Fig 7).

Outer Segment Thickness

The outer segment thickness was calculated in 45 patients and the rate of thinning was 4.2% per year.

The thickness correlated with BCVA in the RE ($r = 0.411$, $P = 0.005$) and in the LE ($r = 0.583$, $P = 0.001$) at $P < 0.05$.

Discussion

Progressive blindness and reduced vision-related quality of life are the main concerns of patients with RP. Functional or useful vision in patients with RP is the ability to perform tasks that require analyzing visual information, such as independent

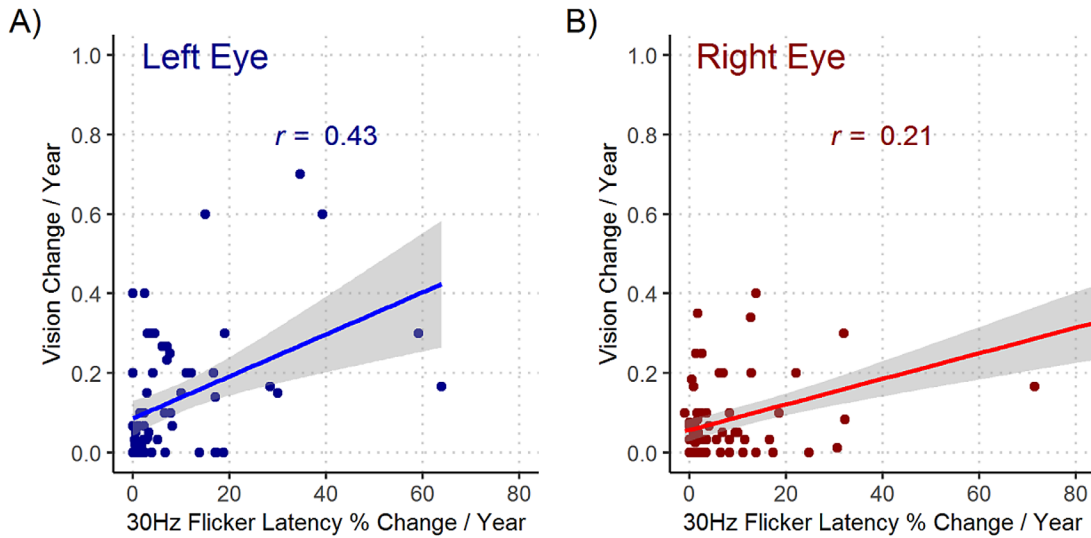


Figure 4. Scatterplot of the percentage change in 30 Hz flicker latency and the percentage change in vision showing positive correlation between them.

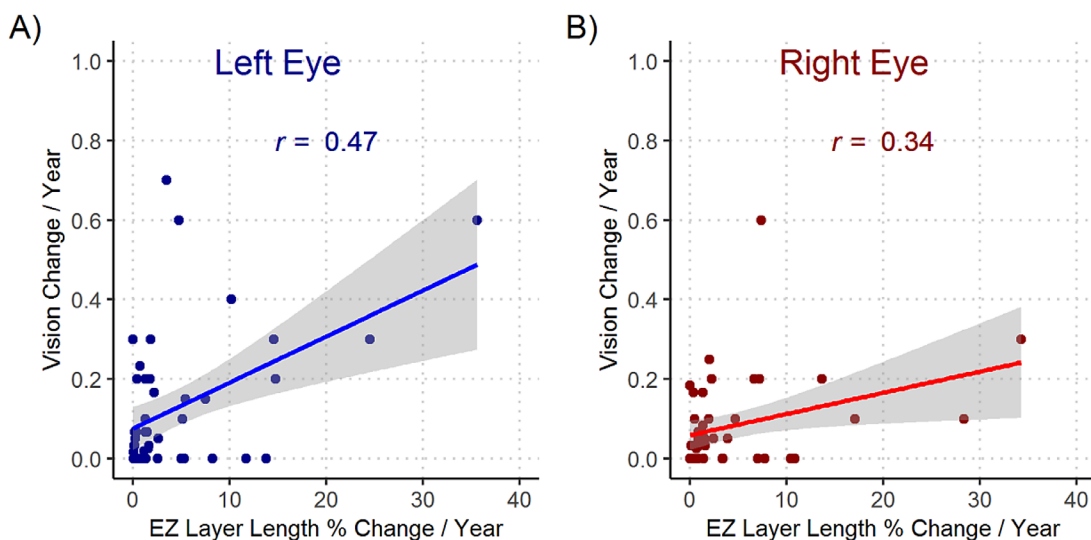


Figure 5. Scatterplot of the percentage change in EZ layer and the percentage change in vision showing positive correlation between them.

navigation, recognizing individuals at a distance, activities of daily living, and visual communication. Loss of central vision has a significant detrimental impact on function. As functional vision is dependent on the central cone photoreceptor function, evaluating the residual cone function provides guidance for patient prognosis. Our study identified the natural decline in central cone-mediated ERG responses, which provides a set of objective parameters that can assist in predicting the rate of change in central vision and hence a patient's overall functional capacity.

Our observation of the correlation between decline in FFamp and 30 Hz b-wave amplitude with decre-

ment in vision are unique, even though there have been reports of correlation among multifocal ERG (mfERG) and visual field,³¹ mfERG and SD-OCT, and visual sensitivity.³²

There exists a significant relationship between rod degeneration and cone survival in RP. Studies have shown that sufficient rod photoreceptors are essential for cone photoreceptor survival.^{33,34} Loss of rod photoreceptor impacts on cone function and survival through several mechanisms, including inadequate factors secreted by rod cells necessary for cone survival,³⁵ migration of microglial cells into outer retina,³⁶ or metabolic stress due to upregulation of certain genes.³⁷

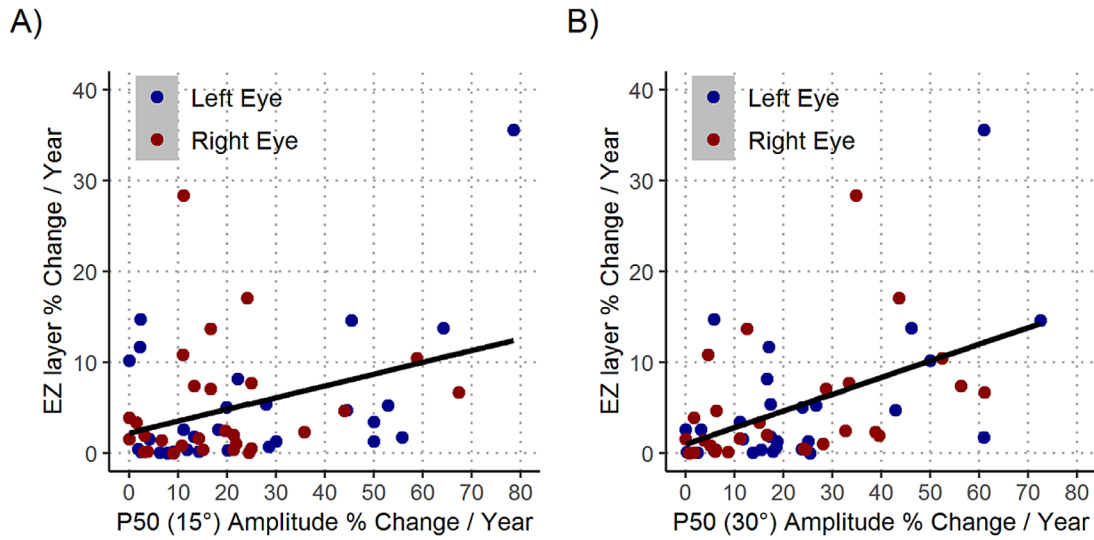
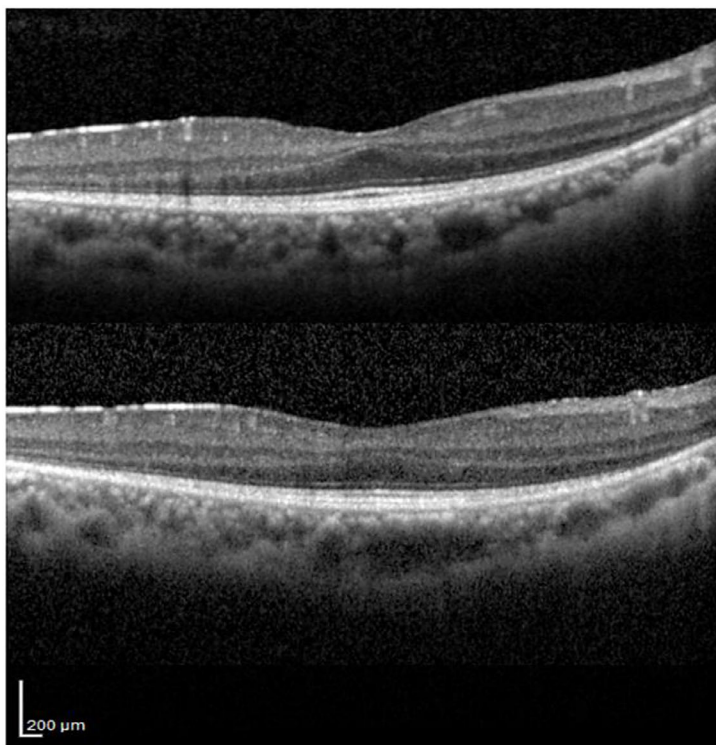


Figure 6. Scatterplot of the percentage change in P50 amplitude per year versus the percentage change in EZ layer per year. The *black line* is the predicted response from generalized estimating equations accounting for intracorrelation between left and right eyes.



30deg field(0.344deg stim)

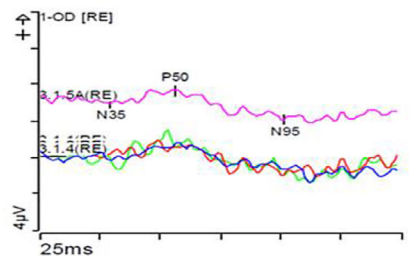
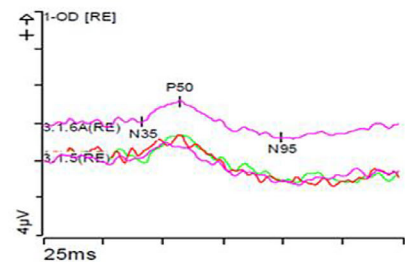


Figure 7. Showing the change in EZ layer and pERG 30 degrees P50 amplitude in one patient after 1 year duration.

Different studies have also reported the structural changes leading to the reduced amplitude and increased latency in the cone ERG parameters, more specifically, changes in cone outer segment, reduced density of the photoreceptors, cell shrinkage, and delay in cone phototransduction.^{38–40}

In our study based on the decrease in FFamp, the global decay rate was noted to be 18.7% and for the 30 Hz amplitude to be 14.6%. Similar rates have been reported by Berson et al.²¹ of 16% to 18.5% change in ERG amplitudes. Studies with smaller sample sizes tend to have higher decay rates than large population

studies.²¹ Difference in measurement of cone function also influences the rate of change, for example, using mfERG techniques, which are focused on the central retina Nagy et al.³¹ found yearly change of 6% to 10%. Even though the mfERG calculates the central cone function, in advanced cases, it is often undetectable or only certain central sectors remain. In addition, mfERG measures the macular cones, which comprise 10% to 12% of the cone photoreceptors in the retina. On the other hand, FFamp and 30 Hz flicker measure global cone function and because of increased averaging can measure smaller responses than the mfERG. It is also difficult to perform mfERG in children as it requires patient cooperation and good fixation. Cone survival rate is also noted to change in different genetic forms of RP,⁴¹ where there is a slower rate of cone decline in patients with autosomal dominant (AD) and Ushers syndrome compared to recessive and sporadic forms. In addition, it is reported that short-term variability in ERG measurement at different visits vary between 25% and 40%,⁴² suggesting that technical (machine-related and electrode coupling) and biological factors (patient factors and viability of cones) can influence the fERG recordings. Interestingly, we noted different rates of decline in different fERG parameters with the maximum decline in the FFamp.

The P50 wave of the pERG has contribution from the outer retina⁸ and is affected in macular dysfunction. In this study, the decline in pERG p50 (30 degrees) did correlate with the decline in BCVA suggesting that this parameter is better at detecting progression. Whereas the pERG p50 (15 degrees) change did not correlate with visual decline and this could be attributed to the small standard deviation and smaller amplitudes of waveforms.

Although not a functional study, the OCT has the advantage of being simpler to undertake, and less technical and time-consuming than ERG with low test-retest variability.⁴³ Hence, finding OCT biomarkers that correlated with visual function decline is useful for the clinic setting. The shortening of the EZ layer has been shown to provide an objective estimate of the residual central cone-mediated visual function.^{44,45} It is the earliest change detected in patients with RP^{27,46,47} and, as it approaches the center, the rate of decline reduces due to increased cone photoreceptor concentration.⁴⁸

The overall rate of EZ shortening and outer segment thinning (4.3% and 4.2% per year, respectively) in this study was a little slower than other reported rates ranging between 5.4% and 7% annually.^{43,49} This could be due to the study cohort that included a significant number of patients with advanced disease and

a small residual foveal island at first review. The EZ length decline and correlation with BCVA decrement has been consistently reported.^{50–55} In our cohort of patients with no measurable EZ line, the FFamp was still recordable providing further evidence of the usefulness of this functional measure in advanced RP. The positive association between vision decline and outer segment thinning further refines the structure-function correlation.

Limitations of our study includes a small sample size and omission of patient's genotyping due to it not being available for all. It will be exciting to find, in future studies, the rate of functional and structural change in different RP genetic forms to better counsel patients.

Conclusion

We quantified the long-term decline of cone function in a cohort of patients with RP utilizing fERG measures of residual cone function – the non-ISCEV standard FFamp and the 30 Hz flicker response as 18.7% and 14.6% per year, respectively. In addition, we demonstrated OCT biomarkers that correlate with this decline in function. These parameters will be useful in both the clinical setting for prognostic counselling at diagnosis as well as monitoring response to treatment in future RP therapeutic clinical trials.

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