



Use of the Heidelberg Retina Tomograph (HRT) in the Ocular Hypertension Treatment Study (OHTS)

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The Confocal Scanning Laser Ophthalmoscopy (CSLO) Ancillary Study to the Ocular Hypertension Treatment Study (OHTS) was initiated in 1995 to investigate the effectiveness of CSLO (Heidelberg Retina Tomograph [HRT], Heidelberg Engineering, Heidelberg, Germany) to objectively and quantitatively detect glaucomatous changes of the optic disc in ocular hypertensive patients and determine whether CSLO measurements are an accurate predictor of the development of primary open-angle glaucoma (POAG) in ocular hypertensive patients.^{1,2} The OHTS, a National Eye Institute–sponsored randomized clinical trial, demonstrated that (1) treatment for ocular hypertension can delay or prevent the onset of POAG; that (2) structural damage is often an early sign of POAG (55% of POAG endpoints were first classified on stereophotograph-based optic disc changes alone); and that (3) baseline stereophotograph-based cup/disc ratio was among the predictors for the onset of POAG.^{3–5} With its large cohort of ocular hypertensive participants without clinically evident optic disc or visual field damage at study entry, the OHTS provides a unique opportunity to evaluate whether baseline HRT parameters are associated with the development of POAG in ocular hypertensive patients. This chapter will briefly summarize the CSLO Ancillary Study to the OHTS published cross-sectional results and will describe the results indicating that baseline HRT measurements are significantly associated with the development of POAG.

STUDY DESIGN

Four hundred and fifty-one subjects from seven of the 22 OHTS clinics participated in the CSLO Ancillary Study to the OHTS (Hamilton Glaucoma Center, University of California, San Diego, California; Devers Eye Institute, Portland, Oregon; Henry Ford Medical Center, Troy, Michigan; Jules Stein Eye Institute, University of California, Los Angeles, California; University of California, Davis, California; Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania; and New York Eye and Ear Infirmary, New York, New York). All participants met the inclusion and exclusion criteria outlined for the OHTS,⁴ that is they had elevated intraocular pressure (IOP) and normal-appearing optic discs and visual fields at study entry. At each CSLO Ancillary Study Center, OHTS participants completed HRT imaging annually at the OHTS dilated visit. Three 10° images centered on the optic disc were obtained on both eyes, and three 15° images were obtained on the right eye. The mean images were used in all analyses. Corneal curvature measurements were used to correct for magnification

error, and corrective lenses were used during image acquisition when astigmatism was greater than one diopter. Standardized quality assessment, image processing, and data analysis were completed at the University of California, San Diego CSLO Reading Center.

SUMMARY OF BASELINE CROSS-SECTIONAL RESULTS

The CSLO Ancillary Study to the OHTS baseline publications^{1,2} suggested the following:

- HRT stereometric measurements were correlated with stereophotograph-based diameter cup/disc ratio measurements even in OHTS participants with normal-appearing optic discs.²
- HRT optic disc measurements describe features that were reflected in standardized assessment of cup/disc diameter ratios from stereophotographs.²
- No associations between HRT measurements and gender, diabetes, systemic hypertension, cardiovascular disease, IOP, or visual function were found.²
- African Americans had significantly larger mean optic discs, cups, neuroretinal rims, and cup/disc ratios, and smaller mean rim/disc ratios than other OHTS CSLO Ancillary Study participants.¹
- Racial differences in topographic optic disc parameters could be largely explained by the larger mean optic disc in African American participants compared with other participants.¹
- Optic disc size should be considered when evaluating the appearance of the optic disc in glaucoma.¹

DEVELOPMENT OF POAG IN THE OHTS⁶

The primary endpoints for the OHTS were the development of either a confirmed visual field abnormality or a confirmed clinically significant stereophotograph-based optic disc deterioration attributed to POAG. With a median follow-up of 48.4 months for eyes developing POAG, five CSLO Ancillary Study to the OHTS participants developed bilateral POAG and 31 developed unilateral POAG. Of the 41 POAG eyes, nine initially reached endpoint based on visual fields alone, 31 initially on stereophotographs alone, and one based on concurrent visual fields and stereophotographs. The median follow-up of the 432 participants (824 eyes) that did not develop POAG was 84.1 months.

BASELINE HRT MEASUREMENTS ARE ASSOCIATED WITH THE DEVELOPMENT OF POAG⁶

Using the CSLO measurements obtained at entry into the CSLO Ancillary Study to the OHTS, baseline HRT stereometric parameters and indices (HRT classification and Moorfields Regression Analysis [MRA]) were found to be statistically significantly associated with the development of POAG among OHTS participants.⁶ (See Table 8.1 adapted from Zangwill et al, *Archives of Ophthalmology*, 2005.⁶) Specifically, compared to a result within normal limits, an overall, global, temporal inferior, and nasal inferior MRA classification as outside normal limits increased the POAG risk by 2.39, 3.37, 5.80, and 4.19, respectively, in multivariate models that controlled for age, IOP, pattern standard deviation, central corneal thickness, history of heart disease, and medication status as a time-dependent covariate. Confidence intervals (CIs) around these estimates were large, with hazards ratios (95% CI) of 2.39, (1.02, 5.62), 3.37 (1.13, 9.99), 5.80 (1.60, 21.00), and 4.19 (1.61, 10.91) respectively. MRA temporal superior region also was associated with the development of POAG, with a hazard ratio (95% CI) of 3.28 (0.98, 10.98).

It should be noted that the majority of eyes with MRA outside normal limits at baseline did not develop POAG within the follow-up period analyzed. The proportion of participants developing POAG with baseline values outside normal limits (positive predictive value) ranged from 14% to 40%. Specifically, among participants with values outside normal limits at baseline, the positive predictive value was 14% by HRT classification (20 of 148), 14% (10 of 71) by MRA overall, 18% (7 of 38) by MRA nasal, 22% (7 of 31) by MRA nasal inferior, 26% (5 of 19) by MRA global, and 40% (4 of 10) by MRA temporal superior. Further analysis is needed to determine whether participants with POAG endpoints and MRA and HRT classification within normal limits at baseline when the visual fields and optic disc photographs were not considered glaucomatous, had measurements outside normal limits during their later follow-up examinations.

On the other hand, the vast majority of eyes with HRT classification or MRA within normal limits did not develop POAG. Specifically, the predictive value of a negative test was high; between 92% and 95% of eyes with HRT classification or MRA within normal limits at baseline did not develop POAG during the follow-up period included in this analysis. These results suggest that HRT indices consistently within normal limits may assist the clinician in identifying ocular hypertensive eyes that have a lower probability of developing glaucoma.

TABLE 8.1: Multivariate Hazard Ratios for the Development of POAG

(Adapted from Zangwill et al, *Archives of Ophthalmology*, 2005 [in press]⁶)

		Multivariate* Hazard Ratio (95% CI)
HRT Measures Significantly Associated with the Development of POAG	Mean height contour (per 0.1 mm greater)	2.69 (1.62, 4.49)
	Cup area-to-disc area (per 0.1 greater)	1.25 (1.02, 1.53)
	Mean cup depth (per 0.1 mm greater)	1.60 (1.15, 2.22)
	Reference height (per 0.1 mm greater)	1.49 (1.03, 2.17)
	Rim area (per 0.2 greater)	0.57 (0.42, 0.78)
	Rim area/disc area (per 0.1 greater)	0.76 (0.62, 0.93)
	Rim volume above reference (per 0.1 mm ³ greater)	0.65 (0.47, 0.91)
HRT Measures Not Significantly Associated with the Development of POAG	Disc area (per 0.4 mm ² greater)	0.86 (0.57, 1.30)
	Cup area (per 0.3 mm ² greater)	1.21 (0.96, 1.53)
	RNFL thickness (per 0.1 mm greater)	0.66 (0.35, 1.23)
	Cup shape (per 0.1 greater)	1.02 (0.62, 1.67)
	Cup volume below surface (per 0.1 mm ³ greater)	1.10 (0.97, 1.25)
	RNFL cross-sectional area (per 0.3 mm ³ greater)	0.72 (0.48, 1.06)
	Cup volume below reference (per 0.1 mm ³ greater)	1.20 (1.01, 1.43)
HRT Indices Associated with the Development of POAG (outside normal limits versus not)	HRT classification	2.54 (1.31, 4.90)
	MRA overall	2.39 (1.02, 5.62)
	MRA global	3.37 (1.13, 9.99)
	MRA temporal inferior	5.80 (1.60, 21.00)
	MRA temporal superior	3.28 (0.98, 10.98)
	MRA nasal inferior	4.19 (1.61, 10.91)
HRT Indices Not Associated with the Development of POAG (outside normal limits versus not)	MRA nasal superior	0.72 (0.11, 4.63)
	MRA nasal	1.59 (0.48, 5.24)
	MRA temporal	2.48 (0.66, 9.22)

* Multivariate model contains baseline age, intraocular pressure, pattern standard deviation, central corneal thickness, and history of heart disease, with medication status as a time-dependent covariate; 112 eyes were excluded from the multivariate analyses due to missing central corneal thickness values.

In addition to the HRT indices, stereometric parameters also were significantly associated with the development of POAG in participants of the CSLO Ancillary Study to the OHTS. A larger baseline HRT mean height contour, mean cup depth, cup area-to-disc area, and cup volume below reference, and a smaller rim area, rim volume, and rim area-to-disc area were significantly associated with the development of POAG in multivariate models. These results are similar to the OHTS finding that a larger baseline stereophotograph-based vertical cup/disc ratio was predictive of the onset of POAG with a multivariate hazards ratio (per .1 larger) of 1.32 (1.19–1.47).³ As our cross-sectional analysis found that the larger optic cups, neuroretinal rims, and cup/disc ratios in African Americans compared with other participants could be explained by their larger disc size, we hypothesized that a large disc may be a significant predictor of the development of POAG in OHTS participants. The results of the current analysis did not confirm this hypothesis; disc area was not significantly associated with the development of POAG.

It should be noted that due to the limited number of POAG endpoints, stereophotograph-based cup/disc ratios were not included in the multivariate models at this time, as the measurements are highly correlated with HRT parameters. Therefore, this study did not yet determine whether the OHTS prediction model that includes baseline HRT measurements is improved over one that includes baseline stereophotograph cup/disc ratio measurements. This analysis will be completed in the future, when a larger number of POAG endpoints are available to adequately address this issue.

Although several HRT measurements were consistent predictors of POAG in the multivariate models, the large confidence intervals with the proximity of the lower confidence limit to one and the limited positive predictive value of the indices suggest that it is not prudent to rely on a single parameter when making clinical decisions. Longer follow-up is needed to better estimate the true predictive ability of the HRT measures. Moreover, as highlighted in other chapters of this primer, clinical decisions should be based on using HRT results with other clinical tools including the clinical examination and tests of visual function.

RESULTS OF BASELINE HRT ASSOCIATIONS WITH THE DEVELOPMENT OF POAG

- Baseline HRT stereometric optic disc parameters and HRT indices are significantly associated with the development of POAG in OHTS participants.
- The vast majority of eyes (92% to 95%) with an MRA result within normal limits at baseline did not develop POAG during the follow-up period.
- Further analysis is needed to determine whether participants with POAG endpoints and baseline HRT results within normal limits (when their visual fields and optic discs also did not appear glaucomatous) had measurements outside normal limits during their later follow-up examinations.

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