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HRT-3 Moorfields Reference Plane: Effect on Rim Area Repeatability and Identification of Progression

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ABSTRACT:

Aims:

To assess the effect of the Moorfields Reference Plane on Heidelberg Retina Tomograph (HRT) rim area repeatability and its effect on progression rates using an event analysis.

Methods:

The HRT reference plane (RP) defines structures above as 'rim' and below as 'cup'. The Moorfields RP applies the Standard RP (located 50 μm posterior to the temporal disc margin) at baseline and maintains the distance between the Standard RP and the reference ring (located in the image periphery) for follow-up images.

The Moorfields RP was applied to an HRT test-retest dataset and rim area repeatability coefficients were calculated. Repeatability coefficients were compared between the Moorfields, Standard and 320 (located 320 μm posterior to the reference ring) RPs.

The Moorfields RP was applied to HRT images from 198 ocular hypertensives, acquired over 6 years. HRT progression required rim area baseline/follow-up differences exceeding the repeatability coefficient in two or more sectors, with confirmation in at least one of two consecutive images. Field progression was assessed using Advanced Glaucoma Intervention Study criteria.

Results:

The Moorfields RP improved rim area repeatability compared to the Standard RP; repeatability was similar between the Moorfields and the 320 RP. The frequency of identified progression using Moorfields RP was 40% compared to 28% for the 320 RP. There was a greater percentage with concurrent field progression - 15.1% (Moorfields RP) compared to 12.1% (320 RP).

Conclusions:

Although rim area repeatability was similar using the 320 RP and the Moorfields RP, the latter resulted in greater rates of detection of change.

INTRODUCTION

Semi-automated optic nerve head (ONH) and retinal nerve fiber layer (RNFL) imaging devices have been commercially available for over a decade. These devices have potential applications in the management of patients with, or at risk of, glaucoma, both in assisting the clinician in the discrimination of normal optic discs from glaucomatous optic discs,[1-4] and in the monitoring of progression.[5-10] No consensus, however, yet exists as to how to best integrate these new technologies into clinical practice and what are the optimal operating criteria to enable their full potential to be realized.

The Heidelberg Retina Tomograph (HRT, Heidelberg Engineering, Heidelberg, Germany), which works on the principle of confocal scanning laser ophthalmoscopy, is the longest established of the scanning imaging devices used in glaucoma management. All new HRT software developments (the Explorer operational software is now in its third version) enable backward compatibility, so that images acquired using older versions of the device, such as the original HRT (now referred to as HRT 'Classic'), can be analyzed.

One approach to monitoring progression using the HRT is to monitor change in a particular stereometric parameter (such as rim area; RA) over time. A number of progression algorithms have been described which assess RA change.[5, 6, 9] RA has been proposed as a good marker for progression as it has been shown to be a repeatable, reliable and clinically meaningful HRT parameter.[11-13]

The greatest challenge in detecting progression is the ability to discriminate true change (disease process) from measurement variability. RA variability is strongly influenced by the position of the reference plane (RP).[11, 13, 14] The RP is parallel to, and below, the retinal surface and is used to define structures above the plane as 'rim' and below as 'cup'. The default RP in the Heidelberg Explorer software is the Standard RP (SRP), located 50 µm posterior to the temporal disc margin. An alternative RP, the 320 RP is located 320 µm posterior to the reference ring (which is located in the image periphery) and has been shown to result in less RA variability.[12] On this basis, our group has previously proposed the use of the 320 RP with RA-based progression algorithms.[6, 9]

We have recently described and tested a novel RP, the Moorfields RP (MRP).[15] The MRP applies the Standard RP in the baseline image and then keeps the height difference between the baseline RP and the reference ring constant for follow-up images (Figure 1).

The aim of this study was to further investigate the performance of the MRP. Firstly, the effect of the MRP on RA repeatability was assessed. Secondly its effect on the detection of glaucoma progression was investigated by applying the MRP to an HRT RA event analysis (EA) algorithm.

MATERIALS AND METHODS

Assessment of Rim Area Repeatability:

Repeatability was assessed by applying the MRP to HRT images acquired as part of an HRT test-retest study which has been described in detail elsewhere.[11, 12] In summary, 43 eyes with ocular hypertension (OHT) and 31 with primary open angle glaucoma (POAG) were imaged by two experienced observers using the HRT Classic on the same date, and on a second date within 6 weeks of the date of the first image acquisition. Subjects had no previous history of intraocular surgery and had prior experience of ONH imaging using the HRT. The acquired HRT Classic single topographies were imported as HRTport files into a beta version of HRT Explorer Version 3.1.2.0, incorporating the MRP, with which mean topography images were generated.

The British Standards Institution definition of measurement error, the repeatability coefficient (RC), was used to quantify RA repeatability.[16] 95% of inter-test differences are expected to lie within the value of the RC. RC was calculated as:

$$RC = 2 * \left(\sqrt{\frac{\sum (observation1 - observation2)^2}{n(observations)}} \right)$$

Interobserver/intervisit RA RCs (using the MRP) were calculated for the 6 predefined HRT sectors – namely superotemporal (ST), inferotemporal (IT), temporal (T), superonasal (SN), inferonasal (IN) and nasal (N). HRT image quality was defined according to the mean pixel height standard deviation (MPHSD). Each subject eye was ranked by MPHSD (taken as the mean MPHSD of observation 1 and observation 2) with good quality images ranked in the upper tertile, medium quality in the middle tertile and poor quality images in the lower tertile. Sector RA RCs generated

using the MRP were compared against previously published RCs generated using the SRP and 320 RP.[6, 12]

Assessment of HRT Progression:

The interobserver/intervisit RA RCs generated using the MRP were used as the basis for 'criteria for change' in an HRT event analysis progression algorithm.[6] In the current study, HRT progression was flagged if a decrease in sector RA (baseline - follow-up) exceeded the sector RA RC for that level of image quality (taken as the mean of the baseline and follow-up MPHSD) in 2 or more sectors and confirmed in at least 2 out of 3 consecutive images. Significant improvement was defined using the same criteria, except requiring an increase in sector RA from baseline to follow-up. This strategy was classified as event analysis 2 (EA2) in our previous report.[6]

The EA2 strategy was applied to HRT mean topographies acquired using HRT 'Classic', from 198 OHT subjects and 21 control subjects followed prospectively with regular HRT and VF testing (1994 to 2001), originally recruited to a betaxolol *versus* placebo study.[17] In brief, OHT was defined as an IOP > 22 mmHg and < 35 mmHg on 2 or more occasions within a 2-week period and a baseline mean Advanced Glaucoma Intervention Study (AGIS) VF score of 0 (Humphrey Field Analyzer, full-threshold 24-2 program).[18] Control subjects were recruited from senior citizens groups or were the spouses or friends of subjects in the OHT cohort; they were not attending the eye clinic as patients and were not seeking care nor undergoing check-ups.[8] Controls had a baseline IOP of less than 21 mmHg, normal baseline VF test results (same criteria as in the OHT group), and were excluded if there was a self-reported family history of glaucoma or any coexistent ocular or neurological pathology. There was no significant age difference between the OHT and control groups ($p = 0.09$, student t-test) and both groups had similar ethnic backgrounds, both being predominantly (> 95%) of European descent. In the current study, the same eye was selected for analysis as had been randomised in the original study. The OHT eye randomisation was based on risk to glaucomatous conversion, classified according to pattern electroretinogram results, IOP, and cup-to-disc area ratio at the time of recruitment;[17] control eyes were selected by simple randomisation.

HRT mean topographies were generated and analysed using a beta version of Heidelberg

Explorer Version 3.1.2.0. (Heidelberg Engineering, Heidelberg, Germany). The MRP was used for all analyses. A single observer (NGS) drew contour lines onto the baseline mean topographies. Contour lines were exported automatically to follow-up images. Manual alignment was used to correct for automatically 'misplaced' contour lines or if there was a magnification change. Each subject had a minimum of 5 HRT mean topographies, with all image qualities included except where satisfactory contour line alignment could not be achieved. In total, 8 mean topographies were excluded from the study, either as a result of 'double imaging' or if the image was so grainy as to prevent adequate visualisation of Elschnig's ring. The baseline HRT image was the first mean topography available for each subject and the baseline VF was taken as the VF test coinciding with, or nearest in acquisition date to, the baseline HRT mean topography.

In the absence of an accepted gold standard for defining glaucomatous progression, two proxy measures were used to generate an estimated 'specificity' for EA2 using the MRP. The first proxy measure was the number of control subjects (of 21) progressing and the second was the number of subjects (of 219) demonstrating significant improvement using the applied 'change' criteria. The number of OHT subjects identified as progressing ('positive hit rate') was compared to the previously published results for the 320 RP applied to the same OHT cohort.[6] HRT progression was compared to VF progression, which was identified if the AGIS VF score increased from 0 to 1 or more and was reproducible in three consecutive VF tests in the same region of the VF.[18] Previous studies have estimated the specificity of the AGIS VF strategy at between 91 – 100 %.[19-21]

The study adhered to the tenets of the Declaration of Helsinki and had local ethical committee approval, in addition to subjects' informed consent. All statistical analyses were performed using Medcalc Version 7.4.2.0 (Medcalc Software, Mariakerke, Belgium).

RESULTS

Interobserver/intervisit RA RCs for the SRP, 320 RP and MRP are shown in Table 1. Regardless of image quality, RA repeatability was generally poorer (higher RC values) for the SRP compared to the 320 RP and MRP. Differences were equivocal between RA repeatability using the 320 RP

and the MRP, except in the temporal sector of medium and poor quality images where the MRP generated RCs of considerably greater magnitude than the 320 RP. A formal comparison of the intertest RA differences used to generate the RCs was performed using the generalized estimating equation technique.[22] This method is related to the standard least squares linear regression, but adjusts for the fact that the RA intertest differences from the six sectors are correlated as they are derived from the same subject (in each of the 74 data sets). Using the MRP, the mean intertest RA difference was 0.001 mm^2 greater than with the 320 RP, although this did not reach statistical significance ($p = 0.229$). Using the SRP, the mean intertest RA difference was 0.004 mm^2 greater than with the 320 RP ($p = 0.04$) and 0.003 mm^2 greater than with the MRP ($p = 0.037$).

The baseline demographics and characteristics of subjects included in the progression analysis are summarised in Table 2.

The specificity for the EA2 strategy following application of the MRP was estimated as follows:

1) Number of Subjects (OHT and Control) Improving = 15 (out of 219)

   Estimated Specificity = (204/219)*100 = 93.2% (95% confidence interval 88.7 – 95.9 %)

2) Number of Controls Progressing = 2 (out of 21)

   Estimated Specificity = (19/21)*100 = 90.5% (95% confidence interval 68.2 – 98.3%)

Application of the MRP to the EA2 strategy resulted in an increased number of OHT subjects identified as progressing by HRT compared to the previously published results for the 320 RP, 24.8% of OHT subjects compared to 16.2% ($p = 0.046$, Fisher's exact test).[6] The agreement between progression identified by EA2 using either the MRP or the 320 RP and progression identified by AGIS criteria is illustrated in a Venn diagram (Figure 2). Of the 43 subjects who progressed according to the AGIS criteria, 70% also progressed by RA using the MRP, compared to 56% who progressed using the 320RP. This difference was not significant ($p=0.265$, Fisher's exact test).

DISCUSSION

The MRP was designed with the intention of combining positive attributes of both the SRP and the 320 RP, whilst at the same time compensating for their respective shortcomings. The 320 RP

is anchored to a reference ring located in the image periphery. As such the height of the reference surface (the retina in the image periphery) is likely to be more stable than the reference surface for the SRP. The SRP is anchored at the temporal disc margin, a location which may shift posteriorly as glaucoma progresses and is subject to artifact in the surface height determination near Elschnig's ring. The SRP does, however, have an advantage over the 320 RP in that it can accommodate the large degree of morphological variation of the ONH, such as oblique insertion. The 320 RP, by contrast, will be prone to generate inaccurate stereometric parameter measurements when applied to such ONHs.

The results of this study indicate that the 320 RP and MRP generate more repeatable RA measurements than the SRP, regardless of image quality. The differences in RA repeatability between the MRP and the 320 RP are equivocal. Our results suggest that the SRP has a greater tendency to generate 'noisy' RA measurements and should therefore not be considered for use when using RA to monitor progression. This does not, however, preclude the application of the SRP for other purposes; it is important to note that the Moorfields Regression Analysis algorithm uses RA measurements generated using the SRP.[2]

Alternative progression algorithms, which are stereometric parameter-independent have been proposed. One such algorithm is topographical change analysis (TCA), which is incorporated into the current Explorer software.[23] Our group has also described a method, statistic image mapping (SIM), which has been adapted from neuro-imaging techniques.[24] Both TCA and SIM measure progression by monitoring pixel-based height change. Unlike RA, the anatomical correlates of SIM and TCA are less easily understood. HRT RA change has a direct anatomical corollorary, which is well understood and may be observed both by clinical examination and by assessment of optic disc stereo-photographs. It is possible that surface height changes within the disc margin, identified by either TCA or SIM, may reflect deformation at the level of the lamina cribrosa, but this has yet to be proven.[25] TCA has been shown to have poor agreement as regards progression with disc stereo-photographs,[26] whereas RA-based techniques have a slightly better agreement with disc photography (O' Leary N, et al. Invest Ophthalmol Vis Sci 2008;49:ARVO E-Abstract 5431). It should be stressed that stereo-photography is not an

absolute gold standard for glaucomatous progression; therefore subjects identified as progressing by TCA or SIM but not by photographic examination may very well still be progressing, but in a fashion which cannot be appreciated using the latter technique. As most of our understanding regarding progressive structural changes in glaucoma has been based on careful clinical observations, we would encourage the continued use of stereometric parameter-based (particularly RA) progression algorithms in practice. This recommendation is not exclusive, however, as SIM and TCA are likely to pick up a proportion of genuine progressors which are different from those identified by RA change.

The MRP identified more OHT subjects as progressing than the 320 RP, with a similar estimated specificity. The MRP showed improved agreement with VF progression, although this was not statistically significant. The estimated specificity range for EA2 using the 320 RP (94.1 – 95.2%) is slightly higher than that generated for EA2 using the MRP (90.5 – 93.2%); given the number of subjects included in these estimates it is likely that there is no real difference in specificity, however, small changes in specificity can have a large effect on the 'positive hit rate'. Given the similar values obtained for our two different approaches to obtain proxy measures of specificity, it is reasonable to postulate that the specificity of the criteria applied to the MRP- and the 320 RP-generated RA are very similar. The comparison between progression rates using the different RPs is therefore fair and the observed differences in 'positive hit rate' are not simply the result of different specificity values.. These results suggest that, at a similar level of specificity, the MRP will identify more subjects as progressing than with the 320 RP and that these subjects are more likely to be genuine progressors. In our previous report we highlighted the higher 'signal to noise' ratio of the MRP and this most probably accounts for the improved detection of progression over the 320 RP, rather than RA repeatability which is similar between the two planes. Although these results require confirmation based on further prospective longitudinal studies, the apparent improved performance of the MRP over the 320 RP in detecting RA progression supports its clinical application in the longitudinal detection of structural change using HRT stereometric parameters

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	T	N	ST	IT	SN	IN
Good Image Quality (MPHSD < 21)						
Standard Reference Plane	0.043	0.033	0.011	0.018	0.017	0.007
320 Reference Plane	0.050	0.014	0.012	0.026	0.008	0.007
Moorfields Reference Plane	0.031	0.023	0.013	0.012	0.009	0.012
Medium Image Quality (MPHSD 21-35)						
Standard Reference Plane	0.083	0.047	0.036	0.047	0.018	0.032
320 Reference Plane	0.058	0.031	0.026	0.026	0.022	0.015
Moorfields Reference Plane	0.082	0.024	0.031	0.025	0.016	0.015
Poor Image Quality (MPHSD > 35)						
Standard Reference Plane	0.134	0.092	0.066	0.065	0.052	0.032
320 Reference Plane	0.109	0.068	0.057	0.046	0.049	0.029
Moorfields Reference Plane	0.161	0.071	0.055	0.049	0.042	0.024

Table 1. Interobserver/intervisit rim area repeatability coefficients (mm^2) for the standard reference plane, 320 reference plane and the Moorfields reference plane.

T = Temporal HRT sector

N = Nasal HRT sector

ST = Superotemporal HRT sector

SN = Superonasal HRT sector

IT = Inferotemporal HRT sector

IN = Inferonasal HRT sector

	OHT	CONTROL
Number of subjects	198	21
Age (Years)	60 (32–79)	65 (41–77)
Length of Follow-up (Years)	6.0 (2.3–7.2)	5.3 (3.1–6.8)
Number of HRT exams	10 (5–16)	9 (8–11)
Number of visual field exams	17 (5–33)	9 (7–14)
Baseline Mean Defect (dB)	+ 0.1 (+ 3.0–2.7)	+ 0.1 (+ 2.6–2.4)
Baseline Global Rim Area (mm^2)	1.24 (0.63–2.31)	1.35 (0.86–2.51)
Image Quality Throughout Study (MPHSD)	20 (7–186)	23 (9–80)

Table 2. Baseline demographics and characteristics of subjects included in the progression analysis. Values are given as the median (range).

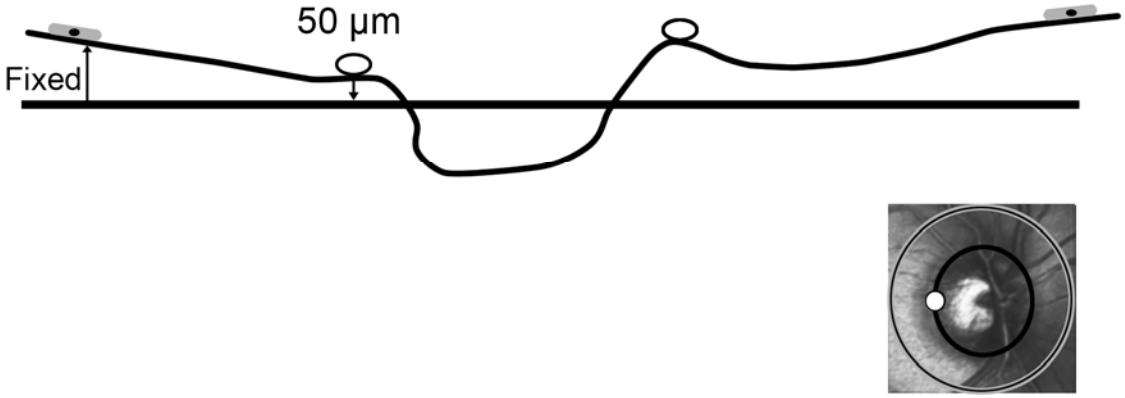

Figure 1. The location of the Moorfields Reference Plane. The height of the reference plane in the baseline image is the same as for the Standard Reference Plane, located 50 µm posterior to the temporal disc margin (white disc with black outline). The height difference between the baseline reference plane and the reference ring (black circle with grey outline) is kept constant for follow-up images.

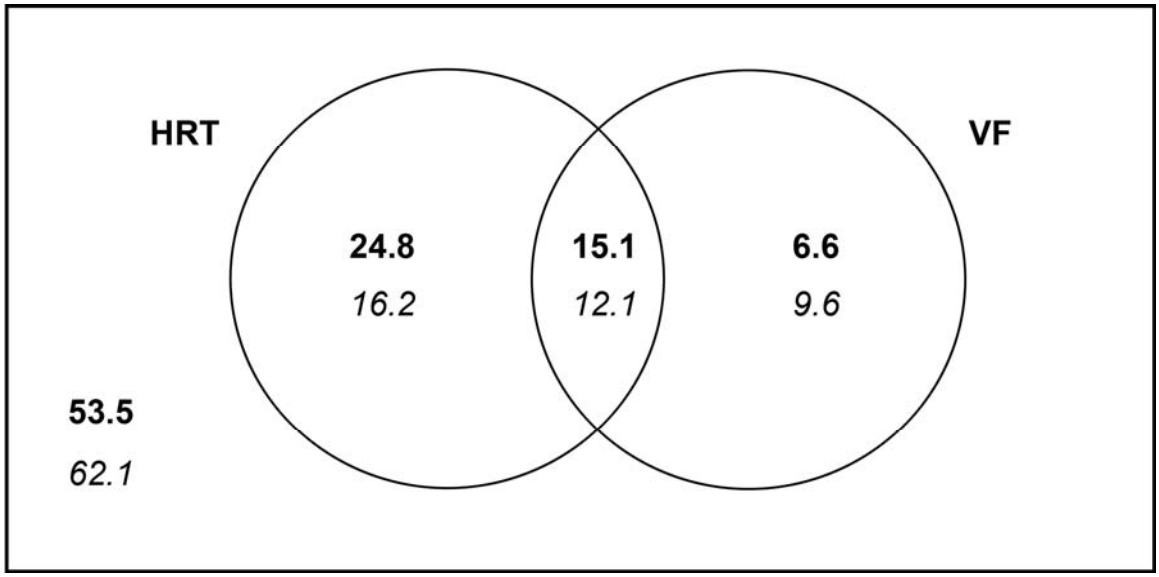

Figure 2. Venn diagram depicting the percentage of ocular hypertensive subjects (of 198) progressing by HRT Event Analysis 2 (EA2) and by AGIS visual field (VF) criteria. Values in bold are for the Moorfields Reference Plane and in italic are for the 320 Reference Plane.[6]. Estimated specificity for the HRT criteria is approximately 93%.