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Assessing disease severity of diabetic retinopathy using novel graphical interpretation of flicker electroretinogram

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ASSESSING SEVERITY OF DIABETIC RETINOPATHY USING NOVEL GRAPHIC INTERPRETATION OF FLICKER ELECTRORETINOGRAM

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ABSTRACT

Purpose: To assess the clinical value of reporting full-field electroretinogram (eg, flicker ERG) findings graphically to determine the severity of diabetic retinopathy (DR) within an office-based setting.
Methods: Patients with type 2 diabetes mellitus were included and classified into varying degrees of DR based on presence and severity. Flicker ERG responses were recorded and compared between groups.
Results: Between the varying disease stages, significant differences in the mean magnitude and phase values were found. There was also a significant difference between the proportions of the magnitude and phase color-coded frequencies between groups of severity and threat to vision.
Conclusion: Magnitude and phase parameters of the flicker ERG test may be used to stage disease severity in patients with ongoing DR and determine risk of worsening. With utilization of these values organized into a visual diagram, interpretation of the recording may be more efficient and facilitate appropriate management of DR within the primary care setting.

INTRODUCTION

As the leading cause of blindness in the world [1], diabetic retinopathy (DR) is one of the most commonly managed diseases in the day-to-day operations of many clinical settings. The mainstay method in prevention involves optimal metabolic control that can reduce the risk of DR progression in diabetic patients. These parameters have been defined as maintaining HbA1c, blood pressure, and low-density lipoproteins levels below 7%, 130/85 mmHg, and 100 mg/dl, respectively [1,2]. Once sight-threatening DR is detected, treatment options are available but limited. Laser photocoagulation and vitrectomy are standard interventions in disease management protocol, however, both carry additional risks of vision loss and neither has been shown to be effective at reversing vision loss incurred by the disease [2,3]. Within recent years, intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has shown to be a safer therapeutic alternative for the treatment of proliferative DR (PDR) and is often used in conjunction with the aforementioned interventions. While these injections have been shown by several clinical trials to effectively improve vision in patients with diabetic macular edema (DME), a common complication of DR [4,5], they are not effective in a large proportion of the population for treating the underlying disease process. Of patients with PDR at baseline, 40% of patients receiving laser treatment alone, 21% of patients treated with anti-VEGF injections (ranibizumab) combined with prompt laser therapy, and 18% in patients treated with anti-VEGF (ranibizumab) with deferred laser treatment showed worsening of retinopathy after three years [3]. Several factors account for these differences and may be attributed to standardized treatment guidelines, which often consist of regimented schedules for intravitreal injections requiring close follow-up and strict compliance for efficiency. Thus, the essentials for best outcomes in managing DR include early detection and prevention through strict glycemic control and close follow-up-- which are, unfortunately, not always easily achieved, particularly in developing nations [1,5].

With the advent of imaging modalities utilized for retinal diseases, several diagnostic techniques have been used as guides for detecting disease progression in the eye, as well as response to treatment. Today, conventional screening includes clinical examinations by ophthalmoscopy, fluorescein angiography (FA), and optical coherence tomography (OCT). The gold standard in diagnosing DR is with stereoscopic color fundus photography in 7-standard fields [2]. With the exception of OCT, these methods require subjective and qualitative assessments with skilled analysts and, particularly with the

gold standard, can be uncomfortable and time-consuming [6]. Increasing utilization of OCT for detecting changes in retinal thickness has made it a prominent tool for following DR and DME. It provides both objective and quantitative measures useful for staging the disease based on the structural components within the posterior pole of the retina [2,5]. The development of imaging studies applied to DR have provided a wealth of evidence to explain the anatomical changes observed late within the disease process, such as microvascular abnormalities and intra-retinal swelling. However, these changes are only clinically apparent once visibly detected and existing diagnostic modalities are limited in value for detecting functional changes before appearance of structural abnormalities. Therefore, routine testing is most helpful once the patient starts to notice a decline in visual function, or under circumstances of vision-threatening DR (VTDR) warranting prompt treatment intervention. Despite technological advancements, there is yet to be established a test that accurately serves as a measure of retinal function in predicting the onset of retinopathy before DR manifests clinically [5,6]. Furthermore, such a test has yet to be implemented in the common clinical setting of managing DR.

Flicker ERG is relatively well-known among practicing ophthalmologists as a test for retinal layer function [1,6]. Like the OCT, it can be analyzed objectively and quantitatively. Through a review of the existing literature, we found that flicker ERG establishes its role as a tool for measuring global retinal function. Several studies have demonstrated the efficacy of ERG for the early detection of retinal dysfunction when screening diabetic patients [1,6]. However, there is often little discussion regarding the implementation of flicker ERG into everyday clinical practice. Conventional ERG methods would previously involve large, bulky equipment and lengthy preparation, causing inconveniences and delays within the confined exam rooms of a fast-paced clinic [1,6]. These issues have largely been resolved by refined, non-mydriatic recording devices that take significantly less time to operate. The Neuro Optic Vision Assessment (NOVA)™ ERG system (Diopsys Inc., Pine Brook, NJ, USA) comes equipped with a handheld dome and disposable skin electrodes that are placed on the outer aspect of the lower eyelids. The compact size and minimal operation time predicate its role for the mass-screening of retinal diseases, not only in specialty ophthalmology clinics but also generalist and primary care practices.

The purpose of the present study was to examine components of the flicker ERG in diabetic patients with ocular involvement of varying severities. Our goal is to highlight the usefulness of graphically analyzing flicker ERG as a means to stage between nonproliferative diabetic retinopathy (NPDR) and PDR, as well as VTDR, from the generalist standpoint. Thus, we aim to establish the clinical value of assessing retinal dysfunction in DR patients through values of NOVA™ flicker ERG parameters organized into a simple and easy-to-understand graph.

METHODS

Subjects

This study is a retrospective, observational, single-center analysis conducted in accordance with the Declaration of Helsinki and is HIPAA compliant. All patients gave their written informed consent prior to being included in the study.

The electronic charts of all patients undergoing routine clinical examinations at the Valley Retina Institute (McAllen, TX, USA) who had received a baseline flicker ERG from the period January 2018 to November 2020 were examined. Of these patients, those who were clinically diagnosed with type 2 diabetes mellitus (T2DM) were included and were classified by severity of DR into five groups: no DR, mild NPDR, moderate NPDR, severe NPDR, and PDR. The diagnosis of T2DM was established according to the diagnostic criteria of the American Diabetes Association (ADA). The diagnosis and classification of DR was established according to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales [7]. Patients were secondarily separated by the presence of VTDR, which was defined as having a diagnosis of either severe NPDR or PDR.

All patients had undergone a comprehensive ophthalmologic examination, including review of medical records, best corrected visual acuity (BCVA), intraocular pressure measurement, slit-lamp biomicroscopy, and indirect ophthalmoscopy with a 20-diopter lens. Retinal function was tested with the NOVA™ flicker ERG system. Age, gender, and race of each patient were recorded. Patients were excluded if they had a history of epilepsy, were unable to tolerate the exam, or if their flicker ERG recordings indicated poor signal quality of response in either eye. A historical control group was used to compare flicker ERG parameters between DR patients and normal controls [8].

Full-field flicker ERG examination

Flicker ERG was performed with the in-office NOVA™ ERG system in an illuminated room free of visual distractions. Patients were not dilated and were seated in front of the device monitor at a distance of about 24 inches. The skin on the lower eyelids was cleansed with lid scrub pads (OCuSOFT®, Inc., Richmond, TX, USA) and the skin on the center of the forehead was prepped with Nuprep™gel (Weaver and Co., Aurora, CO, USA). Disposable, adhesive ERG skin electrodes were positioned on the lower lid of each eye and a disposable electroencephalogram (EEG) electrode was secured to the center of the forehead with Ten20 conductive paste (Weaver and Co., Aurora, CO, USA) as a ground electrode. Patients were asked to hold the mini-Ganzfeld dome over the testing eye while focusing on a target displayed on the device monitor with the fellow eye. The testing eye was simulated by 3 $cd*s/m^2$ light flashes flickering at a frequency of 32 Hz over a white background of 30 cd/m^2 within the handheld dome. The stimulus was presented over a total duration of 20 seconds per eye. The test protocols meet the standard of the International Society of Clinical Electrophysiology of Vision (ISCEV). An age-adjusted normative database provided by the manufacturer for identical testing parameters aided the study interpretation by color-coded reference ranges.

Statistical analysis

Demographic data is summarized as means and standard deviations (SDs) or percentages when appropriate. Flicker ERG parameters of magnitude and phase values are reported numerically, as well as categorically based on color-coded reference ranges. Two-tailed unpaired t-tests were performed for comparisons between DR patients and historical controls, as well as between those with and without VTDR. A one-way analysis of variance (ANOVA) was performed to compare means of magnitude and phase between the five groups of varying DR severity. Similarly, categorical variables were compared between groups with a Chi-squared test. Normality of data distribution was tested by Q-Q plot. The level of significance was set at $P \leq 0.05$. All statistical analysis was performed with R Statistical Software, version 1.3.1073 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

259 eyes of 130 patients were identified and included in this study (60 males and 70 females). The mean ages of DR patients and historical healthy controls were 66.2 ± 10.9 years (range 31-92) and 53.3 ± 16.6 years (range 21-81), respectively. There was no significant difference in age between all groups included in our study (P=0.054). The age difference between our DR patients and the historical control group was statistically significant (P<0.0001). The majority of DR patients identified as Hispanic or Latino (71%) whereas the majority of the control group were reported as Asian (38%). Demographic data is shown in Table 1.

The mean magnitude and phase values were compared between the patients included in our study and normal controls (Table 2). The average flicker ERG magnitude of all DR patients was 7.87 ± 4.8 µV (range 0.06-21.26) and for the control group it was 10.14 ± 3.52 µV. The average flicker ERG phase value of all DR patients was 264.92 ± 50.69 degrees and for the control group it was 305.24 ± 25.55

degrees. Both magnitude and phase averages were both found to be significantly different between our patients and normal controls (P=0.0022).

A flicker ERG recorded from a normal control is shown in Figure 1. Figure 2 shows flicker ERGs recorded from four representative subjects from our study, each with a different degree of DR: mild NPDR, moderate NPDR, severe NPDR, and PDR. Along with reported numerical values, measures of magnitude and phase are organized into a circular graph, called the "Mag/Phase Plot", of which certain regions are demarcated by different colors. The margins depicted as green, yellow, and red indicate retinal function as normal, mild dysfunction, or severe dysfunction, respectively. These color-coded references were used along with the corresponding numerical values of flicker ERG magnitude and phase to assess retinal function between the five groups in this study.

All of the 259 eyes were divided into five groups: no DR (n=6), mild NPDR (n=78), moderate NPDR (n=52), severe NPDR (n=16), and PDR (n=107). The mean magnitude and phase values of the five groups were compared (Table 3). The results indicated significant differences in both the magnitude and phase values between the groups. Furthermore, when comparing proportions of magnitude and phase values based on the color-coded reference ranges between the groups, significant differences were found in both parameters (P<0.0001).

In order to divide subjects into groups with or without VTDR, we further classified patients with no DR, mild NPDR, and moderate NPDR into a "non-VTDR" group (*n*=136) and those with severe NPDR and PDR into a "VTDR" group (*n*=123). The data is demonstrated in Table 4. There were significant differences between the two groups in both means and color proportions for each flicker ERG component.

TABLES AND FIGURES

	Our Study	**Controls**
No. of Patients (*N*)	130	50
Age (mean ± SD)	66.2 ± 10.9	53.3 ± 16.6
Gender (male/female)	60/70	22/28
Race *(% of N)*		
Hispanic or Latino	71%	0%
Asian	0%	38%
Caucasian	9%	32%
African American	0%	18%
*Other**	20%	12%

Table 1. *Demographic data of patients included in our study and historical control group.*
*Declined to specify, unknown, or other unspecified race.

Flicker ERG Parameters	Our patients (n=130)	Control group (n=50)	*p-value*
Magnitude (μV)	7.87 ± 4.8 (0.06-21.26)	10.14 ± 3.52 (9.11-11.17)	0.0022*
Phase (º)	264.92 ± 50.69 (103.13-448.69)	305.24 ± 25.55 (297.74-312.74)	<0.0001*

Table 2. *Mean flicker ERG magnitude and phase values compared between our patients and historical control group.*
*Data is described as [mean ± SD (range)] and analyzed with two-tailed t-test.

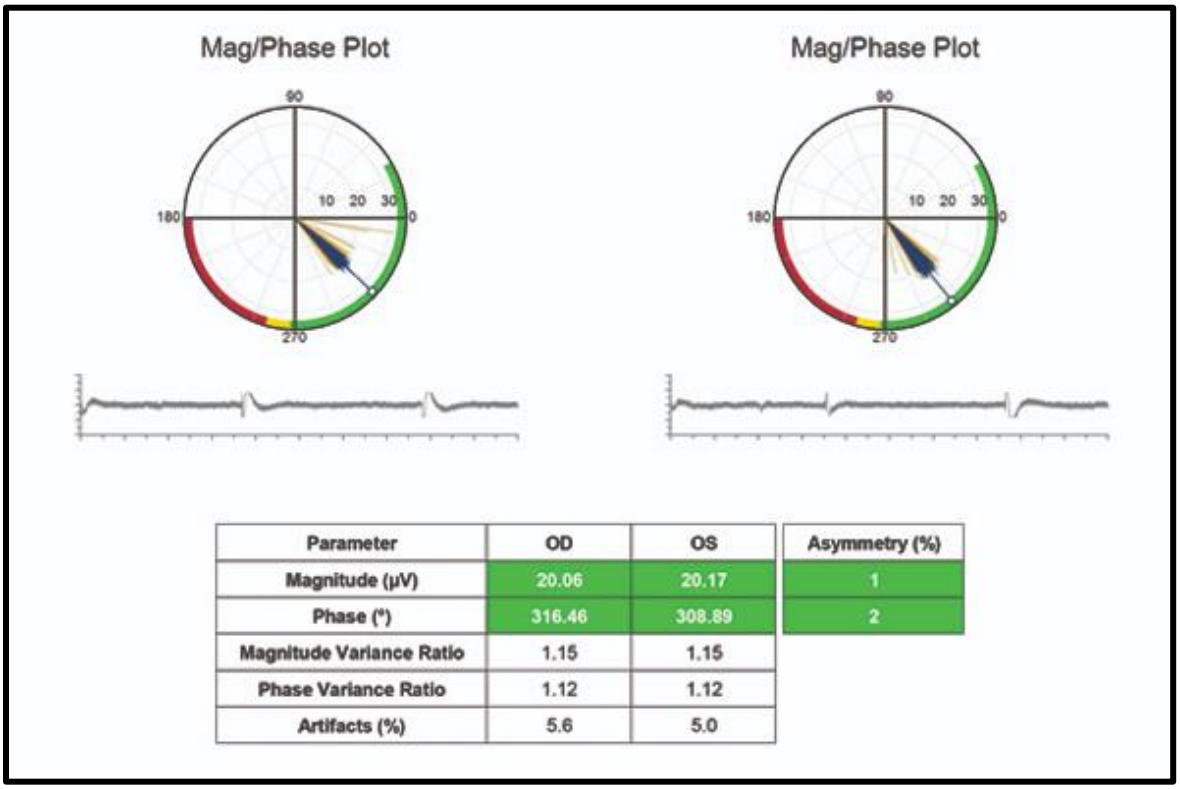

Figure 1. *A representative flicker ERG recording of a pair of normal eyes.* The right eye is depicted on the left (OD) and the left eye is depicted on the right (OS). Response signals of each eye are recorded in parameters of magnitude and phase and are organized qualitatively into a Mag/Phase Plot with the according quantitative values highlighted by color of the appropriate reference range.

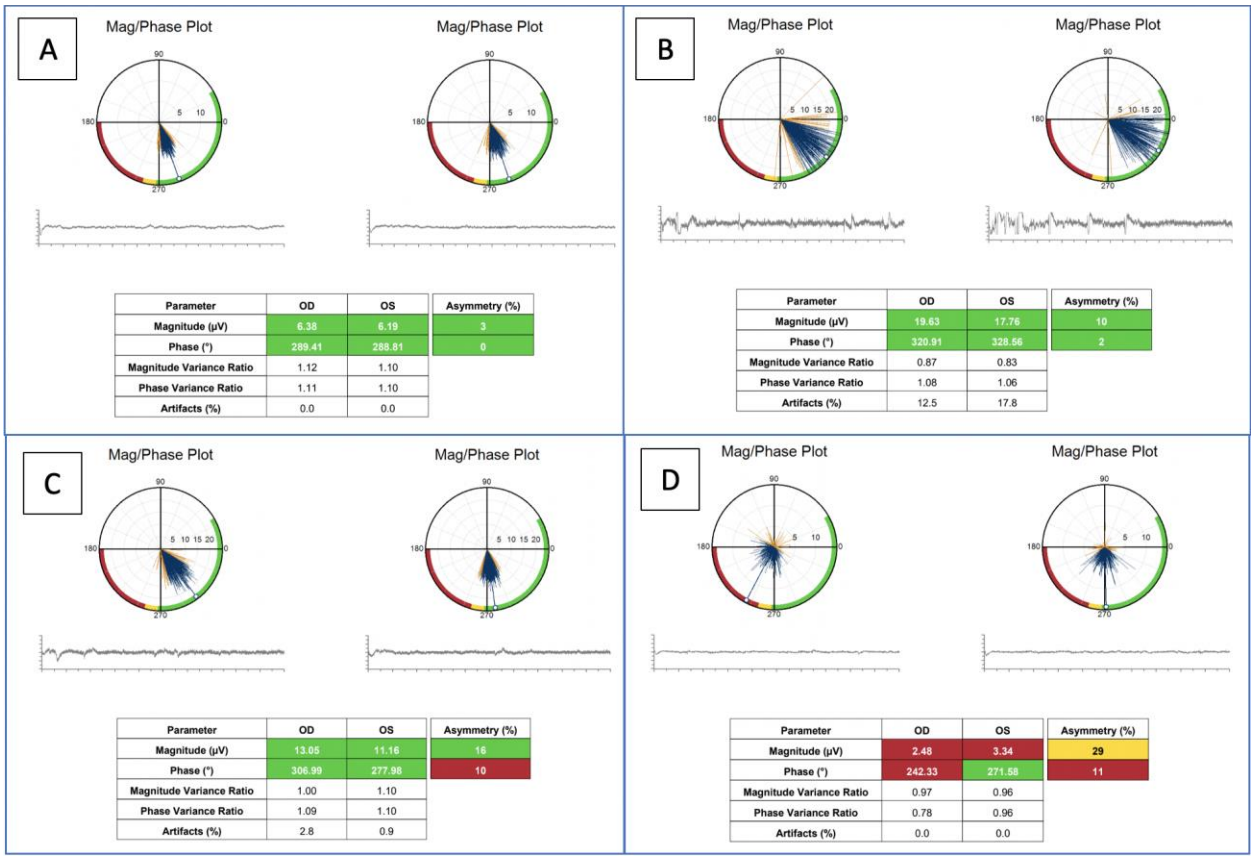

Figure 2. *Representative flicker ERGs recorded from four subjects with various severities of DR, including mild NPDR (A), moderate NPDR (B), severe NPDR (C), and PDR (D).* Increasing degree of severity of DR corresponds to changes in magnitude and phase values based on appearance and position on Mag/Phase plot and color references.

	No DR (n=6)	**Mild NPDR** (n=78)	**Moderate NPDR** (n=52)	**Severe NPDR** (n=16)	**PDR** (n=107)	*p-value*
Magnitude (μV)	7.34 ± 1.87	9.58 ± 4.01	10.87 ± 5.64	6.95 ± 2.95	5.4 ± 3.88	<0.0001*
Green	6	68	41	13	47	**
Yellow	0	6	7	1	24	**
Red	0	4	4	2	36	**
Phase (^{o})	304.37 ± 19.2	267.87 ± 53.93	277.08 ± 42.32	254.99 ± 28.7	256.37 ± 53.65	0.0324*
Green	6	59	32	5	37	**
Yellow	0	6	6	3	10	**
Red	0	13	14	8	60	**

Table 3. *Parameters of flicker ERG test in different groups of DR.*
*Data is described as [mean ± SD] and analyzed with one-way ANOVA.
**Data described as observed counts and analyzed with Chi-squared test with all p-values <0.0001.

	non-VTDR (n=136)	**VTDR** (n=123)	*p-value*
Magnitude (μV)	9.96 ± 4.68	5.6 ± 3.8	<0.0001*
Green	115	60	**
Yellow	13	25	**
Red	8	38	**
Phase (^{o})	272.94 ± 49.23	256.19 ± 51.01	0.0072*
Green	97	42	**
Yellow	12	13	**
Red	27	68	**

Table 4. *Parameters of flicker ERG test in groups of non-VTDR and VTDR.*
*Data is described as [mean ± SD] and analyzed with two-tailed t-test.
**Data described as observed counts and analyzed with Chi-squared test with all p-values <0.0001.

DISCUSSION

In our study, we assess the clinical value of interpreting both magnitude and phase parameters of the flicker ERG test by color as compared between groups of varying degrees of DR, from none to proliferative. We also evaluated the ability of the test to discriminate for VTDR. These parameters were reported with quantitative measures, as well as qualitative measures by depiction through a simple graph, the Mag/Phase Plot. Both measures were associated with color-coded reference ranges supplied by the database of the Diopsys device and were used to assess differences between groups of DR patients. Our results report significant differences of the means and color proportions of the magnitude and phase values between the DR groups, as well as between those with and without VTDR. These findings suggest that the flicker ERG test serves as a promising tool for following disease progression of DR and to guide treatment.

One interesting finding seen in the present study was the relatively large magnitude and phase flicker ERGs in eyes with moderate NPDR (Table 3). It is thought that altered retinal hemodynamics in diabetic individuals would be unable to maintain sufficient perfusion in response to a rapid flicker of light, thereby attenuating the response to flicker ERG testing [9-11]. Changes in different ERG components can also occur depending on various factors, such as glucose load and pupillary size [12,13]. Instances of supernormal flicker ERG parameters in diabetic eyes have been attributed to transduction abnormalities, neuronal activity, and photoreceptor sensitivity loss [6,10], findings that are often present during stages of active disease progression. Given that our threshold cutoff for VTDR was met for any condition worse than moderate NPDR, this may explain the higher flicker ERG values within this group, though these speculations have not been overtly established. Additionally, since our exclusion criteria was limited to maximize the sample size, these values may have been influenced by confounding factors, such as history of intravitreal injections, ocular surgery, laser therapy, and more.

There are a handful of studies that report the feasibility of the flicker ERG test in screening for DR among diabetic patients [1,6,11]. Our findings corroborate these reports, but we also establish a novel method of assessment. Previous studies established their conclusions based on the recorded flicker ERG parameters reported numerically [6,11], whereas we also incorporated their references based on color. By doing so, the time to mentally translate “text” to “numbers” to “associated level of severity” is reduced. Presumably, linking the colors of green, yellow, and red to three broad

classifications (i.e., good, okay, bad) allows a much simpler thought process and eliminates the need to memorize or look up criteria guides for certain disease stages.

To the best of our knowledge, no one has introduced flicker ERG responses organized into a Mag/Phase Plot as an easy modality for the swift diagnosis of retinal diseases. The Mag/Phase plot records retinal signals as lines in response to each flash stimulus during the flicker test; it incorporates the amount of the response (i.e., magnitude; depicted by length of line), speed of response (i.e., phase; denoted by where in the circle the line lies), and reproducibility (i.e., reliability; determined by inverse association to separation of lines from each other). The magnitude of the signal reflects the function of cone cells, which are anatomically distributed throughout the retina, and the phase is a measure of the timing of the response. The variance of these measurements represents the consistency of the strength and speed of the signal. Together, these parameters provide a straightforward analysis of retinal function that may be successfully and efficiently interpreted by clinicians from all backgrounds. By understanding green as “good”, yellow as “okay”, and red as “bad”, the Mag/Phase Plot can be evaluated by the general practitioner to the comprehensive ophthalmologist and beyond.

As seen in our representative sample of patients with DR (Fig. 2), conditions in which the degree of severity is stable within the mild-to-moderate range of DR will have flicker ERG readings mostly in the “green”, where the plot points lie within the lower right quadrant of the graph. In contrast to those ranging in severe NPDR-to-PDR stages, the plot points may make their way closer toward the lower left quadrant zoned with yellow and red color references, which indicate a more drastic underlying disease process. It is important to know, however, that other pre-existing conditions or treatments may alter the retinal response. For example, consider two individuals each diagnosed with moderate NPDR, where one has never received any medical or surgical treatment and the other maintains routinely scheduled appointments for anti-VEGF injections. The flicker ERG of the treatment-naive individual may illustrate a more complex disease picture warranting timely intervention compared to that of the treated patient, whose report may appear to suggest either a stable or improving condition. While flicker ERG alone may not always be the best initial tool to diagnose and stage DR, its value in establishing baseline readings and monitoring for progression during follow-up periods is clear. Furthermore, with improvements in the diagnostic preparation time and portability, flicker ERG may be deployed in smaller spaces and rapidly moving environments.

Our study herein illustrates the applicability of the Mag/Phase Plot to a fast-paced clinical setting. However, there are several limitations to consider. First, our study was limited by the nature of its retrospective design. Another limitation was our small sample size. This has been consistent with prior studies [1,6,11] and bears need for prospective studies with a larger number of participants. Third, as we were unable to locate flicker ERG studies performed on normal or healthy patients seen by the clinic, we compared our study patients to a historical control group that did not appropriately match up by demographic characteristics. Furthermore, we were unable to find existing data regarding evaluation of retinal function as determined by the Mag/Phase Plot, and so no controls were examined for comparison. Considering our limited exclusion criteria, we did not appropriately account for associated or underlying issues, such as diabetic cataracts or glaucoma, which may have influenced our findings. Therefore, a control group would have been especially helpful to determine differences between our patients.

In conclusion, we found that the flicker ERG test interpreted by color can be used as a tool to evaluate for disease severity among patients with T2DM, DR, and VTDR. While the reason why eyes with moderate NPDR tended to have larger magnitude and phase values was not determined, it had no apparent effect on the analysis of flicker ERG reports based on color-coded references. Future directions include addressing the aforementioned limitations and further studies to provide more accurate results of significant differences, as well as determine the detection performance, sensitivity and specificity of the flicker ERGs to discriminate DR stages and VTDR.

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