Transiently Raised Intraocular Pressure Reveals Pattern Electroretinogram Losses in Ocular Hypertension

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Purpose. It is known that the pattern electroretinogram (PERG) of normal subjects is reduced temporarily after short-term elevation of intraocular pressure (IOP). The authors evaluated PERG changes in ocular hypertension during and after transient IOP elevation.

Methods. Steady state (8 Hz) PERGs to sinusoidal gratings (1.7 cyc/deg spatial frequency) were recorded in seven untreated patients with ocular hypertension at medium risk (maximum IOP, 22 to 25 mm Hg; cup–disk ratio, 0.6 to 0.7; normal Humphrey 30-2 visual field results; positive family history), as well as in six age-matched normal subjects. Recordings were obtained for the baseline condition during a short-term (6-minute) IOP elevation (to 30 mm Hg) by using a suction cup apparatus and during a 6-minute recovery period after removal of the apparatus.

Results. During IOP elevation, PERG amplitudes were reduced significantly from baseline values in normal subjects and patients. However, PERG losses were significantly greater in patients (average loss from baseline after 4 minutes of IOP elevation: 72% ± 7.6%) compared to controls (average loss after 2 minutes of IOP elevation: 40% ± 7.5%). In the recovery phase, mean PERG amplitude returned to baseline values in normal subjects but not in patients, whose recovery took longer. In normal subjects, PERG phase did not change either during or after IOP elevation. In patients, however, PERG phase showed a delay from baseline during and after IOP elevation (average delay after 6 minutes of recovery: —41.1° ± 13°).

Conclusions. Results indicate that increasing IOP with scleral suction produces greater PERG losses in eyes with ocular hypertension than in normal eyes. This suggests that the inner retina of eyes with ocular hypertension may have a heightened sensitivity to vascular or mechanical changes induced by transient IOP elevation. Invest Ophthalmol Vis Sci. 1996;37:2663-2670.
jects. A similar approach has not yet been used in patients with OHT. In these patients, because of subclinical abnormalities of the inner retina, acute IOP elevation could induce even enhanced PERG losses compared to those observed in normotensive subjects, thus revealing neural deficits not detectable under baseline conditions.

In this study, PERG changes recorded from patients with OHT during and after acute IOP elevation were compared to those obtained from normal subjects under the same experimental conditions. Results showed that IOP-induced PERG losses were more marked, and had a longer time course of recovery, in patients with OHT than in normotensive controls.

SUBJECTS AND METHODS

Subjects

Seven patients (four men, three women; mean age, 56 years; age range, 36 to 58 years) with a diagnosis of OHT were included in the study. All patients had a history of IOP above 21 mm Hg on two or more separate occasions (maximum ever recorded IOP, 23.6 mm Hg; mean range, 22 to 25 mm Hg); cup-to-disk ratio, 0.6 to 0.7; positive family history for glaucoma; and a normal visual field results (Humphrey 30-2 threshold test). Visual fields were considered normal if their mean deviation and pattern standard deviation significance was >10% and if no localized losses in sensitivity (i.e., two or more adjacent points with a loss of 5 dB or greater) were present. All patients were considered at moderately increased risk for developing glaucoma. None of the patients was under therapy with ocular antihypertensive drugs. On the day of testing, IOP ranged between 19 and 23 mm Hg (mean, 21.2 mm Hg). All patients were free from other ocular or systemic disorders. Their corrected visual acuities, refractive errors, when present, did not exceed ±0.50 sph or cyl diopters. Systolic and diastolic blood pressure, measured at the time of testing, ranged from 120 to 135 and 75 to 90 mm Hg, respectively.

Six normal subjects (four men, two women), age-matched with patients (mean age, 52 years; range, 32 to 58 years) also were tested. All subjects had emmetropia. Their baseline IOP on the day of testing was 15 mm Hg (range, 13 to 18 mm Hg). Systolic and diastolic blood pressure ranged from 115 to 135 and 75 to 90 mm Hg, respectively.

Another reason these normal subjects and patients were selected was that their PERG amplitudes were within the range (±2 SD) of previously established normative values (Falsini and Colotto, unpublished data, 1993). This allowed both groups to be evaluated under comparable functional conditions at baseline.

Informed consent was obtained from all subjects after the nature and possible consequences of the study were fully explained. The research followed the tenets of the Declaration of Helsinki.

Pattern Electroretinogram Recording

Pattern electroretinograms were obtained in response to sinusoidal gratings of 1.7 cyc/deg spatial frequency, sinusoidally modulated in counterphase at 8 Hz. Stimulation was generated electronically on a high-resolution television monitor (mean luminance, 90 cd/m²; contrast, 95%). The stimulating field size was 10° × 15°. Subjects fixated monocularly at a small fixation mark placed in the center of the stimulus field from a distance of 43 cm. All subjects or patients were tested with natural pupils; sizes were measured and did not differ between the groups. Electroretinograms were recorded by a small Ag/AgCl skin electrode placed over the lower eyelid of the stimulated eye. A similar electrode, placed on the eyelid of the contralateral, unstimulated eye, was used as reference. The electrode-skin impedance at the recording sites, checked before and after each recording session, was always below 3 kΩ. Retinal signals were amplified (100,000 times), band-pass filtered between 1 and 30 Hz, sampled with 12-bit resolution (0.5 msec sampling time), and computer averaged (250 events) with automatic artifact rejection. Two blocks of 250 events were recorded at each step of the experimental procedure (see next paragraph) and stored on disk. Discrete Fourier analysis was performed off-line to isolate the response’s second harmonic component, whose amplitude (in µV) and phase (in degrees) were measured.

Artificial Intraocular Pressure Elevation and Experimental Procedure

Intraocular pressure was raised transiently by using a suction cup apparatus according to Ulrich and Ulrich, with outer and inner diameters of 13 and 11 mm, respectively. The suction cup was placed on the temporal sclera after application of one drop of 0.4% oxibuprocarine chloride (Noveside, Sandoz, Milan, Italy), and the IOP was raised by increasing rapidly the negative pressure to the cup, up to a predetermined value corresponding to an IOP of 30 mm Hg. This procedure, which resulted in a more severe IOP elevation in controls than in patients with OHT (see next paragraph), was preferred to that of producing the same magnitude of IOP elevation in all subjects. Indeed, previous studies have shown that, in normal and OHT eyes, the retinal vascular autoregulation is fully effective only if IOP is not elevated above 29 to 30 mm Hg. Increasing IOP by a similar amount in all subjects may have reduced in OHT eyes, but not in normal eyes, the possibility of an autoregulatory response. The negative pressure value required for the
IOP to reach 30 mm Hg was established individually through a calibration procedure performed 2 hours before testing. The suction cup was held in place for 6 minutes. Throughout this period, the artificial IOP elevation resulted in an average relative increase in IOP by 14 mm Hg (SEM, ±1.24 mm Hg) in normal subjects and 10 mm Hg (SEM, ±1.71 mm Hg) in patients with OHT. In normal subjects and patients, systemic blood pressure was measured by sphygmmomanometry either before or during suction cup application. The PP was calculated according to the formula,12 [PP = $\frac{2}{3} P_b - IOP$], where $P_b$ is the mean brachial artery blood pressure. Under artificial IOP elevation, there was an average relative decrease in PP by 43.3% (SEM, ±7.38%) in normal subjects and 24.2% (SEM, ±4.66%) in patients with OHT. After 6 minutes of suction, the cup was removed quickly and IOP and systemic pressure were remeasured. After suction cup removal, IOP decreased and PP increased, compared to baseline values, by an average of 5 mm Hg (SEM, ±1.6 mm Hg) and 10% (SEM, ±5.7%), respectively, in normal subjects and patients.

Controls were made to ascertain whether the suction cup apparatus induced significant changes in either retinal illuminance or contrast of the stimulus used to generate the PERG. Indeed, it is known that a decrease in the stimulus retinal illuminance reduces the amplitude and increases the latency of steady state PERG,14 whereas a decrease in stimulus contrast causes a reduction in PERG amplitude.6 Therefore, changes in these stimulus parameters during suction cup application may have potentially mimicked the effects of acute IOP elevation on the PERG. However, a reduction in stimulus retinal illuminance was reasonably excluded because the suction cup, applied on the temporal sclera, did not interfere with the optical path of the stimulus. A reduction in the effective retinal contrast of the stimulus may have been secondary to refractive changes induced by scleral suction. Changes in the refractive status of the tested eyes during suction cup application were checked out by using an ophthalmometer (Haag–Streit, Bern, Switzerland) and an infrared refractometer (Nidek, Tokyo, Japan). In all cases, the refractive error induced by suction cup did not exceed ±0.50 sph diopters, 0.50 cyl diopters, or both. From preliminary experiments, it was estimated that such a degree of ametropia reduced PERG amplitude by no more than 5% to 10%, leaving the PERG phase unchanged.

Before starting the experiment, each normal subject or patient was adapted for 2 minutes to the stimulus luminance. Thereafter, three PERG records were obtained every 2 minutes throughout a 6-minute period in each of the following experimental conditions: immediately before suction cup application, during suction cup application, and immediately after suction cup removal. In patients with OHT, two to six PERG recordings were obtained every 30 minutes during the 3-hour period after the end of experimental procedure. Although these recordings were not part of the planned ERG protocol, they were undertaken nonetheless to ascertain the full PERG recovery to pre-suction cup values.

### Statistical Analysis

Pattern electroretinogram amplitude and phase changes obtained from normal subjects and patients with OHT during and after acute IOP elevation were evaluated by a three-way, repeated measures analysis of variance evaluating the effect of the group (i.e., normal subjects versus patients with OHT) as a between-subjects factor and the effects of the condition (i.e., the three experimental conditions) and record (i.e., the three records obtained at each condition) as a within-subjects factor. Between-groups comparisons also were performed on the normalized PERG amplitudes (percentage of amplitude change from the first baseline value) and phases (differences in degrees from the first baseline value) to minimize the effects of intersubject variability. These comparisons were made using multiple t-tests with a conservative significance level of $P < 0.005$.

### RESULTS

Figure 1A shows representative examples of steady state PERGs recorded from a normal subject and a patient with OHT before suction cup application (baseline), during artificial IOP elevation by suction cup, and after suction cup removal (recovery). Each PERG is the second of the three records obtained for each condition. The polar plots to the right of each record plot the second harmonic amplitude and phase values for partial averages (two blocks) of the total record. The distance from the origin of each point corresponds to response amplitude, and orientation corresponds to phase angle. Phase lags are measured clockwise from the x-axis. In normal subjects, the PERG amplitude was reduced during IOP elevation compared to either baseline or recovery period values. The PERG phase did not show appreciable changes from baseline values either during IOP elevation or in the recovery period. In patients with OHT, the PERG amplitude was reduced during IOP elevation and during recovery periods compared to baseline values. The amount of amplitude reduction appeared to be larger in patients with OHT than in normal subjects. The PERG phase in patients with OHT, unlike that in normal subjects, was delayed compared to baseline values during IOP elevation and during recovery periods.

Figure 1B shows the mean (± SEM) PERG amplitudes and phases recorded from normal subjects and
patients with OHT at each step of the experimental procedure. The group-averaged amplitude values confirm the trends shown in Figure 1A: During the IOP elevation period (SC), mean amplitude losses of patients were greater than those of controls, and in the recovery period (R), mean amplitudes of patients, unlike those of controls, did not attain baseline (B) values. Analysis of variance on PERG amplitudes showed a significant effect of the condition ($F(2,22) = 25.55; P < 0.001$) and a significant interaction of the group by the condition ($F(2,22) = 3.38; P < 0.05$), whereas the effects of the group ($F(1,11) = 3.56$) and record ($F(2,22) = 0.76$) were not statistically significant.

Mean PERG phases of normal subjects did not change across conditions, whereas those of patients showed a small, but systematic, delay from the baseline values during IOP elevation (at 10 and 12 minutes) and during recovery periods. Analysis of variance on PERG phases showed a significant effect of the group ($F(1,11) = 10.04; P < 0.01$) and a significant interaction of the group by the condition ($F(2,22) = 6.13; P < 0.01$), whereas the effects of the condition ($F(2,22) = 2.34$) and record ($F(2,22) = 2.27$) were not statistically significant.

Figure 2 shows normalized PERG amplitudes (relative amplitudes) and phases (phase changes) recorded individually from normal subjects and patients with OHT at each step of the experimental procedure. For relative amplitudes, the 100% line corresponds to the first baseline amplitude value, whereas for phase changes, the 0 line corresponds to the first baseline phase value recorded from each subject or patient. In most of the patients, the acute IOP elevation by scleral suction induced PERG losses that were greater than those observed in controls. In the recovery period, relative amplitudes of patients tended to be smaller than those of controls and did not attain baseline values. The relative PERG phase of patients, unlike that of controls, showed a delay (expressed by a negative phase difference) from baseline values in the recovery period. The means (± SEM) of normalized PERG amplitudes and phases obtained at each step of the experimental procedure are reported in Table 1 (the first baseline values are omitted because they were all set to 100% for amplitude and 0 for phase); t-tests showed significant differences in relative amplitude between patients and controls during IOP elevation (at 10 and 12 minutes) and in the recovery period (at 14 and 18 minutes). Between-groups differences in phase changes did not reach statistical significance.

An attempt was made to correlate PERG changes obtained in normal subjects and in patients with OHT, during and after IOP elevation, with the corresponding changes in PP. No significant correlations were
Pattern Electroretinogram Loss in Ocular Hypertension

NORMAL SUBJECTS

OHT PATIENTS

FIGURE 2. Normalized pattern electroretinogram amplitudes (relative amplitudes) and phases (phase changes) recorded individually from normal subjects and patients with ocular hypertension at each step of the experimental procedure. For relative amplitudes, the 100% line corresponds to the first baseline amplitude value; for phase changes, the 0 line corresponds to the first baseline phase value, recorded from each subject or patient (B = baseline; SC = suction cup; R = recovery).

Mean PERG amplitudes shown in the figure correspond to the records obtained immediately before PP estimation (i.e., the first record was taken at either baseline or recovery phase and the second record was taken during suction cup application). Absolute and relative (i.e., percent of baseline) values of PERG amplitudes and PPs are plotted in the upper and lower parts of the figure.

TABLE I. Mean Normalized PERG Amplitudes and Phases Recorded in Normal Subjects and Patients With Ocular Hypertension

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Normal Subjects</th>
<th>Patients</th>
<th>Normal Subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100.94 (5.05)</td>
<td>98.11 (5.76)</td>
<td>-15.70 (8.24)</td>
<td>1.03 (9.86)</td>
</tr>
<tr>
<td>6</td>
<td>105.48 (5.40)</td>
<td>92.75 (5.37)</td>
<td>-9.88 (9.28)</td>
<td>14.13 (19.37)</td>
</tr>
<tr>
<td>Suction cup</td>
<td>8</td>
<td>60.50 (7.52)</td>
<td>41.81 (11.52)</td>
<td>-6.68 (9.17)</td>
</tr>
<tr>
<td>10</td>
<td>71.33 (5.58)</td>
<td>28.33 (7.63)</td>
<td>-4.81 (7.98)</td>
<td>-11.17 (9.19)</td>
</tr>
<tr>
<td>12</td>
<td>67.46 (4.55)</td>
<td>34.77 (7.44)</td>
<td>6.13 (15.90)</td>
<td>-19.5 (14.76)</td>
</tr>
<tr>
<td>Recovery</td>
<td>14</td>
<td>90.06 (3.86)</td>
<td>51.12 (8.49)</td>
<td>3.13 (13.13)</td>
</tr>
<tr>
<td>16</td>
<td>86.88 (6.23)</td>
<td>60.81 (7.88)</td>
<td>3.60 (12.21)</td>
<td>-29.60 (8.29)</td>
</tr>
<tr>
<td>18</td>
<td>85.74 (4.13)</td>
<td>48.96 (6.13)</td>
<td>0.95 (10.60)</td>
<td>-41.16 (13.97)</td>
</tr>
</tbody>
</table>

PERG = pattern electroretinogram.

* Percentage of amplitude change from first baseline value.
† Phase difference (*) from first baseline value.
‡ Significant between-groups difference (*test, P < 0.005).
rows of the figure, respectively. It can be noted that in normal subjects and patients, a decrease in PP produced by suction cup application was paralleled by a reduction, with respect to baseline values, in mean PERG amplitudes. A recovery of PP to baseline values after the suction cup removal was associated with an increase in the mean PERG amplitude. Although the decrease in the mean PP during IOP elevation was smaller in patients with OHT than in controls, the corresponding reduction in mean PERG amplitude was much larger in the former than in the latter.

Full PERG recovery to baseline values was evaluated in patients with OHT after the end of the experimental session by obtaining additional recordings every 30 minutes for 3 hours. In four of the seven patients, PERG amplitudes and phases returned to baseline values within 1 hour. In two patients, the full PERG recovery was reached after 2 hours, whereas in one patient, pre-experiment values were attained after 3 hours.

DISCUSSION

Results in normal subjects confirm previous findings that acute, moderate IOP elevation induces transitory reductions in PERG amplitude. There have been, however, two reports in glaucomatous monkey eyes indicating that an acute decrease or increase in IOP may not result in significant PERG changes. Possible explanations for this discrepancy may lie in the different experimental and recording conditions used in these studies. Marx et al did not find changes in the steady state PERG after acute IOP reductions obtained pharmacologically in eyes with laser-induced, chronic (2-month) OHT. However, the effects of chronic OHT may not be comparable with those of short-term IOP elevation. Johnson et al did not report significant effects of acutely raised IOP on transient PERG in response to large (2°) checkerboards. They measured the first positive component (i.e., P50) of the response. However, the P50 component of transient PERG to large checks may not be as sensitive to the effects of acutely raised IOP as either the negative component of the same response (i.e., N95) or the steady state PERG to medium-size stimuli.

It has been suggested that PERG changes during acutely raised IOP levels may be related to vascularly mediated effects of IOP elevation rather than to direct mechanical compression of retinal ganglion cells. Experimental studies in animals support this view. Grehn and Prost by recording ganglion cells' action potentials in the cat under different levels of IOP and vascular PP, found that the electrical function

FIGURE 3. Mean (± SEM) pattern electroretinogram (PERG) amplitudes and perfusion pressures (PP) recorded from normal subjects and patients at baseline during IOP elevation and in the recovery period. Mean PERG amplitudes are those of the records obtained immediately before the PP estimation (i.e., the first record at either baseline or recovery phase, and the second record during suction cup application). Absolute and relative (i.e., percent of baseline) values of PERG amplitudes and PPs are plotted in the upper and lower rows of the figure, respectively.
of ganglion cell axons depends on perfusion pressure and not on the absolute IOP value. Siliprandi et al.,
by altering retinal vascular PP in the cat while leaving IOP levels unchanged, reported PERG changes similar
to those found with acute IOP elevation. Feghali et
al.,
by recording in rabbits the effects of acute IOP
elevation on the PERG, suggested that the rapidity of
onset and reversibility of PERG changes recorded in
their experiments primarily reflect a vascularly medi-
at ed effect of IOP. In the current study, we did not
find evidence of a statistical correlation between IOP-
induced changes in PP and the corresponding
changes in PERG amplitude. However, PP and PERG
amplitude changes had the same direction (i.e., both
parameters decreased and then increased) during and
after acute IOP elevation. It is possible that a direct
correlation between PERG and PP changes may have
been hindered by local autoregulatory mechanisms in
the retinal vascular system, which are known to take
place
under acute IOP elevation. In addition, on the
basis of the current findings, IOP mechanical damage
to retinal ganglion cells cannot be ruled out as an
alternative explanation for the observed PERG
changes.

The effects of acute IOP elevation on the PERG
have not been investigated in patients with OHT. Re-
sults of the current study indicate that, when com-
pared to normal subjects, patients with OHT can ex-
hibit enhanced PERG losses either during or after
acute IOP elevation. Indeed, during IOP elevation,
PERG amplitudes of patients were significantly more
reduced, with respect to baseline values, compared to
those of controls. During the recovery period after
IOP elevation in patients with OHT (unlike control
subjects), PERG amplitudes did not attain baseline
values, and PERG phases were delayed compared to
those recorded at baseline. The PERG losses observed
in patients with OHT, compared to controls, during
and after IOP elevation may reflect a heightened sen-
sitivity of the inner retina to ischemic changes, mecha-
nical compression, or both, induced by an acutely raised
IOP. Retinal ischemia could be caused by reduced
vascular autoregulation. In the current study, we esti-

imated that our artificial IOP elevation induced, on
average, a decrease in PP of 43% in normal subjects
and 24% in patients with OHT. Previous results ob-
tained by using the blue-field entoptic phenomenon

demonstrated that, in normal subjects, the retina was
able to maintain normal blood flow by autoregulation
up to IOP values of approximately 30 mm Hg (i.e.,
the values used in our experiment), corresponding to
a decrease of 36% or less in PP. In patients with or
suspected to have glaucoma, however, Grunwald et
al.
showed, by means of the same methodology, that
the range of acutely increased IOP for which retinal
circulation could maintain a constant flow was re-
duced compared to normal subjects. These previous
findings suggest that in our patients with OHT, abnor-
mal retinal ischemia, because of reduced autoregula-
tion in response to a relatively small decrease in PP,
may have accounted for the enhanced PERG losses
during and after acute IOP elevation. It has already
been reported that the PERG is a sensitive indicator
of inner retinal dysfunction induced by acute and
chronic ischemia in vascular occlusive diseases
and diabetes,
respectively. In addition, anatomic or func-
tional abnormalities of inner retinal neurons, which
presumably were already present in our patients with
OHT, may have been revealed by a moderate, acute
IOP elevation with PP decrement. Indeed, it is known
that a significant loss of retinal ganglion cells may
occur in the retinas of patients with OHT and that
subclinical visual dysfunction not detectable by stan-
dard diagnostic methods can be associated with
chronic OHT (see Stewart and Chauhan
for a recent
review). The ischemic or mechanical effects, or both,
of acute IOP elevation may have acted on an already
anomalous retinal substrate, inducing more severe
PERG loss.

The current data are in general agreement with
psychophysical and visual evoked potential (VEP) re-
sults showing that normal and glaucomatous eyes can
exhibit different responses to acute IOP elevation. By
recording perimetric thresholds at discrete visual field
locations, Krakau et al.
found that in glaucomatous
but not in normal eyes, an acute IOP increment of 20
mm Hg, combined with a decrease in ocular blood
flow, induced a transient loss in differential light sensi-
tivity. The authors suggested that this abnormal loss
of light sensitivity to increased IOP could reflect
microvascular impairment to discrete areas of the optic
nerve. By recording steady state pattern VEPs during
acute, stepwise elevation of the IOP, Stodtmeister and
Pillunat
found that although in normal subjects VEP
amplitude decreased only at critical IOP values of 70
mm Hg or greater, in patients with glaucoma, VEP
amplitude decreased monotonically as a function of
increasing IOP, starting from IOP values of approxi-
ately 40 mm Hg. Stodtmeister and Pillunat
interpreted their findings in patients with glaucoma as evi-
dence of the lack of autoregulation in the circulation
of the optic nerve head. Compared to psychophysical
and VEP techniques, however, the PERG could pro-
vide more direct evidence of impairment of the inner
retina. In addition, the current findings suggest that
retinal ganglion cells in OHT or early glaucoma may
be even more vulnerable to acute IOP elevation than
previously thought.

The results of this study were obtained from pa-
tients at moderately increased risk for glaucoma.
Therefore, our findings cannot be generalized to all
patients with OHT. Patients with low- or high-risk
OHT, as well as those with early glaucoma are, under evaluation in our laboratory with the PERG and scleral suction procedure (Falsini and Colotto, manuscript in preparation). Preliminary findings show that IOP-induced PERG losses in low-risk OHT appear to be more similar to those found in normal subjects, whereas patients with high-risk OHT or early glaucoma can exhibit losses that are comparable to, or even greater than, those observed in the patients included in the current study. Although results on a large sample of patients are needed to validate clinically the current approach, it appears to be potentially useful for revealing, in OHT or glaucomatous eyes, a heightened sensitivity of inner retinal function to vascular or mechanical changes induced by transient IOP elevation.

Key Words
acute intraocular pressure elevation, inner retina, ocular hypertension, pattern electroretinogram, retinal autoregulation

References