The Rate of Visual Field Change in the Ocular Hypertension Treatment Study

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PURPOSE. To assess the rate of change of visual field (VF) mean deviation (MD) in the Ocular Hypertension Treatment Study (OHTS).

METHODS. OHTS data were filtered to exclude eyes that had fewer than 10 reliable VFs or less than 5 years of follow-up or that reached a nonglaucomatous endpoint. The rate of change of MD (MDR) was calculated for each eye. Differences were sought between groups of eyes differing in primary open angle glaucoma (POAG) outcome, how POAG was determined, and original randomization.

RESULTS. In total, 2609 eyes (1379 participants) met the selection criteria. The mean MDR was \(-0.08 \pm 0.20 \text{dB/y} (\pm \text{SD})\). POAG eyes (\(n = 359\)) had significantly worse MDRs (\(-0.26 \pm 0.36 \text{dB/y}\)) than non-POAG eyes (\(n = 2250\); \(-0.05 \pm 0.14 \text{dB/y}; P < 0.001\)). Eyes that reached POAG endpoints based on only VF change (\(n = 74\); \(-0.29 \pm 0.31 \text{dB/y}\)) or only optic disc change (\(n = 158\); \(-0.12 \pm 0.19 \text{dB/y}\)) had significantly worse MDRs than non-POAG eyes (both \(P < 0.001\)). Eyes that reached POAG endpoints for both VF and optic disc change (\(n = 127\)) deteriorated more rapidly (\(-0.42 \pm 0.46 \text{dB/y}\)) than eyes showing only VF change (\(P = 0.017\)) or only optic disc change (\(P < 0.001\)). There was not a significant association between MDR and original OHTS randomization (observed vs. treat, \(P = 0.168\)).

CONCLUSIONS. Eyes that develop POAG have significantly worse MDRs than eyes that do not. Eyes that reached endpoints due to both VF and optic disc change had worse MDRs than eyes displaying change in only one of these. MDR was not significantly associated with randomization, suggesting that MDR may not be the best measure of VF change in early-stage POAG.

The Ocular Hypertension Treatment Study (OHTS) was a randomized clinical trial that demonstrated a benefit of lowering intraocular pressure (IOP) in patients with ocular hypertension. The OHTS found that the proportion of participants with ocular hypertension converting to primary open angle glaucoma (POAG) was approximately 50% lower in those randomly assigned to treatment than in those randomly assigned to observation. Along with this primary result, the OHTS improved our understanding of the associations between certain clinical findings and the risk for conversion to POAG.

Detection of VF change over time is challenging largely because of the numerous factors that can influence VF outcomes. Major clinical trials in glaucoma have formulated different criteria for detecting VF change over time. In the OHTS, for instance, participants were required to have qualifying standard automated perimetry (SAP) VFs that were within normal limits. A change in VFs from within normal limits to outside normal limits (Glucoma Hemifield Test [GHT] outside normal limits or Corrected Pattern Standard Deviation (CPSD)/Pattern Standard Deviation (PSD) greater than the normal 5% level) on originally two, but later three, consecutive reliable examinations was considered confirmation of VF change. This is an event-based approach because progression is deemed to have occurred when a particular event takes place, regardless of how soon after baseline it happens.

One disadvantage of event-based methods is that many intervening VF tests are not used when determining whether change has taken place and no estimate of the rate of change is produced. Other methods for quantifying VF change that use the entire test sequence have been developed. These methods have become known as trend-based techniques because they generate a continuous, numeric trend value (dB/y). Trend-based analyses can be performed using global indices, such as mean deviation (MD) or the newer visual field index (VFI) or using threshold values from individual test locations, such as pointwise linear regression (PLR).

The present study had two main purposes, to examine the rate of VF change in OHTS participants as quantified by the rate of MD change over time (MDR) and to test the hypothesis that the MDR is significantly associated with endpoint status (POAG vs. no POAG), with how the POAG endpoint was established (VF change, optic disc change, or change in both), and with the initial randomization (observed vs. treated).
Rate of Visual Field Change in the OHTS


table 1. MDrs in dB/y for Different Categories of Eyes

<table>
<thead>
<tr>
<th>OHTS Classification</th>
<th>Eyes (n)</th>
<th>Mean MDR (95% CI)</th>
<th>Median (2.5%, 97.5%) MDR for Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All eyes</td>
<td>2609</td>
<td>−0.08 (−0.08 to −0.07)</td>
<td>−0.05 (−0.52, 0.19)</td>
</tr>
<tr>
<td>No POAG end point</td>
<td>2250</td>
<td>−0.05 (−0.05 to −0.04)</td>
<td>−0.04 (−0.35, 0.20)</td>
</tr>
<tr>
<td>All POAG (optic disc and/or VF change)</td>
<td>359</td>
<td>−0.26 (−0.30 to −0.22)</td>
<td>−0.17 (−1.31, 0.12)</td>
</tr>
<tr>
<td>POAG due to VF change only</td>
<td>74</td>
<td>−0.29 (−0.36 to −0.22)</td>
<td>−0.22 (−1.21, 0.07)</td>
</tr>
<tr>
<td>POAG due to optic disc change only</td>
<td>158</td>
<td>−0.12 (−0.15 to −0.09)</td>
<td>−0.09 (−0.60, 0.13)</td>
</tr>
<tr>
<td>POAG due to either VF or optic disc change</td>
<td>237</td>
<td>−0.17 (−0.26 to −0.14)</td>
<td>−0.12 (−0.60, 0.13)</td>
</tr>
<tr>
<td>POAG due to both VF and optic disc change</td>
<td>127</td>
<td>−0.12 (−0.50 to −0.34)</td>
<td>−0.12 (−0.50, 0.34)</td>
</tr>
<tr>
<td>Randomly assigned to observation in OHTS 1</td>
<td>1302</td>
<td>−0.08 (−0.10 to −0.07)</td>
<td>−0.05 (−0.55, 0.19)</td>
</tr>
<tr>
<td>Randomly assigned to treatment in OHTS 1</td>
<td>1307</td>
<td>−0.07 (−0.08 to −0.06)</td>
<td>−0.05 (−0.46, 0.19)</td>
</tr>
</tbody>
</table>
the 2609 linear regressions performed. The mean ± SD was 0.96 ± 0.43 dB. The range was 0.25 to 6.71 dB, with 25th and 75th percentile values of 0.67 and 1.12 dB, respectively.

For participants who remained in the OHTS through its second phase, there was a transition from full threshold to the Swedish interactive thresholding algorithm (SITA standard) testing. We sought an effect of this change in strategy on MD. We fit a linear model of MD against time for each eye while including “strategy” as a binary covariate. We then determined whether the mean coefficient for strategy was significantly different from zero; it was not ($P = 0.752$). We conclude that there was no significant effect of test strategy (full threshold vs. SITA standard) on MD. Similar findings have been reported in the literature.$^{26-30}$

**DISCUSSION**

Perhaps the most striking finding from this study was that the mean MDR in eyes with ocular hypertension, including those that converted to POAG, was slow ($-0.08$ dB/yr). At this rate it would take approximately three decades for a visual field to progress from the normal mean ($MD = 0$ dB) to the 5th percentile of a healthy reference group ($MD \approx -2.2$ dB).

When we applied a criterion of $MD \leq -1$ dB/yr significant at the $P < 0.01$ level$^{31}$ to all 2609 selected eyes, only 16 ($\sim 0.6\%$) were considered to be changing rapidly. No eyes displayed positive trends at the same rate (i.e., $MD > +1$ dB/yr). When we applied a less stringent criterion ($MD \leq -0.5$ dB/yr; $P < 0.05$), 67 eyes (2.6%) were considered to be changing rapidly. The overall proportion of eyes in the wider OHTS study (without the lower limits on follow-up duration and number of tests that we applied in the current analysis) considered to have developed POAG was 11.1% (362/3272 eyes); the rate was 6.2% (204/3272) if we consider only those eyes that reached an endpoint because of confirmed VF change.$^{32}$ These values are substantially higher than the proportions reported for MDR and suggest that monitoring the rate of change of MD in ocular hypertensive eyes may underestimate the number of eyes displaying glaucomatous VF deterioration. It may also suggest that when the VFs of persons with ocular hypertension begin to change during the development of glaucoma, this change occurs at only a small number of VF locations. Local change is more likely to cause CPSD/PSD or GHT, the indices that were used to make a determination of VF change in the OHTS, to move outside their normal limits but will not cause much change in MD. The MD index is designed to “average” data from all VF locations. However, if only a few VF locations change early in the disease, the average will not contain much “change signal” and the application of point-wise methods may be preferable.$^{33,34}$

Not surprisingly, eyes reaching a POAG endpoint based on confirmed VF change had MDRs that were significantly more negative (more rapid deterioration) than non-POAG eyes. However, eyes reaching a POAG endpoint based on change evident in both the VF and the optic disc displayed the most rapid rate of MD change of any subgroup. This suggests that an eye displaying glaucomatous change at the optic disc and within the VF may have a more rapidly progressing form of the disease.

MDR in eyes originally randomly assigned to treatment in the OHTS was not significantly different from that found in eyes originally randomly assigned to observation. This finding initially seems difficult to explain given the significant difference in the number of eyes reaching a POAG endpoint in the two randomization groups.$^1$ However, this finding can be somewhat explained if it is taken together with the number of VF locations that displayed rapid deterioration (median VF

![Figure 1. Histograms of MDRs for different classes of eyes. The number of eyes in each class can be found in Table 1.](https://tvst.arvojournals.org/)
locations, 2) in eyes that displayed confirmed VF change. These findings support the notion that VF change in early glaucoma might be primarily localized. In addition, all participants were offered treatment at the commencement of phase 2 of the OHTS. Because we used the entire VF sequence from each eye, most of the eyes originally randomly assigned to observation were actually treated for a substantial portion of their follow-up. The current analysis was not optimally designed to examine the effect of treatment on MDR because that would require looking at the change in MDR at either side of a change in treatment. This question is the subject of another study.

One limitation of the method used to assess the rate of VF change in this study (linear regression) is the assumption of a constant rate of change (slope) in the calculation of the statistical significance of the slope estimate. It is not yet established that the rate of VF change in glaucoma is constant.

In conclusion, our analyses show that eyes meeting the OHTS definition of a POAG endpoint display significantly faster VF deterioration than eyes not meeting the endpoint definition, regardless of whether POAG was identified by change occurring in the VF or change in the appearance of the optic disc. Ocular hypertensive eyes that develop POAG and display both optic disc and VF change, not necessarily concurrently, had significantly more rapid VF deterioration than eyes developing POAG but only displaying change in their VF or in their optic disc.

References


