Principles and Practice of Clinical Electrophysiology of Vision

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A Year Book Medical Publishers imprint of Mosby-Year Book, Inc.

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

1 2 3 4 5 6 7 8 9 0 CL CL MV 95 94 93 92 91

Library of Congress Cataloging-in-Publication Data
Principles and practice of visual electrophysiology / [edited by]
John R. Heckenlively, Geoffrey B. Arden.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-8151-4290-0
1. Electroretinography. 2. Electrooculography. 3. Visual evoked response. I. Heckenlively, John R. II. Arden, Geoffrey B. (Geoffrey Bernard)
[DNLM: 1. Electrooculography. 2. Electrophysiology. 3. Electroretinography. 4. Evoked Potentials, Visual. 5. Vision Disorders—physiopathology. WW 270 P957]
RE79.E4P75 1991 91-13378
617.7 1547—dc20 CIP
DNLM/DLC
for Library of Congress

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The Pattern Electroretinogram in Glaucoma and Ocular Hypertension

Gary L. Trick

Primary open-angle glaucoma (POAG) is a chronic visual disorder characterized by elevated intraocular pressure (IOP) in the presence of an anatomically open anterior chamber angle, excavation and/or pallor of the optic disc along with the nerve fiber layer defects, and visual field loss. Visual loss in chronic glaucoma results from the destruction of the retinal ganglion cell axons that form the optic nerve. The optic nerve damage in POAG occurs over a protracted period of time (often months or years) and appears to be due to an increase in IOP to an intolerable level. Individuals with elevated IOP who do not exhibit optic disc, nerve fiber layer, or visual field defects (i.e., ocular hypertensives) are considered glaucoma suspects because they are at risk of developing the disease. However, the relationship between elevated IOP and the development of glaucoma remains unclear since many ocular hypertensives may not develop the disease while other individuals with apparently normal IOP develop the optic disc, nerve fiber layer, and visual field abnormalities that are characteristic of glaucoma (i.e., low-tension glaucoma). This suggests that there is considerable interindividual variability in the IOP level necessary to produce optic nerve damage.

The mechanism by which elevated IOP induces optic nerve damage is not known. The two primary hypotheses suggest that elevated IOP either interferes with blood flow at the optic nerve head (the vascular theory) or produces mechanical compression of the retinal ganglion cell axons in the region of the lamina cribrosa (mechanical theory). In either case, there is a slowly progressive loss of retinal ganglion cell axons that eventually results in the development of a characteristic visual field defect (Fig 107–1), upon which the diagnosis of glaucoma is often made. However, the manifestation of a visual field defect may represent a relatively late stage in the progression of the disease, a time when retinal ganglion cell loss is virtually irreversible. Recent estimates suggest that 40% to 50% of the optic nerve axons can be lost prior to the development of a visual field defect that is detectable with manual perimetry.[31] As a result there has been considerable interest in developing more sensitive and more reliable methods for studying the pathogenesis and pathophysiology of retinal ganglion cell damage in glaucoma. The pattern electroretinogram (PERG) is one method that is being used in these studies.

The original suggestion by Maffei and Fiorentini[24] that the PERG could be used to monitor the bioelectrical response of the retinal ganglion cells provided the impetus for a large number of studies on patients with glaucoma. In a general sense these investigations can be characterized as either (1) testing the hypothesis that the PERG has a ganglion cell origin by studying individuals with a disease that is known to directly affect these cells or (2) evaluating the possible clinical value of the PERG for detecting glaucoma. Taken together, these diverse studies have provided considerable insight concerning both the basic properties of the human PERG and the pathophysiology of retinal ganglion cell dysfunction in glaucoma.

Earlier electrophysiological studies of the pathogenesis and pathophysiology of visual dysfunction in glaucoma were hampered by the lack of an appropriate technique for directly evaluating the func-

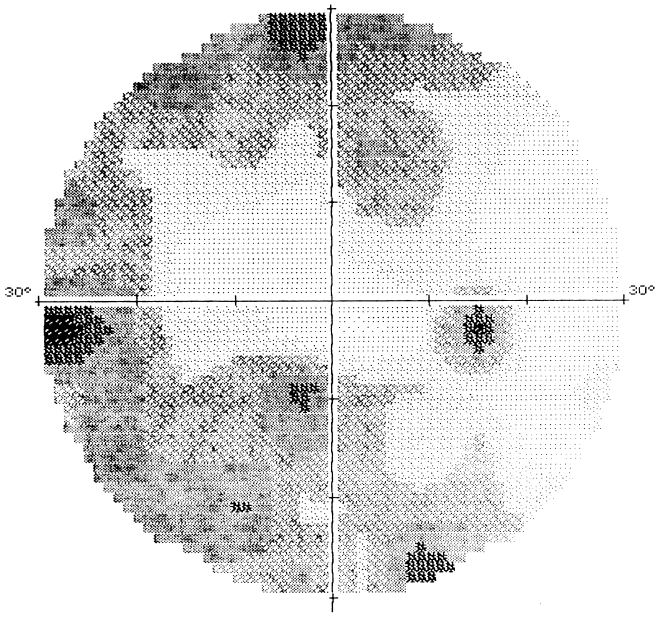

FIG 107–1.
The diagnosis of chronic open-angle glaucoma is often based upon evidence of a visual field defect similar to the visual field loss apparent in this 65-year-old white male. This result was obtained by automated perimetry (Humphrey 30–2).

tional integrity of the neural elements in the proximal retina and, in particular, the retinal ganglion cells. Studies of the flash electroretinogram (ERG) in patients with glaucoma clearly illustrated that the more distal neural elements in the retina were unaffected,[14, 21] at least until relatively late in the disease process.[3, 12] The results of visual evoked potential (VEP) studies in glaucoma patients, on the other hand, indicated that the latency of the bioelectrical responses generated in the primary visual cortex was often increased.[17, 37] Therefore, the flash ERG and VEP results implied that there was a significant deficit within the primary visual pathway of glaucoma patients that was not the result of dysfunction in the neural elements of the distal retina. However, the mechanism whereby a loss in retinal ganglion cell axons would produce an increase in VEP latency remains unclear. Furthermore, the relationship between the VEP latency increase and the nature and extent of the early damage to the optic nerve in glaucoma has not been established, perhaps because the VEP is an indirect reflection of retinal ganglion cell function that is dominated by the bioelectrical response of neural elements within the central 5 to 10 degrees of the visual field.[36] Thus the availability of an electrophysiological technique to monitor a bioelectrical response that includes a component (or components) that originates in the proximal retina and possibly reflects the functional integrity of the retinal ganglion cells that themselves filled an obvious void.

There now have been numerous studies of the PERG in glaucoma patients, and the clear consensus of these studies is that PERG abnormalities frequently are evident in individuals with well-diagnosed POAG (Table 107–1). Both PERG amplitude reductions and latency increases (or phase shifts) have been reported in various studies (Fig 107–2), but because the latency increase is relatively small (about 5 to 8 ms) although statistically significant, the more robust amplitude reductions have drawn the most interest. The results of these investigations indicate that in glaucoma patients PERG amplitude reductions occur in the presence of normal flash and flicker ERGs. Some evidence also indicates that the PERG amplitude reductions become more profound when other signs of glaucoma (i.e., cupping and field loss) indicate an increase in the severity of the disease.[19, 45]

TABLE 107–1.
A Partial Summary of the Studies Demonstrating Significant PERG Abnormalities in Glaucoma Patients and Ocular Hypertensives

Authors	Type of Abnormality
Glaucoma	
Fiorentini et al.[13]	Amplitude reduction
Arden et al.[5]	Amplitude reduction
Trick[38]	Amplitude reduction, latency increase
Markoff et al.[25]	Amplitude reduction
Seiple et al.[34]	Amplitude reduction
Bobak et al.[8]	Amplitude reduction
Wanger and Persson[47]	Amplitude reduction
Papst et al. [28]	Amplitude reduction, latency increase
van Lith et al.[44]	Amplitude reduction
Howe and Mitchell[16]	Amplitude reduction, latency increase
Trick[40]	Amplitude reduction, latency increase
Ringens et al.[33]	Amplitude reduction, phase shift
Wanger and Persson[45]	Amplitude reduction
Drance et al.[9]	Amplitude reduction
Porciatti et al.[29]	Amplitude reduction
Korth et al.[19]	Amplitude reduction
Bach et al.[7]	Amplitude reduction
Weinstein et al.[48]	Amplitude reduction
Ocular Hypertension	
Trick[39]	Amplitude reduction
Wanger and Persson[46]	Amplitude reduction
Porciatti et al.[29]	Amplitude reduction
Wanger and Persson[45]	Amplitude reduction
Weinstein et al.[48]	Amplitude reduction
Trick et al.[41]	Amplitude reduction
Trick et al.[42]	Amplitude reduction
Ambrosio et al.[4]	Amplitude reduction

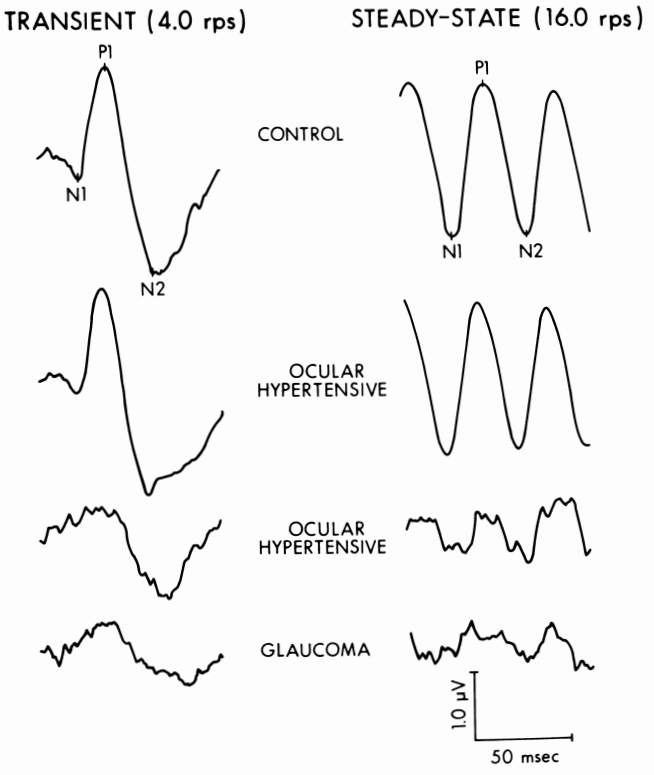

FIG 107–2.
Representative PERGs for low–temporal frequency (transient) and high–temporal frequency (steady-state) conditions are illustrated for an age-matched visual normal (control), two patients with diagnosed ocular hypertension and normal visual fields, and a patient with diagnosed POAG. Note that one ocular hypertensive produced good responses for both test conditions while in the other ocular hypertensive both responses were poor.

Important confirmation of the conclusions drawn from studies of patients with glaucoma has come from studies of experimental glaucoma that is induced in primates by argon laser application to the trabecular meshwork.[11, 26, 27] In this glaucoma model the aqueous outflow facility is decreased, IOP is increased, and there are consequent changes in cupping of the optic nerve head and loss of optic nerve axons that are quite similar to the changes that occur in the human condition.[27, 30] Results from the primate model indicate that PERG amplitude reductions (1) precede the development of significant changes in the optic nervehead, (2) are related to the degree of cupping and nerve fiber loss, and (3) are not diminished when IOP is reduced pharmacologically.[11, 26, 27]

Estimates of the magnitude of the PERG amplitude reductions observed in glaucoma patients vary from 10% to 80% (or more), partially depending upon the spatial and temporal characteristics of the stimulus. Our studies[40] of the spatial and temporal tuning of the PERG abnormality in glaucoma patients indicate that the magnitude of the deficit is greatest when high–temporal frequency stimuli are used to elicit steady-state PERGs (Fig 107–3). Based upon these results and the histological observation that the larger retinal ganglion cell fibers appear to be most susceptible to glaucomatous damage early in the course of the disease,[32] Trick further suggested that this represented a selective loss of the type A retinal ganglion cells that underlie the magnicellular stream of the primary visual pathway.[22] Similarly, in the primate model of glaucoma the largest PERG deficits are observed with high–temporal and low–spatial frequency stimuli, once again supporting the concept of a selective deficit in the magnicellular system.[26, 27] Possible variations in the extent of this selective damage associated with progression of the disease is a topic that requires further investigation.

More recently it has been suggested[15] that the transient PERG includes two semi-independent processes that are evident as the N1-P1 and the P1-N2 components of the waveform (see Fig 107–2). In diseases where damage is localized in the proximal retina and/or optic nerve only the P1-N2 component of the transient PERG is reduced. In diseases that affect the distal retina the N1-P1 component of the transient PERG is reduced (due to the direct influence of the disease on the retinal generators of this compo-

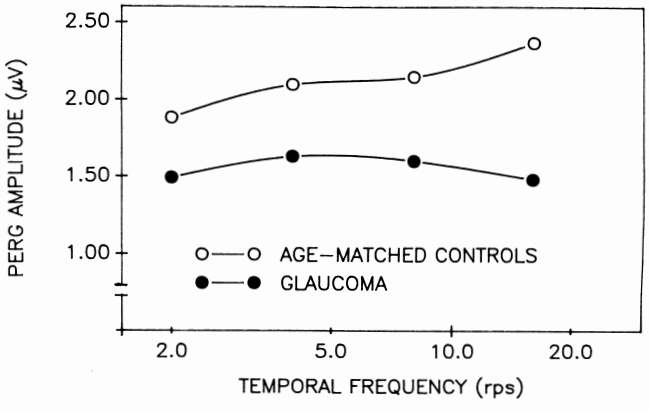

FIG 107–3.
PERG amplitude is plotted as a function of temporal frequency. The data points have been replotted from Trick[40] and represent values for 32 patients with chronic open-angle glaucoma and 32 age-matched controls average across check size.

nent), and the P1-N2 component is also reduced (since the input to the neural elements in the proximal retina/optic nerve is distorted by the effect on the distal retina). Based upon this observation the large-magnitude reduction Trick noted in the steady-state PERG also could be interpreted as resulting from the merging of the N1-P1 and N2-P2 components due to the high temporal frequency. In one study it was observed that the P1-N2 component of the transient PERG was more reduced than the N1-P1 component in glaucoma patients.[48] Certainly, this relationship between the waveform components of both the transient and the steady-state PERG should be more completely evaluated.

Studies of the PERG in patients with ocular hypertension (see Table 107–1) suggest that this retinal potential may provide a sensitive measure of retinal ganglion cell dysfunction that could be used to detect visual loss in ocular hypertensives prior to the development of glaucomatous visual field loss. PERG amplitude reductions are apparent in some, although not all ocular hypertensives (see Fig 107–2). In different studies, however, the percentage of ocular hypertensives with abnormal PERGs has varied considerably. Porciatti et al.[29] reported significant PERG amplitude reductions in 11 of 12 (91.6%) ocular hypertensives who had normal visual fields, while Wanger and Persson[46] observed significant amplitude reduction in four of seven (57.1%) patients with unilateral ocular hypertension. Ambrosio et al.[4] detected PERG amplitude reductions in 75% of the ocular hypertensives tested in their study but failed to indicate whether all of these were significant statistically. On the other hand, Trick et al.[41] found significant PERG amplitude reductions in only of 15 of 130 (11.5%) ocular hypertensives.

The high percentage of ocular hypertensives with PERG abnormalities that has been observed in some studies suggests that this retinal potential may be sensitive to early changes in visual processing that are associated with elevated IOP. However, this high figure also raises questions about the utility of the technique for predicting which patients will develop glaucoma. Epidemiological evidence suggests that 0.5% to 2.0% of patients with mild to moderately elevated IOP (21 to 35 mm Hg) will develop visual loss each year.[20] Long-term follow-up of ocular hypertensives suggests similar values.[18, 23] Thus the high percentages observed in some studies could also suggest that this technique has inadequate specificity (i.e., poorly discriminates the patients with impending glaucomatous visual field loss from other ocular hypertensives). The high percentage of abnormal responses observed in some studies may be partially the result of the small size of the samples tested and a loose definition of a significant deficit. In addition, it is likely that the sample selection criteria influenced the percentage of patients observed to have abnormal responses. Trick[39] demonstrated that over 50% of ocular hypertensives who are considered to be at high risk of developing POAG (based upon a weighted combination of the following risk factors: age, IOP, family history of glaucoma, and cup-to-disc ratio) exhibit significant PERG amplitude reductions while less than 10% of low-risk ocular hypertensives exhibit these deficits. The larger group of ocular hypertensives later tested by Trick et al.[41] were unselected for these risk factors and may have been composed of a large percentage of individuals who were at lower risk than the patients included in other investigations (e.g.. Weinstein et al.[48]). Therefore, a prospective study will be necessary to eventually determine whether PERG amplitude reductions reliably precede the development of a glaucomatous visual field defect in these patients.

The exact relationship between IOP elevations and PERG amplitude reductions has not been determined. There is evidence that large, acute elevations in IOP (as might occur in angle-closure glaucoma or glaucoma secondary to ocular trauma) do produce reductions in PERG amplitude. However, in these cases the PERG amplitude reductions may not reflect only retinal ganglion cell dysfunction since the functional integrity of neural elements in the distal retina, the elements that provide input to the ganglion cells, is also disrupted by acute IOP elevations. It is uncertain whether smaller, chronic changes in IOP produce PERG alterations that are similar to the changes that occur as a result of acute IOP elevation. Among ocular hypertensives the correlation between IOP and PERG amplitude is weak (Fig 107–4), while the association of other factors (such as age and blood pressure) with PERG amplitude may be as strong or stronger. This may simply reflect the variability in pressure tolerance of retinal ganglion cells between individuals, in which case evidence of intraindividual effects of elevated pressure may become obvious when prospective studies are completed. However, in an interesting study designed to separate the influence of IOP and retinal vascular perfusion on the PERG, Siliprandi et al.[35] demonstrated that perfusion pressure rather than IOP plays the major role influencing the PERG. Per-

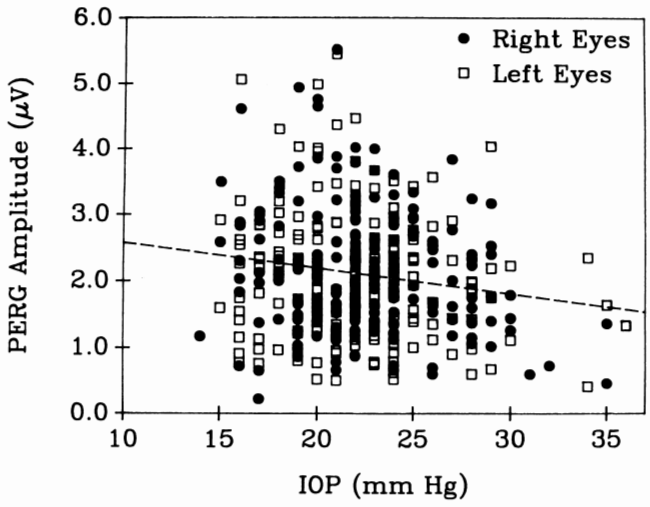

FIG 107–4.
Among ocular hypertensives there is a weak, but statistically significant correlation between PERG amplitude and IOP ($r = -0.16$). The *dashed line* represents the best-fit linear regression (least squares) based upon the data for 153 patients.

haps, therefore, the PERG amplitude reductions associated with chronic glaucoma and ocular hypertension are more directly the result of retinal vascular changes and only indirectly result from elevated IOP.

Visual dysfunction in glaucoma and ocular hypertension has also been revealed in a variety of psychophysical studies. Color vision,[1, 42] contrast sensitivity,[6] and temporal resolution[43] deficits have all been observed in some ocular hypertensives as well as in glaucoma patients. The collective results of these studies suggest that the visual dysfunction associated with the development of glaucomatous damage is not constrained to the retinal areas where the characteristic visual field defects are observed; the damage often involves other retinal areas including the macula. Only color vision deficits have been demonstrated to precede visual field loss in prospective studies of patients developing glaucoma,[10] but many glaucoma patients do not exhibit abnormal color vision,[2, 9] and the percentage of ocular hypertensive patients with color vision deficits exceeds the proportion expected to develop glaucoma.[42] The relationship between these visual deficits and the visual dysfunction underlying the PERG abnormalities of glaucoma patients and ocular hypertensives has been explored incompletely. There is some evidence that the association between the color vision and the PERG deficits in ocular hypertensives is weak, a finding that could imply that different physiological mechanisms are involved in each deficit.

In a recent study Drance et al.[9] examined the sensitivity and specificity of a variety of psychophysical, electrophysiological, and fundus imaging techniques in glaucoma patients, glaucoma suspects, and controls. The results indicated that both sensitivity and specificity were higher for the PERG than for either color vision or contrast sensitivity. Several measures derived from optic disc imaging techniques, however, had higher sensitivity and specificity than did the PERG.

In conclusion, the PERG is a tool that has promise for investigating the pathophysiology of retinal ganglion cell dysfunction in glaucoma. Although it is doubtful that PERG will ever replace perimetry as the method of choice for detecting visual loss in glaucoma patients, it is clear that the technique can be a complement to the visual field in confirming a diagnosis of glaucoma. In addition, PERG studies should be considered in cases where it is difficult to obtain a reliable visual field. Nevertheless, it is important to remember that the precise sensitivity and specificity of the technique for detecting glaucomatous damage remains to be established. The clinical value of PERG for detecting retinal ganglion cell dysfunction in the ocular hypertensives who will develop glaucoma also remains an open question. However, prospective studies of the utility of the PERG in ocular hypertension are underway, so perhaps this issue will be resolved in the not too distant future.

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