The Rate of Functional Recovery from Acute IOP Elevation

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PURPOSE. To evaluate the recovery of retinal function after acute IOP elevation.

METHODS. The electroretinogram (ERG) was measured before, during, and after IOP increased to 50 and 70 mm Hg at different durations in anesthetized, dark-adapted rats (n = 5–7). Signals were collected during bright flashes (−4.95 and 1.0 log cd · s/m²) and in terms of the photoreceptor (P3), postreceptor (P2), and inner retinal (negative scotopic threshold response [nSTR]) responses. Parameters (treatment/baseline, %) were compared across time by using repeated-measures ANOVA and t tests. The rate of recovery was quantified with a logistic function and compared by bootstrap.

RESULTS. IOP spikes induce greater loss (P < 0.01) and slower recovery (P < 0.001) in the nSTR compared with the P2 and P3 responses. IOP spikes having common integral (pressure × duration, 2100 mm Hg · minutes) for insult gave significantly greater P2 and nSTR dysfunction at the higher pressure (70 vs. 50 mm Hg, nSTR reduced to −2.5% ± 0.5% vs. 20.3% ± 6.5%, P < 0.05). The higher pressure also produced significantly slower nSTR recovery (50% recovery time [t0.5] 70 vs. 50 mm Hg: 33.1 vs. 21.7 minutes; P < 0.05). At a given IOP (70 mm Hg), t0.5 showed a linear relationship with duration (15 vs. 30 vs. 60 minutes’ exposure: t0.5 16.7 vs. 33.1 vs. 63.2 minutes; P < 0.05) and integral.

CONCLUSIONS. Ganglion cell function recovers slower than the outer retina after IOP insult, with peak IOP being the principle determinant of functional loss and recovery. For a fixed pressure, functional recovery is linearly related to exposure. (Invest Ophthalmol Vis Sci. 2006;47:4872–4880) DOI:10.1167/iovs.06-0590

Glaucoma is the second leading cause of blindness in the world, with intraocular pressure (IOP) being a well-documented risk factor in its development and progression. It is widely accepted that IOP shows a circadian rhythm, with recent reports indicating that patients with glaucoma show greater diurnal fluctuations than normal. It has been proposed that these undetected spikes in IOP can lead, over time, to cumulative retinal damage. Thus, it is important to understand the effect of short-term IOP spikes on visual function.

Several groups have investigated the effect that transient IOP elevations have on retinal and optic nerve function and histology. Typically, such studies have used cannulation of the anterior chamber to raise IOP above mean arterial pressure (>110 mm Hg), such that ocular perfusion is totally suppressed. However, such high IOPs are not typical of open-angle glaucoma and are only rarely observed in acute angle-closure glaucoma. Not surprisingly, such extreme pressure completely abolishes retinal function, as measured using the electroretinogram (ERG). In addition, many of these functional studies focus on the retinal response to bright flashes known to primarily reflect photoreceptor (a-wave) and bipolar cell (b-wave) activity. However, it is clear that glaucoma manifests as a specific retinal ganglion cell (RGC) loss, which is not reflected in the a- and b-waves. One potentially useful functional measure of ganglion cell activity is the scotopic threshold response (STR). The STR, recorded by using very dim flashes, has been shown to receive contributions from inner retinal neurons. More specifically, in rats the STR depends on the integrity of ganglion cells and thus provides a more specific tool for investigating the effect that IOP spikes have on ganglion cells.

Recently, Bui et al. reported that during IOP elevation (from 10 to 100 mm Hg), STR deficits are observed with moderate IOP elevations (30–50 mm Hg), whereas at higher IOPs (80–100 mm Hg) the functional changes are widespread, involving the b- and a-waves. Although, this study considered a range of IOPs, it did not consider the relationship between IOP peak and duration (IOP integral), which has been shown to be a better predictor of functional damage in rat models of chronic IOP elevation. In particular, it is unclear whether acute IOP elevations of different peak pressures but equivalent integral will lead to the same functional deficit.

The rate of functional loss during IOP elevation is very rapid, making this parameter difficult to quantify. An alternative approach is to quantify the rate of functional recovery of ERG components from acute IOP injury, as this occurs over a longer time course. To our knowledge, the nature of functional recovery immediately after acute IOP spikes has not yet to be considered. Thus, the purpose of this study is to evaluate functional loss, but more important, its rate of recovery after a brief elevation of IOP. For this purpose we adopted more modest IOPs (50 and 70 mm Hg) that yield perfusion pressures of clinical relevance, rather than those in the commonly used ischemia-reperfusion model (≥110 mm Hg).

Based on a previous study, such IOP magnitudes result in greater inner retinal dysfunction, that more closely resembles glutamatic damage. Likewise, our durations are short (15–60 minutes) to replicate the brief spikes in IOP seen in rabbits and may go undetected over a typical diurnal period (e.g., Fig. 8 in McLaren et al. Using the above approach, we compare the effect of IOP spikes of different peak pressures but equivalent integral (by varying duration). We reasoned that if IOP has a “pressure” effect that is duration independent, prolonging the time of pressure application would yield no change in recovery. We also considered the rate of recovery for IOP spikes of fixed magnitude but of varying duration.

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MATERIALS AND METHODS

Animals
All experimental procedures conformed to the guidelines of the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and approval was obtained from our departmental Animal Ethics Committee. Adult Long-Evans rats (8–12 weeks, 200–300 g) were housed in a 20°C environment with the light environment cycling between 12 hours of light and dark (on at 8 AM). Food and water were available ad libitum.

Acute IOP Elevation
Acute IOP elevation in rats was achieved as previously described.22 In brief, animals were dark adapted overnight (>12 hours) and all procedures are conducted under dim red light (λmax = 600 nm). Animals are anesthetized with intramuscular injection of ketamine/xylazine (60 and 5 mg/kg; Troy Laboratories Pty Ltd., Smithfield, NSW, Australia). Corneal analgesia and mydriasis were achieved with 1 drop of proxymetacaine (0.5%, Alcain; Alcon Laboratories, Frenchs Forest, NSW, Australia) and tropicamide (0.5%, Mydriacyl; Alcon Laboratories), respectively. A circulating-water heating pad was applied to maintain body temperature at 37°C. The anterior chamber was cannulated with a 30-gauge needle connected by polyethylene tubing to a pressure transducer (Transpac; Abbott Critical Care Systems, Sligo, Australia). IOP was monitored (ML110G; ADInstruments, Sydney, NSW, Australia) and rat blood pressure was measured using a tail-cuff sphygmomanometer (ML125; ADInstruments). After cannulation, an hour was allowed for stabilization and readaptation before, during, and immediately after IOP elevation.

ERG Recovery from IOP Spikes

ERG Data Analysis
ERG parameters recorded over the time course of IOP insult and subsequent recovery are expressed as a percentage of baseline for the same eye (treatment/baseline, %).

Scotopic Threshold Response. The amplitude of the positive (p)STR and negative (n)STR were measured from baseline at fixed criterion times of 110 and 220 ms, respectively. The total amplitude of the STR was also measured from peak to trough.

Photoreceptor Response. The P3 model introduced by Hood and Birch23 has been well established to fit the leading edge of the photoreceptor a-wave.

ERG Recovery from IOP Spikes

ERG Recovery from IOP Spikes

The rate of functional recovery of the normalized amplitude was quantified by using a logistic function (equation 2), as has been used in studies of cardiovascular recovery in response to ischemic insult.26,27 This function provides a good fit to the recovery of nSTR amplitudes (Figs. 3E, 5) and characterizes the dynamic pattern of the recovery process.

In equation 2, the normalized amplitude (y) as a function of time is given by a maximum recovery amplitude (a), a rate constant (b), and

\[
\frac{y}{1 + \left(\frac{x}{t_b}\right)^2}
\]
the time for 50% amplitude recovery (t_{0.5}, in minutes). Logistic functions were fitted by floating all variables and minimizing the SS merit function for all times after IOP injury (Solver module of Excel; Microsoft).

**Statistical Analysis**

To compare the effect of IOP elevation with baseline control pressure, we normalized ERG parameters of 35 animals at baseline level to their average. This yielded the 99% confidence interval for the mean of each normalized ERG parameter. Thus, parameters falling below this range were considered to be significantly affected by treatment.

When the sensitivity of different ERG components compared with the same IOP treatment (i.e., 50 mm Hg × 42 minutes; Fig. 2), analysis-of-variance (ANOVA; Prism, ver 4.00; GraphPad Software Inc., San Diego, CA) was applied to test the null hypothesis that there is no different effect of IOP across time for individual ERG components. A repeated-measures (RM), two-way ANOVA (ERG components versus time) was used to compare the effect of IOP on different ERG components. An adjusted α of 0.01 was used to limit any type-2 error that may occur with repeated measures. A Student’s t test (unequal variance, two-tailed) was performed to compare the functional deficit at the maximum effect of different IOP treatment (50 mm Hg × 42 minutes vs. 70 mm Hg × 30 minutes; see Fig. 3).

To compare the rate of nSTR recovery between various IOP treatments (Figs. 3E, 5), the 95% confidence interval was established for t_{0.5} using a nonparametric bootstrap. This approach does not assume normality and returns confidence limits appropriate for small samples, as previously described. In brief, the normalized amplitude versus time post-IOP data (for each treatment condition) were resampled with replacement to derive a bootstrap data set. This new bootstrap sample was optimized to give a new estimate of the logistic parameters. By repeating this process (×1000) a nonparametric distribution of the logistic parameters was returned, from which the 2.5 and 97.5 percentiles (95% confidence limit, CL) could be established. The 95% CL allows comparison to be made between IOP treatments, with an effective nonparametric α of 0.05.

**RESULTS**

**ERG Results after IOP Elevation**

To consider the sensitivity of the outer and inner retina to IOP insult, we contrasted the effect of IOP elevation on bright (1.0 log cd · s/m², Fig. 1A) and dim (−4.95 log cd · s/m², Fig. 1B) flashes, respectively. Baseline ERG responses to bright flashes showed the characteristic a-wave negativity, followed by a dominant b-wave. The STR collected with dim flashes showed a positive peak at ~110 ms followed by a negative trough at ~220 ms, consistent with previous studies.

Overlaid in each panel are waveforms from representative animals who had undergone IOP elevation to 50 (thin traces) and 70 mm Hg (thick traces) for 42 and 30 minutes, respectively. In this way, the same integral of insult could be compared (2100 mm Hg × minutes). It is clear from the data in Figure 1 that IOP elevation affected some ERG waveforms more than others. More specifically, IOP elevation to 50 mm Hg had little effect on the bright-flash responses (Fig. 1A, thin traces), but altered the STR (Fig. 1B, thin traces). At the time of maximum ERG deficit (i.e., at 42 minutes post-IOP onset) the nSTR was reduced, and the implicit time of the pSTR was delayed.

IOP elevation to 70 mm Hg resulted in a more severe functional deficit, compared with 50 mm Hg, as shown in Figure 1 (thick versus thin traces, respectively). During the 70 mm Hg insult, the STR was abolished and there was also a

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**Figure 1.** Representative bright flash (A, 1.0 log cd · s/m²) and STR waveforms (B, −4.95 log cd · s/m²) before, during (maximal injury), and after IOP elevation to 50 mm Hg for 42 minutes (thin traces) and 70 mm Hg for 30 minutes (thick traces). Vertical reference lines: fixed criterion times used to quantify amplitude change; horizontal reference lines: baseline.
severe b-wave reduction. In addition, the implicit time of the b-wave was delayed during the insult (Fig. 1A, thick trace). Thus, the higher peak IOP resulted in a more generalized functional deficit.

Although IOP elevation resulted in functional deficits, these changes were not permanent and showed rapid recovery after IOP reduction. The rate of recovery was faster with 50 mm Hg than with 70 mm Hg, which was particularly evident for the STR (Fig. 1B). To consider the rate of recovery more precisely, we normalized the amplitude measured at fixed criterion times after flash onset (Fig. 1, vertical lines) to baseline level.

Figure 2 shows group (mean ± SEM) relative amplitude changes (treatment/baseline, %) over the time course of IOP elevation to 50 mm Hg for 42 minutes. The horizontal axis indicates the time from IOP restoration. It is evident in Figure 2A that different ERG components showed different rates of loss and recovery. During the insult, greater change was observed in the nSTR (reduced to 20.3% of baseline, P < 0.001). The P3 shows a smaller decline to 93.8% ± 6.6%, which is significantly different from the nSTR (RM ANOVA; interaction F1,5 = 4.83, P < 0.001). On IOP restoration, those components that showed a greater deficit also took longer to recover. In particular, the recovery of nSTR amplitude was significantly slower than both the P2 (RM ANOVA; interaction F1,5 = 12.29, P < 0.0001) and P3 (RM ANOVA; interaction F1,5 = 14.77, P < 0.0001) recoveries. The recovery of P2 and P3, however, are not significantly different (RM ANOVA; F1 = 0.003, P = 0.956).

The logic behind using the nSTR as an indicator of inner retinal function is shown in Figure 2B. During the insult, the pSTR (unfilled down triangles) shows a small increase before a slight reduction to 92.5% ± 32.5% at its maximum deficit. As a result, the effect of IOP on the overall STR (peak-to-trough, 45.7% ± 11.4%, RM ANOVA, F1 = 2.89, P = 0.120) is smaller than that of the nSTR (20.3% ± 6.5%, RM ANOVA, F1 = 7.31, P = 0.022). The paradoxical rise of the pSTR during IOP elevation can be attributed to the loss of the nSTR, showing that the pSTR is an unreliable indicator of the effect that IOP has on the retinal function. The nSTR shows greater sensitivity to IOP insult, less variability, and thus will be used to study the IOP-induced deficits.

**Dependency of ERG Recovery on IOP Peak**

Figure 3 shows a comparison of the effect of IOP insults of equivalent integral. The functional change after IOP elevation to 50 mm Hg for 42 minutes is compared with elevation to 70 mm Hg for 30 minutes. Sham control data are also shown for the entire time course of the experiment. The shaded area indicates the 99% confidence interval of mean baseline ERG parameters. Generally, all functional parameters for the sham control group did not deteriorate with time.

In the experimental group, neither insult produced a permanent deficit. All component amplitudes (P3, P2, and nSTR) exhibited a greater loss in the 70 mm Hg than in the 50 mm Hg condition. More specifically, the P3 amplitude (Fig. 3A) was reduced to 74.6% ± 6.9% during a 70 mm Hg insult, but was barely affected during a 50 mm Hg spike (93.8% ± 6.6%, t0 = 2.01, P = 0.075). P3 sensitivity remained unchanged for both IOP insults (Fig. 3B). At 70 mm Hg, the P2 amplitude (Fig. 3C) was almost completely abolished (3.5% ± 4.7%, whereas at 50 mm Hg it was only reduced to 66.9% ± 11.0% (t0 = 4.59, P = 0.001). IOP elevation also delayed the P2 implicit time (Fig. 3D) to an average of 154.3% ± 8.5% of the baseline at 70 mm Hg (treatment/baseline, 131.9 ± 15.0 ms/84.7 ± 5.8 ms), whereas it was only slightly delayed to 114.5% ± 4.8% at 50 mm Hg (treatment/baseline, 93.3 ± 4.0 ms/83.8 ± 1.5 ms, t0 = 3.85, P = 0.004).

Figure 3E shows that not only did IOP elevation to 70 mm Hg induce a greater reduction in nSTR amplitude, but it also gave a slower recovery after IOP restoration, compared with 50 mm Hg. At the maximum effect of 70 mm Hg, the nSTR was completely abolished (~2.5% ± 0.5%), whereas at 50 mm Hg, its amplitude was reduced to 20.3% ± 6.5% (P = 0.017, t-test). The rate of recovery quantified using a logistic function (Fig. 3E, dashed and solid curves, equation 2), revealed a slower recovery for the 70 mm Hg nSTR, as indicated by the prolonged 50% recovery time (t0.5, dashed drop lines), compared with 50 mm Hg nSTR (solid drop line). The 95% confidence interval for t0.5 (Table 1) showed that recovery from an insult of 50 mm Hg (t0.5 = 21.7 minutes [95% CI, 17.0–26.6]) was significantly faster than recovery from 70 mm Hg (t0.5 = 33.1 minute [95% CI, 30.9–37.9]). Overall, both the amount of injury (i.e., the percentage of functional deficit) and the rate of recovery demonstrate that for an equivalent IOP integral (peak × duration), the higher pressure induced greater functional damage. However, the duration of elevated IOP is also known to have an important role in producing functional deficit.

**Quantifying the Effect of Duration of Exposure**

Figure 4 shows representative individual ERG waveforms for injuries from the same peak pressure (70 mm Hg) but different...
durations: 15 (Fig. 4A), 30 (Fig. 4B), and 60 minutes (Fig. 4C). For simplicity, only STR waveforms are shown, as these are the most sensitive to raised IOP. It should be noted that Figure 3B (30 minutes) is a subset of the data shown earlier in Figure 1. All three columns indicate complete suppression of the STR during the IOP insult, with gradual recovery after insult. Note that the recovery waveforms in Figure 4A (15 minute insult) are recorded 3 minutes earlier than those in the other conditions, as ERGs are recorded every 6 minutes from the onset of injury. Nevertheless, despite this earlier timing, they were still larger than those shown in Figures 3B and 3C at all times, consistent with a faster recovery. Likewise, it is evident that the recovery from the 30 minute injury (Fig. 4B) was faster than that from the 60 minute injury (Fig. 4C). This finding is most apparent by the absence of the nSTR at all time points for the 60 minute insult (Fig. 4C).

The normalized nSTR amplitudes in Figure 5 show that functional recovery is slower, given longer durations for a common peak pressure (70 mm Hg). The best-fit logistic functions (dashed curves, thin and thick solid curves) and bootstrapped confidence intervals given in Table 1 confirm that $t_{0.5}$ is significantly prolonged ($P < 0.05$, bootstrap) with longer duration. The effect of duration is further considered in Figure 6, by plotting the 50% recovery times as a function of IOP spike integral. The filled circles indicate $t_{0.5}$ for individual animals, whereas the filled squares and error bars represent the best fit and bootstrap confidence limits, respectively. Figure 6 shows that there was a linear relationship between $t_{0.5}$ and IOP at a pressure of 70 mm Hg. A linear fit passing through 0, shows a strong correlation between individual $t_{0.5}$ and IOP duration ($r^2 = 0.80$, $P < 0.0001$). Also plotted in Figure 6 is the $t_{0.5}$ for an IOP spike of 50 mm Hg for 42 minutes. It is clear that the peak with 50 mm Hg, despite having a longer duration, does not lie along the same linear relationship as that with 70 mm Hg.

### Table 1. Rate of nSTR Recovery for Various IOP Insults

<table>
<thead>
<tr>
<th>IOP and Duration</th>
<th>$t_{0.5}$</th>
<th>2.5% CI</th>
<th>97.5% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mmHg × 42 min (n = 6)</td>
<td>21.7</td>
<td>17.0</td>
<td>26.6</td>
</tr>
<tr>
<td>70 mmHg × 30 min (n = 5)</td>
<td>33.1</td>
<td>30.9</td>
<td>37.9</td>
</tr>
<tr>
<td>70 mmHg × 15 min (n = 6)</td>
<td>16.7</td>
<td>15.0</td>
<td>18.3</td>
</tr>
<tr>
<td>70 mmHg × 60 min (n = 6)</td>
<td>63.2</td>
<td>58.1</td>
<td>67.6</td>
</tr>
</tbody>
</table>

Data are in minutes. Rate of recovery, $t_{0.5}$, derived from best fit of the logistic function to group data for each IOP condition. Confidence limits derived by the nonparametric bootstrap method revealed that all IOP groups are significantly removed from each other ($P < 0.05$).
DISCUSSION

The Selectivity of IOP’s Effect on Retinal Function

Consistent with previous studies, the STR was most affected during IOP elevation, followed by the P2 and then the P3 responses. More important, we extended these observations to show that those components that showed greater deficit during IOP elevation also took longer to recover. Indeed, for a spike of 50 mm Hg (42 minutes) the P2 recovered to 90% of its baseline within a minute after restoration of normal IOP. In contrast, the nSTR took 45 minutes to achieve the same 90% recovery. This pattern of recovery is consistent with greater

FIGURE 4. Effect of IOP duration on the STR. Representative STR waveforms before, during (maximal effect), and after IOP elevation to 70 mm Hg for 15 (A), 30 (B), and 60 (C) minutes. Horizontal reference lines: waveform baselines.

FIGURE 5. Effect of different IOP durations on the nSTR amplitude. Group relative nSTR amplitude (treatment/baseline, mean ± SEM) over the time course of IOP elevation to 70 mm Hg for 15 (n = 6), 30 (n = 5), and 60 (n = 6) minutes. Recovery is described using a logistic function (dashed, thin, and thick curves for IOP duration of 15, 30, and 60 minutes, respectively). Horizontal reference lines: baseline and 50% recovery. Vertical lines: the functional recovery parameter, 50% recovery time (t0.5). Open boxes: durations of IOP elevation.

FIGURE 6. Relationship between the 50% recovery time for nSTR amplitude and the IOP integral for elevation to 70 and 50 mm Hg. Squares: t0.5 fit to the group data; error bars, 2.5% and 97.5% bootstrap confidence limit of the data. Individual logistic fit parameters are also shown and are described with a simple linear regression (solid line: y = 0.016x, r² = 0.80), with intercept set to 0.
insult within the inner retina, based on our current understanding of the cellular origins of ERG components. To our knowledge, this is the first study to investigate the recovery of retinal function, especially the STR, immediately after acute IOP application.

We used the STR as a measure of inner retinal function and the P2 and P3 to reflect ON-bipolar cell and photoreceptor activity, respectively. Although, the cellular origins of the P2 and P3 are well established, the STR has received less attention. Nevertheless, there is strong evidence that STR generation is dependent on intact ganglion cell function. Optic nerve transection severely affects both pSTR and nSTR in rats, without affecting the a- or b-wave. In addition, the STR has been shown to be selectively affected in a nonhuman primate model of glaucoma. Similarly, studies of both acute and chronic IOP elevation have shown that the STR is the component most sensitive to IOP insult. Taken together, our findings show that ganglion cells suffer to a greater degree and undergo a much slower recovery from IOP injury than do the more distal retinal elements, the ON-bipolar cells and photoreceptors.

That the nSTR was more affected by acute IOP is consistent with a previous study in rats. The pSTR, known to reflect ganglion cell activity and sensitive to chronic IOP elevation, was minimally reduced in this study. The absence of a pSTR effect may reflect two possibilities. First, the pSTR is more variable due to its smaller amplitude, which leads to a higher coefficient of variation (pSTR vs. nSTR, 61% vs. 11%). Second, the greater loss of an opposing negative component (nSTR) may mask any pSTR loss.

The mechanism of increased sensitivity of the inner retina may arise due to a vascular compromise and/or mechanical compression of retinal neurons. These factors may be occurring simultaneously, with the optic nerve head (ONH) being the primary site of injury. Greene first suggested that IOP-related stress (force/cross-sectional area) would be magnified at the ONH, due to the stress gradient present at any aperture in a pressurized spherical shell. Therefore, ganglion cell axons and small blood vessels within the lamina are particularly vulnerable to the laminar distortion caused by IOP insult. Given that the inner retinal blood supply may also be compromised by ONH compression, RGCs may receive insult both at their axons and cell bodies located in the retina. During acute IOP elevation in nonhuman primates, Burgoyne et al. detected reversible posterior deformation of the optic disc surface with IOP elevation from 10 to 45 mm Hg for 47 minutes, a magnitude of insult similar to that used in our study (from 13 to 50 mm Hg for 42 minutes). It is worth noting that Morrison et al. have shown that the rat ONH possesses an identifiable laminar cribrosa, with structural proteins that are nearly identical with those of primates. The rate of recovery of laminar cribrosa bowing may underlie our functional recovery. However, this issue requires further investigation.

La Cour et al. showed in porcine retinas, that when IOP is restored from 88 mm Hg to normal levels, ONH oxygen fully recovers within 2 minutes. Such a rapid recovery is inconsistent with the prolonged recovery of the STR. Despite restoration of normal oxygenation, cellular processes involved in generating the STR take a great deal longer to recover. While a purely vascular thesis may account for the rapid b-wave recovery (Fig. 3C), it cannot fully explain the slow recovery of the RGC-derived nSTR (Fig. 3E). The additional mechanical injury of axon at the ONH may contribute to the prolonged RGC dysfunction.

Moreover, the inner retinal blood supply, which enters through the ONH, is more sensitive to IOP insult than is the choroidal circulation. Several studies have demonstrated that the ONH becomes hypoxic at IOPs above 40 mm Hg whereas the choroid is able to withstand higher pressures. The a- and b-wave arising from cellular components closer to the choriocapillaris will be less hypoxic under IOP stress. The susceptibility of optic nerve oxygenation to IOP insult can also contribute to the sensitivity of the STR to modest IOPs.

IOP Spikes of Equivalent Integral

In recent studies of experimental glaucoma, there has been the growing recognition that both peak IOP and its duration are important determinants of injury (IOP integral, pressure × duration). Fortune et al. reported that mean IOP, showed a closer correlation with optic nerve injury than did peak IOP in rats with chronic IOP elevation. In contrast, Chauhan et al. suggest that the peak IOP is a better predictor of optic nerve cupping and ERG loss. However, in studies of chronic IOP elevation, it has been difficult to compare the effect of IOP peak pressure, duration, and integral, given that the infrequent sampling of IOP will yield substantial uncertainties in these values. By considering recovery from short duration IOP spikes, this study shows that peak pressures of 50 and 70 mm Hg having a common IOP integral (2100 mm Hg × minutes), produce different levels of functional injury. Hence, for spikes having equivalent integrals the peak is the critical determinant in setting the degree of functional damage.

However, we cannot dismiss the possibility that a proportional relationship exists for IOPs lower than 50 mm Hg. The IOPs used in this study of 50 and 70 mm Hg may represent critical pressures in terms of ocular perfusion pressure. An IOP of 50 mm Hg has commonly been cited to impair optic nerve oxygenation selectively, without affecting choroidal supply. In contrast, an IOP of 70 mm Hg may induce a more generalized ocular hypoxia. Not surprisingly, a number of studies have shown that outer retinal function becomes impaired when perfusion pressures fall to 30 mm Hg or less, which generally represents an IOP elevation of 70 mm Hg or more.

Thus, 50 and 70 mm Hg are likely to represent different levels of optic nerve and retinal hypoxic insults, making it unlikely that a proportional relationship exists between IOP peak and duration for these pressures.

IOP Spikes of Different Durations with the Same Peak Pressure

In this study, we found a linear relationship between the recovery (t1/2) of the nSTR and IOP duration for a given peak pressure (70 mm Hg), with full recovery generally taking twice as long as the duration of injury. A linear relationship between recovery and insult duration was only found for a fixed pressure, as indicated by the divergence of the 50 mm Hg injury from the 70 mm Hg data. It may be reasonable to predict that a linear relationship also exists for the 50 mm Hg insult but with a shallower slope than the 70 mm Hg data. However, with even longer IOP durations (>60 minutes), the nSTR will take longer to recover, and at some time irreversible damage will ensue. These critical durations for various IOP peak pressures require further investigation. In addition, the linear relationship at lower pressure may provide a potential method for quantifying the clinical concept of “target pressure,” which is that IOP that returns a 0 slope for different durations.

It is worth noting that a pressure of 50 mm Hg represents an increase of approximately 20 mm Hg from baseline pressure for light-adapted rats. Although an elevation of 20 mm Hg is rare in open-angle glaucoma, recent studies suggest that diurnal IOP spikes can occur and may be involved in the patho-
genesis of glaucoma.\textsuperscript{3–7} In addition, diurnal peaks in IOP, together with troughs in blood pressure,\textsuperscript{6,57} may lead to significant reductions in optic nerve perfusion pressure for short periods. Our study suggests that as the peak pressure and duration increases, the time required for recovery also increases. Should such insults occur on a regular nightly basis, ganglion cells may not have enough time to recover fully between troughs in perfusion pressure.

In summary, in this study, the nSTR was more susceptible to acute IOP elevation than the ON-bipolar cell P2 and the photoreceptorial P3. More important, those components with the greater loss displayed slower recovery. For IOP spikes of equivalent integral, the peak IOP is the critical determinant of functional loss and the rate of recovery. For a given IOP peak, the duration plays the key role, so that longer duration prolongs the time needed for recovery. More specifically, for a given IOP, there is an inverse square relationship between the rate of nSTR recovery and IOP duration.

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References