Original article

Ability of Heidelberg Retina Tomograph III to predict progression in patients with early glaucoma or suspected primary open-angle glaucoma

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ABSTRACT

Purpose: To study the ability of Heidelberg Retina Tomography III (HRT 3) measurements to predict perimeter changes in patients with early glaucoma or suspected primary open-angle glaucoma.

Material and methods: One hundred and thirty two eyes with early glaucoma or suspected glaucoma with no changes in basal perimetry were prospectively selected and periodically evaluated over five years. The eyes were divided in two groups depending on the presence or absence of progression (changes in glaucoma perimeter).

The association between morphometric parameters and baseline HRT 3 indices, glaucoma probability score (GPS) and Moorefield's Regression Analysis (MRA), and perimetry progression were studied using Cox multivariate regression analyses. Kaplan-Meier curves were used to illustrate the results.

Results: Forty-eight eyes (36.36%) showed perimeter progression. Perimeter progression showed higher correlations with the disc area (p = 0.001), the cup area (p = 0.002) and the vertical cup disc area (p = 0.001). Multivariate regression analyses showed that eyes with baseline MRA or baseline GPA changes were at a higher risk of having perimeter abnormalities and a faster progression.

Conclusions: MRA and GPA indices are useful to predict perimeter progression in patients with early primary open-angle glaucoma or suspected glaucoma. These indices can be used as risk markers of functional progression in glaucoma.

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Introduction

Glaucoma is one of the main causes of irreversible legal blindness and the second cause of blindness after cataracts. Diagnosis in initial stages and early treatment modify the course of the disease as it halts or slows down functional deterioration (visual field alteration). It seems demonstrated that when the first visual field defects appear, there is already significant loss of retinal ganglionary cells (between 25% and 40%).1

Imaging techniques for structural analysis of the optic nerve head (ONH) and the retina nervous fibre layer (RNFL) allow objective studies and quantitative assessments of the changes in said structures in the course of the disease.2-4

The Heidelberg Retina Tomograph (HRT) is a confocal scan laser that provides precise topographic maps of the optic disc and the peripapillary retina. It yields papillary morphometric parameters at the global level and for each of the six sectors in which the papilla is divided. It also has diagnostic classifications such as the Moorfield Regression (MRA) or the Glaucoma Probability Score (GPS), and follow-up analysis tools such as the Topographic Change Analysis (TCA).5

Zangwill et al6 demonstrated that HRT obtains stereometric and diagnostic parameters such as MRA that have a predictive value for discriminating patients with ocular hypertension that subsequently may progress to glaucoma.

The objective of this study is to assess the value of GPS and MRA papillary morphometric parameters as indices predicting visual field deterioration in patients with incipient glaucoma or suspected glaucoma and assess the probability that the subjects having alterations in said parameters may have of developing functional alterations.

Material and methods

A cohort observational study in which all subjects submitted to an annual regular and complete ophthalmological exploration throughout 60 months (5 years) follow-up which included slit lamp biomicroscopy, gonioscopy, intra-ocular pressure (IOP) with application tonometry, central corneal pachymetry (DGH Technology), ocular fundus evaluation with indirect ophthalmoscopy and slit lamp (with -78 dioptre Volk lens), conventional automated perimetry (AP) optic nerve headtopography with HRT 3.

The subjets included in the study had a baseline AP that was normal or with incipient alterations, ocular hypertension or papillary cup suspecting glaucoma. The age range was 18-70 and their open angle was grade IV.

The study excluded the patients with cataracts above “slight lens opacification” in accordance with the Lens Opacity Classification System III, altered baseline AP (mean standard deviation, p ≤5%), with factors preventing an adequate AP test7 or with neurological or ophthalmological diseases or insulin-dependent diabetes.

With the approval of the ethics committee of the hospital, we obtained the informed consent of all the patients that participated in the study. All the described methods complied...
with the Helsinki declaration guidelines for the use of individuals in biomedical research.

Moorfield’s regression analysis (MRA) is an HRT 3 diagnostic criterion which allows an assessment of the papilla, comparing the values of the neuro-retinal ring area of a subject with normality values included in the standard base, corrected for age and papillary size. In this way, MRA classifies the papillas as normal, suspect or pathological depending on whether the neuro-retinal ring values are within or below the Confidence Interval of 95% or below the 99.9% Confidence Interval for the normality distribution, represented with a green, yellow or red symbol, respectively. This analysis is carried out globally and for each of the 6 sectors (temporal, temporal superior, nasal superior, nasal, nasal inferior and temporal inferior).

The Glaucoma Probability Score (GPS) provides the probability value for a papilla to adjust to a glaucoma model depending on its papillary morphology (depth and verticality of cup walls) and of the peri-papillary retina. The main advantage of GPS over MRA is that it does not require tracing a contour line. The value of 0.65 was chosen as threshold on the basis of the results obtained by Alencer et al that indicate that this is the optimum threshold value for discriminating the presence of glaucomatous damages in the papilla. The values comprised between 0.28 and 0.65 were defined as borderline.

**Study groups**

1. A group with perimetric progression: forty-eight eyes exhibited progression in AP during the 5 years of the study. The progression criterion was taken to be the p value of the mean standard deviation parameter (MSD) from an initial value above 0.05 (patients with normal baseline AP or with incipient changes) up to a value smaller than or equal to 0.05 (MSD p ≤ 0.05, patients with pathological AP).

2. Group without perimetric progression: 84 eyes paired by age were selected (control group) that were assessed during the same period, fulfilled the inclusion criteria and did not exhibit changes in AP.

**Statistical analysis**

The variables analyzed by means of descriptive analysis were clinical variables (age, IOP, pachymetry and cup/vertical disc cup), perimetrical (DM and MSD) and HRT3 morphometric. The influence of the initial variables in the final result was assessed with a Cox proportional risk model or Cox multi-variant regression analysis, stratified according to two parameters: on the one hand the baseline MRA (normal or beyond normal limits) and on the other the baseline GPS (normal, pathological or borderline). The significance level for the statistical analysis was taken to be 5% (p<0.05). Kaplan-Meier curves were used, stratified on the basis of the MRA and GPS parameters to illustrate the survival analysis.

**Results**

A total of 132 eyes with incipient or suspected glaucoma were included in this study, of which 48 eyes exhibited campimetric progression (36.4%) during the follow-up period. The mean follow-up time of patients was of 57.65±13.37 months (range: 11-66 months).

In the Cox multi-variant regression analysis stratified as per the baseline MRA within or beyond normal limits, the parameters that exhibited significant association with visual field progression were disc area (p=0.000), cup area (p=0.016) and the cup/vertical disc quotient (p=0.074).

Figure 1 shows the Kaplan-Meier curve with the aggregated probability of progression in campimetry during the study, stratified on the basis of the MRA baseline value. The probability of progression is higher in eyes having an initial MRA beyond the normality limits (29% progressed to AP with alterations) vis-à-vis eyes with normal baseline values (18% progressed to AP with alterations).

Cox’s multi-variant regression analysis, stratified according to the baseline GPS (normal, pathological or borderline), the ring area parameters (p=0.000), cup volume (p=0.139), cup/vertical disc quotient (p=0.052) and cup area (p=0.056) are the ones that exhibited significant association with visual field progression.

Figure 2 illustrates the aggregate probability of visual field progression with Kaplan-Meier curves in the eyes of the study, stratified as per the GPS baseline classification. The progression of eyes with initial borderline GPA is greater (35% progressed to altered AP) vis-à-vis eyes with pathological baseline GPA (29% progressed) or normal (18% progressed). However, the period of time in which the campimetric progression appeared is shorter in the eyes with a pathological initial GPA than in those that exhibited a borderline baseline GPA. As shown in Table 1, 75% of the 48 eyes comprised in the progression group had exhibited MRA beyond normal values and 37.5% had a baseline pathological GPS, whereas of the 84 eyes without progression only 61.9% exhibited MRA beyond normal limits and 29.76% had a pathological baseline GPS.
Figure 3 shows the aggregate probability of visual field progression with Kaplan-Meier curves in the eyes of the study, stratified according to the GPS baseline classification. It can be appreciated that the progression in eyes with initial borderline values is higher (35% progressed to altered AP) compared to eyes with pathological baseline GPA (29% progressed) or normal baseline (18% progressed). However, the period of time in which the campimetric progression appeared is shorter in eyes with an initial pathological GPA than in those that exhibited a borderline baseline GPA.

The age was significantly higher in the eyes that progressed (56.0±13.11 years) than in those who did not (44.38±15.61 years). No significant differences were found in what concerns the initial IOP and pachymetry between both groups. The cup-disc quotient was higher in the group of eyes that developed glaucomatous alterations in AP but the difference was not statistically significant. The baseline perimetric parameters (DM and MSD) exhibited significant differences between groups (table 2). The morphometric parameters provided by HRT3 that exhibited significant differences between the group of eyes with campimetric progression and without it were the disc, cup and ring areas, as shown in table 3.

Discussion

HRT has a dual usefulness: on the one hand it allows a qualitative assessment of RNFL on the basis of the images it obtains of the papilla, and on the other is provides a quantitative assessment of many ONH parameters, both in area and volumes. The assessment of the RNFL thickness is semi-quantitative as the numbers it yields are obtained by extrapolation of the total retina thickness measured from a reference plane.

It is considered that the technique is reproducible if three images are taken of each eye, but even so variabilities are larger in glaucomatous patients, in vessel areas and in brusque transitions of the cup. The end result depends on factors such as refraction defects, disc area, patient age and the explorer because the latter intervenes in capturing the image, determining the reference plane and, more importantly, in profiling the papilla.

For calculating the parameters, a reference plane must be previously fixed. The HRT software calculates a standard reference plane located 50 microns behind the plane of the height of the retinal contour in the sector located between 350° and 356° of the papillary circumference. The information obtained after the topographic analysis of the papilla provides multiple quantitative parameters of the three-dimensional papillary morphology, but not all exhibit the same sensitivity and specificity for detecting glaucomatous damages. Tan et al demonstrated high reproducibility in all parameters, of which the most reproducible is the ring area.

Table 1 – Stratification of eyes based on the value of Moorfield’s regression analysis (MRA) parameters and the glaucoma probability score (GPS) of baseline exploration

<table>
<thead>
<tr>
<th></th>
<th>Eyes with AP progression (n=42)</th>
<th>Eyes without AP progression (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRA (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beyond normal limits</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>Within normal limits</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td><strong>GPS (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Borderline</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>Normal</td>
<td>13</td>
<td>27</td>
</tr>
</tbody>
</table>

AP: automated perimetry.
Previous studies have determined the existence of a correlation between the HRT and perimetry. According to Uchida et al, the parameters that best defined the presence of glaucomatous damage were those which analyze the cup, followed by those that analyze the neuro-retinal ring and finally those that are dependent on the RNFL measurements. The parameters with highest diagnostic value were CSM (Cup Shape Measure) and the

### Table 3 – Baseline morphometric parameters of the Heidelberg Retina Tomograph III (HRT 3) for the baseline exploration of eyes with and without campimetric progression

<table>
<thead>
<tr>
<th></th>
<th>Eyes with AP progression (n=42)</th>
<th>Eyes without AP progression (n=84)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc area (mm²)</td>
<td>2.02±0.06</td>
<td>2.27±0.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Cup area (mm²)</td>
<td>0.70±0.05</td>
<td>0.85±0.04</td>
<td>0.033</td>
</tr>
<tr>
<td>Ring area (mm²)</td>
<td>1.31±0.03</td>
<td>1.42±0.03</td>
<td>0.037</td>
</tr>
<tr>
<td>Quotient cup/disc area</td>
<td>0.33±0.02</td>
<td>0.36±0.01</td>
<td>0.216</td>
</tr>
<tr>
<td>Cup volume (mm³)</td>
<td>0.21±0.02</td>
<td>0.78±0.02</td>
<td>0.034</td>
</tr>
<tr>
<td>Ring volume (mm³)</td>
<td>0.31±0.01</td>
<td>0.32±0.01</td>
<td>0.237</td>
</tr>
<tr>
<td>Mean cup depth (mm)</td>
<td>0.28±0.01</td>
<td>0.31±0.01</td>
<td>0.099</td>
</tr>
<tr>
<td>Profundidad máxima de la excavación (mm)</td>
<td>0.70±0.03</td>
<td>0.76±0.02</td>
<td>0.083</td>
</tr>
<tr>
<td>Contour height variation (mm)</td>
<td>0.38±0.01</td>
<td>0.39±0.01</td>
<td>0.988</td>
</tr>
<tr>
<td>Measurement of the 3-D cup shape</td>
<td>-1.5±0.01</td>
<td>-0.14±0.01</td>
<td>0.539</td>
</tr>
<tr>
<td>Mean RNFL thickness (mm)</td>
<td>0.24±0.01</td>
<td>0.23±0.01</td>
<td>0.862</td>
</tr>
<tr>
<td>RNFL transversal area (mm)</td>
<td>1.16±0.04</td>
<td>1.22±0.03</td>
<td>0.268</td>
</tr>
<tr>
<td>Quotient of cup/horizontal disc</td>
<td>0.58±0.02</td>
<td>0.61±0.02</td>
<td>0.399</td>
</tr>
<tr>
<td>Quotient of cup/vertical disc</td>
<td>0.46±0.03</td>
<td>0.52±0.19</td>
<td>0.092</td>
</tr>
<tr>
<td>Superior retinal surface point in CL (mm)</td>
<td>-0.08±0.01</td>
<td>-0.07±0.01</td>
<td>0.308</td>
</tr>
<tr>
<td>Modulation of temporal to superior CL (mm)</td>
<td>0.19±0.01</td>
<td>0.19±0.01</td>
<td>0.817</td>
</tr>
<tr>
<td>Modulation of temporal to inferior CL (mm)</td>
<td>0.18±0.01</td>
<td>0.18±0.01</td>
<td>0.864</td>
</tr>
<tr>
<td>Mean variability of points within CL (mm)</td>
<td>0.02±0.00</td>
<td>0.02±0.00</td>
<td>0.939</td>
</tr>
<tr>
<td>Reference plane position (mm)</td>
<td>0.33±0.02</td>
<td>0.34±0.01</td>
<td>0.582</td>
</tr>
<tr>
<td>Multivariant discriminating analysis FSM</td>
<td>0.22±0.22</td>
<td>0.12±0.20</td>
<td>0.748</td>
</tr>
<tr>
<td>Multivariant discriminating analysis RB</td>
<td>1.15±0.12</td>
<td>1.00±0.10</td>
<td>0.383</td>
</tr>
<tr>
<td>Final disc area (mm²)</td>
<td>0.48±0.01</td>
<td>0.54±0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Final cup area (mm²)</td>
<td>0.33±0.01</td>
<td>0.33±0.01</td>
<td>0.088</td>
</tr>
</tbody>
</table>

Mean values were compared with a t for Student test for independent samples, the significance level of which is shown in the column at the right.

RNFL: Retina nervous fibre layers; FSM: discriminating function value according to Lester et al; CL: Contour line; RB: value of the discriminating function according to Burk et al.
cup/disc quotient. The former was more powerful because, when withdrawn from the multi-variant analysis, a greater reduction in the diagnostic performance of the remaining parameters was observed.

In 2008, Moreno-Montañés et al.\textsuperscript{12} published that GPS is more sensitive than MRA but less specific for classifying eyes in hypertensive patients without glaucoma and glaucomatous.

In our follow-up study it can be seen that the HRT parameters that best correlate with the progression of functional alterations are the disc area (p=0.001 in the Cox analysis stratified as per GPS and p=0.006 in the analysis stratified as per MRA) and the ring area (p=0.001 in the Cox analysis stratified as per GPS and p=0.003 in the analysis stratified as per MRA).

The parameters provided by HRT exhibit a high correlation with visual field indices. Thus, Iester et al.\textsuperscript{13} found that the ring area was the parameter which had the best correlation with global perimetry indices (DM and DSPC). This high correlation was also referred by Teesalu et al.\textsuperscript{14}

The initial ocular tension did not exhibit differences between patients with and without campimetric progression, but the final IOP was lower in patients with progression. This can be explained because in these patients topical hypotensor treatment was prescribed in order to hinder the disease progression.

The results of our study demonstrate that the baseline HRT parameters as well as the GPS and MRA indices are predictive of the appearance of alterations in the visual field of patients with incipient glaucoma or suspect of developing glaucoma.

REFERENCES