Ophthalmology Times
eBOOK

A GAME-CHANGER IN DIABETIC RETINOPATHY

Early diagnosis and management guidance using objective, functional vision testing.

by STEVEN M. SILVERSTEIN, MD

We know diabetes is a common and growing problem as well as the leading cause of new cases of blindness in adults.[1] According to the Centers for Disease Control and Prevention, there were an estimated 30.3 million people with diabetes in the United States in 2017.[2] Another recent study found that almost one-third of diabetic adults aged 40 years and older had diabetic retinopathy (DR), and the National Eye Institute projected that the number of Americans with DR would increase by nearly 50% between 2010 and 2030.[1–3] That equates to a lot of new patients walking in your door.

The visual prognosis for patients with diabetic eye disease has been improved with the use of intravitreal anti-VEGF therapy for diabetic macular edema (DME) and diabetic retinopathy (DR), but early detection and intervention are important for optimizing outcomes. With a focus on delivery of value-based care and recognition of the burdens and risks of intravitreal injections, it is also important to avoid overtreatment.

General ophthalmologists and retina specialists need access to tools that enable early diagnosis of diabetic eye disease and guide management decisions. Now, electroretinography (ERG) testing is accessible to ophthalmic practices and is proving valuable for meeting these needs.

Until the advent of optical coherence tomography (OCT), structural evaluation of the retina for evidence of diabetic eye disease relied on fundus photographs and dye-based angiography. Visual acuity (VA) and visual field testing were used for functional assessment. All of these techniques, however, have limitations. Dye-based angiography is invasive and interpretation of its images and of fundus photographs is subjective in nature. Advances in software are aiding the interpretation of visual fields, but visual field and VA testing is subjective since the results depend on the cooperation and responses of the patient.

ERG, a light induced visual response which measures electrical signals generated by cells in the

retina in response to a visual stimulus, is the only diagnostic test available that gives an objective assessment of retinal function. With respect to the need for information that enables early detection and guides management decisions for DR, ERG provides documentation of disease-related damage before retinopathy becomes clinically apparent using other diagnostic modalities.[4] Measuring the function of living cells, ERG identifies cells that are stressed or dying, but that are still viable and may have the potential for functional recovery with effective intervention.

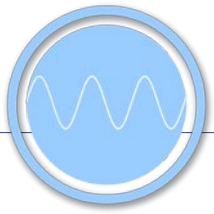
ERG can also guide management decisions because its findings can predict retinal ischemia and DR progression.[4] Unlike visual field testing, the results of ERG testing are completely independent of patient interaction, and flicker ERG in particular is valid even in the presence of media opacities. Because the results are reliable and reproducible, ERG is useful not only as a diagnostic tool for early detection of DR, but also has a role in follow-up evaluations to identify disease progression or response to treatment.

Diopsys ERG Technology

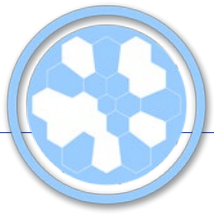
My experience with ERG dates back to the mid-1980s when I was an ophthalmology resident at Tufts-New England Medical Center in Boston where I had the privilege of working with Sam Sokol, PhD, and Ann Moscowitz, PhD, in their research laboratory. At that time, ERG was primarily used for basic and clinical research studies in academic centers because the equipment was expensive and cumbersome, and the testing was time-consuming and utilized multiple invasive sensors. With commercially available equipment from Diopsys, ERG is accessible as a user- and patient-friendly tool for in-practice testing.

Diopsys markets three different platforms that vary in size and portability to provide clinics of all sizes access to visual electrophysiology testing: Diopsys® NOVA™ (cart), Diopsys® ARGOS™ (tabletop), and Diopsys® RETINA PLUS™ (carry case). Each platform can be customized with the testing modules that fit the practice's patient base, with the choice of pattern, flicker, and/or multifocal ERG along with visual evoked potential (VEP) testing (**Figure 1**). In addition to DR with and without macular edema (DME), these techniques have application for evaluating a range of

Flicker ERG is a step of the standard ISCEV full field ERG that flashes at ≥ 30Hz. Flicker ERG testing records the retina's response to the flashes of light, reflecting the electrical activity of cone and bipolar cells.



A **pattern ERG** test records the retina's response to a phase-reversing patterned stimulus, reflecting the electrical activity of retinal ganglion cells.



A **multifocal ERG** test records the retina's response to localized flashes of light, reflecting the electrical activity of mainly bipolar cells, combined with smaller contributions from the photoreceptors.

A **pattern VEP** test records the conductivity of the visual pathway in response to a phase-reversing patterned stimulus, reflecting the electrical activity of the entire vision system, from the retina to the visual cortex.

Figure 1. ERG and VEP testing modules.

diseases affecting the retina and optic nerve, including glaucoma, toxic maculopathy, and optic neuritis.

Pattern and flicker ERG testing with the Diopsys platforms is done with proprietary disposable sensors that are easily applied and comfortable for patients. In contrast to other ERG systems that use an electrode placed on the cornea, the Diopsys sensors are applied to the skin on the forehead and below the eyes, without need for topical anesthetic and with minimal risk for corneal damage or eye irritation.

ERG testing with the Diopsys systems can be performed by practice technicians. Because of the in-person and online training offered by Diopsys and straightforward software, it was readily adopted by the technical support staff in our practice.

Our experience also shows high patient acceptance of ERG testing with the Diopsys systems. To perform the test, patients simply need to cover one eye at a time and look at a screen displaying a series of patterns or flashes of light.

Test interpretation is also intuitive because reference ranges have been established for the tests for help in discriminating healthy eyes and sick eyes. The reports include waveforms, graphs, and data points that are color-coded to identify whether the patient's results are in-range, borderline, or out-of-range (**Figure 2**). Additionally, there are Trend Reports that can track progression or improvement over time.

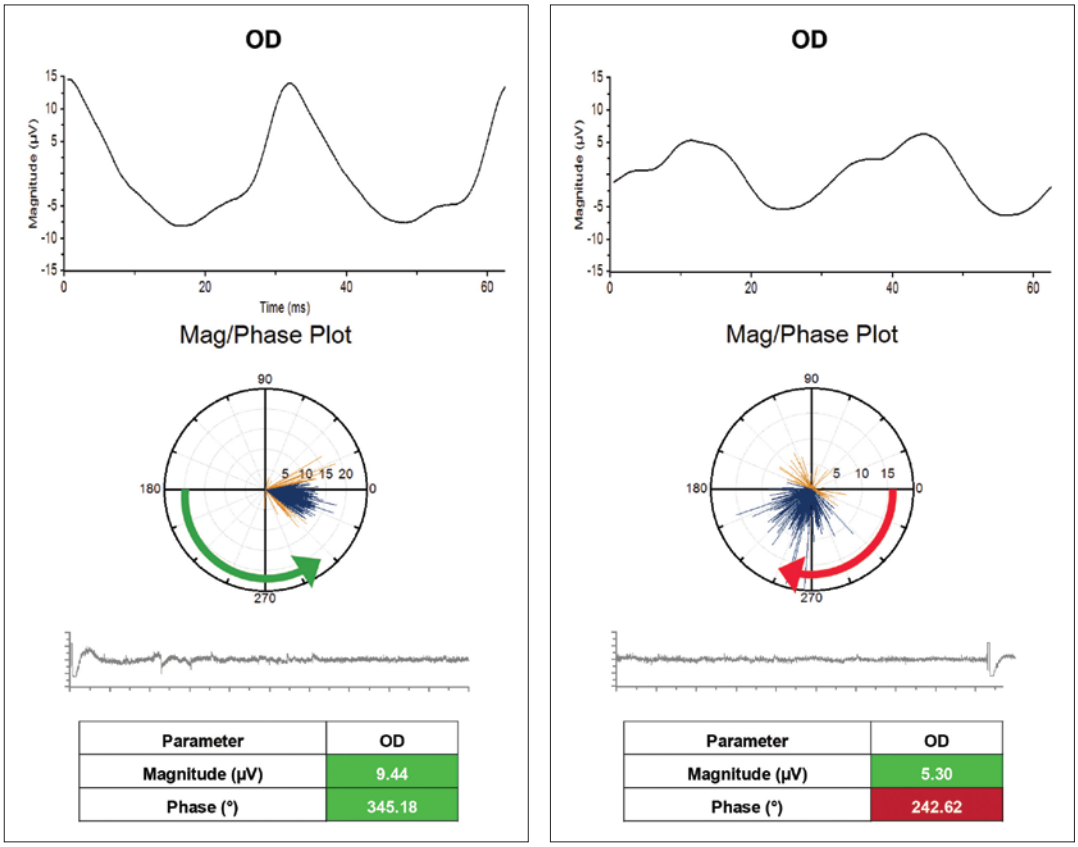


Figure 2. Demonstration Diopsys® ffERG / Fixed Luminance Flicker results of healthy retinal function OD and retinal dysfunction OD.

ERG in Diabetic Patient Care

Pattern and flicker ERG are the test protocols that are relevant for the evaluation and management of DR with and without DME [see **sidebar: Clinical Application of Flicker ERG**].

PATTERN ELECTRORETINOGRAPHY

The value of pattern ERG for evaluating patients with diabetes is demonstrated by results of studies showing that it can pick up preclinical abnormalities and predict disease progression more consistently and reliably than other conventionally used tests, i.e. OCT and fluorescein

CLINICAL APPLICATION OF FLICKER ERG

The following testing examples illustrate how flicker ERG can be applied in clinical practice to optimize the evaluation and care of patients with diabetic eye disease.

Testing Example 1

A 57-year-old woman with a 10-year history of type 2 diabetes mellitus presents reporting a change in her vision. She was previously diagnosed with moderate nonproliferative diabetic retinopathy (NPDR) in both eyes, is poorly compliant with diabetes management, and her hemoglobin A1c indicates poor metabolic control. On clinical examination, there are no changes in her VA nor evidence of new microaneurysms.

Flicker ERG is ordered and shows no change from the prior test result. Therefore, the patient is counselled about the risks of poor metabolic control and counselled to be more compliant with her recommended diabetes management. She is scheduled for a return visit in 1 month and referred to her endocrinologist to receive further evaluation, education, and follow-up for diabetic management.

The same care plan would have been instituted had this woman been newly diagnosed with moderate NPDR and as a baseline test, her flicker ERG was normal. If the woman were an existing patient being followed for DR and the flicker ERG showed worsening, or if she were a new patient with an abnormal flicker ERG, FA would have been ordered to assess for subclinical changes in her DR.

ICD 10 code E11.3393 Type 2 diabetes mellitus with moderate nonproliferative diabetic retinography without macular edema, bilateral

Testing Example 2

A 72-year-old woman with severe NPDR in both eyes and a history of mild DME presents with worsening of a cataract that is impeding visualization of the retina. On examination, she shows a decrease in VA.

Flicker ERG is useful in this situation for determining the underlying global retinal function, planning cataract surgery, and setting proper expectations for postoperative visual recovery. If the flicker ERG is unchanged from a prior test result, the assumption is that the change in VA is explained by cataract progression, and the patient would be scheduled for cataract surgery at her convenience. An abnormal initial flicker ERG or a result showing worsening from a prior test would raise concern about progression of the diabetic eye disease and indicate a need to expedite cataract surgery to enable retinal evaluation. In this situation, the patient would also be counseled that cataract surgery may not fully restore vision and that she is not a good candidate for a presbyopia-correcting IOL.

ICD 10 code E11.3413 (OU) type 2 diabetes mellitus with severe NPDR with macular edema, bilateral

ICD 10 code E11.36 Type 2 diabetes mellitus with diabetic cataract

Testing Example 3

A 61-year-old man with a history of moderate NPDR in both eyes and DME after focal grid photocoagulation is initiated on anti-VEGF therapy. Flicker ERG is repeated to assess the response to the intravitreal injections.

Finding that the flicker ERG results are unchanged or improved from prior testing suggests a positive response to anti-VEGF treatment, and this result considered together with the appearance of the macula on OCT might support starting the patient on a treat-and-extend regimen. If the flicker ERG showed worsening, then a careful examination could be performed looking for uncommonly high IOP or toxic side effects. Consideration might also be given to switching or adding treatment for DME and perhaps shortening the follow-up interval.

ICD 10 code E11.3313 (OU) type 2 diabetes mellitus with moderate NPDR with macular edema, bilateral

angiography (FA).[4–8] By identifying individuals who may be at high risk for DR early, pattern ERG can help clinicians decide whether a patient could benefit from closer surveillance for progression and/or needs stronger reinforcement about the importance of controlling modifiable metabolic risk factors. Pattern ERG test results can also help facilitate co-management conversations with endocrinologists and primary care physicians.

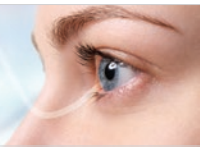
The value of serial testing with pattern ERG to track response to anti-VEGF treatment for DME has also been demonstrated.[9]

FLICKER ELECTRORETINOGRAPHY

Flicker ERG quantifies the level of retinal dysfunction in eyes with DR, and in contrast to the visual field and OCT, which evaluate posterior retina function and structure, flicker ERG provides information about the global function of the cone/bipolar system of the entire retina.[4–8] It therefore gives insight about global retinal ischemia, the potential for progression of DR with the development of proliferative disease and neovascularization. Flicker ERG also helps the clinician in determining whether urgent treatment is appropriate or if the patient may be managed more conservatively with careful observation.

Results of a prospective study of patients with nonproliferative DR and DME showed that serial flicker ERG identified improvement in global retinal function (i.e., global cone function) following initiation of anti-VEGF therapy.[10] By assisting with the assessment of treatment responses and because of its potential to identify improvement or worsening even before changes are observed on OCT or visual fields, flicker ERG can help retina specialists with their decisions on modifying

Figure 3: Patient set-up for flicker ERG vision test.



the anti-VEGF administration regimen. This has important clinical relevance considering evidence from recent studies showing that a treat-and-extend regimen is feasible for reducing the anti-VEGF treatment burden without jeopardizing anatomic or visual outcomes in patients with DME.[11,12]

Conclusion

Diabetic retinopathy is a common and growing problem worldwide and a leading cause of vision loss and blindness among working-age adults in developed countries. As a complement to diagnostic evaluations like VA, visual fields, FA, fundus photographs, and OCT, I find ERG testing using the Diopsys platform is an invaluable tool for evaluating the impact of DR and optimizing management decisions in this patient population. It enables identification of early DR-related retinal dysfunction and intervention before there is irreversible structural damage and permanent loss of vision. Importantly, with anti-VEGF therapy now approved for treatment of DR without DME, ERG is the best modality to guide decisions on its use since it can detect DR and its progression in the absence of DME identified with OCT or FA. ERG testing also allows me to predict whether a patient is at risk for faster progression and to determine whether or not a patient is responding to treatment, allowing me to deliver value-based care that minimizes under or over treatment.

Considering the clinical benefits of ERG, its ease of use, and patient acceptance, I highly encourage my colleagues who have not yet implemented this technology to explore its potential by visiting the Diopsys exhibit booth at a scientific meeting or by contacting the company directly. The number of practices integrating Diopsys visual electrophysiology testing continues to grow worldwide. It offers unique advantages for evaluating retinal and optic nerve function in a number of diseases, and we can expect that its applications will continue to evolve in the future.

Dr. Silverstein is President of Silverstein Eye Centers, Kansas City, MO, and Clinical Professor of Ophthalmology, Kansas City University of Medicine and Biosciences, Kansas City, MO. He is a consultant to Diopsys.

References

1. Centers for Disease Control. Diabetic retinopathy. Available at: https://www.cdc.gov/visionhealth/pdf/factsheet.pdf. Accessed April 4, 2018.
2. Centers for Disease Control. National Diabetes Statistics Report, 2017. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed April 4, 2018.
3. National Eye Institute. Diabetic retinopathy. Available at: https://nei.nih.gov/eyedata/diabetic. Accessed April 4, 2018.
4. Tzekov R, Arden GB. The electroretinogram in diabetic retinopathy. *Surv Ophthalmol.* 1999, 44(1):53–60.
5. Bresnick GH, Palta M. Temporal aspects of the electroretinogram in diabetic retinopathy. *Arch Ophthalmol.* 1987;10(5)5:660–664.
6. Holopigian K, Greenstein VC, Seiple W, Hood DC, Carr RE. Evidence for photoreceptor changes in patients with diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1997;38(11):2355–2365.
7. Kim SH, Lee SH, Bae JY, Cho JH, Kang YS. Electroretinographic evaluation in adult diabetics. *Doc Ophthalmol.* 1997–1998;94(3):201–213.
8. Pescosolido N, Barbato A, Stefanucci A, Buomprisco G. Role of electrophysiology in the early diagnosis and follow-up of diabetic Retinopathy. *J Diabetes Res.* 2015;2015:319692.
9. Ozkiris A. Pattern electroretinogram changes after intravitreal bevacizumab injection for diabetic macular edema. *Documenta Ophthalmologica.* 2010;120(3):243–50.
10. Holm K, Schroeder M, Lövestam Adrian M. Peripheral retinal function assessed with 30-Hz flicker seems to improve after treatment with Lucentis in patients with diabetic macular oedema. *Doc Ophthalmol.* 2015;131(1):43–51.
11. Payne JF, Wykoff CC, Clark WL, et al; TREX-DME Study Group. Randomized trial of treat and extend ranibizumab with and without navigated laser for diabetic macular edema: TREX-DME 1 year outcomes. *Ophthalmology.* 2017;124(1):74–81.
12. Prünte C, Fajnkuchen F, Mahmood S, et al.; RETAIN Study Group. Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study. *Br J Ophthalmol.* 2016;100(6):787–795.