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# Reproducibility of Fixed-luminance and Multi-luminance Flicker Electroretinography in Patients With Diabetic Retinopathy Using an Office-based Testing Paradigm

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## Abstract

**Background:** We evaluated the reproducibility of office-based flicker electroretinography (ERG) in patients with nonproliferative diabetic retinopathy (NPDR).

**Methods:** An observational study was conducted in which ultra-widefield fluorescein angiography (UWF-FA) was performed on 20 patients with mild-to-moderate NPDR; images were graded by the Fundus Photography Reading Center (Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI, USA). Fixed- and multi-luminance flicker ERG was repeated four times (greater than or equal to seven days apart). Recording consistency was assessed using intra-class correlation coefficients (ICCs), coefficients of variation, and Pearson correlations.

**Results:** 82.5% and 17.5% of eyes had mild and moderate NPDR using UWF-FA; 90% of the angiograms were given a high confidence grade. Fixed-luminance phase values were highly reproducible (ICC: 0.949; $P < .001$). There was a significant negative correlation between fixed-luminance phase and log-corrected ischemic index values (−0.426; $P = .015$).

**Conclusions:** Office-based, fixed-luminance phase values are highly reproducible and negatively correlate with retinal ischemia in NPDR, suggesting that global retinal dysfunction may be reliably quantified early in patients with diabetes.

## Keywords

diabetic retinopathy, diagnostic testing, flicker electroretinography retinal dysfunction, ultra-widefield fluorescein angiography

## Introduction

Traditionally, treatment for diabetic retinopathy (DR) is reserved for patients with clinically significant macular edema (CSME),[1,2] severe nonproliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR).[3,4] At these advanced stages of retinopathy, patients can be treated with laser photocoagulation, intravitreal steroids, vascular endothelial growth factor (VEGF) inhibitors, or a combination.[4-10] In 2017, the Food and Drug Administration extended the application of ranibizumab to patients with all stages of DR, with or without diabetic macular edema (DME).[11,12]

Before 2017, no treatment regimens were recommended for patients with mild-to-moderate NPDR without DME.[2] Current guidelines recommend that these patients be monitored every 6-36 months for progression of DR.[4,13] The extended approval of ranibizumab provides new treatment options for patients with mild-to-moderate NPDR without DME. To the best of our knowledge, however, no standardized guidelines have been established for the initiation, duration, or monitoring of ranibizumab treatment in these patients.

Stereoscopic fundus photography is the gold standard for the structural assessment and staging of DR.[14-16] Traditionally, 60° fluorescein angiography has been used

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to aid in classifying DR.[17] More recently, ultra-widefield fluorescein angiography (UWF-FA) has become an invaluable adjuvant for the accurate classification and monitoring of DR.[18-22] UWF-FA, however, still requires a qualitative and subjective assessment of the image.[20-22] Optical coherence tomography (OCT), which has been widely used in the diagnosis and follow-up of eyes with DME,[23,24] is an objective and quantitative test. However, the use of widefield spectral domain OCT, employing a specific montaging software capable of providing a global structural analysis of the retina,[25] has yet to become commonplace in the management of DR.

Full-field electroretinography (ERG; eg, flicker) is the only available technology with the ability to provide objective, quantitative, and global assessment of retinal function. Electrophysiologic studies performed in the laboratory on patients with severe NPDR and PDR have shown flicker ERG to be a sensitive and reliable test[26,27] and an effective assessor of drug efficacy in patients receiving anti-VEGF therapy.[28,29] To date, flicker ERG testing designed to quantify the degree of DR in an office-based setting has yet to be investigated.

We evaluated the inter-session reproducibility of office-based NOVA™ (Diopsys, Inc., Pine Brook, NJ, USA) flicker ERG in patients with mild-to-moderate NPDR. A secondary objective was to investigate the correlation between flicker parameters and the extent of retinal ischemia as defined by UWF-FA.

## Methods

### *Study Design and Patient Population*

The protocol was approved by the Sterling Institutional Review Board and conducted in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. The study was designed as a single-center, observational case series. All research activities were performed at Cumberland Valley Retina Consultants (Hagerstown, MD, USA). The research procedures were explained to all participants, and all 20 patients provided written consent to participate in the study.

All potential participants underwent a comprehensive ophthalmologic evaluation, including review of medical records, best-corrected visual acuity (BCVA) testing, slit-lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, dilated slit-lamp fundus examination with a 90-diopter or fundus contact lens, and indirect ophthalmoscopic examination with a 20-diopter lens. Forty eyes in 20 consecutive patients with presumed mild-to-moderate NPDR without CSME and BCVA better than or equal to 20/50 were included. Eyes with dense cataract or active macular edema were excluded. Other key exclusion criteria included a history of optic neuropathy or vasculopathy known to affect visual function, glaucoma, panretinal photocoagulation, vitreous surgery, focal macular laser (less than or equal to two months), anti-VEGF/intravitreal steroidal therapy (less than or equal to four months), or ocular surgery (less than or equal to six months). Patients with any condition that might impact ERG data acquisition such as tremor, blepharospasm, dry eye, or seizure disorder also were excluded.

### *Procedures*

UWF-FA (Optos 200Tx ultra-widefield™ retinal imaging system, Dunfermline, UK) was obtained on both eyes following standard intravenous infusion with 5 $cm^3$ of 10% sodium fluorescein. Two certified retinal photographers performed the UWF-FA, and images were sent to the Fundus Photography Reading Center (Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI, USA), where a confidence score, area of nonperfusion value, and ischemic index grade were given to each eye by a masked reader.[19-21] The ischemic index grade was calculated by dividing the sum of the areas of nonperfusion by the total visible UWF-FA area for that eye and corrected for using a methodology previously described.[30] A higher ischemic index value indicates a greater amount of fundus capillary closure. A grade of mild or moderate NPDR was given to each eye by evaluating the degree of retinopathy (presence of microaneurysms, intra-retinal hemorrhages, and intra-retinal microvascular abnormalities) within the whole of the UWF angiogram.

Flicker ERG was performed with the in-office NOVA ERG system in an illuminated room, free of visual and audible distractions. Light-adapted participants were not dilated and instructed to fixate on a target using the fellow eye (eye not been tested). Flicker ERG was recorded from both eyes using Diopsys hypoallergenic skin electrodes. For this configuration, three electrodes were used per test: one active/reference electrode positioned at the lower lid of each eye and a ground electrode placed at center of forehead (eg, while testing OD (right eye), the OD lid sensor worked as the active electrode, and the OS (left eye) lid sensor worked as the reference electrode). The skin was thoroughly prepared by cleaning with eyelid cleanser (OCuSOFT®, Inc., Richmond, TX, USA) to ensure good, stable electrical conductivity. Electrode impedances were kept below 5 kΩ. Full-field stimulation was used to provide uniform luminance over the entire retina using a hand-held Mini Ganzfeld Stimulator (LKC Technologies, Inc., Gaithersburg, MD, USA).

For fixed-luminance flicker ERG, the stimulus (as suggested by International Society for Clinical Electrophysiology of Vision [ISCEV] standards) consisted of white flashes flickering at 32 Hz over a white background.[31,32] Onset and offset times were 5 and 26.25 ms, respectively. White flash luminosity was 3 cd *s*$m^{-2}$ over a white background of 28 $cd/m^2$. Signal contaminated by eye blinks or gross eye saccades was rejected automatically over a threshold voltage of 50 μV.

For multi-luminance flicker ERG protocol, a sequence of six steps of increasing luminance was presented. Each step lasted 4 s with a 600-ms break between steps. Luminance increased exponentially (until maximum ISCEV standard was reached) as follows: 0.16, 0.32, 0.64, 1.28, 2.56, and 3.00 cd*s*$m^{-2}$.

Analog signals were amplified 20 000 times, band-pass filtered with cut-off frequencies of 0.5 and 100 Hz, and digitized at 2 048 samples/s. The A-to-D converter (A/D) had a resolution of 12 bits. The voltage range of the A/D was programmed to ±5 V. Synchronized single channel was recorded, generating a time series of 512 data points per analysis window.

Flicker ERGs were repeated on four separate days (greater than or equal to seven days apart) for each participant by one of three certified operators. All four ERG sessions were performed using the same Diopsys machine in the same office location. Two different office locations, each with its own machine, were used. The location of each machine and the ambient lighting in each testing room remained constant for the study duration. Total time was ~20 min/session (90 s of data collection).

### Statistical Analysis

Results are reported as means and standard deviations (SDs). The Shapiro–Wilk test was used as a test of normality given the small sample size. Mean values and normal ranges were analyzed with 95% confidence intervals. Between-session reproducibility determines the ability to detect change over time. Consistency of recordings between visits was calculated using the coefficient of variation (CV) and intra-class correlation coefficients (ICCs). Correlations among flicker ERG variables and UWF-FA ischemic index were calculated using Pearson correlation coefficients. Ischemic index values were assessed for normality, and it was determined that the data had a non-normal, logarithmic distribution. Thus, ischemic index values were logarithmically transformed for the calculation of correlations. SPSS v.20.0 for Windows (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. A $P$-value of $<.05$ was considered statistically significant.

## Results

### Patient Disposition

Twenty consecutive patients with mild-to-moderate NPDR were evaluated. Table 1 provides a per-patient listing of demographic and clinical characteristics. Overall, mean age was 64.5 years (age range 40-75); all patients were white. Seventeen patients had type 2 diabetes; three patients had type 1 diabetes. Mean duration of diabetes was 22 years (range 12-30). Thirty-five percent ($n=14$) of eyes had previous focal macular laser photocoagulation, none of which was performed less than two months prior to enrolment. Eight percent ($n=3$) of eyes had previous anti-VEGF therapy; no eyes had previous intravitreal steroid treatment.

**Table 1.** Individual Patient Listing: Demographic and Clinical Characteristics.

| | | | Diabetes | | Vision | | Previous macular laser | |
|---|---|---|---|---|---|---|---|---|
| Patient # | Age | Sex | Type | Duration, y | Right eye | Left eye | Right eye | Left eye |
| 001 | 61 | F | 2 | 19 | 20/30 | 20/25 | Yes | No |
| 002 | 58 | F | 2 | 15 | 20/30 | 20/40 | No | No |
| 003 | 66 | F | 2 | 12 | 20/20 | 20/20 | No | No |
| 004 | 75 | M | 2 | 27 | 20/25 | 20/25 | No | No |
| 005 | 64 | F | 2 | 15 | 20/40 | 20/25 | No | No |
| 006 | 62 | F | 2 | 17 | 20/20 | 20/20 | No | No |
| 007 | 70 | F | 2 | 25 | 20/25 | 20/20 | Yes | Yes |
| 008 | 72 | F | 2 | 30 | 20/16 | 20/25 | Yes | No |
| 009 | 72 | M | 2 | 30 | 20/30 | 20/25 | No | Yes |
| 010 | 69 | M | 2 | 13 | 20/20 | 20/20 | No | No |
| 011 | 73 | F | 2 | 23 | 20/20 | 20/20 | No | No |
| 012 | 57 | F | 2 | 16 | 20/20 | 20/20 | Yes | No |
| 013 | 65 | F | 2 | 28 | 20/30 | 20/40 | No | Yes |
| 014 | 40 | M | 1 | 23 | 20/20 | 20/20 | No | Yes |
| 015 | 68 | F | 2 | 22 | 20/25 | 20/20 | No | No |
| 016 | 68 | F | 2 | 20 | 20/25 | 20/30 | No | No |
| 017 | 54 | F | 1 | 28 | 20/25 | 20/25 | Yes | Yes |
| 018 | 68 | M | 2 | 29 | 20/50 | 20/50 | Yes | Yes |
| 019 | 58 | M | 1 | 30 | 20/20 | 20/20 | No | Yes |
| 020 | 69 | F | 2 | 18 | 20/20 | 20/20 | No | Yes |

Abbreviations: F, female; M, male.

### UWF-FA

As graded by the Fundus Photography Reading Center, 82.5% ($n=33$) of eyes had mild NPDR; 17.5% ($n=7$) had moderate NPDR. Ninety percent ($n=36$) of eyes had a high confidence score (Figure 1); four eyes had an adequate confidence score. The mean (SD) corrected ischemic index was 0.0116 (0.0227); values ranged from 0.0002 to 0.1219 (Table 2).

### Flicker ERG

Ninety-six percent (307/320) of possible ERG tests were performed. Of 20 patients, 30% ($n=6$), 50% ($n=10$), 15% ($n=3$), and 5% ($n=1$) had their testing completed in four, five, six, and eight weeks, respectively (supplemental Table). The mean testing period was five weeks. Diopsys in-office testing was well tolerated, easily repeatable, and quick to perform.

Fixed- and multi-luminance magnitude values and fixed-luminance phase values were highly reproducible (Table 3). Fixed-luminance phase values were the most reproducible

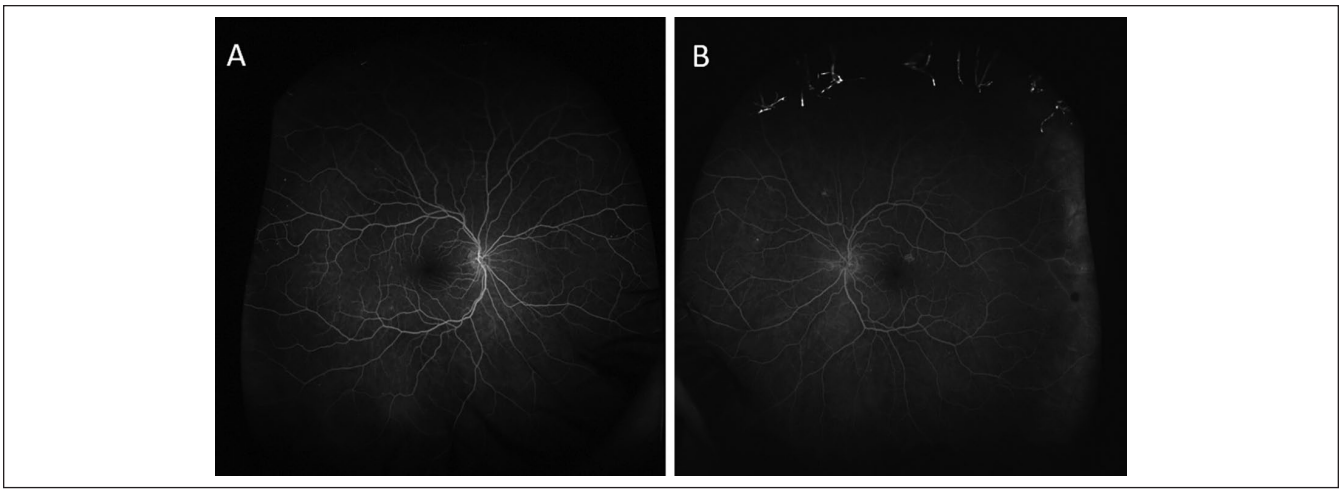


**Figure 1.** UWF-FA results of patient #014 with mild NPDR in both eyes. (a) Right eye with an absent ischemic index. (b) Left eye with an ischemic index of 0.0022 as determined by the Fundus Photography Reading Center.
NPDR, nonproliferative diabetic retinopathy; UWF-FA, ultra-widefield fluorescein angiogram.

**Table 2.** Individual Patient Listing: Wisconsin Reading Center Ultra-widefield Fluorescein Angiogram Results.

| | | | Right eye | | | Left eye | | |
|---|---|---|---|---|---|---|---|---|
| Patient # | Confidence score | Score reason | Area of nonperfusion | Ischemic index | NPDR severity | Area of nonperfusion | Ischemic index | NPDR severity |
| 001 | CS1: High | n/a | Absent | Absent | Mild | 10.60 | 0.0147 | Mild |
| 002 | CS1: High | n/a | 1.89 | 0.0025 | Mild | 3.59 | 0.0045 | Mild |
| 003 | CS1: High | n/a | 1.36 | 0.0018 | Mild | Absent | Absent | Mild |
| 004 | CS2: Adequate | Unknown | 2.17 | 0.0030 | Moderate | 1.57 | 0.0020 | Mild |
| 005 | CS1: High | n/a | Absent | Absent | Mild | Absent | Absent | Mild |
| 006 | CS1: High | n/a | 0.76 | 0.0010 | Mild | 0.59 | 0.0008 | Mild |
| 007 | CS2: Adequate | Patient | 81.53 | 0.1219 | Moderate | 34.71 | 0.0611 | Moderate |
| 008 | CS1: High | n/a | 5.26 | 0.0076 | Mild | Absent | Absent | Mild |
| 009 | CS1: High | n/a | 28.36 | 0.0418 | Moderate | 10.67 | 0.0144 | Moderate |
| 010 | CS1: High | n/a | 2.75 | 0.0046 | Moderate | 8.12 | 0.0120 | Mild |
| 011 | CS1: High | n/a | 16.08 | 0.0241 | Mild | 20.36 | 0.0287 | Moderate |
| 012 | CS1: High | n/a | Absent | Absent | Mild | 8.14 | 0.0104 | Mild |
| 013 | CS1: High | n/a | Absent | Absent | Mild | 2.39 | 0.0030 | Mild |
| 014 | CS1: High | n/a | Absent | Absent | Mild | 1.58 | 0.0022 | Mild |
| 015 | CS1: High | n/a | 1.45 | 0.0020 | Mild | 16.12 | 0.0233 | Mild |
| 016 | CS1: High | n/a | 31.67 | 0.0479 | Mild | 4.17 | 0.0063 | Mild |
| 017 | CS1: High | n/a | 0.78 | 0.0011 | Mild | 0.13 | 0.0002 | Mild |
| 018 | CS1: High | n/a | 2.38 | 0.0036 | Mild | 4.18 | 0.0067 | Mild |
| 019 | CS1: High | n/a | 3.29 | 0.0047 | Mild | 1.63 | 0.0023 | Mild |
| 020 | CS1: High | n/a | 1.61 | 0.0020 | Mild | 1.18 | 0.0016 | Mild |

Abbreviations: CS, confidence score; NPDR, nonproliferative diabetic retinopathy.

(ICC = 0.949; $P < .001$) (Figure 2). Fixed-luminance phase values demonstrated low inter-session variability (Table 3). There was a statistically significant negative correlation between fixed-luminance phase and ischemic index values (−0.426; $P = .015$). No correlations were found between flicker ERG values and eyes with a previous history of macular photocoagulation.

## Discussion

This study found that fixed-luminance flicker phase values are highly reproducible across multiple testing sessions performed at least seven days apart and are negatively correlated with the degree of retinal ischemia in NPDR.

DR is characterized by superficial and deep capillary plexus microangiopathy, chronic microglia-induced inflammation,

**Table 3.** Flicker Inter-session Reproducibility.

| Endpoint | Intra-class correlations | | | Coefficients of variance |
|---|---|---|---|---|
| | ICC[a] | 95% CI | *P*-value | |
| Fixed-luminance ERG | | | | |
| Magnitude | 0.833 | 0.723, 0.907 | <.001 | 0.252 |
| Phase | 0.949 | 0.915, 0.971 | <.001 | 0.036 |
| Multi-luminance ERG | | | | |
| Magnitude | 0.919 | 0.608, 0.846 | <.001 | 0.239 |
| Phase | 0.657 | 0.416, 0.816 | <.001 | 0.086 |

Abbreviations: CI, confidence interval; ICC, intra-class correlation coefficient.
[a]Type A intra-class correlation coefficient using an absolute agreement definition.

and primary hyperglycemia-induced neurodegeneration.[33-38] Diabetic neural and neurovascular dysfunction precedes the onset of overt clinical retinopathy,[39,40] with neurovascular uncoupling preceding neural dysfunction in type 1 diabetic eyes.[41] In addition, electrophysiologic studies on patients with type 1 and type 2 diabetes have confirmed the existence of retinal dysfunction in the absence of visible microvasculopathy.[42-44] Thus, flicker ERG, a test assessing global retinal cone and bipolar cell function, may be a more effective metric of diabetes-induced retinal damage than a structural evaluation designed to address ischemia and morphology such as fluorescein angiography.[45,46]

In addition to the primary pathologic effect that chronic hyperglycemia has on the neuroretina, choroidal and choriocapillary alterations have been reported on postmortem diabetic eyes,[47-49] and in-vivo choriocapillary flow impairment has been documented with swept-source optical coherence tomography angiography.[50] These findings suggest the potential for hyperglycemia-driven, choroid-induced photoreceptor dysfunction. As a result, diabetes-induced choroidal alterations may theoretically contribute to flicker ERG responses that are primarily cone-driven. To summarize, all major cell types and layers of the retina are altered in diabetes, with retinal dysfunction being the result of the pathologic interplay between endothelial cells, microglia, astrocytes, Müller cells, and neurons.[33] Flicker ERG offers a unique opportunity to quantify the total effect of this pathologic interplay on cone and bipolar cell function.

Photopic ERG implicit time delays have been shown to increase significantly as the severity of DR progresses from mild to severe NPDR.[51] Moreover, 30-Hz flicker ERG B-wave implicit times obtained in the laboratory have long been described as a reliable, objective diagnostic tool in quantifying global retinal dysfunction in DR.[52-54] In particular, 30-Hz flicker B-wave implicit times are delayed in DR, with the magnitude of delay increasing with increasing disease severity.[52,55,56] Thus, flicker implicit times can theoretically be used to detect and quantify early disease and potentially be implemented to monitor DR progression.

Recently, mydriasis-free ERG recording with skin electrodes in healthy eyes has been described.[57] Furthermore, this hand-held device, which utilizes skin electrodes, has been proven to be an accurate screening test for identifying the absence of vision-threatening DR.[27] High intra-session reproducibility of the fixed-luminance phase parameter (ICC = 0.98) using office-based Diopsys NOVA technology, a testing methodology that also employs skin electrodes and mydriasis-free recording, has previously been established in healthy eyes.[58] This study, which utilized a similar testing methodology, sought to additionally determine the inter-session reproducibility of the Diopsys NOVA flicker ERG in a clinical setting of diseased eyes with mild-to-moderate NPDR.

Of the four parameters tested, the fixed-luminance phase value, a frequency domain analog of the time domain B-wave implicit time, was the most highly reproducible across testing sessions. This finding is especially noteworthy, as multiple variables such as blood pressure, renal status, patient age, duration of disease, pupil size, time of day when testing was performed, and retinopathy grade could theoretically impact retinal performance and thus confound the degree of inter-session reproducibility over a four- to eight-week testing period. Furthermore, similar to previous reports investigating ERG and retinal ischemia in DR,[52-55] flicker phase in our study was found to negatively correlate with ischemic index as measured using UWF-FA and therefore, possibly the degree of retinopathy severity. Thus, the phase value of the fixed-luminance flicker test is highly reproducible and could be used as a functional metric to quantify the level of baseline retinopathy and also be used to monitor retinopathy progression.[56]

Thirty-five percent (14/40) of eyes had a previous history of a single episode of focal macular photocoagulation, most of which had been performed years previously. A separate analysis comparing the flicker ERG values of these eyes with those of eyes without a previous history of macular photocoagulation yielded no significant between-group difference in electrophysiologic responses. This finding is not surprising given that the vast majority of the total cone population in the human retina is located outside the macular area.[59-61] Flicker ERG, being a full-field electroretinographic test, stimulates the majority of the retinal surface, even through an undilated pupil.[27,57] As such, one would not expect to discern a difference in flicker ERG responses in eyes with limited macular cone loss from previous focal photocoagulation.

The Diabetic Retinopathy Severity Scale (DRSS), which divides DR into 13 levels ranging from absence of retinopathy to severe vitreous hemorrhage, is used to describe overall retinopathy severity and change in severity over time.[14,15] Two classes of intravitreal therapies have been shown to benefit DRSS: anti-VEGF therapy and corticosteroids.[62-66] Intravitreal ranibizumab and aflibercept have been shown to reduce the risk of worsening retinopathy and improve DRSS in a significant percentage of patients.[63,64,67,68] Moreover,

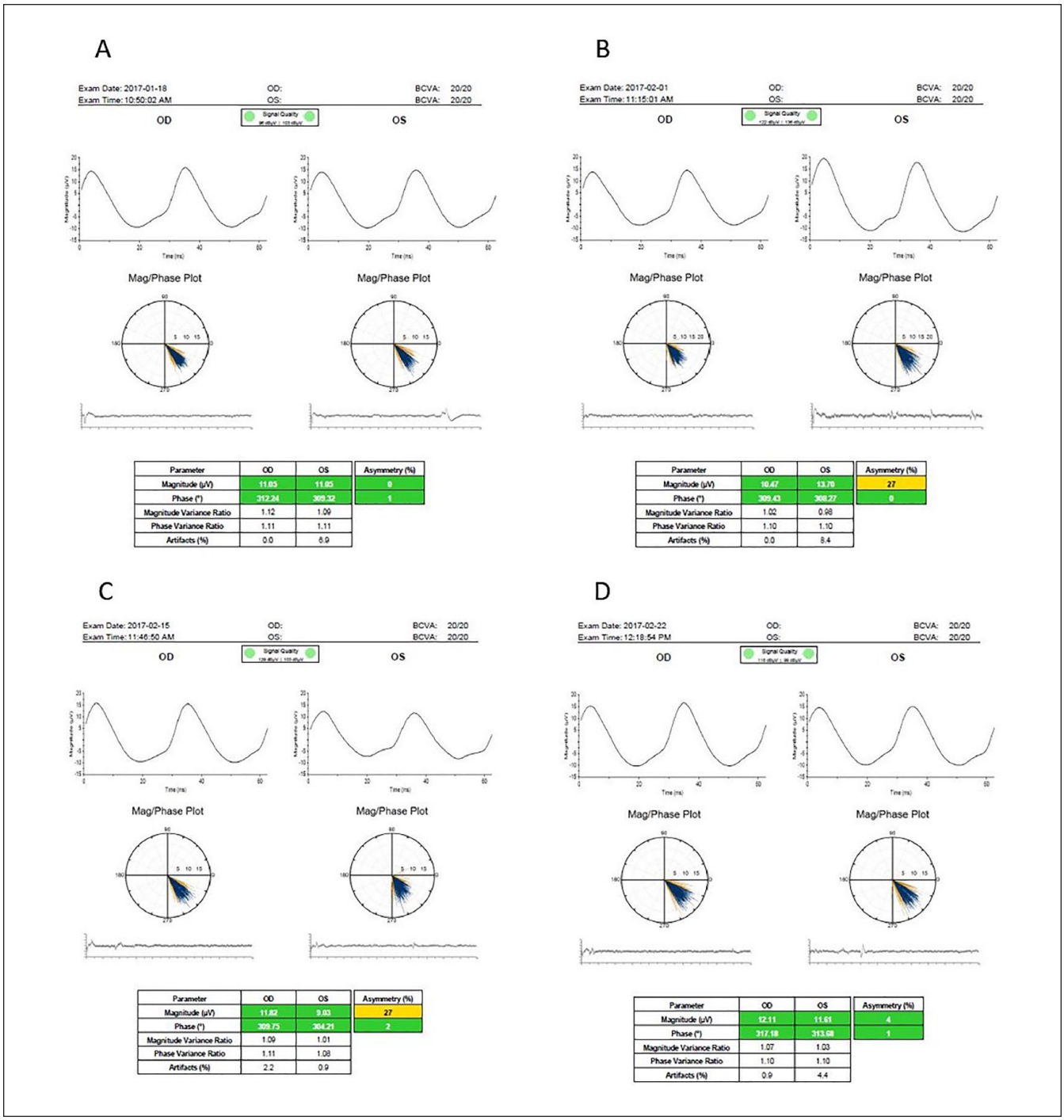


**Figure 2.** (a-d) Diopsys reports illustrating fixed-luminance magnitude and phase values of the right and left eyes of patient #014 acquired over a five-week testing period. The mean phase values of the right and left eyes were 312.15 and 308.87, respectively, which were highly reproducible. The left eye had a lower mean phase value, which corresponded with a greater degree of retinal ischemia, as determined by the Fundus Photography Reading Center (see Figure 1).

treatment with both ranibizumab and aflibercept can be associated with reperfusion of areas of retinal capillary closure as demonstrated with UWF-FA.[69] Thus, in light of the aforementioned negative correlation between flicker phase and retinal capillary nonperfusion, it is reasonable to suggest that flicker ERG could theoretically be utilized to help clinicians decide when to initiate anti-VEGF therapy in eyes with mild-to-moderate NPDR, as well as when to extend the treatment interval and eventually discontinue treatment.[29]

To date, office-based flicker ERG testing designed to longitudinally quantify the degree of diabetic retinal dysfunction in a clinical setting has yet to be reported. Furthermore, this is the first study designed to evaluate the reproducibility of office-based flicker ERG. As such, a detailed comparative analysis with similar studies is not possible owing to our unique, in-office study design. However, ERG studies performed in the laboratory on patients with mild-to-severe NPDR and PDR have been reported and have shown ERG to be a sensitive and reliable test of retinal dysfunction.[70]

Study limitations primarily include the size and characteristics of the patient population, which limit the extent to which the results can be extrapolated to the general population of patients with DR. That is, the sample size of 20 white patients (40 eyes) was small, and the age range was relatively narrow. Moreover, the majority (85%) of patients had type 2 diabetes. However, INDIGO a larger, multicenter, longitudinal, observational study quantitatively evaluating retinal dysfunction in patients with DR using office-based flicker ERG is currently underway. INDIGO is recruiting patients with diverse demographic (eg, age range) and clinical (eg, type of diabetes and duration of disease) characteristics.

Our preliminary findings suggest that office-based flicker ERG, especially the fixed-luminance phase parameter, is highly reproducible and could be reliably used as a biomarker to initially characterize and quantify global retinal cone and bipolar cell dysfunction in diabetes and potentially be employed to follow eyes with mild-to-moderate NPDR over time. Additional potential applications include serving as an adjuvant to fluorescein angiography and supporting the management of anti-VEGF therapy.

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## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This study was funded by Diopsys, Inc. Dr Wroblewski serves as a speaker for Diopsys, Inc. Dr Gonzalez is an employee of Diopsys, Inc. Ms Pickel was an employee of Diopsys, Inc. at the time the study was conducted. None of the other authors have relevant financial disclosures.

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## Supplemental Material

Supplemental material for this article is available online.

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