Anatomic Relationship between Lamina Cribrosa, Intraocular Space, and Cerebrospinal Fluid Space

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

PURPOSE. The lamina cribrosa, as the main structural element of the optic nerve head, forms a pressure barrier between the intraocular space and the retrobulbar space. The function as a pressure barrier may have importance for the pathogenesis of ocular diseases related to intraocular pressure and/or cerebrospinal fluid (CSF) pressure, such as the glaucomas. The purpose of the present study was to examine the anatomic relationship between the lamina cribrosa, the intraocular pressure space, and the retrobulbar cerebrospinal pressure space in eyes with glaucoma.

METHODS. The study included 53 globes enucleated because of malignant choroidal melanoma (n = 42) without involvement of the optic nerve (control group) or because of painful absolute secondary angle-closure glaucoma (n = 11; glaucoma group). Anterior–posterior histologic sections through the pupil and the optic disc were morphometrically evaluated.

RESULTS. In the glaucoma group compared with the control group, the lamina cribrosa was significantly (P < 0.001) thinner, the part of the outer lamina cribrosa surface directly exposed to the pia mater and indirectly exposed to the CSF space was significantly (P = 0.001) wider, and the shortest distance between the intraocular space and the CSF space was significantly (P < 0.001) shorter. The posterior lamina cribrosa surface in direct contact with the pia mater was located close to the optic disc border.

CONCLUSIONS. The thickness of the lamina cribrosa and the anatomic relationships between the intraocular space and the CSF space differ significantly between normal and glaucomatous eyes. The findings may be of importance for the pathogenesis of glaucomatous optic neuropathy. (Invest Ophthal mol Vis Sci. 2003;44:5189–5195) DOI:10.1167/iovs.03-0174

The lamina cribrosa forms the bottom of the optic cup on the inner surface of the optic nerve head. On the outer surface of the optic nerve head, the posterior part of 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 extracocular space. Because of the barrier function, the lamina cribrosa prevents a 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, which has a higher pressure, and the retrobulbar space, which has a lower pressure, a pressure gradient exists across the lamina cribrosa, which is the intraocular pressure minus the pressure in the retrobulbar cerebrospinal fluid space. This trans-lamina cribrosa 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.1–3 An abnormal pressure gradient influences the physiology of the optic nerve fibers, with their orthograde and retrograde axoplasmic flow,4–7 and the pressure in the retinal veins.8,9 Because the pathophysiologic effect of an abnormal trans-lamina cribrosa pressure gradient on the structures in and around the lamina cribrosa may depend on the anatomy of the lamina cribrosa itself, it was the purpose of the present study to examine histomorphometrically the anatomy with the spatial relationships between the lamina cribrosa and the surrounding intraocular and retrolaminar tissue.

MATERIALS AND METHODS

Fifty-three globes of 53 patients were included in the study and were divided into two groups: 42 (79%) eyes that had been enucleated because of malignant choroidal melanoma (control group) and 11 (21%) eyes that had been enucleated because of painful absolute secondary angle-closure glaucoma (glaucoma group). Because the optic disc morphology varies significantly between highly myopic and less myopic eyes,10,11 globes with an axial length of more than 27 mm were generally excluded. Patients in both study groups did not vary significantly (P > 0.10) in age, and eyes did not differ in axial length or in horizontal or vertical diameter of the globe.

In the glaucoma group, vision was completely or almost completely lost. Enucleation became necessary because of intractable pain that could not be treated by medication. Reasons such as perforating corneal injuries and diabetic retinopathy had been responsible for the closure of the angle. Intraocular pressure ranged between 30 and 60 mm Hg. In the tumor group, which served as a nonglaucoma control group, intraocular pressure was within the normal range without antiglaucoma medication. Migrating cells of the malignant choroidal melanoma did not infiltrate the trabecular meshwork, either 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 en-doresection of the tumor or radiologic brachytherapy were available or were thought 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 approximately 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 segment going through the pupil and the optic nerve was cut out of the fixed globes. These segments were dehydrated in alcohol, embedded in paraffin, sectioned for light microscopy, and stained by the periodic acid–Schiff (PAS) method. For all

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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. In histologic sections of eyes with chorio-
dal melanoma (control group; Figs. 1, 2) and eyes with secondary
angle-closure glaucoma (glaucoma group; Figs. 3, 4) we measured the
following (see Table 1):

- The thickness of the lamina cribrosa in five locations: 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
- The length of the anterior and posterior surfaces of the lamina
  cribrosa
- The length of the posterior surface of the lamina cribrosa directly
  exposed to the pia mater and therefore indirectly exposed to the
cerebrospinal fluid space
- The shortest distance between the intraocular space (inner sur-
  face of the lamina cribrosa) and the cerebrospinal fluid space
- The shortest distance between the intraocular space (inner sur-
  face of the lamina cribrosa) and the inner surface of the pia mater

For statistical analysis, means and standard deviations as well as
medians and ranges are presented. For the comparison of the two
study groups, statistical tests for unpaired samples were applied. The
level of significance was 0.05 (two-sided) in all statistical tests. To test
the statistical significance of differences in frequencies, we applied the
$\chi^2$ test with the Yates correction. The statistical analyses were per-
formed on computer (SPSSWIN, ver. 11.5; SPSS Science, Chicago, IL).

RESULTS

In the glaucomatous eyes (Figs. 3, 4), the lamina cribrosa was
significantly ($P < 0.001$) thinner than in the nonglaucomatous
control eyes (Figs. 1, 2), and the difference held true for all
locations measured (Table 1). The ratio of the inner to the
outer lamina cribrosa length was significantly lower in the
control group than in the glaucoma group. Correspondingly, in
the control group, the posterior lamina cribrosa was signi-
ficantly ($P < 0.001$) longer than the anterior lamina cribrosa, in
contrast to the glaucoma group, in which the lengths of the
anterior lamina cribrosa and the posterior lamina cribrosa did
not vary significantly ($P = 0.32$).

The part of the posterior lamina cribrosa surface that was in
direct contact with the pia mater and therefore in indirect
contact with the cerebrospinal fluid space was significantly
($P < 0.001$) larger in the glaucoma than in the control group
(Table 1). In 7 (64%) eyes of the glaucoma group (Figs. 3, 4)
and in 36 (86%) eyes of the control group (Figs. 1, 2), a part of
the posterior lamina cribrosa surface was in direct contact with
the pia mater, without optic nerve fibers interposed between
the lamina cribrosa posterior surface and the pia mater. The
difference between the two study groups in the frequency of a
posteriorly exposed lamina cribrosa was significant ($P = 0.01$;
$\chi^2$ test). In all eyes in which a part of the posterior surface of
the lamina cribrosa was in direct contact with the pia mater,
this region of the lamina cribrosa was located at the optic disc
border.
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), and the shortest distance between the intraocular space and the inner surface of the pia mater were significantly ($P < 0.001$) smaller in the glaucoma group than in the control group (Table 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 frequency of detected central retinal vessels in the optic nerve did not vary significantly between the two study groups ($P = 0.58$).

**DISCUSSION**

In the lamina cribrosa, the tissue pressure is reduced from the pressure level of the intraocular space to the pressure level of the retrolaminar space. Because the lamina cribrosa is not indefinitely thin, the pressure may decrease gradually or in steps along the whole thickness of the lamina cribrosa. The pressure gradient across the lamina cribrosa leads to a backward bowing of the lamina cribrosa. This bowing is the reason that, under normal circumstances, a normal-sized optic disc is cupped in its center and does not have a prominent central part. In glaucoma, optic disc cupping enlarges. An important parameter for shape and extent of glaucomatous optic cup enlargement may be the tissue behind the lamina cribrosa allowing or inhibiting progressive backward bowing of the lamina cribrosa. In those regions of the optic disc in which the lamina cribrosa faces the central trunk of the optic nerve, backward bowing may be less marked than in the peripheral regions of the optic disc in which the lamina cribrosa may have indirect contact with the cerebrospinal fluid space. The latter, in contrast to the solid trunk of the optic nerve, may more easily allow the backward movement of the lamina cribrosa. This example serves to suggest that the anatomic relationships between the lamina cribrosa and its surrounding tissue may be significant in optic nerve diseases with a pathogenesis associated with the trans-lamina-cribrosa pressure gradient. These diseases include conditions in which the intracerebral pressure is abnormally low or in which the intraocular pressure is abnormally high, and vice versa. Clinical examples are chronic ocular hypotony; diseases associated with an elevated intracerebral pressure, such as pseudotumor cerebri and epidural hematomata; and the different types of glaucoma.

The findings of the present study indicate that the lamina cribrosa is thinner in glaucomatous than in control eyes (Table 1). The deformation and condensation of the lamina cribrosa has already been described by Quigley et al. and other researchers. The question arises whether thinning and condensation of the lamina cribrosa is a primary event caused by...
the increased trans-lamina-cribrosa gradient in eyes with increased intraocular pressure and leading secondarily to a damage of optic nerve fibers in the lamina cribrosa or whether the condensation is a secondary phenomenon, in that the loss of fibers leaves the lamina cribrosa pores open and may induce a scarring process. The intralaminar scar formation may fill up the open pores preventing aqueous humor in the vitreous cavity from leaving the eye through the lamina cribrosa. The scar formation may also lead to a shrinkage of tissue, explaining the sagittal condensation of the lamina cribrosa in glaucomatous eyes. Morgan et al.3 examined the translaminar fluid space (Table 1; Figs. 1–4).

The thinning of the lamina cribrosa may be one of the reasons that the distance between the intraocular compartment and the cerebrospinal fluid space was smaller in the glaucoma group. The pressure decrease in this region would occur across both the lamina and pia mater, whereas the pressure decline in the more central lamina cribrosa facing the retrobulbar optic nerve tissue would occur only across the lamina cribrosa. Morgan et al.3 examined the translaminar pressure gradient but also the pressure decrease across the pia mater, which in dogs was an additional 4 mm Hg at its lowest. It is possible that this additional decrease in pressure adds additional compressive forces to the lamina and pia mater tissues in this region. Thus, in the present study, anatomic measurements were obtained where the pressure gradient has been shown to exist.

Another result of the present study is that glaucomatous eyes compared with control eyes significantly more often showed the peripheral posterior surface of the lamina cribrosa to be directly exposed to the pia mater, and as a result, indirectly to the cerebrospinal fluid space. In the present study, anatomic measurements were obtained where the pressure gradient has been shown to exist.

### Table 1. Histomorphometric Measurements of the Lamina Cribrosa

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Glaucoma Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>42</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Lamina cribrosa thickness (μm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central region</td>
<td>457.7 ± 163.7</td>
<td>201.5 ± 251.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>464.0</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>92–1008</td>
<td>39–868</td>
<td></td>
</tr>
<tr>
<td>Midperipheral region</td>
<td>463.5 ± 167.6</td>
<td>175.3 ± 191.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>441.5</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>135–1013</td>
<td>30–684</td>
<td></td>
</tr>
<tr>
<td>Peripheral region</td>
<td>455.3 ± 130.6</td>
<td>161.4 ± 184.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>447.0</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>82–714</td>
<td>38–658</td>
<td></td>
</tr>
<tr>
<td>Ratio of inner to outer lamina cribrosa surface</td>
<td>0.88 ± 0.12</td>
<td>0.99 ± 0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Median</td>
<td>0.87</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.57–1.35</td>
<td>0.85–1.0</td>
<td></td>
</tr>
<tr>
<td>Length of the posterior surface of the lamina cribrosa directly exposed to the pia mater and indirectly to the cerebrospinal fluid space (μm)</td>
<td>39.4 ± 99.6</td>
<td>310.2 ± 299.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>321</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–334</td>
<td>0–842</td>
<td></td>
</tr>
<tr>
<td>Shortest distance (μm) between inner surface of the lamina cribrosa and cerebrospinal fluid space</td>
<td>847.0 ± 224.8</td>
<td>606.9 ± 382.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>810.5</td>
<td>511</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>384–1488</td>
<td>307–1710</td>
<td></td>
</tr>
<tr>
<td>Shortest distance (μm) between inner surface of the pia mater</td>
<td>557.9 ± 172.1</td>
<td>335.4 ± 266.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>546.0</td>
<td>314</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>185–998</td>
<td>99–1079</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD. P is the significance of the differences (Mann-Whitney test) between the two study groups.
cribrosa to the pia mater (and indirectly to the cerebrospinal fluid space) is that, because of the pathologic process in glaucoma, the optic nerve volume inside the pia mater shrinks, decreasing the diameter of the optic nerve within the pia mater. Because the cerebrospinal fluid will not resist a focally accentuated backward bowing of the lamina cribrosa, a circumscibed herniation of the lamina cribrosa into the retrobulbar cerebrospinal fluid space may occur in predisposed eyes. The herniation may be enhanced by the anatomy of the lamina cribrosa itself, which has larger pores and less pronounced interpore connective tissue close to the optic disc border, compared with the center of the optic disc. A herniation of the lamina cribrosa into the widened cerebrospinal fluid space at the optic disc border may be the pathohistologic equivalent of acquired pits in the optic nerve head in glaucomatous eyes, as described by Spaeth et al. and Radius et al. The exposed region of the posterior surface of the lamina cribrosa to the cerebrospinal fluid space may also have importance for the pathogenesis of congenital pits of the optic nerve head which usually occur in abnormally large optic discs and are located close to the optic disc border.

The region with the shortest distance between the intracocular space and the cerebrospinal fluid pressure space was located in the periphery of the optic nerve head. Considering that a short distance between the intracocular space and the cerebrospinal fluid space steepens the pressure gradient, and assuming that a steep pressure gradient increases the susceptibility of optic nerve fibers to glucoma, one may infer that optic nerve fibers located in the optic disc periphery should be more susceptible to glaucoma than fibers running through the optic disc center. Clinically, the first glaucomatous visual field defects are often detected close to the nasal step, corresponding with a loss of retinal ganglion cells adjacent to the temporal fundus raphe. 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, in agreement with the concept that the pressure gradient may be steeper at the border of the optic disc, leading to an increased susceptibility to glucoma of the optic nerve fibers located in that region.

The anatomic relationship between the lamina cribrosa’s architecture, the intracocular space, and the retrobulbar cerebrospinal fluid space may affect the path of glaucomatous neuroretinal rim loss. Studies of the morphology of the optic disc and the distribution of visual field defects have shown that the optic nerve damage in glucoma usually does not occur in a strictly diffuse manner. Glaucomatous loss of neuroretinal rim occurs in a pattern, with early changes predominating in the temporal inferior and temporal superior disc sectors, leading to notches in the neuroretinal rim relatively often associated with disc hemorrhages and localized defects in the visual field. In eyes with medium advanced glaucomatous optic nerve damage, rim loss is most marked in the temporal horizontal disc sector. In patients with far advanced glaucoma, rim remnants are found in the nasal disc sector with a larger rim area in the nasal superior disc region than in the nasal inferior disc sector. The pattern of glaucomatous rim loss with early damage preferentially in the temporal inferior and temporal superior disc sectors suggests an increased susceptibility to glaucomatous damage in these disc regions. This pattern may have several causes, such as the regional distribution of the large and small lamina cribrosa pores, the spatial relationship between the exit of the central retinal vessel trunk on the lamina cribrosa surface and the disc sector with the most marked glaucomatous damage, the physiologic configuration of the neuroretinal rim according to the so-called inferior, superior, nasal, temporal (ISNT) rule, the regional distribution of the thin and thick optic nerve axons, the course of the optic nerve fibers through the lamina cribrosa with a more serpentine course of the axons in the periphery compared with the center of the lamina cribrosa; and the biomechanical properties of the lamina cribrosa. According to the present study, an additional factor in local susceptibility to optic nerve fiber loss in glucoma may be the spatial relationship between the lamina cribrosa and its surrounding tissues. The region with the shortest distance between the intracocular space and the cerebrospinal fluid space was located in the periphery of the optic disc where neuroretinal rim notches usually occur.

The terms glaucoma and the glaucomas encompass a whole variety of different diseases that, independent of the primary etiology, have in common damage to the optic nerve. Often, intraocular pressure is slightly or markedly elevated, whereas in some patients, intraocular pressure remains in the statistically normal range. The intraocular pressure is given and measured as the pressure difference between the intracocular space and the space in front of the eye. It is determined as the transcorneal pressure gradient. These values are only relative. Expressed in absolute terms, the intraocular pressure would be the sum of the atmospheric pressure plus the transcorneal pressure difference. For the optic nerve, however, the intraocular pressure measured as the transcorneal pressure gradient is not the most important pressure parameter. Because the optic nerve leaves the eye at the backside and is surrounded by cerebrospinal fluid, the pressure parameter relevant for the optic nerve is the pressure difference between the intracocular space and the cerebrospinal fluid space. This assumption is further strengthened by the fact that it is not the intraocular pressure as such, but the trans–lamina-cribrosa pressure difference that is presumably harmful to the optic nerve fibers. Underwater divers at the depth of 100 m have an 11-fold increase in tissue pressure and a corresponding increase in intraocular pressure, but with the transmural pressure gradient presumably remaining constant, symptoms of glucoma do not occur. If the so-called intraocular pressure is elevated from 20 to 40 mm Hg, as in acute angle-closure glucoma, the intraocular pressure is elevated by just 20/780 mm Hg or 2.7%. The transmural pressure difference, however, is elevated by 100% and leads to glaucomatous damage. Assuming that besides the difference in pressure between the intracocular space and the retrobulbar space, the thickness of the lamina cribrosa as one of the determinants of the steepness of the pressure gradient plays a role in susceptibility to glucoma, one may conclude that in different types of glucoma the primary thickness of the lamina cribrosa may play a pathogenic role. Studies have shown that highly myopic eyes have a significantly thinner lamina cribrosa than less myopic eyes, which may explain why highly myopic eyes may have a higher susceptibility to glucoma than emmetropic eyes, which arise whether patients with so-called normal-pressure glucoma primarily have an abnormally thin lamina cribrosa, leading to an increased steepness of the pressure gradient with a normal pressure difference between the intracocular space and the retrobulbar space. In addition, the cerebrospinal fluid pressure may be abnormally low in patients with normal-pressure glucoma, leading to an increased pressure difference between the intracocular and retrobulbar space.

There are factors limiting the present study. Because of postmortem swelling of the tissue after enucleation and because of the histologic preparation of the slides, the measurements given in this study do not represent dimensions as determined intravitally. 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 ob-
tained in glaucomatous eyes with the measurements taken in control eyes. The systemic error that was introduced by the histologic preparation of the slides would affect the specimens in the glaucoma and control groups in a similar manner, because the preparation did not vary between the study groups. Thus, such an error may not have markedly affected 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, however, were highly significant, despite the relatively small number of eyes. This limitation of the study may thus serve only to strengthen the conclusions drawn. 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 in eyes with the more common primary open-angle glaucoma and in eyes with an early stage of the disease. The present investigation may thus be taken as a pilot study highlighting the importance of the retrobulbar cerebrospinal fluid space and its pressure as a counterbalance for the intraocular pressure in pseudotumor cerebri. IOVS, 2003;87:361–362.


