Reversible Pattern ERG Loss in Glaucoma

Restoring the activity of dysfunctional retinal ganglion cells in patients with early disease.

BY LORI M. VENTURA, MD, AND VITTORIO PORCIATTI, DSc

Although glaucomatous visual field loss has traditionally been considered permanent,[1] some studies have shown that visual dysfunction in glaucoma may be, to some extent, reversible. As early as the 1970s, reports indicated that visual fields improved by either lowering pressure[2-4] or increasing retinal circulation using calcium-channel blockers.[5] Fluctuations of the visual field have been the main deterrent in the confirmation of reversible dysfunction. Recently, other psychophysical[6] and electrophysiological[7] measures showed that reversing visual dysfunction in patients with glaucoma is possible.

DYSFUNCTIONAL RETINAL GANGLION CELLS

One potential mechanism for the loss of visual function is that viable retinal ganglion cells become dysfunctional in response to a noxious stimulus such as elevated IOP or impaired vascular autoregulation. If this dysfunction is not reversed, then apoptosis and the premature death of retinal ganglion cells ensue.

The potential rescue of retinal ganglion cells in the dysfunctional phase is suggested by primate models of experimental glaucoma in which the chronic elevation of IOP may result in a loss of 6 to 12 dB of perimetric sensitivity with little-to-no retinal ganglion cell losses (0% to 10%).[8] Pattern electroretinogram (ERG) amplitude losses have occurred before changes in disc cupping with elevated IOP.[9,10] Primate models of glaucoma have also shown that, in response to elevated IOP, the cell bodies and dendritic arbors of viable retinal ganglion cells may shrink significantly.[11,12] These shrunken cells are less responsive, particularly to patterned stimuli and stimuli presented at increased temporal frequencies.[13]

RESTORING PHYSIOLOGICAL ACTIVITY

Recently, Gandolfi et al[6] reported that the psychophysical contrast sensitivity of glaucoma patients improved after trabeculectomy. These results are strong evidence that lowering IOP may reverse the IOP-dependent dysfunction of retinal ganglion cells.[6] Ventura and Porciatti[7] recorded the physiological response of retinal ganglion cells with the pattern ERG before and after lowering IOP with topical medications.[7] They demonstrated that reducing IOP in patients with early glaucoma (who had normal or high baseline IOPs) may significantly improve the abnormal pattern ERG amplitude. In contrast, the pattern ERG amplitude in control subjects did not change with decreased IOP (Figures 1 and 2).

> "A reduction of the pattern ERG amplitude in glaucoma may be due to a lack of activity from dead or missing retinal ganglion cells, the reduced activity of viable retinal ganglion cells, or a combination of the two."

PATHOPHYSIOLOGICAL IMPLICATIONS

The pattern ERG amplitude reflects the total amount of electrophysiological activity of the retinal ganglion cells. A reduction of the pattern ERG amplitude in glaucoma may be due to a lack of activity from dead or missing retinal ganglion cells, the reduced activity of viable retinal ganglion cells, or a combination of the two. Research by Ventura and Porciatti[7] implied that a population of retinal ganglion cells was dysfunctional, at least in part, as a consequence of a higher IOP than the retinal ganglion cells could tolerate. The function of these cells could be restored to some degree by reducing the IOP. The results do not exclude the possibility that changes occurring deep in the inner retina, which have an impact on retinal ganglion cells, could affect the pattern ERG.

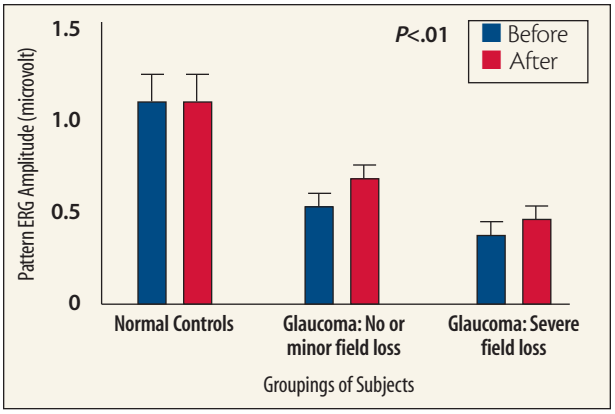

Figure 1. This graph shows the pattern ERG amplitude before and after IOP-lowering treatment in normal controls and in glaucoma patients with visual field defects of two different levels of severity. Note that the improvements in the amplitude are greater in eyes with few or no visual field defects as compared to those with severe defects. No changes in the pattern ERG occurred in treated normal controls.

After lowering patients' IOPs, researchers observed some cases of improved pattern ERG amplitude, not only in patients with ocular hypertension or chronic open-angle glaucoma (OAG), but also in individuals with normal-tension glaucoma (NTG).[7] It is noteworthy that such improvements in patients with NTG were associated with smaller reductions in IOP compared with patients who had chronic OAG. Since the amount by which IOP may be lowered is smaller in NTG, the retinal ganglion cells of these patients may have a lower IOP threshold for dysfunction due to vascular or unknown factors. Consequently, in NTG, the dysfunction of retinal ganglion cells occurs at lower levels than in chronic OAG, and an improvement in pattern ERG occurs with smaller reductions in IOP.

A pattern ERG is unlikely to show an improvement when the baseline test is already normal. At the opposite end of the spectrum, as in advanced glaucoma, improvement is unlikely when the amplitude of the pattern ERG is severely reduced due to extensive retinal ganglion cell dropout. A larger population of retinal ganglion cells with reversible dysfunction exists in patients who have early field loss compared with patients who have advanced glaucoma. A pattern ERG amplitude that fails to improve with IOP lowering may indicate that either (1) the mechanism of loss is not related to pressure or (2) the loss of retinal ganglion cells is so extensive that it is not possible to measure an improvement in function from a small, residual population of dysfunctional cells.

CLINICAL IMPLICATIONS

An improvement in pattern ERG amplitude after a reduction in IOP challenges the current opinion that structural changes of the optic nerve fiber layer precede functional changes, as measured by standard automated perimetry (SAP).[14,15] It is important to consider, however, that pattern ERG and SAP probe different retinal regions and different aspects of visual function. SAP is relatively insensitive to early losses of retinal ganglion cells in the central area, where there is high retinal ganglion cell density and redundancy. In contrast, the pattern ERG, representing the summed activity of central retinal ganglion cells, may be able to discern the early generalized dysfunction of viable neurons. Given that retinal ganglion cell function is restored, at least in part, with a decrease in IOP, several multicenter studies may now have a neurophysiological basis to indicate that reducing IOP delays the onset or the progression of visual field deterioration in ocular hypertension and glaucoma.[16-19]

FUTURE CHALLENGES

Recent technical advances that allow easy and reproducible recordings from skin electrodes[20] make the pattern ERG more inviting to clinicians for the management of glaucoma suspects and patients with early stages of the disease. In principle, the pattern ERG may be used to assess the neuroprotective effects of drugs or other therapeutic strategies based on an improvement of retinal ganglion cell function on a very short time scale.

In addition, pattern ERGs may help clinicians to set an individual's target pressure to optimize retinal ganglion cell function. The standard goals for lowering IOP cur-

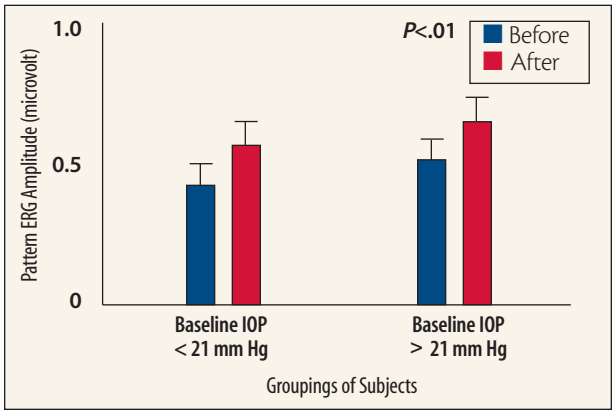

Figure 2. This graph shows the pattern ERG amplitude before and after IOP-lowering treatment in glaucoma patients with two different levels of baseline IOP. Note that a significant improvement in the pattern ERG amplitude may occur for patients with a baseline IOP that is either lower or higher than 21 mm Hg.

rently used by clinicians may not be stringent enough. Recent pattern ERG results suggest a nonlinear relationship between reductions in IOP and improvements in pattern ERGs.[21] A certain critical IOP must be reached by lowering pressure before the pattern ERG shows significant improvement. One case in point showed little improvement in pattern ERG amplitude when pressure was reduced from 38 to 20 mm Hg; only when IOP decreased to the midteens was there a significant reversal of dysfunction.[21] Various psychophysical techniques (including white-on-white contrast sensitivity, short-wavelength automated perimetry, and frequency doubling perimetry) show promise as early indicators of functional loss in glaucoma and may contribute to these aims.[6,22,23]

CONCLUSION

A significant reversal of dysfunction may not occur in all individuals with an abnormal pattern ERG. First, the number of pretreatment dysfunctional retinal ganglion cells must be relatively high for a measurable effect. This situation is expected to occur early in the disease. In older patients with more advanced stages of the disease, retinal ganglion cell losses are more extensive, and the restoration of function is less likely.

Second, dysfunctional retinal ganglion cells may exist due to factors other than IOP. The recovery of function, therefore, would not be expected from lowered IOP. Finally, pathophysiological mechanisms of glaucoma are elusive and multifactorial, and they vary from patient to patient. As a result, lowering pressure may have a demonstrable impact on one individual but not on another. ❑

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