Flash and Pattern Electroretinograms During and After Acute Intraocular Pressure Elevation in Cats

R. Siliprandi, M. G. Bucci, R. Canella, and G. Cormignoro

Retinal functionality during short-term intraocular pressure (IOP) elevation and simultaneous systemic blood pressure (BP) variations was evaluated in the cat by recording the electroretinogram in response to both homogenous flickering light (FERG) and contrast reversing gratings (PERG). The mean arterial blood pressure (BPm) was pharmacologically adjusted to different levels and a large range of IOP values was tested. Results indicate that both FERG and PERG responses are impaired when the eye perfusion pressure (PP = BPm - IOP) is reduced and they disappear at a critical PP value of about 20 mm Hg, irrespective of the absolute value of the IOP. In addition, when the critical perfusion pressure is maintained for periods longer than 5 min, the recovery of the PERG response, when present, is always delayed compared to the full recovery of the FERG response. These findings support the hypothesis that vascular factors, i.e., the impairment of the retinal blood supply, may be responsible for the disappearance of the retinal electrical activity during short-term IOP elevation. Furthermore, the retinal ganglion cells, presumably the main source of the PERG response, appear less likely to recover from the acute ischemic episode.

In man, the most common manifestations of glaucoma, i.e., visual field defects together with optic disk cupping, have been related to anatomical and functional abnormalities of the retinal ganglion cell axons at the level of the lamina cribrosa. Two different hypotheses have been proposed concerning the possible causes of the early development of the disease. According to the "mechanical" hypothesis, the distortion of the optic nerve axons, consequent to elevated intraocular pressure-induced compression against the glial-collagen framework of the lamina cribrosa, is mainly involved. According to the "vascular" hypothesis, a local ischemia due to reduction of the blood supply of the retina and optic nerve head is the primary damage caused by the elevated intraocular pressure (IOP).

The diagnosis of glaucoma has long been based on the assessment of the visual field perimetry and examination of the optic disk. Recently, the electroretinogram in response to a patterned stimulus (PERG), generated in the proximal retina and mainly related to the electrical activity of the retinal ganglion cells, has been applied in the clinical evaluation of retinal and optic nerve diseases. In particular, in patients suffering from unilateral glaucoma the PERG response is dramatically reduced or absent in the affected eye, while the electroretinogram in response to a flash of light (FERG) (related to the activity of the more distal retinal layers) has comparable amplitudes in the two eyes.

The importance of the PERG technique in the diagnostic procedures of glaucoma is based on its efficacy in detecting ganglion cell damage. This PERG property is particularly important in the early diagnosis of the disease since a massive loss of ganglion cell axons can occur in open-angle glaucoma before detectable visual field deficits become evident. In addition, a reduction in the PERG amplitude was recently reported to be greater for those hypertensive subjects who were at high risk for developing glaucoma when compared to low-risk hypertensives. However, despite such considerable improvement in the diagnosis and prognosis of glaucoma, the identification of glaucoma pathogenesis is still uncertain. In this respect, it is noteworthy that nerve damage can occur without increased IOP, as observed in low-tension glaucoma.

In the present study an acute model of glaucoma in the cat was used to evaluate whether or not the effects of short-term IOP elevation originate from vascular insufficiency. In particular, following simultaneous variations of systemic blood pressure (BP) and IOP, we determined whether or not the impairment of retinal functionality, as assessed by both FERG and PERG recordings, depends on the abso-
lute value of the IOP (mechanical effect), or whether it matches the eye perfusion pressure \( (\text{PP} = \text{BP} - \text{IOP}; \text{vasogenic effect}) \). Moreover, in some animals cortical visual evoked potentials (VEPs) in response to contrast reversing gratings, together with FERG and PERG, were recorded in order to monitor the functionality of the optic pathway from the retina to the visual cortex. This approach allows the identification of the occurrence of possible damage to the optic nerve which is not yet detectable at the retinal level. This seems to be particularly relevant in view of the fact that in glaucoma the pathological alterations mainly occur at the optic nerve head.

Materials and Methods

General Surgery and Anaesthesia

Experiments were performed on 30 adult cats. Animal care and treatment in this investigation were in compliance with the ARVO Resolution on the Use of Animals in Research.

An endotracheal tube, one arterial and two venous cannulas were inserted under halothane anaesthesia. At the end of the surgical procedures, all the operated areas were infiltrated with local anaesthetic (Novocaine®, Hoechst AG, Frankfurt, West Germany). The animal was then mounted in a stereotactic apparatus and paralyzed with a continuous infusion of Pavulon® (Pancuronium Bromide, N.V. Organon OSS, The Netherlands) 0.1–0.6 ml/kg/hr. Artificial ventilation was supplied with a mixture of \( \text{NO}_2 \) (75%) + \( \text{O}_2 \) (25%) and completed with 0.5% halothane in the gas mixture. Body temperature was maintained at 38°C, \( \text{PCO}_2 \) (3.8–4.2%), and heart rate and electroencephalogram (EEG) were monitored throughout the experiments.

BP Assessment and Variations

The arterial blood pressure (BP) was continuously monitored by a pressure transducer connected to a heparinized catheter inserted into the femoral artery. The BP was pharmacologically manipulated, when necessary, during the recording sections: a persistent lowering of BP was achieved by a continuous intravenous infusion of Na-Nitroprusside (Sigma Chemical Co., St. Louis, MO) (0.2–0.4 mg/kg/hr); a persistent elevation of BP was achieved by the use of Angiotensin I (Sigma) (60–90 \( \mu \)g/kg/hr). The mean BP \( (\text{BP}_m) \) was calculated as follows: \( \text{BP}_m = \text{Diastolic Pressure} + \frac{1}{2} \text{(Systolic Pressure} - \text{Diastolic Pressure}) \).

IOP Assessment and Variations

The anterior chamber of the eye was incannulated and the IOP was recorded by a pressure transducer. Another cannula was connected to a Ringer reservoir and the IOP was artificially varied by adjusting the reservoir at the appropriate height. In some animals the IOP was additionally measured through a pressure tonometer (Model 30 R, Digilab, Inc., Cambridge, MA).

The eye perfusion pressure is defined as the difference between the \( \text{BP}_m \) and the IOP:

\[
\text{PP} = \text{BP}_m - \text{IOP}
\]

Ocular Preparation, Recordings and Visual Stimulation

Nictitating membranes were retracted with phenylephrine and pupils dilated with atropine. Platinum wire electrodes for ERG recording were applied to the corneas. Optically neutral contact lenses with artificial pupils of 3 mm diameter were applied to protect corneas and refraction was corrected, when necessary, with additional lenses. In addition, a screw electrode was positioned in the skull above the cortical projections of area centralis (area 17) for measurements of both VEPs and EEG.

For visual stimulation the papillae of both eyes were projected on a tangent screen placed 40 cm from the eyes using the technique described by Fernald and Chase. The screen was then replaced by a display (Hewlett-Packard Model 1304A, Palo Alto, CA) in order to cover the central part of the visual field of either eye (field size: 38° by 30° at 40 cm viewing distance). Sinusoidal gratings of various spatial frequencies and contrasts were generated on the display (mean luminance: 10 cd/m²) and shifted in spatial phase by 180° (pattern reversal) at the rate of 8 Hz (16 reversal/sec). Contrast is defined as:

\[
C = \frac{\text{L}_{\text{max}} - \text{L}_{\text{min}}}{\text{L}_{\text{max}} + \text{L}_{\text{min}}}
\]

where \( \text{L}_{\text{max}} \) and \( \text{L}_{\text{min}} \) are the maximum and minimum luminance, respectively. The same display was used to present a flicker stimulation (ON-OFF luminance modulation at 8 Hz; \( \text{L}_{\text{min}}: 0.7 \text{ cd/m}^2 \), \( \text{L}_{\text{max}}: 18 \text{ cd/m}^2 \)).

For ERG and VEP recordings, both responses were filtered between 1–50 Hz, conventionally amplified, recorded over 125 msec epoch and averaged on-line by a computer (MINC 23, Digital, Maynard, MA). Usually 150–200 responses were averaged in order to sufficiently improve the signal-to-noise ratio. The noise level was usually of the order of 0.1–0.4 \( \mu \)V.

The noise level was defined as the amplitude of the 16 Hz component of a record obtained in the absence of a contrast stimulus (sampling temporal frequency: 8 Hz). The averaged responses were pooled off-line (300–800 stimulus period), Fourier analyzed and plotted on a X-Y plotter. The amplitude of the second harmonic was used to evaluate both ERG and VEP responses to alternating gratings, the am-
plitude of the first harmonic was used to evaluate the ERG response to flickering light at 8 Hz.12

Results
FERG and PERG Impairment and Disappearance
Retinal electrical activity monitored through FERG and PERG recordings was evaluated at decreasing levels of the eye PP. This was achieved either by increasing the IOP and/or by decreasing the BPr.

Moreover, in some cases, the functionality of the visual pathway from the retina to the visual cortex was also monitored by recording VEPs in response to contrast reversing gratings. Results obtained show that FERG, PERG and VEP response amplitudes decrease as the PP is reduced, irrespective of the absolute value of the IOP and disappear when the PP reaches a critical value (PPcrit).

Figures 1 and 2 show in detail the results of two experiments in which the PP was lowered by increasing the IOP to 80 mm Hg, the highest value tested in this study (Fig. 1), and by diminishing the BPr to 60
mm Hg, one of the lowest value tested in this study (Fig. 2). In the upper row of Figure 1 are shown FERG and PERG response amplitudes recorded at physiological conditions of BP\textsubscript{m} (120 mm Hg) and IOP (20 mm Hg). When the IOP is increased to 70 and subsequently to 80 mm Hg (PP = 50 and 40 mm Hg respectively) both the responses are still at control levels despite these very high values of IOP. However, when the PP is further reduced to 25 mm Hg by slightly lowering the BP\textsubscript{m} to 105 mm Hg, the amplitudes of the FERG and PERG responses both decrease, and they disappear when the PP is additionally reduced to 15 mm Hg, by further reducing the BP\textsubscript{m} to 95 mm Hg. The PP at which both the responses are abolished represents the PP\textsubscript{crit}. The lowering of BP was obtained via an endovenous infusion of Na-Nitroprusside which, as will be described in the next experiment, does not alter by itself the electrical responses of the retina. Furthermore, Figure 1a, b also shows that when the physiological levels of IOP and BP\textsubscript{m} are reestablished, FERG and PERG responses fully recover to control levels in a few minutes.

In the experiment shown in Figure 2a, b the IOP was kept at control levels and the PP was reduced by decreasing the BP via a continuous infusion of Na-Nitroprusside. FERG and PERG response amplitudes recorded at physiological conditions of BP\textsubscript{m} (140 mm Hg) and IOP (20 mm Hg) are shown in the upper row of the figure. Similar to what was observed in the experiment reported in Figure 1a, b, FERG and PERG are normal at the PP of 45 mm Hg; this value of PP is obtained by lowering the BP\textsubscript{m} to 65 mm Hg and by maintaining the IOP at normal levels (20 mm Hg). When the PP is further reduced by slightly increasing the IOP to 35 mm Hg (PP = 30 mm Hg), both the responses decrease and disappear when the PP reaches the critical value of 20 mm Hg (BP\textsubscript{m} = 60 mm Hg; IOP = 40 mm Hg). FERG and PERG fully recover to control levels within a few minutes as the control values of PP are reestablished. In both the above mentioned experiments, VEP recordings were also performed (Fig. 1c; Fig. 2c). Results show that VEP responses, similarly to FERG and PERG responses, are reduced as the PP is lowered, irrespective of the absolute value of the IOP. Moreover, the impairment of the VEPs does not precede the impairment of the PERG. Noteworthy is that Na-Nitroprusside by itself does not alter the electrical responses since FERG, PERG and VEP responses amplitudes did not change even when the drug was used to greatly reduced the BP\textsubscript{m} to 65 mm Hg (see Fig. 2).

These results (i.e., as the eye PP is reduced towards the PP\textsubscript{crit}, FERG, PERG and VEP responses disappear and the disappearance of the PERG response does not precede that of the FERG response, and the disappearance of the VEP response does not precede that of the PERG response) were confirmed, with no exceptions, in a large number of experiments in which the eye PP was lowered by varying both the IOP and the BP over a wide range of values. Figure 3 summarizes all the results obtained and reports the critical PP which results in the loss of FERG, PERG and VEPs (open symbols; n = 6) and in the loss of FERG and PERG (filled symbols; VEPs were not recorded; n = 27).

Statistical evaluation of the data indicates that a high correlation exists between the IOP and the BP\textsubscript{m} (correlation index R = 0.96). When the BP\textsubscript{m} is set at high values, the IOP must be fixed at high values for the ERGs to disappear; vice-versa, when the BP\textsubscript{m} is set at low levels, the ERGs disappear when the IOP is at relatively low or at normal levels. Similar results were obtained when VEP responses were also monitored (six experimental eyes). Hence, the loss of the ERGs and VEPs appears to be closely correlated to the critical PP and not to the absolute value of the IOP. The mean PP\textsubscript{crit} was calculated to be 20.9 ± 0.76 mm Hg (n = 33).

The dependence of a normal ERG response on the eye PP is further demonstrated by the particular experiment reported in Figure 4. In this unusual cat the BP\textsubscript{m} underwent very fast variations in response to the Na-Nitroprusside. In particular, while the BP\textsubscript{m} rap-
Fig. 4. Relationship between BPa and PERG amplitudes as a function of time. The Na-Nitroprusside infusion started at minute 0. IOP was fixed at 75 mm Hg and BPa varied between 135 mm Hg and 80 mm Hg. Each point represents PERG amplitude in response to an alternating grating stimulus: 0.35 c/deg, contrast: 40%. White arrows: PERG amplitude recorded at normal levels of both IOP and BPa. Black arrow: noise level.

Fig. 5. Recovery of FERG (dashed line) and PERG (continuous line) amplitudes following 10 min of complete ischemia. The PP was fixed to 0 mm Hg (BP = IOP = 90 mm Hg). Black arrows: noise levels. White arrows: control recordings of PERG (left) and FERG (right) before inducing the ischemic conditions (BP = 120 mm Hg, IOP = 24 mm Hg).

Table 1. Differential effect of ischemia on FERG and PERG recovery

<table>
<thead>
<tr>
<th>Cat</th>
<th>Ischemic episode (min)</th>
<th>FERG recovery (min)</th>
<th>PERG Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>20</td>
<td>40</td>
<td>*</td>
</tr>
<tr>
<td>C2</td>
<td>10</td>
<td>50</td>
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<td>C3</td>
<td>10</td>
<td>30</td>
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<tr>
<td>C4</td>
<td>20</td>
<td>20</td>
<td>60†</td>
</tr>
<tr>
<td>C5</td>
<td>5</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>C6</td>
<td>15</td>
<td>10</td>
<td>60†</td>
</tr>
<tr>
<td>C7</td>
<td>30</td>
<td></td>
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</tbody>
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* No recovery was seen after 1 hr. Further recordings were not performed.
† No recovery was seen after 2 hr. Further recordings were not performed.
‡ Partial recovery.

FERG and PERG Recovery

The disappearance of both PERG and FERG responses when the PP is reduced to threshold values for a very short time (<5 min) is completely reversible (see Fig. 1a, b and Fig. 2a, b). However, when the eye PP is maintained at or below threshold values for longer times (5–30 min), a clear dissociation between the recovery of the two ERG responses occurs in all the animals examined (Table 1). Note that after the ischemic episode PERG response does not recover (cats: C1, C2, C3, C7), or it recovers only partially (cat C4), while the FERG response always returns to normal. In cats C5 and C6 the PERG response fully recovers, but later than the full recovery of the FERG response. Figure 5 reports in detail one of these experiments (Table 1, cat C3): both FERG and PERG responses disappear during a complete block of the retinal blood supply. This was achieved by maintaining the PP at 0 mm Hg (IOP = BPa = 90 mm Hg) for 10 min. Fundus ophthalmoscopic investigations revealed the occurrence of dramatic shrinkage of the retinal blood vessels during such a time period (data not shown). When the physiological level of PP was reestablished (IOP = 20 mm Hg, BPa = 120 mm Hg), the FERG recovers to normal within 30 min, while the PERG is still completely impaired even 1 hr after the ischemic episode.

In order to examine whether or not in the preceding experiments longer times of IOP elevation cause a selective impairment of the PERG by inducing a me-
mechanical compression at the level of the ganglion cell axons, the following experiment was performed (Fig. 6). By a continuous infusion of Angiotensin I, the cat BP_m was elevated to 180 mm Hg and the IOP was also raised to 90 mm Hg. These pressure levels were maintained for 30 min. In such a way a normal PP of the eye (PP = 90 mm Hg) was maintained despite the high IOP value. Figure 6a shows PERG, FERG and VEP responses recorded in normal conditions (IOP = 20 mm Hg; BP_m = 120 mm Hg). Figure 6b shows that not only both PERG and FERG responses are normal 10, 20 and 30 min after setting the IOP at 90 mm Hg and the BP_m at 180 mm Hg, but also that the VEP response is at all times normal. When physiological conditions of both IOP and BP were restored, no changes in PERG, FERG and VEP responses were observed (Fig. 6c). Thus, the normal functionality of the whole retina as well as the normal impulse conduction of the optic nerve axons are preserved even when the IOP is set at a very high value, provided that a normal eye PP is maintained.

**Discussion**

**Impairment of FERG and PERG Responses During Acute Short-Term IOP Elevation**

The results reported suggest that the impairment of the electrical retinal activity induced by either acute short-term IOP elevation or diminished systemic blood pressure is caused by a reduction of the eye PP and thus may be considered ischemic in origin. During the induction of ischemia, the PERG disappearance does not precede the FERG disappearance, thus suggesting that the inner retinal layers are not more sensitive to ischemia than the outer retinal components. Moreover, as the PP is reduced, an impairment of the VEP response is also observed, but it never precedes the impairment of the PERG response. This suggests that ganglion cell axons are not more susceptible to ischemia with respect to the cell bodies. Noteworthy is that, during acute IOP elevation in monkeys, the b-wave of the ERG and the optic tract response are similarly impaired as the eye PP is reduced. Comparable reductions in the ERG b-wave during short-term IOP elevations were also reported to occur in human subjects.

Our results are in agreement with those of Grehen and Prost. These authors reported that the impulse conduction of ganglion cell axons, impaired during short-term IOP elevation, is correlated to the eye PP irrespective of the absolute value of the IOP.

It may be suggested that the use of drugs like Na-Nitroprusside might interfere with the ERG and VEP responses. This possibility appears unlikely since no direct correlation was found between the impairment of the responses and the absolute value of the BP_m. (see Figs. 2, 3). Alternatively, it may be argued that this drug could affect the autoregulative properties of the retinal vasculature. Again, this appears unlikely as the critical perfusion pressure values obtained in our experiments are similar (approximately 20 mm Hg) both when the eye PP has been lowered through lowering of the BP_m, ie, using Na-Nitroprusside, or when the eye PP has been lowered by simply increasing the IOP without any manipulation of the BP_m.

**Recovery of FERG and PERG Responses After Short-Term IOP Elevation**

The recovery of the FERG and PERG responses differentially varies with the duration of the ischemic episode. In particular, both the FERG and the PERG responses fully recover to control values in a few minutes, provided that the ischemic episode is very short (not more than 5 min). However, when the PP is kept at or below threshold for longer times, thus inducing longer times of ischemia, the time course of FERG and PERG recovery differs: the former was always found to return to normal values earlier than the latter. In some cases (see Table 1) the PERG, in contrast to the FERG, was completely impaired even 1 or 2 hr after the ischemic insult. The ischemic origin of the selective impairment of the PERG recovery
is further suggested by the experiment described in Figure 6: even by setting the IOP at extremely high values for 30 min, both ERG and VEP responses were normal provided that a relatively normal PP was maintained by increasing the cat systemic blood pressure. The above findings are in agreement with Maffei and Fiorentini, who showed that when the IOP was increased until no response could be recorded at the lateral geniculate nucleus, the PERG recovered later than the FERG, provided that the high value of the IOP was maintained for 20–25 min. In contrast, when the IOP elevation lasted for 30 min no recovery of the PERG response was observed. Similar results were obtained following induction of a complete transient retinal ischemia via clamping of the retinal artery. Although obtained in chronic IOP elevation experiments, a decrease of the PERG response amplitudes, in contrast to the FERG response amplitudes, was also reported to occur in monkeys. Taken together, these data suggest that retinal ganglion cells, presumably the main source of the PERG response, are less likely to recover from prolonged ischemia compared to the other retinal neurons. Although underlying mechanisms are still unknown, differences in neuronal vulnerability to ischemic episodes are common features of the central nervous system neurons. Hypothetically, the selective vulnerability of the inner retinal layers to ischemia may be related to differences in circulatory properties. The cat inner retinal layers are supplied by branches of the ciliary artery, while the avascular outer retinal layers are supplied by diffusion from the choroidal vessels. As the autoregulative properties of these vessels are still under debate, it is tempting to speculate that the differential circulatory regulation of these two types of vessels may perhaps underlie the differences in vulnerability to ischemic episodes. Alternatively, the metabolic demand of the retinal cell types may differ: the neurons of the inner retinal layers may have a higher metabolic demand per se and hence a higher susceptibility to oxygen deprivation.

In conclusion, our results indicate that short-term IOP elevation induces a reduction of the eye perfusion pressure which results in the disappearance of both FERG and PERG as well as VEP responses. The impairment of the retinal as well as optic nerve function is also observed when the eye perfusion pressure is reduced by diminishing the systemic blood pressure. This phenomenon is completely reversible, provided that the ischemic conditions do not last more than a few minutes. For longer times, a selective functional impairment of the proximal retinal layers occurs with respect to the more distal retinal layers. It is noteworthy that, in the present study, we inves- gated the acute effects of ocular hypertension. These experimental conditions are similar to the episodes of severe attacks of intraocular hypertension in man, like those occurring in angle-closure glaucoma, and therefore our results could well be relevant to this pathology. As regards open-angle glaucoma, which is characterized by moderate but chronic ocular hypertension, other factors, like mechanical compression on ganglion cell axons, could be involved in the alterations occurring in this disease.

**Key words:** flash and pattern electroretinograms, eye perfusion pressure, ischemia, ganglion cells, cat

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