Dorzolamide Effect on Ocular Blood Flow

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PURPOSE. To evaluate the effect of dorzolamide on ocular blood flow in normal and glaucomatous eyes.

METHODS. Twenty-six eyes with documented open-angle glaucoma of 26 patients and 13 normal control eyes of 8 age-matched subjects were included in this study. All eyes underwent color Doppler imaging for measuring peak-systolic velocity, end-diastolic velocity, and resistance index in the ophthalmic and central retinal arteries and the maximal and minimal velocities in the central retinal vein. Eyes were grouped in control and initial and advanced glaucoma categories. Measurements were made in all groups before and after application of topical dorzolamide. Intragroup comparisons between baseline and dorzolamide conditions were made using paired Student's t-test. Intergroup comparisons under baseline conditions between normal and glaucomatous eyes were made by using the one-way ANOVA test. Statistical significance was set at $P < 0.05$.

RESULTS. The peak-systolic velocity of the central retinal artery in glaucomatous eyes and the end-diastolic velocity of the ophthalmic and central retinal arteries in all groups were significantly higher after application of dorzolamide. The minimal velocity of the central retinal vein showed significantly higher values after dorzolamide, whereas the maximal velocity remained unchanged. The peak-systolic velocity of the ophthalmic artery in all groups and the peak-systolic velocity of the central retinal artery in normal eyes also remained unchanged. The resistance index...
was significantly lower in the ophthalmic and central retinal arteries in all groups after dorzolamide. The intraocular pressure was significantly reduced in all groups after dorzolamide. Under baseline conditions normal control eyes and glaucomatous eyes showed differences in various measurements. Peak-systolic velocity was significantly lower in glaucomatous eyes than in normal control eyes with the exception of the ophthalmic artery in the initial glaucoma group. End-diastolic velocity was lower in glaucomatous eyes than in control eyes in both arteries. Maximal and minimal velocities of the central retinal vein were lower in glaucomatous eyes than in normal control eyes. Resistance index was higher in glaucomatous eyes than in normal control eyes in the ophthalmic artery but not in the central retinal artery.

**Conclusions.** Most hemodynamic parameters of intraocular and perilocular vessels improve after application of topical dorzolamide in both normal control and glaucomatous eyes. Dorzolamide should be regarded as a useful drug for treatment of glaucoma not only because it reduces intraocular pressure but also because it improves the ocular blood supply. *(Invest Ophthalmol Vis Sci. 1999;40:1270-1275)*

Although it is widely accepted that elevated intraocular pressure (IOP) is an important factor in glaucoma, local and systemic vascular alterations have been implicated in the development of glaucomatous damage. It has been observed, for instance, that migraine, vasospasm, and low blood pressure are present in some patients with glaucoma. Recently, a population-based study demonstrated that the risk for glaucoma is higher when diastolic perfusion pressures are below 40 mm Hg. Measurements of systemic blood pressure through the periocular vessels have been described in patients with normal tension glaucoma. Dorzolamide should be considered the most relevant, and interest in the blood flow supplies in both normal and glaucomatous eyes.

**Methods**

We studied 13 eyes of 13 patients with initial primary open-angle glaucoma, 13 eyes of 13 patients with advanced primary open-angle glaucoma, and 13 control eyes of 8 healthy subjects. Suitable patients were collected from our clinic. The mean age of the control group was 66.5 ± 9.1 years (mean ± SD), ranging from 52 to 79 years. The mean age of the patients with initial glaucoma was 64.8 ± 11.3 years, ranging from 49 to 79 years. The mean age of the patients with advanced glaucoma was 64.3 ± 8.7 years, ranging from 49 to 79 years. None of the subjects was using systemic β-blockers or calcium channel blockers.

Visual field examinations were performed in all subjects with program 24/2 on the Humphrey visual field analyzer (Humphrey Instruments, San Leandro, CA). Glaucomatous field defects were defined as at least the presence of a cluster of three abnormal points in the same hemifield with a pattern deviation less than 2% and with at least one point less than 1% or at least two adjacent points with a pattern deviation less than 1%. The visual field defect of the affected eye was qualitatively classified into two stages defined as initial glaucoma and advanced glaucoma. Subjects with initial glaucoma were characterized by the presence of relative or absolute paracentral scotoma or relative arcuate scotoma in one hemifield. Subjects with advanced glaucoma were characterized by the presence of more severe field defects such as absolute arcuate scotoma in one hemifield, paracentral scotomas in both hemifields, or central or nasal island of vision.

Eyes were divided into three groups. Group A included 13 normal control eyes from 8 healthy subjects with no ocular abnormality, normal optic discs, and IOP below 20 mm Hg in both eyes. In those subjects who had both eyes included in this study, Doppler examinations were made at least 15 days apart on each eye. The eyes of this group were randomly selected for testing. Group B included 13 eyes with initial glaucoma. Group C included 13 eyes with advanced glaucoma. All eyes from groups B and C had primary open-angle glaucoma and were undergoing treatment with β-blockers (timolol) and dorzolamide. Timolol was maintained throughout the study, whereas dorzolamide was discontinued and a washout period of 15 days allowed. Patients with previous filtering surgery, diabetes mellitus, or other systemic or cardiovascular diseases were excluded. Informed consent was obtained from all subjects at the beginning of the study, and the tenets of the Declaration of Helsinki were followed.

All color Doppler imaging examinations (model SSA-340A; Toshiba Medical Systems, Tustin, CA) were performed by the same sonographer who was unaware of the status of each eye. A 6-MHz vector array transducer was applied to the closed eyelid using a coupling gel, taking care to avoid any pressure on the eye. During the examination, subjects were in supine position, with the head tilted forward at about a 30° angle. The ophthalmic artery (OA), the central retinal artery (CRA), and the central retinal vein (CRV) were examined following procedures indicated elsewhere. Measurements of OA flow were performed approximately 10 mm to 15 mm posterior to the globe, where the Doppler signals are stronger. The CRA and CRV were measured 2 mm to 3 mm behind the surface of the optic disc. During the approximately 30-minute examination, systolic and diastolic blood pressure and heart rate were measured by sphygmanometry and by palpation of radial pulse, respectively, every 10
minutes. These parameters remained constant in each individual throughout all the examinations.

Peak-systolic velocity (PSV), end-diastolic velocity (EDV), and resistance index (RI) were used to describe the highest and lowest recorded pressure (measured with an applanation tonometer) was determined in all eyes. Because the time-velocity waveform recorded by the color Doppler system consists of multiple velocities, most investigators use PSV and EDV to describe blood flow velocity in arteries. PSV represents the maximal value of blood velocity at the beginning of the systolic phase of the cardiac cycle. Blood flow in the CRV produces a smoother Doppler waveforms than in the OA and CRA, and therefore the terms maximal velocity and minimal velocity are used to describe the highest and lowest recorded velocities during the cardiac cycle.

In group A, two measurements of these hemodynamic parameters were made: first under no treatment (baseline measurement) and then 2 hours after two drops of dorzolamide (2%) were instilled into the lower conjunctival sac without punctual occlusion (dorzolamide measurement). Intraocular pressure (measured with an application tonometer) was determined before each Doppler examination to obtain IOPs under baseline and dorzolamide conditions. In groups B and C, the same measurements and procedures were performed after the 15-day dorzolamide washout period was completed.

Intragroup mean values and SDs were calculated for PSV, EDV, and RI in the OA and CRA and for MXV and MIV in the CRV for each of the groups A, B, and C. The hemodynamic effects of dorzolamide were evaluated by intragroup comparisons made between the values obtained under baseline and dorzolamide conditions in groups A, B, and C. For this purpose, a paired Student’s t test was used. \( P \leq 0.05 \) was considered significant. To establish whether there were differences between normal control eyes and glaucomatous eyes, comparisons were made with the values obtained under baseline conditions between groups A and B and between groups A and C. Differences between initial and advanced glaucomatous eyes were assessed by comparing the values of groups B and C. The one-way ANOVA test was used for these statistical procedures. \( P < 0.05 \) was considered significant.

RESULTS

Mean values and SDs of blood flow velocities and RI of the OA, CRA, and CRV together with the IOP are summarized in Table 1. The hemodynamic values of these vessels measured under baseline and dorzolamide conditions are graphically represented in Figure 1.

Neither the ophthalmic PSV nor the MXV of the CRV showed statistically significant changes \( (P > 0.05) \) after dorzolamide application in any of the groups. The PSV of the CRA did not change in control eyes (group A) but showed a statistically significant increase after dorzolamide application \( (P < 0.05) \), from 10.5 ± 1.2 to 12.5 ± 1.6 cm/s in group B and from 10.2 ± 1.0 to 11.5 ± 2.0 cm/s in group C. The EDV of the OA and CRA and the MIV of the CRV showed statistically significant higher values \( (P < 0.05) \) under dorzolamide than under baseline conditions in all groups. The RI of both arteries was statistically significantly lower in all three groups under dorzolamide than under baseline conditions \( (P < 0.05) \).

Statistical comparisons between the hemodynamic values of control (group A) and glaucomatous eyes (groups B and C) measured under baseline conditions showed significant differences in many parameters. The PSV of the OA and the EDV of the OA and CRA together with the MXV and MIV of the CRV were statistically significantly lower \( (P < 0.05) \) in glaucomatous than in control eyes. The PSV of the OA did not show statistically significant differences between control eyes (group A) and initial glaucomatous eyes (group B) under baseline conditions. On the contrary, advanced glaucoma eyes showed lower PSV in the OA than in control eyes \( (30.3 ± 2.0 \text{ and } 34.1 ± 3.2 \text{ cm/sec, respectively}) \). No significant differences were observed in the RI of the CRA between control and glaucomatous eyes. The RI of the OA was higher in glaucomatous than in control eyes. Under baseline conditions we found no statistically significant differences in hemodynamic parameters between initial and advanced glaucomatous eyes.

DISCUSSION

Color Doppler ultrasound imaging allows simultaneous two-dimensional imaging of ocular and periocular structures and the assessment of blood flow velocities. Reproducible results can be obtained in the OA, central retinal vessels, and, to a lesser degree, in the short posterior ciliary arteries. This is so because posterior ciliary arteries are tortuous, multiple and varied in number, which makes difficult to accurately angle the ultrasound beam. Although color Doppler is widely used to assess hemodynamics of ocular and periocular vessels, attenuation of ultrasound in tissue, volume sample, low flow velocities, and the angle of insonation are sources of error, mostly for measurements made on small-caliber vessels. To minimize the inaccuracies they may have caused in our measurements, we placed the ultrasound beam at those angles to the vessel flow for which the signal/noise ratio was optimal. Moreover, to ensure reliable measurements, we waited until all the time-velocity waveforms of the same vessel appearing on the screen were identical. Thus, even though we used one blood flow measurement for statistical purposes, we took special care to meet these requirements for each measurement. Indeed, in those cases in which we measured several waveforms recorded from the same vessel the variability we observed was minimal.

It must be pointed out that the color Doppler ultrasound technique does not provide information about flow in terms of volume per time unit but rather about flow velocity. However, if the blood perfusion pressure and blood viscosity remain constant, an increase in flow velocity is invariably associated
TABLE 1. Hemodynamic Parameters Measured in This Study

<table>
<thead>
<tr>
<th>Measurement Group</th>
<th></th>
<th>Baseline</th>
<th>Dorzolamide</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PSV OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>34.1 ± 3.2</td>
<td>34.8 ± 4.1</td>
<td>0.144 (NS)</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.442 (NS)</td>
<td>32.1 ± 4.4</td>
<td>33.8 ± 4.3</td>
<td>0.117 (NS)</td>
</tr>
<tr>
<td>C, advanced glaucoma</td>
<td>0.029</td>
<td>30.3 ± 2.0</td>
<td>31.0 ± 1.8</td>
<td>0.250 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSV CRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>12.1 ± 1.3</td>
<td>12.9 ± 1.5</td>
<td>0.112 (NS)</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.005</td>
<td>10.5 ± 1.2</td>
<td>12.5 ± 1.6</td>
<td>0.000</td>
</tr>
<tr>
<td>C, advanced glaucoma</td>
<td>0.001</td>
<td>10.2 ± 1.0</td>
<td>11.5 ± 2.0</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MXV CRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>5.5 ± 0.8</td>
<td>5.9 ± 0.9</td>
<td>0.209 (NS)</td>
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<tr>
<td>B, initial glaucoma</td>
<td>0.035</td>
<td>4.7 ± 0.8</td>
<td>5.5 ± 0.7</td>
<td>0.200 (NS)</td>
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<tr>
<td>C, advanced glaucoma</td>
<td>0.005</td>
<td>4.4 ± 0.6</td>
<td>4.9 ± 0.7</td>
<td>0.165 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDV OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>9.2 ± 2.5</td>
<td>11.5 ± 2.4</td>
<td>0.000</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.018</td>
<td>6.8 ± 2.3</td>
<td>11.4 ± 3.4</td>
<td>0.000</td>
</tr>
<tr>
<td>C, advanced glaucoma</td>
<td>0.005</td>
<td>6.2 ± 1.2</td>
<td>8.8 ± 1.8</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDV CRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>3.7 ± 0.9</td>
<td>4.7 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.012</td>
<td>2.7 ± 0.8</td>
<td>4.0 ± 0.7</td>
<td>0.000</td>
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<tr>
<td>C, advanced glaucoma</td>
<td>0.003</td>
<td>2.5 ± 0.6</td>
<td>3.7 ± 0.6</td>
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<tr>
<td></td>
<td></td>
<td>MIV CRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>2.7 ± 0.7</td>
<td>3.5 ± 0.8</td>
<td>0.009</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.010</td>
<td>1.6 ± 0.7</td>
<td>2.8 ± 0.7</td>
<td>0.000</td>
</tr>
<tr>
<td>C, advanced glaucoma</td>
<td>0.000</td>
<td>1.5 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RI OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>72.9 ± 6.1</td>
<td>66.9 ± 5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.049</td>
<td>78.7 ± 6.8</td>
<td>67.2 ± 6.7</td>
<td>0.000</td>
</tr>
<tr>
<td>C, advanced glaucoma</td>
<td>0.021</td>
<td>79.5 ± 3.5</td>
<td>71.6 ± 4.6</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RI CRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>69.2 ± 7.4</td>
<td>63.5 ± 5.9</td>
<td>0.005</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.254 (NS)</td>
<td>74.5 ± 7.6</td>
<td>67.5 ± 7.8</td>
<td>0.005</td>
</tr>
<tr>
<td>C, advanced glaucoma</td>
<td>0.175 (NS)</td>
<td>75.0 ± 6.7</td>
<td>67.3 ± 5.9</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A, control</td>
<td></td>
<td>15.4 ± 4.9</td>
<td>14.6 ± 2.7</td>
<td>0.362 (NS)</td>
</tr>
<tr>
<td>B, initial glaucoma</td>
<td>0.010</td>
<td>24.2 ± 5.3</td>
<td>19.5 ± 3.6</td>
<td>0.000</td>
</tr>
<tr>
<td>C, advanced glaucoma</td>
<td>0.000</td>
<td>24.1 ± 4.1</td>
<td>19.6 ± 3.1</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Values of hemodynamic parameters (mean ± SD) under baseline and dorzolamide conditions are shown in the two central data columns. PSV, peak systolic velocity; MXV, maximal velocity; EDV, end-diastolic velocity; MIV, minimal velocity; RI, resistance index; IOP, intraocular pressure; NS, not statistically significant. Blood flow velocity is given in cm/sec.

* Values shown for the initial glaucoma group (B) result from the intergroup comparison with the control group (A). Values shown for the advanced glaucoma group (C) result from the intergroup comparison with the control group (A).

† P for baseline versus dorzolamide.

with an increase in flow in terms of volume per time unit. Indeed, there is a general agreement that blood flow velocity assessed by color Doppler ultrasonography correlates with volume blood flow, provided there is no evidence of vascular stenosis or changes in perfusion pressure.6

Open-angle glaucoma seems to be associated with a decreased mean flow velocity and an increased mean RI in the CRA and the short posterior ciliary arteries. Reduced EDV and increased RI in the OA, reduced MXV and MIV in the CRV, and reduced PSV in the CRA and short posterior ciliary arteries have been observed in eyes with primary open-angle glaucoma when compared with normal control eyes.6 These findings largely agree with the observations we made in the present study. Indeed, in our sample, glaucomatous eyes showed impaired blood flow velocities in the CRA and CRV together with an increased RI of the OA when compared with normal eyes. We found no evidence of hemodynamic systemic effects caused by instillation of dorzolamide.

We observed that the PSV in the OA did not change with dorzolamide either in control eyes or in glaucomatous eyes. On the contrary, the EDV of the OA shows higher values in all eyes after dorzolamide. The blood flow velocities in the OA vary with systemic blood pressure1 and probably with the posture of the subject.12 Because in our subjects systemic blood pressure was constant and because care was taken to reproduce the same postural conditions in all measurements, it is likely that the perfusion pressure in the OA was constant. Thus, the increase in EDV with constant PSV that we observed in this vessel is congruent with a vascular relaxing effect of dorzolamide. An additional factor to explain the EDV increase that we found in the OA could result from a relaxation of the periocular vasculature supplied by this vessel. This would also explain the finding that the RI of the OA significantly decreased after dorzolamide application.
the CRA increased after dorzolamide in both groups of glaucomatous eyes but not in normal control eyes. The EDV of this artery increased in all three groups. The MIV of the CRV remained without change in control and glaucomatous eyes, whereas the MIV of this vessel increased in all groups. These findings suggest a mixed interaction between vascular relaxation and the effect of the IOP on intracocular vasculature. Carbonic anhydrase inhibitor may have vasoactive effects by disturbing the CO₂ metabolism. Local vasodilatory effects of CO₂ on intracranial vasculature have been described. The increase in PSV of the CRA that we have observed after dorzolamide in glaucomatous eyes could also be influenced by the reduction of IOP induced by the drug. Indeed, we found a significant decrease in IOP only in glaucomatous eyes, precisely where the changes in PSV were observed. Studies made by using a suction cup showed that systolic, mid-diastolic, and end-diastolic peak velocities in the CRA progressively diminished and that the RI increased when the IOP increased. In contrast, hemodynamics of the OA seem to be independent of the IOP. This agrees with our observation that ophthalmic PSV is not altered by dorzolamide.

Because the observed increase of EDV in the CRA of all groups in our study seems to be an IOP-independent effect, it is likely that it could be caused by a CO₂-mediated, relaxing effect of dorzolamide on the wall of the artery. Indeed, the increase of EDV in the CRA was also observed in control eyes in which no significant changes in IOP were observed after dorzolamide. As a consequence of these changes the RI of the CRA improves, showing lower values.

The increase of the MIV in the CRV in all groups seems to be a direct effect of the increase in EDV of the CRA also observed in all groups. Similarly, the MXV in the CRA of control eyes seems to follow the absence of changes in PSV of the CRA in these eyes. It is not clear, however, why the MXV of the CRA of initial and advanced glaucomatous eyes does not significantly increase despite the increase of PSV in the CRA. This may be due to the failure in vascular autoregulation observed in glaucomatous eyes. Indeed, indirect studies of the optic nerve indicate that autoregulation in the optic disc vessels may be disturbed with changes in IOP.

Our finding that dorzolamide has hemodynamic effects on ocular and periocular vasculature dissents from the findings reported by Harris et al. in normal eyes. These investigators observed that dorzolamide has no apparent effect on the hemodynamics of these vessels. In agreement with their report, we found no changes in the PSV of the OA and CRA of normal eyes. However, in our study EDV was significantly increased and RI significantly reduced in these vessels of normal eyes.

In our study, initial and advanced glaucoma eyes seem not to differ in their hemodynamic response to dorzolamide. It is there-
fore not clear whether the vascular regulation might be equally impaired in these two situations. This observation suggests that the possible vascular dysfunction underlying the glaucomatous process is not tightly related to the stage of the disease.

Topical dorzolamide reduced the IOP in our patients with glaucoma (groups B and C). Our measurements showed that both, initial and advanced glaucomatous eyes, have lower IOPs (19.5 ± 3.6 and 19.6 ± 3.1 mm Hg, respectively) after dorzolamide application than under baseline conditions (24.2 ± 5.3 and 24.1 ± 4.1, respectively). Moreover, we have also observed that the IOP increased in groups B and C after the initial dorzolamide withdrawal. Our observation that dorzolamide reduces the IOP in glaucomatous eyes and that it shows an additive effect with β-blockers fully agrees with the observations reported in the literature. On the other hand, in our study this hypotensive effect was not observed in healthy eyes.

In summary, the main finding in the present study was that dorzolamide induces changes in ocular and periocular hemodynamics, improving blood perfusion of the eye. Improvement of blood flow, however, was not similar in all studied vessels. Hemodynamic changes in the OA were similar in normal and glaucomatous eyes. In this vessel the PSV seems not to be affected, whereas the EDV and the RI were improved. On the contrary, dorzolamide induced different hemodynamic changes in the CRA of normal and glaucomatous eyes. In this vessel, the PSV increased in glaucomatous eyes but not in normal eyes. The effect of the drug on the remaining hemodynamic parameters of the CRA and CRV was similar in normal and glaucomatous eyes. This differential effect of dorzolamide on the CRA of normal and glaucomatous eyes may be explained by the more prominent effect of the drug in lowering the IOP in the second group of eyes.

Acknowledgments

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References


Epitope Mapping of Anti-Rhodopsin Antibodies from Patients with Normal Pressure Glaucoma

Carmelo Romano,1 Zhengzhi Li,1 Anatol Arendt,2 Paul A. Hargrave,2 and Martin B. Wax1

PURPOSE. The presence of anti-rhodopsin antibodies in patients with normal pressure glaucoma (NPG) has been previously demonstrated with western blot analysis and enzyme-linked immunosorbent assay. To learn more about the characteristics, origin, and possible significance of these antibodies, the epitopic specificity of the anti-rhodopsin antibodies was examined in four NPG patients.

METHODS. Antibodies in patient sera were assayed by western blot analysis against purified bovine rhodopsin. Peptides derived from particular segments of the rhodopsin sequence were tested for activity in competing for rhodopsin-antibody binding.

RESULTS. Of a series of nine peptides that constitute most of the hydrophobic regions of rhodopsin, only one, consisting of the C-terminal 25 amino acids, prevented binding of the patient antibodies to rhodopsin. Higher resolution mapping using a set of dodecamers of overlapping sequences from the C-terminal region demonstrated that...