The Influence of Intraocular Pressure on Visual Field Damage in Patients With Normal-Tension and High-Tension Glaucoma

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There have been several reports to suggest that the type of visual field damage in open-angle glaucoma is influenced by intraocular pressure (IOP). This study was undertaken to determine the extent to which patients with normal-tension (NTG) and high-tension glaucoma (HTG) could be differentiated on the basis of some features of their visual fields. The results from 40 pairs of NTG and HTG patients were matched closely for the extent of visual field damage, pupil size, and visual acuity. Using this pooled material, the authors increased the IOP difference between the two groups in either direction, ie, by either progressively lowering the highest recorded IOP allowed for inclusion in the NTG group or by progressively increasing that required for inclusion in the HTG group. They compared the normal areas of the patients' visual fields by using simple visual field indices designed to quantify the undisturbed field. Using receiver operating characteristics (ROC) analysis, they showed that changing the inclusion criterion in the NTG group resulted in no better separation between the groups. However, when the inclusion criterion was changed in the HTG group, the two groups tended to become more separable. In this case, the degree of separation appeared to be related to the difference in the highest recorded IOP between the two groups although the separation was not complete. These findings show that pressure has a greater influence on the type of visual field damage at the higher end of the IOP spectrum encountered in open-angle glaucoma and suggest that there is no common single pathophysiologic mechanism in this disease.

Functional and structural damage in open-angle glaucoma occurs with a wide range of intraocular pressures (IOP). Several investigations attempting to isolate differences in features of visual field damage and optic disc appearances between glaucoma patients with “normal” IOP (low- or normal-tension glaucoma, NTG) and those with “elevated” IOP (high-tension glaucoma, HTG) have been undertaken but they are controversial in their findings. 1-7 This may be due partly to differing sampling criteria and the nature and extent of differences that were sought. It is important to understand whether the characteristics of field and disc damage depend on IOP since it would determine if factors other than IOP play a role in the pathogenesis of glaucoma.

The emphasis on finding pressure-dependent features in glaucomatous field damage has shifted from mostly descriptive and qualitative to more quantitative ones. Recent evidence showed that using automated perimetry and visual field indices, 8,9 the visual field in NTG patients tends to be affected in a more localized manner, 10,11 whereas in HTG patients, the localized damage is accompanied with diffuse damage. 12 This supports the hypothesis that diffuse damage may be influenced by IOP and that localized damage may be due to other, possibly vascular, factors. 13

It is unlikely that localized and diffuse damage are independent. The visual field indices used by the Octopus perimeters (Interzeag AG, Schlieren, Switzerland) to indicate localized and diffuse damage, ie, corrected loss variance and mean defect, respectively, were found to be highly correlated in a sample of glaucoma patients and glaucoma suspects. 14 In a recent study using simple indices to quantify normal areas of the visual field in pairs of NTG and HTG and in patients matched very closely for the extent of damage, we showed that approximately two thirds of the NTG patients had more localized damage than their paired HTG counterparts. 15 Although our data generally agree with the above hypothesis, in roughly...
one third of the pairs, the NTG patients had more diffuse damage. These findings suggest that IOP is not the only determinant of damage in these two groups of patients, or that IOP may be a factor in some cases of NTG.16,17

This investigation is an extension of our previous study. We wanted to study more closely the effect of IOP on the normal areas of the visual field in NTG and HTG patients. We wanted to determine if increasing differences in the highest recorded IOP between the two groups (firstly by lowering the highest recorded IOP allowed for inclusion in the NTG group and secondly by increasing the highest recorded IOP required for inclusion in the HTG group) could lead to a better separation between them on the basis of the remaining normal parts of their visual fields.

Materials and Methods

Patients for this study were obtained from the University of British Columbia Glaucoma Clinic and divided into NTG and HTG groups. For inclusion in the NTG group, patients had to have a highest ever recorded IOP not exceeding 22 mm Hg in both eyes during clinical follow-up, which in nearly all cases included diurnal pressure curves. In the HTG group, the highest ever recorded IOP had to be at least 30 mm Hg in the study eye. Inclusion criteria common to both groups were: abnormal optic disc, pupil size of at least 3 mm, visual acuity of 6/9 (20/30) or better, and at least one reliable examination (fixation losses less than 20% and false-positive and false-positive responses less than 33%)18 using of program 30-2 on the Humphrey Field Analyzer (Allergan Humphrey, San Leandro, CA).

Fifty-five patients with 263 Humphrey 30-2 examinations qualified for the NTG group, and 79 patients with 297 examinations qualified for the HTG group. Clinical consent to do standard perimetric testing was obtained from all patients. To indicate total damage, we used the index mean deviation9 which is a weighted mean of the deviation of the light sensitivity measurements from normal age-corrected values. The weighting is applied to reflect the normal inter-individual variability in light sensitivity at each test location. Matching each NTG examination with each HTG examination resulted in 78,111 possible pairs from which pairs were selected by identification, in sequence, of the minimum paired differences in mean deviation, pupil size, and visual acuity. The maximum allowable difference in mean deviation was 0.50 dB, and only one eye per patient and one examination per eye were included. Forty pairs of NTG and HTG patients qualified for the study. The mean difference ± 1 standard deviation in mean deviation was −0.01 ± 0.14 dB (NTG group: −5.04 ± 3.56 dB; HTG group: −5.03 ± 3.49 dB), in pupil size was 0.00 ± 1.34 mm (NTG group: 4.20 ± 1.14 mm; HTG group: 4.20 ± 1.04 mm), and in visual acuity (logMAR) was 0.03 ± 0.24 (NTG group: 0.17 ± 0.18; HTG group: 0.14 ± 0.20). A discussion of these and the other background variables have been given elsewhere.15 These patients constituted the pooled material.

For each visual field examination we identified those locations where the sensitivity was equal to or higher than the age-corrected value and termed them normal locations. A cluster analysis which recognizes randomly scattered normal (or abnormal) locations from clustered ones19 was then done on these locations. We computed three simple indices: (1) the number of normal locations, (2) the number of clustered normal locations, and (3) the size of the largest cluster of normal locations.

Using the pooled material containing the 40 pairs of NTG and HTG patients, we constructed receiver operating characteristics (ROC) curves20 on which the probability of detecting a NTG patient was plotted against the probability of detecting a HTG patient at each possible value for the three indices. The area under the ROC curve (A) and its standard error were computed according to the method of Hanley and McNeil.21 In this case, A represents the probability of a randomly selected NTG patient having a greater value for a given index than a randomly selected HTG patient. Its computation makes no assumptions about the underlying distribution of any index in either group. The ROC curve of the number of normal locations for the pooled material is shown as an example in Figure 1.

To increase the pressure difference between the two groups, we successively redefined the two groups by first progressively lowering the highest recorded IOP allowed for inclusion in the NTG group in steps of 1 mm Hg. At each such step, the value of A and its standard error were computed. We removed pairs using this successive elimination so that the remaining NTG patients were still matched with HTG patients for the extent of damage, pupil size, and visual acuity. Although the pressure difference between the two groups could have been increased until all patients were eventually removed from the analysis, large standard errors of A due to decreasing sample sizes would have resulted. For this reason, an arbitrarily chosen “final step” of IOP level where only ten pairs remained was selected. Starting with the pooled material of 40 pairs, we then progressively increased the highest recorded IOP required for inclusion in the HTG group in steps of 1 mm Hg. As previously, A and its standard error were computed at each step,
Fig. 1. The receiver operating characteristics (ROC) curve for the number of normal locations in the pooled material of 40 pairs of normal-tension glaucoma (NTG) and 40 high-tension glaucoma (HTG) patients. The shaded region represents the area under the ROC curve ($A_z$). The dashed line represents the line of no discrimination.

and pairs were removed until the final step when only ten pairs remained was reached. For each index, we looked at the relationship of $A_z$ with the mean difference in the highest recorded IOP between the NTG and HTG groups at each step.

Results

The distribution of the highest recorded IOP in the pooled material of the 40 pairs of NTG and HTG patients is shown in Figure 2. The mean values ± 1 standard deviation were 18.73 ± 1.99 mm Hg and 37.48 ± 5.56 mm Hg in the NTG and HTG groups, respectively. The mean paired difference of 18.75 ± 5.78 mm Hg was highly significant ($P = 0.000$, Wilcoxon matched-pairs test).

$A_z$ and its standard error at each step for the number of normal locations, the number of clustered normal locations, and the size of the largest cluster of normal locations are given in Table 1. Due to the larger range of IOP in the HTG group, there were more available steps as the highest recorded IOP required to be included in this group was progressively increased. Five values of $A_z$ were available when the inclusion criterion in the NTG group was changed, and 12 values of $A_z$ available when that in the HTG group was changed. Descriptively, these results show that as the highest recorded IOP allowed for inclusion in the NTG group was lowered, the value of $A_z$ on the whole, remained lower than that of the pooled material. This was apparent for all three indices. On the other hand, as the highest recorded IOP required for inclusion in the NTG group was increased, for all indices, $A_z$ was nearly always higher than that of the pooled material. The standard error of $A_z$ increased from the pooled material to the final step. This was due to decreasing sample sizes, and although the increases were very slight initially, they were more evident toward the final step.

For each index we plotted $A_z$ as a function of the mean difference in the highest recorded IOP between the NTG and HTG groups (Fig. 3). To ensure that the pressure differences between the groups were roughly equivalent as the inclusion criterion was changed from either direction, we first included in our analysis values of $A_z$ only for the pooled material and the first five steps. These results show that when the inclusion criterion for the NTG group was changed, the regression of $A_z$ on the mean difference in highest recorded IOP was not statistically significant for any index ($P > 0.750$). In addition the slopes were close to zero. This shows that the separation between the NTG and HTG groups was not significantly different as the as the pressure difference between the groups was increased by lowering the highest recorded IOP allowed to be included in the NTG group. When the IOP difference between the groups was increased by increasing the highest recorded IOP required to be included in the HTG group, the results contrasted sharply. The regression slopes in this case were statistically significant ($P < 0.025$) for all indices, which showed that there tended to be a greater separation between the two groups as the pressure difference between them increased.

Since more steps were available when the entry criterion in the HTG group was progressively changed, these additional data are shown in Figure 4. For all indices, the relationship between $A_z$ and the mean difference in the highest recorded IOP between

Fig. 2. The distribution of the highest recorded intraocular pressure (IOP) in the normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) patients.
Table 1. The number of pairs of NTG and HTG patients remaining at each step for each of the indices

<table>
<thead>
<tr>
<th></th>
<th>No. of pairs</th>
<th>No. of normal locations</th>
<th>No. of clustered normal locations</th>
<th>Size of largest cluster of normal locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled material</td>
<td>40</td>
<td>0.604 ± 0.067</td>
<td>0.579 ± 0.071</td>
<td>0.576 ± 0.073</td>
</tr>
<tr>
<td>Highest IOP in NTG group (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;22</td>
<td>37</td>
<td>0.591 ± 0.071</td>
<td>0.566 ± 0.074</td>
<td>0.564 ± 0.076</td>
</tr>
<tr>
<td>&lt;21</td>
<td>32</td>
<td>0.586 ± 0.075</td>
<td>0.562 ± 0.080</td>
<td>0.572 ± 0.081</td>
</tr>
<tr>
<td>&lt;20</td>
<td>26</td>
<td>0.567 ± 0.085</td>
<td>0.547 ± 0.089</td>
<td>0.555 ± 0.090</td>
</tr>
<tr>
<td>&lt;19</td>
<td>16</td>
<td>0.546 ± 0.110</td>
<td>0.522 ± 0.120</td>
<td>0.504 ± 0.119</td>
</tr>
<tr>
<td>&lt;18</td>
<td>10</td>
<td>0.610 ± 0.137</td>
<td>0.570 ± 0.156</td>
<td>0.590 ± 0.155</td>
</tr>
<tr>
<td>Highest IOP in HTG group (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>38</td>
<td>0.610 ± 0.061</td>
<td>0.583 ± 0.073</td>
<td>0.580 ± 0.075</td>
</tr>
<tr>
<td>&gt;31</td>
<td>36</td>
<td>0.621 ± 0.071</td>
<td>0.583 ± 0.075</td>
<td>0.584 ± 0.077</td>
</tr>
<tr>
<td>&gt;32</td>
<td>33</td>
<td>0.649 ± 0.073</td>
<td>0.616 ± 0.078</td>
<td>0.607 ± 0.081</td>
</tr>
<tr>
<td>&gt;33</td>
<td>29</td>
<td>0.654 ± 0.077</td>
<td>0.612 ± 0.084</td>
<td>0.595 ± 0.086</td>
</tr>
<tr>
<td>&gt;34</td>
<td>25</td>
<td>0.667 ± 0.080</td>
<td>0.623 ± 0.092</td>
<td>0.615 ± 0.093</td>
</tr>
<tr>
<td>&gt;35</td>
<td>23</td>
<td>0.682 ± 0.085</td>
<td>0.621 ± 0.099</td>
<td>0.619 ± 0.100</td>
</tr>
<tr>
<td>&gt;36</td>
<td>20</td>
<td>0.718 ± 0.089</td>
<td>0.635 ± 0.111</td>
<td>0.621 ± 0.111</td>
</tr>
<tr>
<td>&gt;37</td>
<td>17</td>
<td>0.673 ± 0.100</td>
<td>0.581 ± 0.122</td>
<td>0.561 ± 0.124</td>
</tr>
<tr>
<td>&gt;38</td>
<td>14</td>
<td>0.680 ± 0.109</td>
<td>0.607 ± 0.132</td>
<td>0.592 ± 0.131</td>
</tr>
<tr>
<td>&gt;39</td>
<td>13</td>
<td>0.676 ± 0.113</td>
<td>0.602 ± 0.136</td>
<td>0.587 ± 0.133</td>
</tr>
<tr>
<td>&gt;40</td>
<td>11</td>
<td>0.745 ± 0.112</td>
<td>0.705 ± 0.134</td>
<td>0.667 ± 0.137</td>
</tr>
<tr>
<td>&gt;41</td>
<td>10</td>
<td>0.740 ± 0.120</td>
<td>0.690 ± 0.146</td>
<td>0.650 ± 0.145</td>
</tr>
</tbody>
</table>

The groups was maintained, suggesting that the level of separation between the groups was dependent on the pressure difference. This was most evident in the case of the number of normal locations where the regression slope was the steepest and statistically the most significant. The highest value of \( A_z \) attained was 0.745 which occurred when the mean pressure difference between the groups was 25.5 mm Hg.

**Discussion**

The extent to which IOP plays a role in the pathogenesis of open-angle glaucoma is important in our understanding of this disease. If IOP had the same influence in producing damage in all glaucoma patients, the features of their visual field and optic disc damage would be expected to be similar, irrespective of their IOP. It is becoming increasingly apparent that pressure-dependent differences in glaucomatous damage, although not clear-cut, do exist.

Our study shows that by progressively lowering the highest recorded IOP used by us to classify patients as having NTG and by studying the nature and extent of that part of the visual field which was undisturbed, a better separation between these patients and those who had HTG was not achieved. In fact, the separation between the two groups, on the whole, became worse. Conversely, at the other end of the IOP spectrum, as the highest recorded IOP required to be included in the HTG group was increased, the two groups tended to become more separable.

These findings have some implications for the role of IOP in visual field damage in glaucoma. Since the extent to which the NTG and HTG groups could have been separated generally increased only when the inclusion criterion in the HTG group was changed strongly suggests that IOP does not have the same influence on visual field damage in all glaucoma patients. This provides evidence that factors other than IOP may be responsible for the production of damage in some cases of glaucoma. Increasing the pressure difference between the groups had different effects on \( A_z \) depending on which end of the IOP spectrum the inclusion criterion was changed from.

Our data suggest that IOP affects the type of damage in glaucoma patients with high IOP. There is more evidence for this since we were able to increase the pressure difference between the groups further by continuing to increase the highest recorded IOP required to enter the HTG group and maintaining at least ten pairs of NTG and HTG pairs for analysis (Fig. 4). The effect of IOP on the type of visual field damage in glaucoma patients with relatively low IOP is not clearly apparent in our study.

Due to the narrower range of highest IOP measurements in the NTG group, we could not obtain the same number of steps when the entry criterion was changed in either group. Obtaining the same number of steps to allow a fuller comparison would have required at least ten NTG patients whose highest recorded IOP was less than 11 mm Hg. Such patients
are rarely encountered in clinical practice. This is an unavoidable limitation of our study. Using only five steps (in addition to the pooled material) in either direction still showed an increasing $A_z$ as the inclusion criterion was changed in the HTG group but not when that in the NTG group was changed. Having only six observations available for the regression analysis may be offset, to a degree, by the design of the study. The 40 pairs of NTG and HTG patients were matched tightly for the extent of damage in addition to the other background variables. The pairing was maintained even with the successive elimination when the pressure difference between the two groups was increased. Additionally, the visual field indices used to describe the undisturbed visual field were simple and made no assumptions of the nature and distribution of field damage.

It is important to note that NTG and HTG patients are conventionally separated by an arbitrary IOP level. We were able to show that by including in the HTG group only those patients whose highest recorded IOP was greater than 41 mm Hg, a better separation between NTG and HTG patients was attained than by including in the HTG group those whose highest recorded IOP was greater than only 29 mm Hg. The NTG and HTG distributions of any field index used in this study, however, were far from bimodal. With a mean difference in the highest re-

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Fig. 3. The area under the receiver operating characteristics (ROC) curves ($A_z$) as a function of the mean difference in highest recorded intraocular pressure (IOP) between the normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) groups for the first five steps. Open circles represent data for change in the inclusion criterion in the NTG group and the dotted line shows the best linear fit through the data points. Closed circles represent data for change in the inclusion criterion in the HTG group and the dashed line shows the best linear fit through the data points. The solid line shows the value of $A_z$ for the pooled material. Top: data for the number of normal locations; slope of dotted line = $-0.002$ ($P = 0.820$); slope of dashed line = $-0.025$ ($P = 0.001$). Center: data for the number of clustered normal locations; slope of dotted line = $0.002$ ($P = 0.780$); slope of dashed line = $-0.016$ ($P = 0.016$). Bottom: data for the largest cluster of normal locations; slope of dotted line = $-0.001$ ($P = 0.929$); slope of dashed line = $-0.012$ ($P = 0.024$).

Fig. 4. The area under the receiver operating characteristics (ROC) curve ($A_z$) as a function of the mean difference in highest recorded intraocular pressure (IOP) between the normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) groups for all steps when the inclusion criterion in the HTG group was changed. The dashed line shows the best linear fit through the data points. The solid line shows the value of $A_z$ for the pooled material. Top: data for the number of normal locations; slope = $-0.016$ ($P = 0.000$). Center: data for the number of clustered normal locations; slope = $-0.011$ ($P = 0.012$). Bottom: data for the size of the largest cluster of normal locations; slope = $-0.006$ ($P = 0.058$).
corded IOP of 25.5 mm Hg between the groups, the value of $A_z$ for the number of normal locations (the maximum obtained) was 0.745. This means that even with such a large pressure difference between the groups, there was less than a 75% chance of a randomly selected NTG patient having more normal locations (hence more localized damage) than a randomly selected HTG patient. Assuming that different mechanisms are responsible for producing selective types of field damage, it seems unlikely, therefore, that even at these extremes of IOP, the mechanisms responsible for damage to the optic nerve in glaucoma are independent.

The use of the highest recorded IOP is a clinically convenient method to separate two groups of glaucoma patients. In terms of the pathophysiology of glaucoma, however, the method is probably not a good one, since as far as visual field damage is concerned, the distinction between the groups is not unequivocal. Although this study suggests that IOP affects to a different extent the type of visual field damage in glaucoma patients, pressure may be only one of many factors which have varying influences on field and disc damage in open-angle glaucoma.

Key words: normal-tension glaucoma, high-tension glaucoma, intraocular pressure, automated perimetry

References