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**CHANGE IN OPTIC NERVE HEAD TOPOGRAPHY IN HEALTHY VOLUNTEERS  
AN ELEVEN-YEAR FOLLOW-UP**

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## **ABSTRACT**

**Aim:** To study longitudinal changes in optic nerve head (ONH) topography in healthy volunteers.

**Methods:** One eye each of 36 healthy volunteers was prospectively followed for 11 (7-13) years with the Heidelberg Retina Tomograph I (HRT I). All eyes had normal visual fields, non-glaucomatous ONHs, no defects on red-free nerve fibre layer photographs, and intraocular pressure (IOP) <22 mmHg. During the follow-up, no eye developed glaucoma; VFs remained normal, and no longitudinal changes appeared in nerve fibre layers assessed from red-free photographs or ONHs assessed from stereophotographs. The median baseline and follow-up IOPs were comparable (15 mmHg; range 10-20 mmHg, and 16 mmHg; 10-22mmHg, respectively;  $P=0.38$ ). Images were re-evaluated with HRT III and ONHs graded as normal, borderline, or glaucomatous with the Moorfield's Regression Analysis (MRA).

**Results:** Significant changes in HRT parameters indicating increased ONH cupping were detected in Cup Area ( $P=0.013$ ), Cup-to Disc Area ratio ( $P=0.015$ ), Rim Area ( $P=0.015$ ), Mean Cup Depth ( $P=0.006$ ), and Cup Shape Measure ( $P<0.001$ ). With the MRA classification, nine eyes (9/31, 29%) had a change to the worse in the global or any of the sector classifications.

**Conclusion:** Age-dependent changes occur in ONH topography detectable with the HRT.

## **INTRODUCTION**

Detection of progressive optic nerve head (ONH) changes in follow-up of glaucoma is fundamental. We know from histological studies, however, that non-glaucomatous eyes also undergo a decline in the number of nerve fibres in the ONH with age.[1, 2] Up-to-date technologies for ONH imaging provide high resolution and high reproducibility [3-5] and may be more sensitive than are clinicians in detecting ONH changes.[6, 7] The question arises whether the normal age-dependent decline in the number of optic nerve fibres causes detectable changes in ONH topography as measured with scanning laser ophthalmoscopy (SLO); this has been suggested in some cross-sectional studies[8, 9] whereas others have found no change with age. [10]

We studied longitudinal changes in ONH topography with SLO in non-glaucomatous healthy volunteers.

## **MATERIALS AND METHODS**

Forty-three healthy volunteers were recruited among hospital staff and their friends for a prospective follow-up of the ONH with SLO. One eye of each volunteer was randomly chosen for follow-up. Each underwent a complete ophthalmic examination at the study entry and the follow-up visit: best corrected visual acuity (VA) tested with Snellen charts, refraction, Goldmann applanation tonometry, slit-lamp biomicroscopy and funduscopy after pupillary dilatation with 10% phenylephrine hydrochloride. Inclusion criteria were: VA at least 0.8 Snellen Equivalent (SE), intraocular pressure (IOP) <22 mmHg, open angles on gonioscopy, non-glaucomatous ONH (no notching of the rim or diffuse enlargement of the disc cupping, fulfilment of the Inferior-Superior-Nasal-Temporal (ISNT) rule, a difference in the cup-to-disc ratios between fellow eyes of  $\leq 0.2$ , and cup-to-disc ratio was  $\leq 0.6$ ), and no signs related to exfoliation or pigment dispersion syndromes. All eyes examined fulfilled the inclusion criteria.

Visual field (VF) examinations (Octopus perimetry program G1 and G2, Interzeag Ag, Schlieren, Switzerland) were obtained and considered normal in all eyes on both visits, because of no three or more adjacent points of >5dB loss each, no two or more adjacent points of  $\geq 10$ dB loss each, nor any difference of  $\geq 10$ dB between two or more adjacent points across the nasal horizontal meridian.[11]

The retinal nerve fibre layer was assessed from red-free photographs on both visits. No eyes had signs of slit-like or diffuse nerve fibre layer defects. ONH stereophotographs were taken on both visits. In a masked fashion, M.H. and E.V. separately evaluated the red-free photographs and ONH stereophotographs for any glaucomatous progression.

Scanning laser ophthalmolmoscopy of the ONHs was performed with the HRT I (Heidelberg Retina Tomograph I, Heidelberg Engineering, Dossenheim, Germany) on both visits. Scanning was performed pupils dilated patients fixating on a target 4 m away. The ONH was scanned using a  $10 \times 10^\circ$  degree field. The software (version 2.01) creates a topographic image representing the surface height in every pixel. Keratometry values were used for correction of magnification errors. The operator draws a contour line at the inner border of the scleral ring, and the software creates stereometric variables. ONH stereophotographs were used to aid in placement of contour lines. A mean of three topographic images acquired, and approved by the internal quality program of the software, were used in analyses. The contour lines were drawn on the mean baseline images and automatically exported to follow-up mean images. The same examiner drew all contour lines.

All images were acquired with the HRT I. Images were also copied to a separate computer with a newer software, the HRT III. Baseline and follow-up images of 31 eyes were successfully re-analysed with the new HRT version to gain the Moorfield's Regression Analysis (MRA) and Glaucoma Probability Scores (GPS) classifications. [12-15] In five eyes, the conversion from HRT I to HRTIII failed. The Actual Rim Areas of the MRA output and the GPS score of the GPS output were used for statistical analysis. Global and predefined sector parameters were separately examined.

Statistical analyses were performed with the SPSS software package (version 15.0 for Windows, SPSS, Chicago, IL, USA). The Wilcoxon signed ranks test served for paired comparisons and the Spearman's correlation coefficient for correlation analyses. Summary statistics are reported as median (range). Significance was set at  $P=0.05$ . The study followed the tenets of the Declaration of Helsinki and was approved by the Helsinki Eye Hospital Ethics Committee. Informed consent was obtained from volunteers.

## RESULTS

From 43 volunteers recruited, seven failed to attend the follow-up visit in 2005. Thus, 36 volunteers (29 women, 7 men; median age 47 years, range 24-68 years) were followed for 11 (7-13) years.

At study entry, no eyes had cataracts, and all had VA at least 0.8 SE, with a median refraction in spherical equivalent of 0.0 (-3.0 - +3.0) D. Median IOP was 15 (10-20) mmHg.

One volunteer had ankylosing spondylarthritis at study entry. No other systemic diseases were reported, and none were undergoing systemic treatment. The father of one volunteer had glaucoma, while the others reported no glaucoma history among first- or second-degree relatives.

During follow-up, no eye developed glaucoma; VFs remained normal, and no longitudinal changes appeared in nerve fibre layers, as assessed from red-free photographs, or in ONHs assessed from stereophotographs. The median baseline and follow-up IOPs were comparable (15 mmHg; range 10-20 mmHg, and 16 mmHg; 10-22mmHg, respectively;  $P=0.38$ ). One eye had an increase in IOP from 20 mmHg to 22 mmHg, but others remained normotensive with IOP < 22 mmHg.

One eye developed exfoliation syndrome during the follow-up but had IOP 18 mmHg both at study entry and follow-up visit. One eye had undergone a cataract operation during the study, whereas three developed slight cataract changes, but VA still remained 1.0 SE. In three eyes with small macular pathologies (macular drusen or incipient macular degeneration), VA also remained 1.0 SE. There occurred no changes in refraction in spherical equivalent between baseline (0.0 D; -3 to 3.0 D) and follow-up visit (0.0 D; -4 to 3.0 D;  $P=0.44$ ).

Some volunteers developed systemic diseases during the follow-up; seven took medication for systemic hypertension, three for hypercholesterolemia, one for diabetes mellitus, and one for cardiac arrhythmia. One had been diagnosed with breast cancer.

With the contour line automatically exported to the follow-up image, no change was detected in Disc Area (DA, Table 1). Statistically significant changes indicating increased ONH cupping were detected

in Cup Area (CA), Cup-to Disc Area ratio (C/D), Rim Area (RA), Mean Cup Depth (MnCD), and Cup Shape Measure (CSM). Of these, the change in CSM was significantly correlated with age (correlation coefficient  $R=0.41$ ,  $P=0.012$ ). The Maximum Cup Depth (MxCD) decreased significantly at follow-up compared to baseline and this change was negatively correlated with age ( $R=-0.44$ ,  $P=0.007$ ). Figure 1 shows the distribution of percentage change in RA in relation to RA.

Table 1. Median (range) baseline and follow-up Heidelberg Retina Tomograph I (HRT I) parameters.

HRT parameter	Baseline	11-year follow-up		P	Median change Range
	Median Range	Median Range			
Disc area (mm <sup>2</sup> )	1.868	1.868		0.26	0.000 0.000, 0.000
	1.431, 2.955	1.431, 2.955			
Cup area (mm <sup>2</sup> )	0.372	0.394		0.013	0.031 -0.199, 0.405
	0.029, 1.574	0.010, 1.732			
Cup/disc area ratio	0.208	0.213		0.015	0.017 -0.107, 0.184
	0.012, 533	0.007, 0.597			
Rim area (mm <sup>2</sup> )	1.390	1.401		0.015	-0.031 -0.405, 0.199
	1.194, 2.392	0.892, 2.377			
Height variation contour (mm)	0.376	0.390		0.064	0.021 0.148, 0.155
	0.287, 0.533	0.187, 0.606			
Cup volume (mm <sup>3</sup> )	0.074	0.067		0.48	-0.001 -0.104, 0.224
	0.001, 0.614	0.000, 0.615			
Rim volume (mm <sup>3</sup> )	0.409	0.401		0.48	0.008 0.143, 0.138
	0.224, 0.865	0.120, 0.072			
Mean cup depth (mm)	0.207	0.218		0.006	0.008 -0.033, 0.072
	0.081, 0.420	0.067, 0.436			
Maximum cup depth (mm)	0.636	0.557		0.005	-0.028

	0.258, 0.918	0.211, 0.952		-0.153, 0.112
Cup shape measure	-0.206	-0.149	<0.001	0.041
	-0.333, -0.073	-0.293, -0.020		-0.034, 0.173
Mean RNFL thickness (mm)	0.261	0.259	0.86	-0.003
	0.196, 0.356	0.125, 0.408		-0.085, 0.096
RNFL cross section area (mm <sup>2</sup> )	1.285	1.335	0.89	-0.020
	1.003, 1.794	0.660, 2.021		-0.425, 0.457

RNFL = Retinal nerve fibre layer

At baseline, the MRA classified the global Rim Area as borderline in three eyes and glaucomatous in one eye. If also sector parameters were considered (i.e. the global parameter or any of the sector parameters were affected) MRA classified seven eyes as borderline and four as glaucomatous.

In three eyes (3/31, 10%) the global MRA classification changed towards a worse classification during follow-up; in 2 eyes a normal global classification changed to borderline and in 1 case, a global borderline classification changed to glaucoma. Nine eyes (9/31, 29%) had a change to the worse in the global or any of the sector classifications. One of these had a change from normal to glaucoma, and one from borderline to glaucoma. The other seven changed from normal to borderline. The median percentage change in RA in these nine eyes (-8%, -31 to 5%) did not differ from the percentage change in RA in eyes without change in MRA classification (-1.5%, -14 to 17 %; P = 0.13).

The medians of the global and predefined sector Actual Rim Areas extracted from the MRA outputs were calculated. The median global, temporal, and the temporal superior sector RA decreased statistically significantly from baseline to follow-up (Table 2).

Table 2. Actual rim areas (mm<sup>2</sup>) from the Moorfields Regression Analysis after conversion of images from HRT I to HRT III. Median (range) baseline and follow-up values are presented.



	Baseline	11-year follow-up	
Rim Area (mm <sup>2</sup> )	Median	Median	P
	Range	Range	
Global	1.54	1.46	0.018
	1.07, 2.63	1.04, 1.99	
Temporal	0.25	0.23	0.029
	0.12, 0.60	0.11, 0.41	
Temporal Superior	0.19	0.18	0.013
	0.12, 0.32	0.10, 0.29	
Temporal Inferior	0.21	0.20	0.11
	0.12, 0.37	0.11, 0.30	
Nasal	0.43	0.42	0.32
	0.30, 0.67	0.24, 0.56	
Nasal Superior	0.22	0.21	0.058
	0.12, 0.38	0.11, 0.31	
Nasal Inferior	0.23	0.23	0.071
	0.17, 0.34	0.16, 0.34	

At baseline visit, the global GPS classification suggested 6 eyes as borderline and four as glaucomatous. When the sector GPS classification was considered, five eyes were classified borderline and five as glaucomatous. If any sector had other than a normal classification, the global classification was always the same. In 7/10 eyes with borderline or glaucomatous GPS classification, all the sector and global GPS classifications had the same classification. Neither the global nor the sector GPS scores changed statistically significantly during the follow-up. GPS changed to worse in 1 eye (global classification).

## DISCUSSION

Scanning laser ophthalmoscopy has provided the clinician with an objective and highly reproducible means of examining the ONH.[3-5] Despite high reproducibility, and because of the large variation in

normal ONH topography, the diagnostic performance of HRT parameters is moderate but improves with application of linear discriminant functions or regression analyses combining several parameters.[12, 16]

The high reproducibility of scanning laser ophthalmoscopy with the HRT makes it a promising tool for follow-up to detect ONH progression in glaucoma, and various sophisticated strategies for progression analysis exist.[17-21] One concern would be that true disease progression is detected and not a physiological change over time.

In a set of healthy volunteers we found statistically significant changes in most HRT parameters indicating increased ONH cupping. From histological studies, we know that a certain degree of ONH nerve fibre loss occur in normal, non-glaucomatous eyes with age.[1, 2] It is thus tempting to assume that we were able to detect this physiological age-dependent nerve fibre loss with HRT.

The high normal variability in ONH topography may make it difficult to show any correlation between HRT parameters and age in cross-sectional studies. This may explain why Gundersen et al.,[22] in their cross-sectional study with HRT, failed to detect any age-related changes in ONH topography. Also Vernon et al.,[10] , in their cross-sectional population-based study, found no correlation between age and HRT parameters. Their study was, however, limited to include people older than 65 years of age. On the other hand, other cross-sectional studies have reported age-related ONH changes with HRT.[8, 9] Changes detected with age in cross-sectional studies could be due to population change occurring with time. To determine whether age-related differences represent an aging effect or a cohort defect, a longitudinal approach is needed.[8] However, when using HRT for longitudinal follow-up, possible change in the reference plane may cause artefactual change in the topographical parameters. Nevertheless, we found that most HRT parameters in healthy volunteers changed statistically significantly even if no glaucoma was suspected in any other follow-up method used. This indicates that HRT is sufficiently sensitive to detect age-dependent nerve fibre loss in healthy eyes in long-term follow-up.

Our finding also highlights the importance of age-specific databases. Both the Moorfield's Regression Analysis and Glaucoma Probability Score may overestimate the likelihood of glaucoma in elderly patients, perhaps because of a sub-optimal age correction in the algorithms.[13, 14, 23] In this study, one third of eyes had a change in the global or at least one sector in the MRA classification even though no change could be found by other means. This highlights that the HRT changes of the ONHs in these normal eyes are not only statistically significant but may also be clinically relevant indicating normal change with age. The percentage change in RA did not differ significantly in eyes with a change in MRA classification compared with those without change in classification. However, the subgroups were quite small. Furthermore, there could be large percentage changes in some eyes within a classification of normal or borderline, and on the other hand, in other eyes only a small percentage change could cause a change in classification.

If the age-dependent ONH change is also dependent on the age of the patient (the change in CSM was correlated with patient age), this makes the development of progression and analysis software even more complex. Furthermore, it is unknown whether any age-dependent ONH change is linear with age and in our study, participants had a wide range of age. Therefore it could be inappropriate to make age-specific or quantitative conclusions about ONH change from this study. Adding to this complexity, the ONH topography may also change as IOP changes during follow-up.[15, 24]

It may be appropriate to include senescent change in any future HRT progression software applications in order to avoid considering normal age-dependent ONH change to be glaucomatous progression. Topographical change analysis (TCA) provided by HRT III software estimates the probability that clusters of pixels have changed more than expected, taking into account local variability.[18, 25] Unfortunately, the participants in this prospective study had only one examination at baseline and one follow-up examination. The TCA requires several images for determination of baseline. Therefore, no TCA interpretation of possible change was available.

The re-evaluation of HRT I images with HRT II or III software may be affected by technical differences between versions. The older HRT I images were acquired using a 10 x 10° degree field. HRT II and III use 20 x 20° degree fields. In this study, the GPS classification seemed inappropriate as one third of

normal eyes were classified as borderline or glaucomatous and in 7/10 eyes with borderline or glaucomatous classification, all sectors and global classifications were the same. Also MRA classification resulted in an unexpectedly high frequency of eyes considered borderline or glaucomatous. This suggests that the sample is not representative of a normal population, or that it is not appropriate to analyse HRT I scans with HRT III. Because all eyes were found non-glaucomatous with other means at baseline and follow-up, our impression was that GPS classification of  $10 \times 10^\circ$  images is more or less arbitrary in some eyes and should not be used at least for clinical purposes. Also MRA classification of HRT I scans should be interpreted with caution.

Despite an uneven distribution among sexes and a small sample size, we believe that the study population was appropriate and represented a set of healthy eyes without glaucoma. They had no changes in VFs, ONHs, or nerve fibre layer photographs, and had no significant rise in IOP. However, there is a probability that, because of the limited sample size and certain morphometric inclusion criteria, the study population do not well represent a population of normals.

Even though accommodation was controlled for by having the subject fixating on a distant target, it is possible that age-dependent changes accommodation could affect the results. Even though the mean DA was identical at baseline and follow-up visit, the P-value was not 1. This is explained by that there were individual eyes (7 out of 36) in which the DA changed slightly; all changed by  $0.001 \text{ mm}^2$ . The changes in DA were minimal because the contour lines from the baseline images were automatically exported to the follow-up images. However, it is possible that minor changes in DA could actually happen. If this is true, using the same contour line could be a source of error when measuring the other HRT parameters. Automatic export of the contour line does, however, exclude subjective examiner-dependent bias and reduces variation.

In conclusion, the senescent changes in ONH topography in healthy eyes previously described in cross-sectional studies seem to be confirmed in this longitudinal series.

#### **LICENCE FOR PUBLICATION**

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## COMPETING INTERESTS

None

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## **FIGURE LEGENDS**

Figure 1. Percentage change in Rim Area in relation to RA

