Vascular Risk Factors for Primary Open Angle Glaucoma

The Egna-Neumarkt Study

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Objective: To assess the impact of vascular risk factors on the prevalence of primary open angle glaucoma.

Design: Population-based cross-sectional study.

Participants: Four thousand two hundred ninety-seven patients more than 40 years of age underwent a complete ocular examination in the context of the Egna-Neumarkt Glaucoma Study.

Intervention: Ocular examinations were performed by trained, quality-controlled ophthalmologists according to a predefined standardized protocol including medical interview, blood pressure reading, applanation tonometry, computerized perimetry, and optic nerve head examination.

Main Outcome Measures: Prevalences of ocular hypertension, primary open-angle glaucoma, normal-tension glaucoma, and other types of glaucoma were determined. Correlation coefficients were calculated for the association between systemic blood pressure and age-adjusted intraocular pressure (IOP) and between age and both intraocular and systemic blood pressures. Odds ratios were computed to assess the risk of primary open-angle glaucoma and normal-tension glaucoma in relation to systemic hypertension or antihypertensive medication, blood pressure levels, diastolic perfusion pressure, and a number of other cardiovascular risk factors.

Results: A positive correlation was found between systemic blood pressure and IOP, and an association was found between diagnosis of primary open-angle glaucoma and systemic hypertension. Lower diastolic perfusion pressure is associated with a marked, progressive increase in the frequency of hypertensive glaucoma. No relationship was found between systemic diseases of vascular origin and glaucoma.

Conclusions: Our data are in line with those reported in other recent epidemiologic studies and show that reduced diastolic perfusion pressure is an important risk factor for primary open-angle glaucoma. Ophthalmology 2000;107:1287–1293 © 2000 by the American Academy of Ophthalmology.

In the pathogenesis of primary open-angle glaucoma (POAG), it is generally agreed that, in addition to ocular hypertension (OH), other risk factors may also play an important and, in certain cases, even a predominant role. Particularly worthy of note are risk factors of a vascular nature; systemic hypertension,1–3 atherosclerosis, vasospasm, and other vascular diseases have been listed as potential factors capable of increasing the risk of POAG.4–14 Drance15 has reported numerous cases of low-tension glaucoma probably related to previous hemodynamic crises.

A number of authors claim that alongside high-pressure glaucoma, where the damaging factor is OH, there also exists a type of glaucoma in which the pathogenesis is mainly or exclusively the result of vascular disorders.13,16,17 In particular, the intervention of vascular factors is regarded as likely in the pathogenesis of normal-tension glaucoma (NTG).4–7,15,18

The data available on these points are often contradictory and hard to interpret.19 In most cases, the data are based on clinical case series and may present problems of selection bias.

The aim of this study was to present a series of data on vascular risk factors obtained in the course of the Egna-Neumarkt Glaucoma Study. This was a population-based epidemiologic study conducted in a specific area of northern Italy, according to a standardized protocol, to ascertain the prevalence of the various types of glaucoma in the area and to evaluate any risk factors associated with the disease. Data on the distribution of ocular pressure and the prevalence of the various forms of glaucoma have been published in a previous article, which also details the protocol.20
Patients and Methods

The entire population more than 40 years of age from the Egnatia-Neumarkt area of the South Tyrol, Italy, comprising 11 rural districts in the vicinity of Bolzano, was eligible.

The investigation was carried out in a specially equipped screening center by specifically trained medical staff, periodically subjected to quality control, according to procedures described in a prepared operating manual.

The study was conducted in three phases. At the first screening visit, a medical history questionnaire was administered that included information on educational status; profession; smoking habits; coffee and alcohol intake; family history of cardiovascular disease, diabetes, and sudden death; pathologic history of heart attacks, intermittent claudication, cerebrovascular accidents, hypertension, diabetes, and headache; and any therapies implemented. Body weight and height were also recorded. Two blood pressure readings in the sitting position were taken, after 5 minutes of rest, with the sphygmomanometer cuff placed on the right arm at the level of the heart. A Riva-Rocci mercury sphygmomanometer was used.

A complete ophthalmologic examination was carried out, including application tonometry using a Goldmann tonometer under topical anesthesia with 0.4% benoxinate; computerized examination of the visual field using the Armaly full-field screening program, with a threshold-related three-zone strategy by means of a Humphrey 640 perimeter (Zeiss, San Leandro, CA); and evaluation of the optic disc by means of direct ophthalmoscopy.

Patients regarded as glaucoma suspects underwent a second examination that included: computerized examination of the visual field with the 30-2 full threshold program by means of a Humphrey 640 perimeter, evaluation of the optic disc under stereoscopic vision with the pupil dilated, repeated tonometric examinations, and gonioscopy.

For patients whose diagnosis remained uncertain, further investigations were conducted by the Ophthalmology Division of Bolzano General Regional Hospital, with all the examinations regarded as necessary for each individual case. Referral criteria and the definitions of glaucoma suspects, glaucomatous abnormalities of the optic disc, and glaucomatous visual field defects were reported as in the previous study.20

For the purposes of this investigation, the following diagnostic criteria were adopted.

OH. Intraocular pressure (IOP) of 22 mmHg or more without visual field or optic disc abnormalities in the absence of an occludable anterior chamber angle and no signs of secondary glaucoma.

POAG. At least two of the following criteria: IOP of 22 mmHg or more; glaucomatous optic disc abnormalities; glaucomatous visual field abnormalities (Humphrey 30-2 Statpac II program) and anterior chamber angle not occludable and devoid of goniosynechiae or signs of secondary glaucoma. In the POAG category we also included those with capsular pseudoexfoliation.

NTG. Glaucomatous optic disc and glaucomatous visual field abnormalities with IOP less than 22 mmHg, confirmed at the second and third examinations.

Diastolic hypertension. Diastolic blood pressure more than 95 mmHg.

Systolic hypertension. Systolic blood pressure more than 160 mmHg.

Actual hypertension. Systolic blood pressure more than 160 mmHg, diastolic blood pressure more than 95 mmHg, or both in the absence of antihypertensive therapy.

Table 1. Overall Prevalence of Different Forms of Glaucoma (Values not Standardized)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>% (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4087</td>
<td>95.1 (92.1–98.1)</td>
</tr>
<tr>
<td>OH</td>
<td>89</td>
<td>2.1 (1.7–2.6)</td>
</tr>
<tr>
<td>POAG</td>
<td>60</td>
<td>1.4 (1.1–1.8)</td>
</tr>
<tr>
<td>NTG</td>
<td>24</td>
<td>0.6 (0.4–0.9)</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>0.8 (0.6–0.9)</td>
</tr>
<tr>
<td>Total</td>
<td>4297</td>
<td>100</td>
</tr>
</tbody>
</table>

CI = 95% confidence intervals; NTG = normal-tension glaucoma; OH = ocular hypertension; Other = primary angle-closure glaucoma and secondary glaucoma; POAG = primary open-angle glaucoma.

Systemic hypertension. Systolic blood pressure more than 160 mmHg, diastolic blood pressure more than 95 mmHg, or both, or antihypertensive therapy in progress, even with blood pressure values below the limits at the time of measurement.

Diastolic perfusion pressure. Diastolic blood pressure minus IOP.

Systolic perfusion pressure. Systolic blood pressure minus IOP.

Mean perfusion pressure. (systolic blood pressure – 1/3 [systolic – diastolic pressure]) – IOP.

IOP. IOP of right eyes was used to calculate diastolic, systolic, and mean ocular perfusion pressure (no significant difference in IOP was found between right and left eyes).

Statistical Analysis

The SAS version 6.12 statistical program (SAS Institute Inc, Cary, NC, USA) was used. Numerical frequencies, percentages, and 95% confidence intervals were calculated for the various conditions examined. Correlation analysis was used to assess the effects of differences in blood pressure on IOP and to evaluate IOP and blood pressure variability in relation to age. Those with POAG and NTG were considered cases, and those with OH were considered controls. Perfusion pressure values were divided into tertiles. Multivariate regression analysis was used to assess the increased risk of POAG, NTG, and of either form of glaucoma taken together as a result of the presence of a given risk factor. Age-adjusted odds ratios and 95% confidence intervals were computed. The Mantel–Haenszel chi-square test for trends was used to evaluate the increased risk of glaucoma in relation to increased blood pressure.

Results

One thousand eight hundred eighty-two men and 2415 women were examined from a total population of 5816 for an overall participation rate of 73.9%. The composition of the sample together with the participation rates according to sex and age have been analyzed in detail in a previous article.20 Table 1 shows the overall prevalence of OH and of the different forms of glaucoma in the population studied. Table 2 gives details of the association between systemic blood pressure and age-adjusted IOP. Intraocular pressure correlates with blood pressure, although by no means closely. The correlation is statistically significant (P < 0.001) for both systolic and diastolic pressure. In fact, a 10-mmHg increase in systolic blood pressure is associated with only a 0.24 mmHg increase in IOP. In the case of diastolic blood pressure, the same 10-mmHg increase is associated with a 0.4 mmHg increase in IOP.
Table 2. Association between Blood Pressure and Age-adjusted Mean Intraocular Pressure

<table>
<thead>
<tr>
<th>Age Group</th>
<th>IOP (mean ± SE)</th>
<th>Systolic Blood Pressure (mean ± SD)</th>
<th>Diastolic Blood Pressure (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;110</td>
<td>14.71 ± 2.47</td>
<td>134.76 ± 16.93</td>
<td>85.48 ± 9.56</td>
</tr>
<tr>
<td>110–129</td>
<td>15.07 ± 6.66</td>
<td>143.88 ± 19.91</td>
<td>88.64 ± 10.26</td>
</tr>
<tr>
<td>120–139</td>
<td>15.29 ± 2.82</td>
<td>151.65 ± 20.83</td>
<td>86.23 ± 9.51</td>
</tr>
<tr>
<td>130–149</td>
<td>15.39 ± 2.86</td>
<td>155.54 ± 21.33</td>
<td>86.65 ± 9.25</td>
</tr>
<tr>
<td>140–159</td>
<td>15.50 ± 3.17</td>
<td>157.42 ± 20.07</td>
<td>84.52 ± 10.48</td>
</tr>
</tbody>
</table>

Table 3 shows that both IOP and systolic blood pressure increase significantly with age (P < 0.001). In our sample, this is not the case with IOP and diastolic blood pressure. It should be noted, however, that between the two extreme age groups in our sample (40–49 years and 80–89 years), the mean increase in IOP is quantitatively very limited, not reaching even as much as 1 mmHg (+5.37%), whereas the increase in systolic blood pressure (+22.66 mmHg = +16.81%) is considerably greater.

Having established, in this population, that both IOP and systolic blood pressure increase with age, just as the prevalence of POAG increases as reported in our previous study,20 we sought to determine to what extent the apparent correlation between POAG prevalence and blood pressure was actually related to changes in blood pressure and to what extent it was simply the result of aging. To this end, the data were further analyzed after adjusting for age. Sex-adjusted data were also analyzed.

The data relating to a possible association between glaucoma diagnosis and actual hypertension, taking antihypertensive medication, and systemic hypertension are given in Table 4. It should be noted that systemic hypertension is not just equal to actual hypertension and taking antihypertensive medication, because people with high blood pressure who are taking antihypertensive medication are present in both the actual hypertension group and the antihypertensive medication group. With regard to the diagnosis of POAG, age- and sex-adjusted odds ratios invariably yielded values more than 1, whereas for the NTG diagnosis, the values ranged from 0.8 to 0.4. It should be noted, however, that all values lay within fairly broad confidence limits. Overall, this may suggest a correlation between POAG and systemic hypertension regardless of the age of the patients. No such correlation, however, emerged for NTG.

Figure 1 was constructed to assess whether ocular perfusion pressure was related in some way to the prevalence of glaucoma. The figure clearly shows that the prevalence of glaucoma decreases progressively with increased diastolic perfusion pressure, whereas no correlation is detectable with either systolic or mean perfusion pressure.

This phenomenon is confirmed for POAG, but not for NTG, by the more detailed analysis presented in Table 5 in which, for reasons of simplicity, only diastolic perfusion pressure is considered.

From the responses to the questionnaire administered to those studied, we obtained the frequencies of five previous diseases regarded as indicative of possible systemic vascular involvement. As can be seen in Table 6, none of the conditions considered was significantly associated with glaucoma.

The questionnaire was also used to obtain data regarding possible associations between glaucoma diagnosis and a series of hypothetical risk factors considered in other studies. These include body weight, body mass index, coffee consumption, tobacco and alcohol intake, and the presence of frequent headaches. As emerges from Tables 7 and 8, none of these factors was found to be significantly associated with glaucoma.

Discussion

Although OH is generally regarded as being the main risk factor for glaucoma, there can be no doubt, especially in the primary open-angle form, that other factors make a decisive contribution toward increasing the vulnerability of the optic nerve and generating the typical anatomic–functional damage that characterizes this disease.

According to the vascular or ischemic hypothesis, glaucomatous damage is caused by, or at least facilitated by, inadequate perfusion of the proximal portion of the optic nerve. In systemic hypertension, this may be the result of increased peripheral resistance in the small vessels. It is often stressed, however, that a reduction in systemic blood pressure may also have a deleterious effect by creating insufficient perfusion pressure in the optic disc. In other words, both systemic hypertension and hypotension could, with different mechanisms, be risk factors for glaucoma. In light of this, the concept of perfusion pressure may be highly important, which, in the case of the eye, expresses the difference between arterial and venous pressure, the latter being conventionally regarded as equal to IOP.

Other causes of abnormal perfusion of the optic disc may be linked to various kinds of anatomical or functional abnormalities, or both, of the minor vessels. Among these we should consider atherosclerosis of the vessels upstream of the disc, arteriolar sclerosis, and vasospasm phenomena. Various authors have found a greater prevalence of cardiac, cerebral, and peripheral vascular disorders in glaucoma and...
particularly in the normal-tension forms in their study populations. 1,6,8,13,16,21

More than one mechanism has been postulated for the possible effects of blood pressure in the pathogenesis of glaucoma. On the one hand, various investigators have found a positive correlation between systemic hypertension and OH.1,3,22–26 Although we realize that blood pressure in the eye is different from blood pressure in the arm, we used brachial diastolic pressure for calculating ocular perfusion pressure in our study, as was used by other investigators.25–27 Moreover systemic hypertension, through the increase in peripheral vascular resistance that accompanies it, may play a direct role in the pathogenesis of a number of ischemic eye diseases.28 In a report by Wilson et al, 2 systemic hypertension, along with being black, would appear to be the main risk factors for glaucoma. However, there has also been considerable insistence in the literature on the possibility that habitual or episodic systemic hypotension may lead to a decisive degree of deterioration of optic nerve head perfusion and thus generate those defects that we regard as being typical of chronic glaucoma.9–12,15 This would appear to be particularly important in the pathogenesis of NTG. 1,7,13,14,18,27,29

On analyzing our entire study population, we observed the effective existence of a positive correlation between systemic pressure and IOP. This proved statistically significant for both systolic and diastolic blood pressures. The increase in systemic blood pressure should therefore be regarded as effectively capable of producing a slight increase in IOP. Our data provide no indication of mecha-

![Figure 1](image_url)

**Figure 1.** The prevalence of open-angle glaucoma (primary open-angle glaucoma and normal-tension glaucoma) in relation to the level of perfusion pressure.
vessels responsible for this phenomenon. It should be noted, however, that it is a very weak correlation and that the increases in IOP in response to 10-mmHg increments in systolic and diastolic blood pressures are only 0.24 and 0.40 mmHg, respectively. These data confirm the findings reported by Carel et al\textsuperscript{22} and by McLeod et al\textsuperscript{3} and, in quantitative terms, closely reflect the findings of the Balti-
more\textsuperscript{25} and Rotterdam\textsuperscript{26} studies, which closely resemble our own with regard to the number of patients making up the study population. The correlation between higher IOP and higher arterial blood pressure was observed in the study population as a whole and thus did not depend on the presence of glaucoma. Furthermore, although real, it was of such modest proportions as to be of no clinical importance in the pathogenesis of glaucomatous disease. Despite this, the finding is still undeniably of theoretical interest.

Worthy of separate mention is the correlation between diagnosis of glaucoma and diagnosis of systemic hypertension. The data obtained in our study would appear to indicate not so much a clearly demonstrable correlation as a weak tendency toward an association between POAG and systemic hypertension. This seems to be particularly true as far as systolic blood pressure is concerned. However, no positive correlation is discernible between systemic hyper-
tension and NTG. These data are at variance with the findings reported by Wilson et al\textsuperscript{2} who asserted that systemic hypertension is one of the main risk factors for glaucoma, but the data are in good agreement with the statements made by many authors,\textsuperscript{1,7,9–13,15,18,25,27,29} who believe that glaucoma is more often associated with low levels of systemic blood pressure.

One obvious explanation for this association may be the fact that low blood pressure accompanied by higher IOP can only render the degree of perfusion of the optic nerve head more precarious. In fact, Leske et al\textsuperscript{27} found in their study population that glaucoma was more frequent in patients with minimal differences between systemic pressure and IOP. Tielsch et al\textsuperscript{25} convincingly demonstrated the existence of an inverse correlation between glaucoma and diastolic perfusion pressure of the ocular tissues.

The data obtained in our study are in excellent agreement with these findings. Although no demonstrable correlation is observed between systolic and mean perfusion pressure and glaucoma prevalence, lower diastolic perfusion pres-
sure is associated with a marked, progressive increase in the frequency of glaucoma. This correlation appears to be highly significant for POAG but, surprisingly, is nonexistent in the case of NTG, that is, precisely in the form of glaucoma that is most insistently indicated to be the most classic example of glaucoma of vascular origin. In this connection, there is good reason to suspect that, in our study population, the lack of any significant correlation between these variables may be related to the limited number of cases in the NTG group.

An appreciable difference between Tielsch et al’s\textsuperscript{25} data and ours is the numerical relationship between the level of diastolic perfusion pressure and the increase in glaucoma prevalence. The latter, in the Baltimore study, begins to increase at diastolic perfusion pressure values less than 50

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients with/without (%) Cardiovascular Risk Factor</th>
<th>Sex-adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POAG NTG Controls</td>
<td>POAG NTG Total</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more of the above</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
mmHg, whereas in our study population, the phenomenon is already apparent at diastolic perfusion pressure values just less than 70 mmHg. This discrepancy may be attributable to racial differences (approximately half the Baltimore study population were African American) or to the different definitions of glaucoma. The data obtained by Leske et al\textsuperscript{27} appear to lie midway between ours and those reported by Tielsch et al\textsuperscript{25} considering that in the Barbados population (the vast majority of whom are of African origin) the mean diastolic perfusion pressure was 63 ± 14.9 mmHg in healthy persons as opposed to 53.8 ± 14.9 mmHg in the patients with glaucoma. On the basis of our own data as well as those of Tielsch et al\textsuperscript{25} Leske,\textsuperscript{27} and Drance et al\textsuperscript{12} we may conclude that there is an important increased risk of glaucomatous damage when the ocular diastolic perfusion pressure is less than 55 mmHg.

The absolute importance of the perfusion pressure of ocular tissues as a risk factor for glaucoma should not, however, be overrated. In fact, only 23% of our glaucoma cases had ocular perfusion pressure less than 50 mmHg. Essentially, we can safely claim that reduced diastolic perfusion pressure is only one of the mechanisms whereby OH damages the optic nerve and is probably not the most important in terms of frequency.

The hypothesis put forward by many authors\textsuperscript{7,8,13,16,18} of a link between glaucoma and the presence of diseases of other organs of an obviously vascular nature, such as angina, infarct, stroke, transient ischemic attack, and intermittent claudication, was not confirmed in our study either for POAG or NTG. This would appear to be in line with the findings of Armaly,\textsuperscript{30} Drance,\textsuperscript{15} and Klein and Klein\textsuperscript{23} reported in publications specifically devoted to this aspect. Additional risk factors assessed in other studies and listed in Tables 7 and 8 also failed to show any significant correlation with the presence of glaucoma.

The final conclusion of the study may be that there is a correlation between higher systemic blood pressure and higher IOP that is unrelated to age. However, this produces effects that are too slight to be regarded as risk factors for glaucoma. In contrast, the diastolic perfusion pressure of the ocular tissues is confirmed as an important factor in the pathogenesis of glaucomatous damage. The lower the perfusion pressure, the more likely occurrence of damage becomes. Because this is a variable that is easy to calculate

<table>
<thead>
<tr>
<th>Risk Factors for Cardiovascular Diseases</th>
<th>Patients with/without (%) Risk Factor</th>
<th>Sex-adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POAG NTG Controls</td>
<td>POAG NTG Total</td>
</tr>
<tr>
<td>Headache</td>
<td>44/15 (74.6) 16/7 (69.6)</td>
<td>1.1 (0.6–2.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>26/34 (43.3) 4/20 (16.7)</td>
<td>1.2 (0.7–2.2)</td>
</tr>
<tr>
<td>Coffee consumption</td>
<td>55/3 (94.8) 12/2 (91.7)</td>
<td>0.3 (0.1–1.0)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>43/17 (71.7) 13/11 (54.2)</td>
<td>1.5 (0.8–2.8)</td>
</tr>
</tbody>
</table>

BMI = body mass index; BW = body weight; CI = confidence interval; Controls = normal or nonglaucomatous ocular hypertension; NTG = normal-tension glaucoma; POAG = primary open-angle glaucoma; Total = all primary open angle glaucoma including both POAG and NTG.
and does not require either complex or invasive investigations, it would be advisable to take this factor into account in the clinical evaluation of patients.

We cannot rule out the possibility that vascular diseases arising in other organs may contribute to the pathogenesis of glaucoma, but the results reported here have furnished no evidence to support this hypothesis.

References