Lamina Cribrosa Thickness and Spatial Relationships between Intraocular Space and Cerebrospinal Fluid Space in Highly Myopic Eyes

Jost B. Jonas,1 Eduard Berenshtein,1 and Leonard Holbach2

PURPOSE. To evaluate the spatial relationships of the intraocular space, the cerebrospinal fluid space, and the lamina cribrosa in highly myopic eyes.

METHODS. The study included 36 human globes with an axial length of more than 26.5 mm that showed marked glaucomatous optic nerve damage (n = 29; highly myopic glaucomatous group) or in which the optic nerve was affected by neither glaucoma nor any other disease (n = 7; highly myopic normal group). Two non–highly myopic control groups included 53 globes enucleated because of malignant choroidal melanoma (n = 42; non–highly myopic normal group) or because of painful absolute secondary angle-closure glaucoma (n = 11; non–highly myopic glaucomatous group). Anterior–posterior histologic sections through the pupil and the optic disc were morphometrically evaluated.

RESULTS. In both highly myopic groups compared with both non–highly myopic groups and in the highly myopic glaucomatous group compared with the highly myopic normal group, the lamina cribrosa was significantly (P < 0.001) thinner. Correspondingly, the distance between the intraocular space and the cerebrospinal fluid space was significantly (P < 0.05) shorter in the highly myopic normal group than in the non–highly myopic normal group and in the highly myopic glaucomatous group than in the highly myopic normal group.

CONCLUSIONS. In highly myopic eyes, the lamina cribrosa is significantly thinner than in non–highly myopic eyes, which decreases the distance between the intraocular space and the cerebrospinal fluid space and steepens the translaminar pressure gradient at a given intraocular pressure, which may explain the increased susceptibility to glaucoma in highly myopic eyes. As in non–highly myopic eyes, thinning of the lamina cribrosa gets more pronounced in highly myopic eyes if glaucoma is also present. (Invest Ophthalmol Vis Sci. 2004;45: 2660–2665) DOI:10.1167/iovs.03-1363

Highly myopic eyes show ophthalmoscopic and histologic characteristics of the optic nerve head that differentiate them from non–highly myopic eyes, such as a scleral crescent in the peripapillary area and a secondary, or acquired, macrodisc, to mention only a few.1–5 In addition, highly myopic eyes compared with non–highly myopic eyes have been presumed to have a higher susceptibility to glaucomatous optic nerve damage at a given intraocular pressure.1–15 It was the purpose of the present study to search for histomorphometric findings that may give pathogenic hints to explain the presumably increased susceptibility to glaucoma in highly myopic eyes.

METHODS

The study included 36 human globes with an axial length of more than 26.5 mm that showed marked glaucomatous optic nerve damage (n = 29; highly myopic glaucomatous group) or in which the optic nerve was neither affected by glaucoma nor any other disease on gross inspection and microscopic examination (n = 7; highly myopic normal group). For determination of the axial length, a linear shrinkage factor of 1.5% was taken into account. Two non–highly myopic control groups included 53 globes divided into a non–highly myopic normal group of 42 (79.2%) eyes of 42 patients who had undergone ocular enucleation because of malignant choroidal melanoma and a non–highly myopic glaucomatous group of 11 (20.8%) eyes of 11 patients who had undergone ocular enucleation because of painful absolute secondary angle-closure glaucoma. The two non–highly myopic groups had already been investigated separately in a previous study.13 The study’s protocol adhered to the provisions of the Declaration of Helsinki.

In the highly myopic and non–highly myopic glaucomatous groups, vision was completely or almost completely lost. Enucleation became necessary, usually because of intractable pain that could not be treated by medication. In the highly myopic normal and the non–highly myopic normal groups, intraocular pressure was within the normal range without antiglaucoma medication. Migrating cells of the malignant choroidal melanomas did not infiltrate the trabecular meshwork directly or indirectly. The parapapillary region was free of tumor. Visual acuity depended on the degree of cataract, vitreous opacity, and foveal involvement by the tumor. At the time when the eyes were enucleated, no other treatment modalities, such as enucleation of the tumor or radiologic brachytherapy, were available, or such treatments were thought not to be suitable for tumor removal because of its location and size.

Immediately after enucleation, the globes were fixed in a solution of 4% formaldehyde and 1% glutaraldehyde. They remained in the fixation agent for about 1 week before they were further processed for histologic sectioning. The preparation of the globes did not vary between the glaucomatous and nonglaucomatous eyes. The globes were prepared in a routine manner for light microscopy. An anterior–posterior section was cut from the fixed globes, going through the pupil and the optic nerve. These segments were dehydrated in alcohol, embedded in paraffin, and sectioned for light microscopy. Most of the eyes were stained by the periodic acid–Schiff (PAS) method, and the remaining eyes were stained with hematoxylin-eosin. In all eyes, one section running through the central part of the optic disc was selected for further evaluation. The histologic slides were digitized and morphometrically analyzed. The resolution at which the measurements were performed was 1030 × 1300 pixels per image at ×25 magnification (Fig. 1). We measured the following:

1. The thickness of the lamina cribrosa in five locations: in the center of the optic disc, at the optic disc border, and in the...
intermediary positions between the center and the border of the optic disc.
2. The length of the anterior surface and posterior surface of the lamina cribrosa.
3. The shortest distance between the intraocular space (inner surface of the lamina cribrosa) and the cerebrospinal fluid space.

To evaluate the reproducibility of the technique, 10 randomly selected histologic optic disc sections were evaluated 10 times. The reproducibility was determined as the coefficient of variation defined as the ratio of the mean of the standard deviations of the reevaluations divided by the mean of the means. Most of the parameters of the eyes of the two non–highly myopic groups, had been measured in a previous study. The data are presented in the present investigation to compare the measurements of the two highly myopic groups with those of the two non–highly myopic groups.

For statistical analysis, means and standard deviations, as well as medians and ranges, are presented. For the comparison of the study groups, statistical tests for unpaired samples were applied. The level of significance was 0.05 (two-sided) in all statistical tests. The statistical analysis was performed on computer (SPSSWIN, ver. 11.5; SPSS Science, Chicago, IL).

**Figure 1.** Histologic sections through the optic disc of highly myopic eyes. (B, D, F) Anterior and posterior borders of the lamina cribrosa. (B, arrows) The five measurement points of the thickness of the lamina cribrosa. The length of the anterior surface and posterior surface of the lamina cribrosa is identical with the anterior and posterior border line of the lamina cribrosa. The shortest distance between the intraocular space (inner surface of the lamina cribrosa) and the cerebrospinal fluid space is in this example at the optic disc border (arrow).
Table 1. Histomorphometric Measurements of the Lamina Cribrosa

<table>
<thead>
<tr>
<th>Eyes (n)</th>
<th>Glaucoma Group</th>
<th>Normal Group</th>
<th>P*</th>
<th>Non-Highly Myopic Eyes</th>
<th>Glaucoma Group</th>
<th>Normal Group</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamina cribrosa thickness (μm)</td>
<td>29</td>
<td>7</td>
<td></td>
<td>11</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central region</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>77.7 ± 52.4</td>
<td>206.7 ± 59.2</td>
<td>&lt; 0.001</td>
<td>201.5 ± 251.5</td>
<td>457.7 ± 163.7</td>
<td>&lt; 0.001</td>
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<tr>
<td>Midperipheral region</td>
<td>49 (16-1789)</td>
<td>212.0 (140-335)</td>
<td></td>
<td>75.9 (39-806)</td>
<td>464 (92-1008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>76.4 ± 49.7</td>
<td>208.5 ± 68.9</td>
<td>&lt; 0.001</td>
<td>173.3 ± 191.2</td>
<td>463.3 ± 167.6</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Midperipheral region</td>
<td>50 (15-167)</td>
<td>183 (140-335)</td>
<td></td>
<td>62 (30-684)</td>
<td>442 (133-1013)</td>
<td></td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>69.8 ± 50.2</td>
<td>207.9 ± 50.9</td>
<td>&lt; 0.001</td>
<td>188.9 ± 241.3</td>
<td>461.3 ± 189.6</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Peripheral region</td>
<td>53 (19-199)</td>
<td>207 (127-291)</td>
<td></td>
<td>84 (28-850)</td>
<td>441 (111-1355)</td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>66.6 ± 52.3</td>
<td>162 ± 34.6</td>
<td>&lt; 0.001</td>
<td>161.4 ± 184.2</td>
<td>435.3 ± 136.6</td>
<td>&lt; 0.001</td>
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<tr>
<td>Median (range)</td>
<td>40 (14-185)</td>
<td>172 (114-202)</td>
<td></td>
<td>99 (38-658)</td>
<td>447 (82-714)</td>
<td></td>
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<tr>
<td>Peripheral region</td>
<td>61.4 ± 45.3</td>
<td>214.2 ± 70.1</td>
<td>&lt; 0.001</td>
<td>162.6 ± 194.1</td>
<td>464.9 ± 190.6</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>49 (16-177)</td>
<td>220 (121-320)</td>
<td></td>
<td>60 (33-665)</td>
<td>458 (71-1290)</td>
<td></td>
<td></td>
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<tr>
<td>Ratio of inner-to-outer lamina cribrosa surface</td>
<td>1.12 ± 0.43</td>
<td>0.95 ± 0.43</td>
<td>0.12</td>
<td>0.88 ± 0.12</td>
<td>0.99 ± 0.05</td>
<td>0.002</td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>1.06 (0.88–3.29)</td>
<td>1.00 (0.11-1.56)</td>
<td></td>
<td>0.87 (0.57–1.35)</td>
<td>1.0 (0.85–1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortest distance (μm) between inner lamina cribrosa surface and cerebrospinal fluid space</td>
<td>374.8 ± 102.5</td>
<td>461.4 ± 42.4</td>
<td>0.026</td>
<td>355.4 ± 266.6</td>
<td>557.9 ± 172.1</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>357 (205-597)</td>
<td>564 (386-677)</td>
<td></td>
<td>314 (99-1079)</td>
<td>546.0 (185-998)</td>
<td></td>
<td></td>
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</tbody>
</table>

Data are expressed as the mean ± SD.

* Significance of differences (Mann-Whitney t test) between the two highly myopic groups.
† Significance of differences (Mann-Whitney t test) between the two non-highly myopic groups.

RESULTS

In the highly myopic glaucomatous group, the lamina cribrosa was significantly (P < 0.001) thinner than in the highly myopic normal group (Table 1). This held true for all locations measured (Table 1). The ratio of the inner lamina cribrosa length to the outer lamina cribrosa length did not vary significantly (P = 0.12) between the two study groups (Table 1). The shortest distance between the intraocular space (i.e., the inner surface of the lamina cribrosa) and the cerebrospinal fluid space (i.e., outer surface of the pia mater) was significantly (P = 0.009) smaller in the highly myopic glaucoma group than in the highly myopic control group (Table 1; Fig. 1). In all eyes included in the study, the region with the shortest distance between the intraocular space and the cerebrospinal fluid space was located in the periphery of the optic nerve head. The peripheral posterior surface of the lamina cribrosa was significantly more often directly exposed to the pia mater and, by that, indirectly to the cerebrospinal fluid space in the highly myopic glaucomatous eyes (24/29; 83%) than in the highly myopic normal eyes (0/7; 0%; P < 0.001; χ² test).

Comparing the highly myopic normal study group with the non–highly myopic normal group showed that the lamina cribrosa was significantly (P < 0.001) thinner in the highly myopic group than in the non–highly myopic control group (Table 1). The ratio of the inner lamina cribrosa’s length to the outer lamina cribrosa’s length did not vary significantly between the two study groups (Table 1). The shortest distance between the intraocular space and the cerebrospinal fluid space was significantly (P < 0.001) shorter in the highly myopic normal group than in the non–highly myopic normal group (Table 1).

Applying the Bonferroni correction for multiple statistical comparisons showed that the differences between the groups remained statistically significant. The coefficient of variation for the remeasurement of the thickness of the lamina cribrosa was 0.143.

DISCUSSION

The bottom of the optic cup on the inner surface of the optic nerve head is formed by the lamina cribrosa. On its outer surface, the lamina cribrosa faces the anterior region of the optic nerve. The main functions of the lamina cribrosa are to allow the retinal ganglion cell axons and the central retinal vein to leave the eye, to allow the central retinal artery to enter the intraocular space, and to stabilize the intraocular pressure by forming a barrier between the intraocular space and the extracellular space. Because of its barrier function, the lamina cribrosa prevents major leakage of aqueous humor from the intravitreal space into the retrobulbar cerebrospinal fluid space surrounding the retrobulbar part of the optic nerve. Because the lamina cribrosa forms the border between the intraocular space with a higher pressure and the retrobulbar space with a lower pressure, a pressure gradient exists across the lamina cribrosa as the difference in intraocular pressure minus pressure in the retrobulbar cerebrospinal fluid space. This translamellar pressure gradient is of importance in ocular diseases in which the pressure on one or both sides of the lamina cribrosa is either abnormally high or abnormally low.14–16 An abnormal pressure gradient influences the physiology of the optic nerve fibers, with their orthograde and retrograde axoplasmic flow.17–20 The translamellar pressure gradient depends on the difference in pressure and the thickness of the lamina cribrosa. Because the lamina cribrosa is not indefinitely thin, the pressure reduction does not occur in an indefinitely thin layer of the lamina cribrosa, but the pressure may decrease gradually or in steps along the whole thickness of the lamina cribrosa.

The findings of the present study indicated that the lamina cribrosa was thinner in highly myopic eyes than in non–highly myopic eyes (Table 1). Assuming that at a given difference in pressure between the intraocular space and the retrobulbar space the pressure gradient is negatively influenced by the thickness of the lamina cribrosa, one may infer that the reduced thickness of the lamina cribrosa in highly myopic eyes is the histologic correlate of an increased susceptibility to glau
coma, as assumed clinically.\textsuperscript{4–12} Taking into account that the myopic stretching of the globe and the secondary enlargement of the optic nerve head increases with increasing axial myopia,\textsuperscript{1} one may suggest that the susceptibility to glaucomatous optic nerve fiber loss is related to the degree of high axial myopia and indirectly to the size of the enlarged optic disc. It may mean clinically that in highly myopic eyes, the target pressure may be set at a lower level than in emmetropic eyes and that, within the highly myopic group, the target pressure may be lower in severely myopic eyes with markedly enlarged optic discs than in moderately myopic eyes with moderately enlarged optic nerve heads.

The finding of a thin lamina cribrosa, possibly explaining an increased susceptibility to glaucoma in highly myopic eyes may have a counterpart in the group of non–highly myopic eyes, in which glaucomatous eyes have a significantly thinner lamina cribrosa than do normal eyes,\textsuperscript{13} possibly explaining the increased risk of further progression of glaucoma with advancing stages of the disease.\textsuperscript{21–23} This is in agreement with previous studies in which a blockade of the orthograde axoplasmic flow has been shown experimentally in eyes with markedly elevated intraocular pressure, pointing to the lamina cribrosa as the principal location of glaucomatous damage to the optic nerve fibers.\textsuperscript{17–20} In a recent clinical study, the investigators did not find a major influence of the degree of myopic refractive error on the amount of glaucomatous optic nerve damage, suggesting that myopia may not be a major risk factor for glaucoma.\textsuperscript{25} Since highly myopic eyes with a myopic refractive error exceeding \textasciitilde 8 D were excluded from that clinical study, the findings do not contradict the present histologic investigation in which highly myopic eyes with an axial length of more than 26.5 mm were primarily included.

In non–highly myopic glaucomatous eyes, the question has been raised of whether the deformation and condensation of the lamina cribrosa already exists before the development of glaucoma. At least in highly myopic eyes, the thinning of the lamina cribrosa, as also been described by Quigley et al.\textsuperscript{26,27} and others,\textsuperscript{28} is a primary event caused by the increased translaminar gradient in eyes with increased intraocular pressure and leads secondarily to damage of optic nerve fibers in the lamina cribrosa, or whether the condensation of the lamina cribrosa is a secondary phenomenon, since the loss of optic nerve fibers leaves the lamina cribrosa pores open and may induce a scarring process in it, with tissue shrinkage and sagittal condensation of the lamina cribrosa in eyes with glaucoma. At least in highly myopic eyes, a thinning of the lamina cribrosa already exists before the development of glaucomatous optic nerve damage, suggesting that at least in this group of eyes, stretching and secondary thinning of the lamina cribrosa may be one of the primary reasons for the increased susceptibility to glaucoma in that group.

Another result of the present study is that, in highly myopic glaucomatous eyes compared with highly myopic control eyes, the peripheral posterior surface of the lamina cribrosa was significantly more often directly exposed to the pia mater and, by that, indirectly to the cerebrospinal fluid space. The posteriorly exposed region of the lamina cribrosa is located close to the optic border. The reason for the exposure of the posterior surface of the lamina cribrosa to the pia mater (and indirectly to the cerebrospinal fluid space) is that, due to the myopic stretching of the optic nerve head, the optic disc diameter enlarges, whereas the diameter of the optic nerve inside the pia mater does not show major changes. In highly myopic glaucomatous eyes, the optic nerve also shrinks because of the loss of optic nerve fibers, increasing the gap between the optic nerve itself and the posterior surface of the enlarged optic disc and the stretched lamina cribrosa. It has been assumed that the exposure of the posterior surface of the lamina cribrosa to the cerebrospinal fluid space in eyes with glaucomatous optic nerve damage is the reason for acquired optic nerve head pits, which can occur in the periphery of the optic disc, as has been described in non–highly myopic eyes by Spaeth et al.\textsuperscript{29} and Radius et al.\textsuperscript{30} In contrast to non–highly myopic eyes, highly myopic eyes with glaucoma usually do not have acquired optic disc pits. The reason may be that, because of the myopic stretching of the lamina cribrosa in highly myopic eyes, the lamina cribrosa is thinned, but is so tightly stretched that a local herniation of the lamina cribrosa into the cerebrospinal fluid space may not commonly occur. Correspondingly, congenital pits of the optic nerve head which have also been considered a local herniation of a lamina cribrosa pore into the cerebrospinal fluid space have not been described frequently in highly myopic eyes.\textsuperscript{31}

The periphery of the optic nerve head was the region with the shortest distance between the intraocular space and the cerebrospinal fluid space. Assuming that a short distance between the cerebrospinal fluid space and the intraocular space steepens the pressure gradient and that a steep pressure gradient increases the susceptibility to glaucoma of optic nerve fibers, one may infer that optic nerve fibers located in the optic disc periphery would be more susceptible to glaucoma than fibers running through the optic disc center. In non–highly myopic eyes, the first glaucomatous visual field defects are often found close to the nasal step, corresponding with a loss of retinal ganglion cells adjacent to the temporal fundus raphé.\textsuperscript{32–34} The axons of these ganglion cells run in the deep part of the retinal nerve fiber layer and are located close to the optic disc border.\textsuperscript{55–56} Which agrees with the concept that the pressure gradient may be steeper at the border of the optic disc, leading to an increased susceptibility of the optic nerve fibers located in that region to glaucoma. Although perimetric studies have not been performed to the same extent in highly myopic eyes as in non–highly myopic eyes, one may assume, that due to the anatomy of the stretched lamina cribrosa, the optic nerve fibers located in the periphery of the optic nerve head in highly myopic eyes are more vulnerable to glaucoma than fibers running closer to the center of the optic nerve head.

There are several factors limiting the present study, similar to those that limited the preceding study.\textsuperscript{13} Because of post-mortem swelling of the tissue after enucleation and because of the histologic method used to prepare the slides, the measurements in this study do not represent dimensions as determined intravitreally. It was not the purpose of the present investigation, however, to evaluate the measurements of the lamina cribrosa and its surrounding tissues in real dimensions, but to compare the measurements of the lamina cribrosa obtained in highly myopic eyes with those taken in non–highly myopic eyes. The systemic error that was introduced by the histologic preparation of the slides affected the specimens in the highly myopic and non–highly myopic groups in a similar manner, because the preparation did not vary between the study groups. Thus, it may not have markedly affected the conclusions of the study. Another limitation of the study was that serial sections of the globes were not available, and therefore it was not possible to determine whether the histologic section was located in the very center of the optic disc or whether it ran slightly paracentrally. Because there were no marked differences in the myopic thinning of the lamina cribrosa between the central region and the peripheral region of the optic disc, the inaccuracy in the exact localization of the histologic section may not have markedly influenced the determinations of the lamina cribrosa’s thickness and the conclusions of the study. Another limitation of the study is the relatively small number of eyes included in the investigations. The differences in the lamina cribrosa measurements between the two study groups were statistically significant, however, despite the relatively small number of eyes. This limitation of the study may thus only serve to strengthen the conclusions drawn. Another
factor limiting the present investigation may be that only eyes with end-stage glaucomatous damage were studied what may be the most advantageous method to find differences between normal eyes and eyes with glaucoma. It may be considerably more difficult to find thinning of the lamina cribrosa early in the neuropathy. In fact, in a recent study by Bellezza et al., the lamina cribrosa, although clearly posteriorly deformed, was actually thicker in perfusion-fixed prime eyes with very early experimental glaucoma than in the contralateral normal eyes. This difference in thickness may have been due to tissue-swelling secondary to a blockade of the axoplasmic flow. Conclusions drawn from the present study may therefore be only that thinning of the lamina cribrosa, perhaps in a sense of compression or collapse, is a finding present in the relatively late stages of the glaucomatous optic neuropathies.

An additional factor limiting the present study may be that the glaucoma group consisted of eyes with severe secondary glaucomatous optic nerve damage. The histopathology of these eyes may be markedly different from the pathomorphology of eyes with the more common primary open-angle glaucoma and from the pathomorphology of eyes at an early stage of glaucoma. Another potentially limiting factor of the present study is that the optic disc could not be covered during measurement of the lamina cribrosa’s thickness, so that a bias in the assessment of the data cannot be excluded. In view of the marked differences between the groups, however, it is unlikely that this possible flaw may have markedly influenced the results of the investigation. The present investigation may thus be taken as a pilot study highlighting the importance of the lamina cribrosa’s anatomy in highly myopic eyes in regard to the spatial relationship between the retrobulbar cerebrospinal fluid space and the intraocular space, showing that in high myopia, marked morphologic changes can occur in the lamina cribrosa and that these changes may influence the pathophysiology of the optic nerve head. In that context, one should take into account that, besides the thickness of the lamina cribrosa, several other anatomic parameters of the optic nerve head and the peripapillary region, such as size of the optic disc and thickness of the peripapillary sclera, may have a major impact on the biomechanics of the lamina cribrosa and the biomechanical part of the pathogenesis of glaucomatous optic nerve damage, as has already been pointed by Burgoyne and Morris and Downs et al.

In conclusion, the present study suggests that the lamina cribrosa is thinner, that the posterior lamina cribrosa surface is more often directly exposed to the pia mater and indirectly exposed to the cerebrospinal fluid space, and that the shortest distance between the intraocular space and the cerebrospinal fluid space is smaller in highly myopic eyes than in non-highly myopic eyes. This may steepen the translaminar pressure gradient at a given intraocular pressure and may thus explain an increased susceptibility to glaucoma in highly myopic eyes. As in non-highly myopic eyes, thinning of the lamina cribrosa became more pronounced in highly myopic eyes if glaucoma was also present, which may suggest that, in highly myopic eyes, as has already been demonstrated in non-highly myopic eyes, the susceptibility to further progression of glaucoma at a given intraocular pressure increases with advancing glaucoma.

References


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