OCULAR PERFUSION PRESSURE VS ESTIMATED TRANS–LAMINA CRIBROSA PRESSURE DIFFERENCE IN GLAUCOMA: THE CENTRAL INDIA EYE AND MEDICAL STUDY (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

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ABSTRACT

Purpose: To test the hypothesis that taking translamina pressure difference into consideration changes associations between ocular perfusion pressure and glaucomatous optic neuropathy.

Methods: The population-based Central India Eye and Medical Study included 4711 subjects. Ocular perfusion pressure was calculated as follows: \( \frac{1}{3} \left[ \text{diastolic blood pressure} + \frac{2}{3} \times (\text{systolic blood pressure} – \text{diastolic blood pressure}) \right] – \text{IOP} \). Cerebrospinal fluid pressure (mm Hg) was estimated as follows: 0.44 body mass index (kg/m\(^2\)) + 0.16 diastolic blood pressure (mm Hg) – 0.18 × age (years) – 1.91. Translamina pressure difference was IOP minus cerebrospinal fluid pressure.

Results: In multivariate analysis, higher open-angle glaucoma prevalence was associated with higher IOP \((P<.001; \text{odds ratio [OR], 1.19; 95% CI, 1.15, 1.24})\) or with higher translamina pressure difference \((P<.001; \text{OR, 1.15; 95% CI, 1.10, 1.19})\), but not with ocular perfusion pressure \((P>.37)\). A smaller neuroretinal rim area was correlated with higher IOP \((P<.001; \text{standardized coefficient beta} –0.09)\) or larger translamina pressure difference \((P<.001; \beta –0.10)\), but not with ocular perfusion pressure \((P=.26)\). Greater prevalence of angle-closure glaucoma was associated with higher IOP \((P<.001; \text{OR, 1.22; 95%CI, 1.15, 1.28})\) or higher translamina pressure difference \((P<.001; \text{OR, 1.19; 95% CI, 1.13, 1.25})\) or lower ocular perfusion pressure \((P<.04; \text{OR, 0.95; 95%CI, 0.90, 0.996})\). Correlation coefficients were highest for the association with IOP and lowest for ocular perfusion pressure. A smaller rim area was correlated with higher IOP \((P<.001; \text{beta} –0.08)\) and higher translamina pressure difference \((P<.001; \text{beta} –0.08)\); rim area and ocular perfusion pressure were not significantly associated \((P=.25)\).

Conclusions: The present study provides information on the relationship of translamina pressure difference to the development of optic nerve damage in what is presently called glaucoma. It does not provide support of the idea that ocular perfusion pressure plays a major role in the pathogenesis of optic neuropathy.


INTRODUCTION

Previous studies have shown an association between glaucoma, in particular open-angle glaucoma, and decreased ocular perfusion pressure.\(^{11-13}\) The latter has usually been defined as the difference between the mean intraocular arterial blood pressure and intraocular pressure (IOP). These studies revealed that a lower ocular perfusion pressure was associated with a higher prevalence and a more severe stage of glaucomatous optic neuropathy. A low ocular perfusion pressure has subsequently been considered to be a major risk factor for glaucomatous optic nerve damage, particularly for patients with so-called normal-pressure glaucoma.\(^{14-15}\) Other studies have suggested associations between a greater prevalence of glaucoma or more marked glaucomatous optic nerve damage and a lower body mass index.\(^{16,17}\) Anatomic investigations and recent small-scale pilot studies have suggested that the orbital cerebrospinal fluid pressure may be an additional risk factor, other than IOP, in the pathogenesis of glaucomatous optic neuropathy (Yablonski M, et al. IOVS 1979;18:ARVO E-Abstract 165).\(^{16-25}\) The orbital cerebrospinal fluid pressure is one of two determinants of the translamina cribrosa pressure difference, which has been defined as IOP minus cerebrospinal fluid pressure.\(^{16,17}\)

Because it may be important to differentiate between the influences of ocular perfusion pressure vs translamina pressure difference or IOP and glaucomatous optic neuropathy, we conducted this study to compare the associations of glaucomatous optic neuropathy with these three different pressure parameters, ie, ocular perfusion pressure, IOP, and translamina pressure difference. We hypothesized that taking the translamina pressure difference into consideration changes the associations between ocular perfusion pressure and glaucomatous optic neuropathy. We studied patients with open-angle glaucoma and with angle-closure glaucoma, because in open-angle glaucoma, extraocular risk factors may be involved in the pathogenesis of the optic nerve damage, whereas in angle-closure glaucoma, the reason for the increased IOP and the damage of the optic nerve has been considered to be located intraocularly. We corrected the dependence of IOP on central corneal thickness (CCT) and corneal curvature to reduce the risk of a confounding effect by these two parameters.\(^{26-28}\) Because measurement of cerebrospinal fluid pressure as one part of the equation to calculate the translamina pressure difference is invasive, we estimated the cerebrospinal fluid pressure based on diastolic blood pressure, age, and body mass index, using a formula that was derived in a previous investigation on the relationship between these four parameters.\(^{29}\) Finally, we chose a population-based study design to avoid the potential bias due to referral-related selection of study participants.

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METHODS

The Central India Eye and Medical Study is a population-based cross-sectional study that has been described in detail previously. The Medical Ethics Committee of the Medical Faculty Mannheim of the Ruprecht-Karls-University Heidelberg and the ethical committee of Suraj Eye Institute/Nagpur prospectively approved the study, and all participants gave informed written consent, according to the Declaration of Helsinki. The Central India Eye and Medical Study is one of several population-based studies in ophthalmology in India or on Indian populations. These studies include the Aravind Comprehensive Eye Survey, the Chennai Eye Disease Incidence Study, the LV Prasad Eye Institute Glaucoma Epidemiology and Molecular Genetic Study, the Singapore Indian Eye Study, the Andhra Pradesh Eye Disease Study, and the India Study of Age-Related Eye Diseases. Out of a total population of 13,606 villagers, 5885 subjects met the inclusion criterion of an age of 30+ years. Of these 5885 eligible subjects, 4711 subjects (80.1%) participated. The mean age was 49.5 ± 13.4 years (median, 47 years; range, 30-100 years). The demographic and socioeconomic data of the study population have been described in detail elsewhere. Among the 1174 nonparticipants were 685 men (58.3%); the mean age was 48.6 ± 14.1 years (median, 45 years; range, 30-95 years). The group of study participants and the group of nonparticipants did not differ significantly in age (P=.06), whereas the proportion of men was significantly (P<.001) higher in the group of nonparticipants.

All examinations were carried out during a day-long stay at a hospital to which the study participants were transported by bus. After participants underwent an interview conducted by trained social workers regarding socioeconomic background, living conditions, tobacco use, and alcohol consumption, we recorded pulse, arterial blood pressure, and body height and weight. A detailed ophthalmologic examination included visual acuity measurement, refractometry, frequency-doubling perimetry, Goldmann applanation tonometry, slit-lamp biomicroscopy, sonographic corneal pachymetry and biometry (PacScan; Sonomed, Lake Success, New York), gonioscopy, digital photography of the cornea, lens, optic disc, and macula, and confocal laser scanning tomography (HRT; Heidelberg Engineering, Heidelberg, Germany) of the optic disc. Glaucoma was defined according to the criteria of the International Society of Geographic and Epidemiological Ophthalmology (ISGEO), or by a glaucomatous appearance of the optic disc. The optic nerve head was glaucomatous (1) if the inferior-superior-nasal-temporal (ISNT) rule of the neuroretinal rim shape was not fulfilled in early glaucoma in eyes with a normally shaped optic disc (ie, the rim width at the inferior disc pole or at the superior disc pole was equal to or smaller than the temporal rim width; it included a notch in the neuroretinal rim in the inferotemporal and/or superotemporal region); or (2) if an abnormally large cup was present in a small optic disc, which normally would not show cupping. In all eyes with glaucoma, the visibility of the retinal nerve fiber layer was locally and/or segmentally reduced.

The assessment of the optic disc photographs was carried out in a masked manner without knowledge of IOP or the perimetric results. Each photograph of a glaucomatous optic disc was independently adjudicated by two senior graders (V.N. and J.B.J.). In the ISGEO definition of glaucoma, criteria for a category 1 diagnosis (structural and functional evidence) were a vertical cup-disc diameter ratio or an inter-eye asymmetry in the vertical cup-disc diameter ratio of ≥97.5th percentile for the normal population, or a neuroretinal rim width reduced to ≤0.1 vertical cup-disc diameter ratio (between the 11:00 and 1:00 o’clock or the 5:00 and 7:00 o’clock position), in addition to a definite visual field defect consistent with glaucoma. Criteria for the category 2 diagnosis (advanced structural damage with unproven visual field loss) were a vertical cup-disc diameter ratio or a vertical cup-disc diameter ratio asymmetry ≥99.5th percentile for the normal population. Criteria for a category 3 diagnosis (eyes for which the optic nerve head could not be examined or for which a visual field examination was not possible) were a visual acuity <3/60 combined with either an IOP ≥99.5th percentile or definite indication of glaucoma in medical records, such as filtering surgery history. The reason that two definitions of glaucomatous optic neuropathy were used is that the ISGEO definition of glaucoma has not been universally accepted (except by many ophthalmic epidemiologists) and that the morphologic definition based on the appearance of the optic nerve head has been accepted.

The entire glaucoma group was differentiated into subjects with open-angle glaucoma and with primary angle-closure glaucoma. Open-angle glaucoma was characterized by an open anterior chamber angle, in addition to a normal depth of the anterior chamber as assessed by slit-lamp biomicroscopy. In angle-closure glaucoma, the anterior chamber angle was occluded or occludable. The anterior chamber angle was defined as occludable if ≥270° of the posterior trabecular meshwork could not be seen on gonioscopy. In addition, other features for angle-closure glaucoma were iris whirling and glaukomflecken in the anterior subcapsular lens region, in combination with a narrow anterior chamber angle.

The main outcome parameters were IOP, estimated cerebrospinal fluid pressure, translimina pressure difference, and ocular perfusion pressure.

The measured IOP was corrected for its dependence on CCT and anterior corneal curvature radius. The reason for correcting the IOP for its dependence on the corneal parameters was that the ocular perfusion pressure may be associated more strongly with the real IOP than with the measured IOP. Correcting for the confounding corneal parameters of CCT and corneal curvature radius may have given values that were closer to the real IOP than if the raw measurements of IOP had been taken. In our study population, IOP was significantly associated with thinner CCT (P<.001) and shorter corneal curvature radius (P<.001) after adjusting for parameters such as shallower anterior chamber depth, longer axial length, younger age, higher pulse rate, higher prevalence of arterial hypertension, and higher blood concentration of triglycerides and cholesterol. The regression coefficients of the associations between IOP and CCT or corneal curvature were used for the formula of the corrected IOP:

\[
IOP_{\text{corrected}} = IOP_{\text{measured}} + (513.8 – \text{CCT} [\mu\text{m}]) \times 0.02 + (44.62 – \text{Corneal Refractive Power} [\text{Diopters}]) \times 0.125.
\]
Mean CCT in our study population was 513.8 µm, and mean corneal refractive power was 44.62 D. This formula was partially different from the one developed by Kohlhaas and colleagues, in which an approximately 1 mm Hg correction for every 25 µm deviation from a CCT of 550 µm was suggested. In our formula, the correction for each 25 µm difference from the mean CCT (of 532 µm) was 0.50 mm Hg. The difference between the formula of Kohlhaas and the formula applied in the present study was that in the Kohlhaas formula the dependence of IOP measurements on corneal curvature was not taken into account and that it was based on Caucasian eyes, in which the mean CCT is markedly thicker compared to Indian eyes.

The transamina pressure difference was calculated as IOP minus estimated cerebrospinal fluid pressure. As described recently, we used lumbar cerebrospinal fluid pressure measurements for the calculation of a formula to estimate the cerebrospinal fluid pressure. The measurements had been taken in a previous study of 74 patients (mean age, 42.0 ± 13.4 years) who underwent lumbar puncture for neurological diseases such as peripheral neuropathy, intracranial hypertension, spontaneous intracranial hypotension, cavernous sinus syndrome, meningitis, multiple sclerosis, unilateral ischemic optic neuropathy, unilateral optic neuritis, optic nerve atrophy, and head injury. The mean cerebrospinal fluid pressure was 12.6 ± 4.8 mm Hg. Out of the total group, we randomly formed a training group consisting of 32 patients, and a group including the remaining 42 patients. In multivariate analysis in the training group, cerebrospinal fluid pressure was best described by the formula as follows: cerebrospinal fluid pressure (mm Hg) = 0.44 × body mass index (kg/m²) + 0.16 × diastolic blood pressure (mmHg) − 0.18 × age (years) − 1.91. The association between higher cerebrospinal fluid pressure and younger age, higher body mass index, and higher blood pressure had also been reported in other studies. The formula was then tested in the independent test group, in which the measured lumbar cerebrospinal fluid pressure (12.6 ± 4.8 mm Hg) did not differ significantly (P=.29) from the calculated cerebrospinal fluid pressure (13.3 ± 3.2 mm Hg). The Durbin-Watson value was 2.08, indicating a nonsignificant autocorrelation for the residuals in the multiple regression models. The intraclass correlation coefficient was 0.71. The Bland-Altman analysis revealed that 40 of 42 measurements were within the 95% limits of agreement.

Mean ocular perfusion pressure was defined as follows:

$$\frac{2}{3} [\text{Diastolic Blood Pressure} + \frac{1}{3} \times (\text{Systolic Blood Pressure} – \text{Diastolic Blood Pressure})] – \text{IOP}.$$  

Only those subjects with assessable optic disc photographs and measurements of blood pressure, body height and weight, IOP, and central corneal thickness and corneal curvature were included in the study. Statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 21.0; SPSS, Chicago, Illinois). The normal distribution of the values of parameters was tested using the Kolmogorov-Smirnov test. Continuous data were presented as mean ± standard deviation. In the first step of the analysis, we evaluated differences between individuals included in the study and individuals excluded from the study (Table 1). Differences in pressure-related parameters between glaucomatous groups and the nonglaucomatous group were then examined using the Mann-Whitney U test for unpaired samples (Table 2). Associations between the presence of glaucoma and pressure-related parameters were assessed using linear regression analysis (Table 3). We calculated odds ratios (OR) and their 95% confidence intervals (CI). The values were 2-sided and were considered statistically significant when the values were <.05.

### RESULTS

Of the 9422 eyes (4711 subjects), optic disc photographs and measurements of body height and weight, blood pressure, IOP, CCT, and corneal curvature were available for 8768 eyes (93.1%) of 4534 subjects (96.2%). The mean age of the 4534 participants (2438 [53.8%] women) was 48.9 ± 13.0 years, mean refractive error was −0.10 ± 1.73 D, and mean axial length was 22.62 ± 0.87 mm (Table 1). The group of excluded subjects, as compared with the group of subjects included in the study, was significantly older (P < .001).
and more myopic ($P<.001$), whereas the two groups did not differ significantly in axial length ($P=.32$), IOP ($P=.44$), and gender ($P=.06$) (Table 1).

### TABLE 2. DIFFERENCES IN PRESSURE-RELATED PARAMETERS BETWEEN INDIVIDUALS WITH OPEN-ANGLE GLAUCOMA, INDIVIDUALS WITH ANGLE-CLOSURE GLAUCOMA, AND INDIVIDUALS WITHOUT GLAUCOMA IN THE CENTRAL INDIA EYE AND MEDICAL STUDY

<table>
<thead>
<tr>
<th>GROUP</th>
<th>ALL-GLAUCOMA GROUP</th>
<th>NONGLAUCOMATOUS GROUP</th>
<th>P VALUE *</th>
<th>OPEN-ANGLE GLAUCOMA</th>
<th>P VALUE †</th>
<th>ANGLE-CLOSURE GLAUCOMA ‡</th>
<th>P VALUE ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected IOP (mm Hg)</td>
<td>17.1 ± 6.9</td>
<td>13.7 ± 3.2</td>
<td>&lt;.001</td>
<td>16.5 ± 5.8</td>
<td>&lt;.001</td>
<td>22.3 ± 11.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Corrected IOP (mm Hg)</td>
<td>17.2 ± 6.8</td>
<td>13.7 ± 3.1</td>
<td>&lt;.001</td>
<td>16.6 ± 5.7</td>
<td>&lt;.001</td>
<td>22.1 ± 11.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Estimated CSF pressure (mm Hg)</td>
<td>7.6 ± 3.7</td>
<td>10.0 ± 3.6</td>
<td>&lt;.001</td>
<td>7.6 ± 3.8</td>
<td>&lt;.001</td>
<td>8.2 ± 3.0</td>
<td>.01</td>
</tr>
<tr>
<td>Translamina pressure difference (mm Hg)</td>
<td>9.5 ± 7.8</td>
<td>3.6 ± 4.2</td>
<td>&lt;.001</td>
<td>9.0 ± 6.0</td>
<td>&lt;.001</td>
<td>13.9 ± 13.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ocular perfusion pressure (mm Hg)</td>
<td>48.2 ± 12.6</td>
<td>46.9 ± 8.8</td>
<td>.03</td>
<td>48.8 ± 12.0</td>
<td>.03</td>
<td>43.9 ± 16.4</td>
<td>.94</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; IOP, intraocular pressure.

*Statistical significance (Mann-Whitney $U$ test for unpaired samples) of the difference between the nonglaucomatous group and the all-glaucoma group.
†Statistical significance (Mann-Whitney $U$ test for unpaired samples) of the difference between the open-angle glaucoma group and the nonglaucomatous group.
‡Statistical significance (Mann-Whitney $U$ test for unpaired samples) of the difference between the angle-closure glaucoma group and the nonglaucomatous group.

### TABLE 3. ASSOCIATIONS (UNIVARIATE ANALYSIS) BETWEEN THE PREVALENCE OF OPEN-ANGLE GLAUCOMA OR ANGLE-CLOSURE GLAUCOMA AND NEURORETINAL RIM AREA WITH PRESSURE PARAMETERS IN THE CENTRAL INDIA EYE AND MEDICAL STUDY

<table>
<thead>
<tr>
<th>OPEN-ANGLE GLAUCOMA IN ASSOCIATION WITH:</th>
<th>P VALUE</th>
<th>ODDS RATIO</th>
<th>95% CI</th>
<th>COX &amp; SNELL $R^2$</th>
<th>NAGELKERKE $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected IOP (mm Hg)</td>
<td>&lt;.001</td>
<td>1.16</td>
<td>1.13, 1.20</td>
<td>.009</td>
<td>.05</td>
</tr>
<tr>
<td>Corrected IOP (mm Hg)</td>
<td>&lt;.001</td>
<td>1.18</td>
<td>1.14, 1.22</td>
<td>.010</td>
<td>.06</td>
</tr>
<tr>
<td>Translamina pressure difference (mm Hg)</td>
<td>&lt;.001</td>
<td>1.20</td>
<td>1.17, 1.24</td>
<td>.019</td>
<td>.11</td>
</tr>
<tr>
<td>Ocular perfusion pressure (mm Hg)</td>
<td>.008</td>
<td>1.02</td>
<td>1.01, 1.04</td>
<td>.001</td>
<td>.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NEURORETINAL RIM AREA (mm$^2$) IN ASSOCIATION WITH:</th>
<th>P VALUE</th>
<th>REGRESSION COEFFICIENT B</th>
<th>95% CI</th>
<th>STANDARDIZED COEFFICIENT BETA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected IOP (mm Hg)</td>
<td>&lt;.001</td>
<td>-.01</td>
<td>-.01, -.01</td>
<td>-.09</td>
</tr>
<tr>
<td>Corrected IOP (mm Hg)</td>
<td>&lt;.001</td>
<td>-.01</td>
<td>-.01, -.01</td>
<td>-.09</td>
</tr>
<tr>
<td>Translamina pressure difference (mm Hg)</td>
<td>&lt;.001</td>
<td>-.01</td>
<td>-.01, -.01</td>
<td>-.10</td>
</tr>
<tr>
<td>Ocular perfusion pressure (mm Hg)</td>
<td>.26</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
IOP, intraocular pressure.

*The Cox and Snell $R^2$ and Nagelkerke $R^2$ are coefficients of determination, with $R^2$ summarizing the proportion of variance in the dependent variable associated with the predictor or independent variables. The Cox and Snell $R^2$ is based on the logarithmic likelihood for the model compared to the logarithmic likelihood for a baseline model. Since, with categorical outcomes, its theoretical maximum value is <1.0, the Nagelkerke $R^2$ was calculated as an adjusted version of the Cox & Snell $R^2$ that adjusts the scale of the statistics to cover the full range from 0 to 1.

Mean estimated cerebrospinal fluid pressure was 10.0 ± 3.6 mm Hg (median, 10.2 mm Hg; range, −1.9 to 27.3 mm Hg), mean uncorrected IOP was 13.8 ± 3.4 mm Hg (median, 14.0 mm Hg), mean corrected IOP was 13.8 ± 3.3 mm Hg (median, 13.6 mm Hg), mean translamina pressure difference was 3.8 ± 4.4 mm Hg (median, 3.5 mm Hg), and mean ocular perfusion pressure was 46.9 ± 8.9 mm Hg (median, 46.0 mm Hg; range, 5.0 to 95.5 mm Hg) (Figure 1). All pressure-related parameters were not normally distributed ($P < .001$).

Using the optic nerve head criteria for the definition for glaucomatous optic neuropathy, glaucoma was detected in 185 eyes (2.11%; 95% CI, 1.81, 2.41) of 109 subjects (2.4%). According to gonioscopic findings, the entire glaucoma group was differentiated into open-angle glaucoma (n=165 eyes) and angle-closure glaucoma (n=20 eyes) groups. Using the criteria of the ISGEO, glaucoma was detected in 128 eyes, with 119 eyes fulfilling the criteria for open-angle glaucoma.

Comparing the whole glaucoma group with the nonglaucomatous group in univariate analysis showed that IOP was significantly higher ($P < .001$) and that translamina pressure difference was significantly higher ($P < .001$) in the glaucoma group, whereas ocular perfusion pressure was marginally significantly ($P = .03$) higher in the glaucoma group than in the nonglaucomatous group (Table 2).

### OPEN-ANGLE GLAUCOMA

Comparing the open-angle glaucoma group with the nonglaucomatous group revealed that IOP (uncorrected and corrected) ($P < .001$), translamina pressure difference ($P < .001$), and ocular perfusion pressure ($P = .03$) were significantly higher in the open-angle glaucoma group (Table 2) (Figures 1 through 3). The finding of a marginally significantly ($P = .03$) higher ocular perfusion pressure in the open-angle glaucoma group was due to the observation that the mean blood pressure was significantly ($P < .001$) higher in the open-angle glaucoma group (98.0 ± 15.9 mm Hg) than in the nonglaucomatous group (90.9 ± 13.5 mm Hg). The differences between the open-angle glaucoma group and the nonglaucomatous group in IOP or translamina pressure difference were higher than the difference in ocular perfusion pressure, expressed in absolute units (mm Hg) and expressed in relative units with the difference as percentage of the measurement (Table 2). Correspondingly, the associations between neuroretinal rim area (as quantitative measure of the glaucomatous optic nerve damage) and IOP or translamina pressure difference were statistically significant and stronger (ie, lower $P$ values and higher correlation coefficients) than the association between neuroretinal rim area and ocular perfusion pressure, which was not significantly ($P = .26$) associated with neuroretinal rim area (Table 3).

If two pressure parameters were included in the analysis, in this case IOP and translamina pressure difference, a higher prevalence of open-angle glaucoma was significantly associated with higher translamina pressure difference ($P < .001; OR, 1.23; 95% CI, 1.17, 1.28$) but not with IOP ($P = .25$). If only IOP and ocular perfusion pressure were included in the analysis, a higher prevalence of open-
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angle glaucoma was significantly associated with higher IOP ($P<.001$; OR, 1.20; 95%CI, 1.16, 1.25) and with higher ocular perfusion pressure ($P<.001$; OR, 1.04; 95%CI, 1.02, 1.05). If only translamina pressure difference and ocular perfusion pressure were included in the analysis, a higher presence of open-angle glaucoma was significantly associated with higher translamina pressure difference ($P<.001$; OR, 1.28; 95% CI, 1.24, 1.33) and with higher ocular perfusion pressure ($P<.001$; OR, 1.08; 95% CI, 1.07, 1.10). As also shown in a multivariate analysis in a previous study, a higher prevalence of open-angle glaucoma was associated with higher age ($P<.001$), lower body mass index ($P=.007$), lower level of education ($P=.01$), prevalence of myopic retinopathy ($P<.001$), longer axial length ($P<.001$), and higher IOP ($P<.001$; B = 0.18; OR, 1.19; 95% CI, 1.15, 1.24). If IOP was replaced by translamina pressure difference, similar results were obtained: a higher prevalence of open-angle glaucoma was associated with higher age ($P<.001$), lower level of education ($P=.01$), higher prevalence of myopic retinopathy ($P<.001$), longer axial length ($P<.001$), and higher translamina pressure difference ($P<.001$; B = 0.14; OR, 1.15; 95% CI, 1.10, 1.19). If IOP was replaced by ocular perfusion pressure, the prevalence of open-angle glaucoma was not significantly associated with ocular perfusion pressure ($P<.37$).

**FIGURE 1**
Histogram showing the distribution of intraocular pressure corrected for its dependence on central corneal thickness and corneal curvature in the Central India Eye and Medical Study.

**FIGURE 2**
Histogram showing the distribution of the translamina cribrosa pressure difference for its dependence on central corneal thickness and corneal curvature in the Central India Eye and Medical Study.

**FIGURE 3**
Histogram showing the distribution of ocular perfusion pressure in the Central India Eye and Medical Study.
If only patients with open-angle glaucoma and nonglaucomatous subjects were included in the analysis and the amount of glaucomatous damage was quantified as neuroretinal rim area, the association between smaller rim area and higher IOP was similar to the association between smaller rim and higher trans lamina pressure difference, whereas rim area and ocular perfusion pressure were not significantly associated with each other (\(P=.26\)) (Table 3).

**ANGLE-CLOSURE GLAUCOMA**

Comparing the angle-closure glaucoma group with the nonglaucomatous group revealed that IOP (uncorrected and corrected) (\(P<.001\)) and trans lamina pressure difference (\(P<.001\)) were significantly higher in the angle-closure glaucoma group, whereas ocular perfusion pressure (\(P=.94\)) did not differ significantly between the two groups (Table 2; Figures 1 through 3). The differences between the glaucomatous group and the nonglaucomatous group in IOP (8.4 mm Hg vs 2.9 mm Hg) and in trans lamina pressure difference (10.2 mm Hg vs 5.3 mm Hg) were higher for angle-closure glaucoma than for open-angle glaucoma. The differences between the angle-closure glaucoma group and the nonglaucomatous group were higher for IOP and trans lamina pressure difference than for ocular perfusion pressure, expressed in absolute units (mm Hg) and expressed in relative units with the difference as percentage of the measurement (Table 2). Correspondingly and in a similar manner as for open-angle glaucoma, the associations between neuroretinal rim area and IOP or trans lamina pressure difference were statistically significant and stronger (ie, lower \(P\) values and higher correlation coefficients) than the association between neuroretinal rim area and ocular perfusion pressure, which was not significantly (\(P=.25\)) associated with neuroretinal rim area (Table 3). Comparing the associations between the prevalence of angle-closure glaucoma and each of the three pressure parameters separately in univariate analysis showed that the correlation coefficients were similar for the association between the prevalence of angle-closure glaucoma and IOP and for the association between the prevalence of angle-closure glaucoma and trans lamina pressure difference, whereas the prevalence of angle-closure glaucoma was not significantly associated with ocular perfusion pressure (\(P=.20\)) (Table 3).

As also shown in a multivariate analysis in a previous study, a higher prevalence of angle-closure glaucoma was associated with older age (\(P=.003\)), shallower anterior chamber (\(P=.046\)), shorter axial length (\(P=.009\)), and higher IOP (\(P<.001\); \(B = 0.20\); OR, 1.22; 95% CI, 1.15, 1.28).\(^{45}\) If IOP was replaced by trans lamina pressure difference, higher prevalence of angle-closure glaucoma was associated with higher trans lamina pressure difference (\(P<.001\); \(B = 0.17\); OR, 1.19; 95% CI, 1.13, 1.25). If IOP was replaced by ocular perfusion pressure, a higher prevalence of angle-closure glaucoma was significantly associated with lower ocular perfusion pressure (\(P<.04\); \(B = -0.05\); OR, 0.95; 95% CI, 0.90, 0.996). The correlation coefficients were highest for the association between angle-closure glaucoma prevalence and IOP, followed by the association between angle-closure glaucoma prevalence and trans lamina pressure difference, and they were lowest for the association between higher angle-closure glaucoma prevalence and lower ocular perfusion pressure.

If only patients with angle-closure glaucoma and nonglaucomatous subjects were included in the analysis and the amount of glaucomatous damage was quantified by neuroretinal rim area, the association between smaller rim area and higher IOP was similar to the association between smaller rim and higher trans lamina pressure difference, whereas rim area and ocular perfusion pressure were not significantly associated with each other (\(P=.25\)).

Using the criteria of the ISGEO, glaucoma was detected in 128 eyes (1.51 ± 0.13%; 95% CI, 1.25, 1.77), with 119 eyes fulfilling the criteria of open-angle glaucoma. Using the ISGEO-defined open-angle glaucoma group for the statistical analysis led to similar results as previously described. The prevalence of ISGEO open-angle glaucoma was significantly associated with IOP (\(P=.003\)) and with trans lamina pressure difference (\(P=.02\)), but not with ocular perfusion pressure (\(P=.17\)).

**DISCUSSION**

In our population-based study, IOP, trans lamina pressure difference, and ocular perfusion pressure were significantly higher in the open-angle glaucoma group than in the nonglaucomatous group. In univariate analysis, the correlation coefficients for the significant (\(P<.001\)) associations between neuroretinal rim area and pressure-related parameters were highest for trans lamina pressure difference and IOP, whereas the association between neuroretinal rim area and ocular perfusion pressure was not statistically significant (\(P=.26\)) (Table 3). In multivariate analysis, higher open-angle glaucoma prevalence was significantly (\(P<.001\)) associated with higher IOP or with higher trans lamina pressure difference but not with ocular perfusion pressure (\(P>.37\)). In angle-closure glaucoma, IOP (\(P<.001\)) and trans lamina pressure difference (\(P<.001\)) were significantly higher than in the nonglaucomatous group, whereas ocular perfusion pressure (\(P=.94\)) did not differ significantly between both groups. In multivariate analysis, higher angle-closure glaucoma prevalence was associated with higher IOP (\(P<.001\)) or with higher trans lamina pressure difference (\(P<.001\)) or lower ocular perfusion pressure (\(P<.04\)). Correlation coefficients were highest for the association with IOP and lowest for ocular perfusion pressure. Smaller neuroretinal rim area was significantly (\(P<.001\)) correlated with higher IOP or with higher trans lamina pressure difference, whereas neuroretinal rim area and ocular perfusion pressure were not significantly (\(P=.25\)) associated with each other.

These results confirm previous studies and contradict others. In the population-based cross-sectional Egna-Neumarkt Study with more than 4000 participants, Bonomi and colleagues\(^{1}\) found that lower diastolic perfusion pressure was associated with a higher prevalence of hypertensive glaucoma. The investigators concluded that a reduced diastolic perfusion pressure was an important risk factor for primary open-angle glaucoma. In the population-based cohort study of the Barbados Eye Study with almost 3000 participants, Leske and coworkers\(^{2}\) reported that the 4-year incidence of open-angle glaucoma was inversely associated with higher baseline prevalence of arterial hypertension or with higher baseline systolic blood pressure, and as a corollary, higher glaucoma
incidence was positively correlated with a lower baseline perfusion pressure. In the Rotterdam study of more than 5000 participants, Hulsman and colleagues found that in persons treated for systemic hypertension, low diastolic perfusion pressure of less than 50 mm Hg was inversely associated with the prevalence of normal-pressure glaucoma. In the Early Manifest Glaucoma Trial, Leske and associates detected that besides other factors such as age, family history of glaucoma, and higher IOP, were risk factors for the progression of open-angle glaucoma. In the Low-pressure Glaucoma Treatment Study, de Moraes and colleagues reported that lower mean ocular perfusion pressure increased the risk for progression of glaucoma. In the Thessaloniki Eye Study of more than 2500 participants, Topouzis and colleagues concluded that a low diastolic ocular perfusion pressure may be associated with an increased risk for primary open-angle glaucoma, in particular if the patients were treated for systemic hypertension. Similar conclusions were drawn by Flammer and colleagues, Cherecheanu and associates, Sommer, and Costa and coworkers. In contrast to these studies cited, the Beijing Eye Study did not find a clear association between ocular perfusion pressure and prevalence of glaucoma. The reasons for the discrepancy between the studies has remained unclear. A potential reason may be differences in the statistical analysis, in particular whether a multivariate analysis was performed and, if yes, which parameters were included in the list of independent variables.

Interestingly, the prevalence of open-angle glaucoma was associated with higher IOP and with higher ocular perfusion pressure, if no other parameters were included in the statistical analysis. In a similar manner, the prevalence of open-angle glaucoma was associated with higher translamina pressure difference and with higher ocular perfusion pressure, if no other parameters were included in the statistical analysis. The unexpected finding of an association between higher prevalence of open-angle glaucoma and higher ocular perfusion pressure was probably due to a confounding effect, since higher ocular perfusion pressure was additionally associated (univariate analysis) with other parameters, such as older age, female gender, higher body mass index, lower educational level, and longer axial length. These parameters were also related to open-angle glaucoma. Consequently, the multivariate analysis including all these parameters revealed that the prevalence of open-angle glaucoma was not significantly associated with ocular perfusion pressure ($P<.37$).

The results of the present study on a statistically significant association between higher translamina pressure difference (and indirectly, lower cerebrospinal fluid pressure) and higher prevalence and severity of open-angle glaucoma and, to a lesser degree, the results on a statistically significant association between higher translamina pressure difference and higher prevalence and severity of angle-closure glaucoma, are in agreement with investigations from the Beijing Eye Study, in which similar observations were made.

For example, in an eye with an “IOP” of 20 mm Hg, the true physical pressure is 760 mm Hg (from the atmosphere) plus 20 mm Hg. It leads to the phenomenon that the difference in pressure between an eye with an IOP of 20 mm Hg and another eye with an IOP of 40 mm Hg is not 100% but just 780/800, or 2.5%. For the optic nerve head, however, where likely the glaucomatous optic nerve damage primarily takes place, the transcorneal pressure difference may be less important than the pressure difference between the intraocular compartment and the surrounding external atmosphere. For example, in an eye with an “IOP” of 20 mm Hg, the true physical pressure is 760 mm Hg (from the atmosphere) plus 20 mm Hg. It leads to the phenomenon that the difference in pressure between an eye with an IOP of 20 mm Hg and another eye with an IOP of 40 mm Hg is not 100% but just 780/800, or 2.5%. For the optic nerve head, however, where likely the glaucomatous optic nerve damage primarily takes place, the transcorneal pressure difference may be less important than the pressure difference between the intraocular compartment (ie, the so-called IOP) and the pressure behind the lamina cribrosa (ie, the retrolaminar optic nerve tissue pressure and the orbital cerebrospinal fluid pressure). It was therefore discussed that the translamina pressure difference as compared with the IOP may be more important for the pathophysiology of glaucomatous optic neuropathy. This notion was supported by clinical studies in which some patients with glaucomatous optic nerve damage and normal IOP had an abnormally low cerebrospinal fluid pressure or other signs of a low cerebrospinal fluid pressure.

The potential role of the cerebrospinal fluid pressure in the pathogenesis of glaucomatous optic neuropathy was suggested several decades ago by studies and articles by Volkov, Morgan, and others. Berdahl and colleagues performed a retrospective clinical chart analysis on patients who had undergone lumbar cerebrospinal fluid pressure measurements for a variety of reasons. They found that the lumbar cerebrospinal fluid pressure was highly significantly lower in the glaucoma group than in the nonglaucomatous group. As a corollary, patients with ocular hypertension had significantly higher lumbar cerebrospinal fluid pressure measurements than the control group and the glaucoma group. In a prospective study by Ren and associates, patients with normal-pressure glaucoma and patients with high-pressure glaucoma underwent for various reasons a neurological examination including a lumbar puncture with lumbar cerebrospinal fluid pressure measurement. They were compared with individuals of a nonglaucomatous control group. It revealed that the patients with normal-pressure glaucoma had significantly lower lumbar cerebrospinal fluid pressure measurements than those with high-pressure glaucoma or those in the control group. Wang and associates showed that the width of the orbital cerebrospinal fluid space as measured by magnetic resonance imaging was significantly smaller in patients with normal-pressure glaucoma than in patients with high-pressure glaucoma or in a control group. Since the width of the orbital cerebrospinal fluid space is associated with the cerebrospinal fluid pressure, one concluded that the patients with normal-pressure glaucoma had lower cerebrospinal fluid pressure. In a recent experimental study, Yang and colleagues decreased the cerebrospinal fluid pressure by a lumbo-peritoneal shunt in monkeys and found that the monkeys of the study group, as compared to monkeys of a control group, developed an optic nerve damage.

Interestingly, other studies suggested a physiological correlation between cerebrospinal fluid pressure and IOP in patients without major neurological or ophthalmological diseases. This would fit with other similarities between IOP and cerebrospinal fluid pressure, such as in the composition of their underlying fluids, their physiological pressure range, and their response to changes of...
intra-abdominal and intrathoracic pressure.\textsuperscript{87,88} In a parallel manner, cerebrospinal fluid pressure has been found to be related to blood pressure and higher blood pressure is correlated with higher IOP.\textsuperscript{25,53,89,90} One may assume a physiological association between IOP, cerebrospinal fluid pressure, blood pressure, and IOP in a triangular association. The mechanism behind such a relationship has remained unclear so far. In a recent experimental study by Samuels and colleagues,\textsuperscript{91} chemical stimulation of the dorsomedial/periforinal hypothalamic region evoked substantial increases in IOP, cerebrospinal fluid pressure, and translamina pressure difference in rats. The investigators postulated that the dorsomedial and periforinal hypothalamic neurons may be a key effector pathway for circadian regulation of the autonomic tone by the suprachiasmatic nucleus. Interestingly, as early as 1955, von Sallmann and colleagues\textsuperscript{92-94} already examined the region of the diencephalon influencing the regulation of IOP.

Besides the static measurements of IOP, cerebrospinal fluid pressure, and blood pressure, dynamic aspects in the relationship between these three pressure parameters may also have to be taken into account. Studies by Morgan and colleagues\textsuperscript{66,67} have revealed that the pressure wave starting at the heart arrives first in the brain and orbital cerebrospinal fluid space before it leads to a pulse-synchronous IOP increase. It could indicate that the translamina pressure difference fluctuates due to the different pulse-related changes in the orbital cerebrospinal fluid pressure and IOP. During an early and brief period of the pulse phase, the orbital cerebrospinal fluid pressure may increase in relation to the IOP, so that the translamina pressure difference decreases. If, for this short fraction of the pulse phase, the orbital cerebrospinal fluid pressure may even become higher than the IOP, the translamina pressure difference could briefly be reversed. The pulse-synchronous swinging of the translamina pressure difference may be of physiological importance, since it could help the retrograde axoplasmic flow entering the eye.\textsuperscript{66,67} Any change in the dynamics of pulse-synchronous changes of IOP and cerebrospinal fluid pressure could thus result in a change of the undulation of the translamina pressure difference with consequences for the axoplasmic flow.

In addition to the pulse-synchronous changes in cerebrospinal fluid pressure, IOP, and translamina pressure difference, both IOP and cerebrospinal fluid pressure also change in relationship to the body position, such as both increase in headstand.\textsuperscript{76,77,95-102} It has remained unexplored yet whether the body position–associated changes in IOP and cerebrospinal fluid pressure occur in a parallel and similar manner, or whether IOP vs cerebrospinal fluid pressure may change more markedly or faster or vice versa.

Interestingly, other studies revealed associations between cerebrospinal fluid pressure and other parameters, such as retinal vein diameter and retinal vein pressure, incidence of retinal vein occlusions, prevalence, incidence and severity of diabetic retinopathy, hypertensive retinopathy, and subfoveal choroidal thickness.\textsuperscript{103-105} These findings may show the potential importance of the cerebrospinal fluid pressure for a variety of ocular parameters and disorders.

Our study has potential limitations. First, the definition of the ocular perfusion pressure was based on IOP instead of on the central retinal vein pressure. The latter can be estimated applying a modified form of ophthalmodynamometry.\textsuperscript{106,107} A recent study by Stodtmeister and colleagues\textsuperscript{108} showed that using the central retinal vein pressure instead of the IOP in the formula for the calculation of the ocular perfusion pressure should result in more valid figures, since it is the vein pressure, and not the IOP, that primarily influences the retinal capillary blood pressure and the blood outflow from the eye. Second, the statistical analysis depended on a formula to calculate the cerebrospinal fluid pressure. As already discussed, the study in which the basis parameters for that formula were assessed included a relatively small number of subjects, and these subjects had a clinical reason to undergo lumbar puncture.\textsuperscript{29} Although the clinical neurological examination and the further clinical course retrospectively revealed that it was unlikely that the lumbar cerebrospinal fluid pressure measurement in that study group was markedly influenced by the reason to perform the lumbar puncture, one has to keep in mind that the participants in that study were not randomly selected normal subjects. One may, however, also consider that it would not have been appropriate to measure cerebrospinal fluid pressure invasively in a population-based study. Third, the formula to estimate the cerebrospinal fluid pressure was derived in an investigation on Chinese, and it has remained unclear whether this formula based on Chinese subjects can be transferred to Indians. Fourth, IOP was measured only once, so that diurnal variations in IOP were not taken into account. One may also raise the question of how representative the single IOP measurement was for the subject’s IOP in general. Fifth, the statistical analysis for the angle-closure glaucoma group was limited by the relatively small sample size in that subgroup. Sixth, the design of our study as a cross-sectional investigation did not allow addressing questions on dynamic changes in cerebrospinal fluid pressure and translamina pressure difference with age, so that a causal relationship between translamina pressure difference and glaucoma subtypes has to be examined in future longitudinal studies. Seventh, this study, as preceding investigations, used the same definition of ocular perfusion pressure except that this formula has been validated. Furthermore, the main parameter would be the blood flow to the capillaries of the optic nerve head, and this may not accurately be predicted by measuring or estimating pressure in the ophthalmic artery, in the central retinal artery, and certainly not in the brachial artery. Eighth, if the estimated cerebrospinal fluid pressure had been close to a constant, the translamina pressure difference would have simply been equal to the IOP minus a constant. If that had been the case, the study would have assessed only the relationship of IOP to glaucoma damage, without adding new information. The estimated cerebrospinal fluid pressure ranged, however, between −1.9 mm Hg and 27.3 mm Hg, which may show that this range was sufficient to give the parameter of estimated cerebrospinal fluid pressure sufficient influence in the statistical analysis. Ninth, the standardized correlation coefficients beta in the associations between neuroretinal rim area and IOP or translamina pressure difference were relatively low and ranged between −0.08 and −0.10 (Table 3). A standardized correlation coefficient beta of −0.10 indicated that an increase of 1 SD in IOP resulted in a statistically (P<0.001) significant decrease of 0.10 SD in neuroretinal rim area. It was, however, not the purpose of our study to assess associations between IOP (or translamina pressure difference) and the amount of glaucomatous optic nerve damage, but to compare IOP or translamina pressure difference with ocular perfusion pressure in their influence on glaucomatous optic nerve damage. The relationship between ocular perfusion pressure and neuroretinal rim area in open-angle glaucoma and angle-closure glaucoma was not statistically significant. 

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significant \((P=.26\) and \(P=.25\), respectively), thus showing a difference between ocular perfusion pressure vs translamina pressure difference or IOP in their associations with glaucoma.

In conclusion, higher prevalence of open-angle glaucoma and more marked optic nerve damage in open-angle glaucoma were strongly correlated with translamina pressure difference but not with ocular perfusion pressure in multivariate analysis. In patients with angle-closure glaucoma, prevalence of angle-closure glaucoma was considerably more strongly correlated with translamina pressure difference than with ocular perfusion pressure. The present study provides information on the relationship of translamina cribrosa pressure with the development of optic nerve damage in what is presently called glaucoma. The present study does not provide support of the idea that ocular perfusion pressure plays a major role in the pathogenesis of optic neuropathy; this, however, does not relate to difficulties in determining ocular perfusion pressure with validity.

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