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Electroretinography in glaucoma diagnosis

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Abstract

Purpose of review—Electrophysiological measures of vision function have for decades generated interest among glaucoma researchers and clinicians alike because of their potential to help elucidate pathophysiological processes and sequence of glaucomatous damage as well as to offer a potential complementary metric of function that might be more sensitive than standard automated perimetry. The purpose of this article is to review the recent literature in order to provide an update on the role of the electroretinogram (ERG) in glaucoma diagnosis.

Recent findings—The pattern reversal ERG (PERG) and the photopic negative response (PhNR) of the cone-driven full-field, focal or multifocal ERG provide objective measures of retinal ganglion cell function and are all sensitive to glaucomatous damage. Recent studies demonstrate that a reduced PERG amplitude is predictive of subsequent visual field conversion (from normal to glaucomatous) and an increased rate of progressive retinal nerve fiber layer thinning in suspect eyes, indicating a potential role for PERG in risk stratification. Converging evidence indicates that some portion of PERG and PhNR abnormality represents a reversible aspect of dysfunction in glaucoma.

Summary—PERG and PhNR responses obtained from the central macula are capable of detecting early-stage, reversible glaucomatous dysfunction.

Keywords

electroretinogram; electroretinography; glaucoma; retinal ganglion cell; intraocular pressure

Introduction

Electroretinography is a minimally invasive technique that provides a direct, objective assessment of retinal function [1]. An electroretinogram (ERG) is a compound field potential recorded at the surface of the eye in response to a visual stimulus, which in its simplest form consists of a brief flash of light that uniformly fills the field of vision. The morphology of an ERG response varies with the intensity and duration of the stimulus flash as well as with the state of light adaptation, which itself depends on the intensity and duration of exposure to any background illuminant. When a healthy eye is completely dark-

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Conflicts of interest

There are no conflicts of interest.

adapted and the stimulus flash is within ~2 log units of psychophysical detection threshold, the ERG has a monophasic waveform consisting of a single, positive “B-wave” with a peak (implicit time) around 100 msec. For brighter flashes, the ERG of a healthy eye will exhibit a more complex waveform consisting of an initial negative deflection (“A-wave”) followed by a B-wave with an increasingly steeper rise and faster peak upon which are superimposed higher-frequency oscillations known as “oscillatory potentials” (OPs). Since rod photoreceptors vastly outnumber cones, the dark-adapted (or “scotopic”) ERG A-wave is dominated by the collective response of the rods and the scotopic B-wave by the response of rod bipolar neurons. The OPs are thought to arise within the inner plexiform layer as a consequence of inhibitory feedback loops involving primarily amacrine cells [2].

In a light-adapted state (with rod responses saturated), the normal photopic ERG waveform is always more complex, exhibiting an A-wave, B-wave and prominent OPs. The photopic ERG is also smaller than the scotopic response to a stimulus flash with the same nominal intensity. The increased complexity of the photopic ERG reflects in part the fact that the photopic system contains both “on” and “off” cone bipolar neurons, which depolarize and hyperpolarize, respectively, in response to light onset [3]. These opposing contributions can be teased apart by extending the duration of the stimulus or by using “saw-tooth” periodic stimulation [4, 5]. Because the photopic ERG originates with cone responses, the chromaticity of both stimulus and background also influence response amplitude and morphology.

Thus the ERG is an important diagnostic tool capable of identifying the origin of vision loss in terms of specific retinal neuronal cell type and physiological mechanism [6, 7]. This is true particularly for retinal neurons that are aligned along the optical axis of the eye since the current loops their responses generate are readily detected as a voltage change at the front of the eye. However, historically, the full-field flash ERG has not been useful for glaucoma diagnosis since it is dominated by the responses of neurons of the distal retina, namely photoreceptors and bipolar cells (though the OPs are thought to be generated by amacrine cell signal processing within the inner plexiform layer). Generally the full-field flash ERG does not reflect the responses of retinal ganglion cells (RGCs), which are the primary neuron affected by glaucoma [8, 9]. Though it remains a matter of some mild controversy, the evidence that outer retinal (e.g. photoreceptor) damage occurs in glaucoma is limited, at least until later-stages of disease with long-standing vision loss secondary to RGC death and axon degeneration [10–12]. In this regard, the full-field flash ERG can be a useful adjunct for glaucoma management insofar as it can help to determine if a patient is also suffering from additional disease processes affecting the outer retina. For a thorough review of the historical literature on this issue, the reader is referred to Holopigian et al [13]; for a review of more recent studies on outer retinal changes in glaucoma, see Wilsey et al (under review).

Yet there are features or components of the full-field ERG that have been shown to depend on intact RGC responses. The scotopic threshold response (STR), for example, can be recorded under deep dark adaptation for stimulus flashes that are ~2 log units dimmer than the scotopic B-wave “threshold” observed under typical clinical conditions [14, 15]. The requirements of stringent dark adaptation and signal averaging to overcome lower signal-to-

noise ratio preclude widespread use of the STR as a clinical diagnostic, though it remains useful for assessment of RGC function in experimental animal models of glaucoma [16–18]. In contrast, the photopic negative response (PhNR) is much easier than the STR to record in a clinical setting and is similarly dependent on intact RGC responses [19–21]. The PhNR has thus proven to be an effective objective clinical diagnostic test for assessment of RGC function in optic neuropathies, including glaucoma (for excellent recent reviews, see Machida [21] and Bach and Poloschek [9]). There are additional types of ERG recordings based on alternative stimulus and recording paradigms rather than full-field flashes, such as the well known pattern reversal ERG (PERG) [22] and multifocal ERG (mfERG) [23], which can also be obtained in a routine clinical setting and offer meaningful objective measurements of RGC function in glaucoma [9]. The purpose of this article is to review the recent literature in order to provide an update on the role of ERG in glaucoma diagnosis, with one section each for PERG, PhNR and mfERG.

Pattern Electrophoretogram (PERG)

As its name implies, the PERG is a retinal response to a *patterned* stimulus, that is, one with spatial and temporal contrast modulation rather than uniform field illumination. The spatial pattern is commonly a checkerboard or stripes, which can be either fine or coarse, but usually limited to the central field, thus stimulating only the macula. The stimulus ‘event’ is defined by temporal modulation whereby brighter elements switch to dark and vice versa (e.g., a “reversal” of black and white checks or stripes). The goal of the stimulus presentation is to maintain a constant space-averaged luminance. In this way, the cone photoreceptor and cone bipolar cell responses tend to cancel each other and allow the RGC (with center-surround receptive field) responses to manifest and dominate the recording. Therefore, theoretically the best PERG stimuli have gradual (e.g. sinusoidal), not abrupt spatial and temporal contrast modulation and a gradual (e.g. Gaussian) outer boundary or window to blend into a steady surround with equivalent mean luminance. It is more difficult to minimize luminance responses when the stimulus elements like checks or stripes are large, but smaller checks require optimal refractive correction and clear ocular media. Steady, central fixation is also necessary for these reasons.

Another important clinical consideration is that the PERG like any test of RGC function depends on a cascade of intact outer retinal signals, so without a multifocal ERG to evaluate specifically the macular cone and cone bipolar responses, the PERG alone is not a specific assay of RGC function. The PERG will yield abnormal findings in patients with middle and outer retinal damage. This is important since most glaucoma patients are older and may suffer concomitant age-related decline of outer retinal function too. In addition, since the PERG is a small signal, it is prone to interference from environmental noise and blinking artifact. While it is independent of patient motor and cognitive skills (unlike perimetry), it still requires careful control of fixation, refraction and stimulus distance.

Nevertheless, the PERG is the most well established ERG technique for glaucoma diagnosis with a long proven history of efficacy (for thorough reviews of PERG historical background and utility for glaucoma diagnosis, see e.g., [9, 22, 24–27]). The results of two recently published PERG studies in particular, however, warrant special consideration for their

implications. The first by Banitt and colleagues [28] evaluated longitudinal rates of change for peripapillary retinal nerve fiber layer (RNFL) thickness and PERG amplitude in glaucoma suspects. They found that the glaucoma suspect eyes with the smallest baseline PERG amplitude (50% of its age-adjusted normative value) had the fastest rate of RNFL thickness decline over the subsequent 5 years [28]. Banitt et al concluded that a glaucoma suspect with a severely reduced PERG indicates a need for “*closer monitoring or treatment as he or she will have a higher rate of RNFL thinning*” [28].

The second recently published noteworthy study on PERG and glaucoma was also a longitudinal study of suspects [29]. In this study, Bode and colleagues found that the PERG “*detected glaucoma patients 4 years before visual field changes occurred, with a sensitivity/specificity of 75%/76.*” [29]. Another interesting finding in the study by Bode et al was that the predictive capacity of PERG for eventual conversion from normal to glaucomatous visual field damage “*was roughly constant from conversion to 4 years before conversion, fitting with the view that PERG changes occur early and then saturate, thus rendering the PERG a poor biomarker for monitoring advanced disease*” [29]. Although the outcome measure in the Bode et al study was visual field conversion, their result is similar to the observation by Banitt et al [28] that RNFL thickness did not exhibit loss until PERG amplitude was severely reduced (implying that PERG amplitude cannot decline much further and would thus not be useful for monitoring moderate-to-advanced glaucoma).

The evidence from this pair of recent studies indicates that PERG may be most beneficial as an adjunct in the diagnosis and management of glaucoma suspects (with normal or near normal visual fields and/or RNFL thickness) by helping to stratify risk: for those suspect eyes with a severely reduced PERG (and no other evidence of outer retinal dysfunction), it may be prudent to increase frequency of follow-up and/or initiate therapy.

It is worth noting that the methods used by Banitt et al [28] differ from those used by Bode et al [29] in terms of the PERG stimulus, electrodes and response analysis, yet readers may find it reassuring that the results were nonetheless similar and that the same differences did not substantially impact diagnostic accuracy when compared directly in another recent study by Bach and colleagues [30].

Photopic Negative Response (PhNR)

The PhNR is a slow negative component that manifests after the b-wave of the cone driven full-field ERG as first characterized by Viswanathan et al [19, 20]. Like the PERG, the PhNR is dependent on intact RGC responses, which in turn of course also depend on intact feed-forward responses of cone photoreceptor and cone bipolar neurons [19, 21]. Since the PhNR is elicited by a uniform full-field stimulus, in contrast to the PERG, it is not as critically dependent on accurate refraction, clear optics or exquisite fixation control, which is potentially advantageous for clinical testing. Another distinct advantage over the PERG is that the PhNR enables simultaneous assessment of distal retinal function (cone photoreceptor and cone bipolar cell responses) from the same recording. However, the reliability and diagnostic efficacy of the PhNR are likely improved by recording with dilated pupils, which is a disadvantage for clinical testing and unlike the PERG. Since the PhNR is

also a newer technique than PERG, there is even less consensus on the best protocol to use for glaucoma in terms of stimulus characteristics (intensity and chromaticity) and signal analysis (amplitude measurement details) [20, 31–37].

An excellent review of PhNR clinical applications was published by Machida in 2012 [21]. Since that time, several other studies have been published on the PhNR that are relevant to glaucoma and considered here. First is the careful study by Niyadurupola and colleagues [38], which provides a compelling demonstration of improvement in the PhNR amplitude within 1–2 months of IOP lowering by standard clinical therapy. The eyes that did not achieve significant IOP reduction (<25% reduction) did not have any change in PhNR amplitude over the same period. In the group of eyes that did achieve significant IOP reduction (>25% reduction), the improvement in PhNR amplitude was related to the degree of IOP lowering [38]. The authors discussed how this might be a reflection of improved RGC function and/or due to a change in spatial buffering of potassium ion by retinal and optic nerve head glia. They also discuss how their results using the PhNR were similar to earlier reports of improved PERG amplitude after IOP lowering [39, 40].

The second notable paper was published this year by Machida and colleagues, who used a focal stimulation technique to evaluate topographic variation in the relationship between PhNR (as well as a-wave and b-wave) amplitudes and the thickness of the ganglion cell complex measured by spectral domain optical coherence tomography (SD-OCT) [41**]. They found that the PhNR made was more prominent in central macular ERG responses (15 degrees of retina) as compared with responses elicited by annular stimuli around the central macula (15–30 degrees). Further, Machida et al found that PhNR amplitudes were well correlated with the thickness of the ganglion cell complex within the central macula, but only weakly correlated outside of the central macula. These investigators discussed the likely explanation that RGC density is highest in the central macula and that therefore the central macular PhNR exhibits the largest relative contribution from RGC responses, supporting the use of the focal macular ERG technique for glaucoma assessment [41**]. However, one aspect of their data that the investigators did not mention is the fact that there was much more overlap between open-angle glaucoma and healthy eyes for PhNR amplitude (and PhNR/b-wave amplitude ratio) than there was for the ganglion cell complex measured by SD-OCT [41**]. This means that the diagnostic utility of the PhNR is substantially lower than OCT measurements of ganglion cell complex thickness (a fast and completely non-invasive test); indeed, there were very few examples of glaucoma eyes with a normal ganglion cell complex thickness but abnormal focal PhNR amplitude.

The third recently published study we chose to consider here was a direct comparison of PERG and PhNR diagnostic utility by Preiser and colleagues [36]. The paper by Preiser et al provides a good review of the field (for a primary research paper), so it is recommended reading for that reason alone. Importantly, Preiser et al found that the PERG and the PhNR performed about equally well, achieving relatively high diagnostic accuracy in patients with “manifest glaucoma” (documented visual field defects) and above chance in patients with “pre-perimetric glaucoma”. Although these investigators noted a relatively poor correlation between the PERG and PhNR amplitudes within eyes, the fact that these two technique performed equally well might reflect the likelihood that these two different ERG signals

represent currents with the same origin [42]. Preiser and colleagues ultimately concluded that practical clinical aspects of recording might guide the choice between these two alternatives: *“The PhNR has the advantage of not requiring clear optics and refractive correction; the PERG has the advantage of being recorded with natural pupils.”*

Multifocal Electroretinogram (mfERG)

The multifocal technique pioneered by Sutter [43–46] was a major advance for the field of electrophysiology. The technique enables assessment of multiple independent stimulus locations (up to hundreds) simultaneously, thereby vastly decreasing the time required to accomplish a topographic representation of ERG and visual evoked cortical responses. Another important aspect of the technique is the rapid calculation of non-linear response component estimates, which were initially hoped to offer new insights into glaucomatous abnormalities of RGC function [43, 46]. Thorough reviews of the clinical applications of multifocal ERG and VEP were published by Hood in 2000 [23] and 2003 [47], respectively. Though abnormalities can be readily detected in mfERG recordings from glaucomatous eyes, the advantage of topographic analysis offered by the technique has not proven important for glaucoma diagnosis [48–51]. Specific features of mfERG response arrays thought to represent an optic nerve head component [52, 53] hold great promise for evaluation of glaucoma, but remain extremely challenging to extract and quantify. Alternatives to the standard fast luminance modulation stimulus (typically 75 Hz) may enhance the optic nerve head component [54, 55], but this is still difficult to extract and quantify in all healthy eyes. Numerous studies have used such stimuli to discriminate glaucoma from healthy eyes [51, 56–61], but to date, none have demonstrated a clear role for any mfERG technique as a diagnostic aid in glaucoma, let alone the holy grail of a direct, non-invasive topographic readout of RGC function that is more sensitive and less variable than psychophysical perimetry. It remains puzzling why mfERGs recorded from monkey eyes contain such a greater enrichment of RGC signals as compared with human eyes [62–69] though it may relate to differences in eye size and spatial relationships between current sources and recording electrodes.

One might predict that a combination of a patterned stimulus with the multifocal technique would prove to be highly effective for glaucoma diagnosis. However, unfortunately results to date reveal only a general amplitude reduction centrally with little or no topographic relationship to even advanced visual field loss.[49, 70, 71] Similarly, Kaneko and colleagues recently published a study in which they used the multifocal technique to rapidly record from 5 macular retinal locations in order to assess the mfERG homologue of the PhNR in glaucoma [72**]. Their results were quite similar to what they had demonstrated using the focal macular PhNR technique [41**] insofar as there was selective reduction of the mfERG “N2” component (likely the PhNR homologue) in glaucoma with little or no effect on N1 or P1 (analogous to the photopic a-wave and b-wave, respectively), but this held only for the central 15 degrees with no loss of any component beyond that out to 40 degrees. Loss of mfERG N2 amplitude in the central macular region was related to the severity of glaucoma, but there was substantial overlap between healthy eyes and the “early damage” glaucoma group. Moreover, the ganglion cell complex thickness measured by SD-OCT for the

corresponding central macular region was far superior for discriminating glaucoma from healthy eyes [72**].

Conclusion

What emerges from the recently published literature on ERG and glaucoma is that there is a very limited role for specific types of ERG such as PERG and PhNR to aid the clinician caring for glaucoma patients. This role includes objective assessment of RGC function, limited to the central macula in early stages of glaucoma (including suspects), where dense psychophysical perimetric testing of function may be much more time consuming, relatively insensitive and more variable. In such cases, with or without subjective complaints of vision impairment, a markedly reduced PERG or PhNR (preferably focal or multifocal for the central 15 degrees) is indicative of RGC dysfunction and warrants careful follow-up and potentially advancement of therapy, especially when accompanied by evidence of structural loss (such as thinning of the macular inner retinal layers, reduction of peripapillary RNFL thickness, progressive optic disc changes and/or splinter hemorrhages). In this regard, the PERG and PhNR may serve to help stratify risk for glaucoma progression, no doubt an important consideration. The converging evidence that PERG and PhNR measurements may also reveal some reversible aspect of glaucomatous dysfunction has important implications; future studies will hopefully uncover the source and mechanism of these effects. However, for objective topographic assessment of vision function in glaucoma, the mfVEP is far superior to any form of ERG, though its sensitivity is about the same as psychophysical perimetry [47, 73–75].

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Abbreviations

ERG	electroretinogram
OPs	oscillatory potentials
RGC	retinal ganglion cell
STR	scotopic threshold response
PhNR	photopic negative response
PERG	pattern reversal ERG
mfERG	multifocal ERG
RNFL	retinal nerve fiber layer
SD-OCT	spectral domain optical coherence tomography
IOP	intraocular pressure

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Key points

- The pattern ERG (PERG) and the photopic negative response (PhNR) of the cone-driven ERG, elicited either by full-field, focal or multifocal stimulation of the macula are objective measures of retinal ganglion cell function and sensitive to glaucomatous damage.
- Recent studies have demonstrated that a reduced PERG amplitude is predictive of subsequent visual field conversion (from normal to glaucomatous) and an increased rate of progressive retinal nerve fiber layer thinning in suspect eyes, indicating a potential role for PERG in risk stratification.
- Converging evidence indicates that some portion of PERG and PhNR abnormality represents a reversible aspect of dysfunction in glaucoma.
- Improved methods are required for reliably extracting and quantifying the optic nerve head component from multifocal ERG (mfERG) response arrays, which may then offer another complementary technique to PERG and PhNR for ERG assessment of glaucoma.
- Advancements in retinal and optic nerve head imaging, such as ocular coherence tomography have narrowed the limited role for ERG in glaucoma diagnosis.