Ville Saarela

STEREOMETRIC PARAMETERS OF THE HEIDELBERG RETINA TOMOGRAPH IN THE FOLLOW-UP OF GLAUCOMA

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Abstract

Glaucoma is a progressive neuropathy of the optic nerve. It causes degeneration of ganglion cell axons resulting in defects in the retinal nerve fibre layer (RNFL) and characteristic changes in the optic nerve head (ONH). The Heidelberg Retina Tomograph (HRT) is a confocal scanning laser imaging device, which measures the topography of the ONH and the adjacent RNFL. To quantify the measurements of the ONH topography, various stereometric parameters are calculated.

The change in the stereometric parameters of the HRT was studied in 34 eyes with glaucomatous progression in RNFL photographs and 34 eyes without progression. The change in only one stereometric parameter, the cup shape measure, showed a statistically significant correlation with the progression of the RNFL defect. An optimised change in the best three-parameter combination had 77% sensitivity and 79% specificity for progression.

The change in the stereometric parameters was compared in 51 eyes with glaucomatous progression in stereoscopic ONH photographs and 425 eyes without progression. The parameters having the best correlation with progression include cup:disc area ratio, vertical cup:disc ratio, cup volume and rim area. The parameter with the largest area under the receiver operating characteristics curve (0.726) was the vertical cup:disc ratio. A change of 0.007 in the vertical cup:disc ratio had a sensitivity of 80% and a specificity of 65% for progression.

The factors having the most significant effect on the sensitivity and specificity of the stereometric parameters for progression were the reference height difference and the mean topography standard deviation, indicating image quality. The change in image quality and age also showed a consistent, but variably significant influence on all parameters tested.

Exercise was associated with an increase in variance in 17 of the 18 stereometric parameters.

In conclusion, the change in the stereometric parameters provides useful information on ONH topography, especially when image quality is excellent. However, the evaluation of glaucomatous progression should not rely solely on the stereometric parameters of the HRT.

Keywords: glaucoma, Heidelberg Retina Tomograph, optic nerve head, progression, retinal nerve fibre layer.
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Abstract

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Keywords: glaucoma, Heidelberg Retina Tomograph, optic nerve head, progression, retinal nerve fibre layer
To my family
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Oulu, October 2010

Ville Saarela
### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AGIS</td>
<td>Advanced Glaucoma Intervention Study</td>
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<tr>
<td>CIGTS</td>
<td>Collaborative Initial Glaucoma Treatment Study</td>
</tr>
<tr>
<td>CLM</td>
<td>Contour Line Modulation</td>
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<tr>
<td>ECC</td>
<td>Enhanced Corneal Compensation</td>
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<td>EGPS</td>
<td>European Glaucoma Progression Study</td>
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<td>EMGT</td>
<td>Early Manifest Glaucoma Trial</td>
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<td>GCP</td>
<td>Glaucoma Change Probability</td>
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<tr>
<td>GDx</td>
<td>Imaging device using scanning laser polarimetry</td>
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<td>GPA</td>
<td>Glaucoma Progression Analysis</td>
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<td>GPS</td>
<td>Glaucoma Probability Score</td>
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<tr>
<td>HRT</td>
<td>Heidelberg Retina Tomograph</td>
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<tr>
<td>IOP</td>
<td>Intraocular Pressure</td>
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<tr>
<td>LDF</td>
<td>Linear Discriminant Function</td>
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<tr>
<td>MD</td>
<td>Mean Deviation</td>
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<tr>
<td>MRA</td>
<td>Moorfields Regression Analysis</td>
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<tr>
<td>OCT</td>
<td>Optical Coherence Tomography</td>
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<tr>
<td>OHTS</td>
<td>Ocular Hypertension Treatment Study</td>
</tr>
<tr>
<td>ONH</td>
<td>Optic Nerve Head</td>
</tr>
<tr>
<td>POD</td>
<td>Proper Orthogonal Decomposition</td>
</tr>
<tr>
<td>RNFL</td>
<td>Retinal Nerve Fibre Layer</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristics</td>
</tr>
<tr>
<td>SAP</td>
<td>Standardised Automated Perimetry</td>
</tr>
<tr>
<td>SIM</td>
<td>Statistical Image Mapping</td>
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<tr>
<td>TCA</td>
<td>Topographic Change Analysis</td>
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<tr>
<td>TSD</td>
<td>Topography Standard Deviation</td>
</tr>
<tr>
<td>VCC</td>
<td>Variable Corneal Compensation</td>
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List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:


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1 Introduction

Glaucoma is the second leading cause of blindness in the world (Quigley & Broman 2006). The visual impairment due to glaucoma is irreversible. In Finland, there are 80000 patients diagnosed with glaucoma. The prevalence increases with age, being up to 10% in a population over 80 years of age (Mitchell et al. 1996). The course of glaucoma is typically a slowly progressing one, but the rate of progression varies (Airaksinen et al. 1992, Heijl et al. 2002). Since the progression of glaucomatous damage can be prevented or delayed with treatment (Leske et al. 2003, Maier et al. 2005), it would be important to identify the patients with a high rate of progression.

Glaucoma causes degeneration of ganglion cell axons. The structural damage can be seen as defects in the retinal nerve fibre layer and as topographic changes in the optic nerve head. The corresponding functional damage can be detected in the visual fields (Quigley et al. 1982, Airaksinen et al. 1985). However, glaucomatous changes in the optic nerve head, the retinal nerve fibre layer and the visual fields may manifest themselves at different times during follow-up (Tuulonen et al. 2003).

Glaucomatous damage in the optic nerve head can be detected with ophthalmoscopy, fundus photography and scanning laser ophthalmoscopy. Both ophthalmoscopy and the evaluation of photographs are subjective methods and subject to high variation between observers (Lichter 1976, Varma et al. 1992). A quantitative analysis of optic nerve head topography can be achieved with scanning laser ophthalmoscopy.

The Heidelberg Retina Tomograph is a confocal scanning laser imaging device, which measures the topography of the optic nerve head and the adjacent retinal nerve fibre layer (Zinser et al. 1989). To quantify the measurements of the optic nerve head topography, various stereometric parameters are calculated (Burk et al. 1990). The change in stereometric optic nerve head parameters may be used for detecting glaucomatous progression. The aim of the research was to study how the change in the stereometric parameters correlates with glaucomatous progression. Factors that may affect the correlation with progression were also evaluated.
2 Review of the literature

2.1 Summary of the literature search

A literature search in PubMed was performed on 2nd of March 2010. After the exclusion of case reports and articles not related to the topic or using irrelevant methodology, 40 articles written in English were included. An additional 16 articles were identified in the references of the 40 articles and the Cochrane database. The specifics of the search are given in Figure 1.

PubMed search with keywords “glaucoma” and “progression”:
\[ n = 1668 \]
\[ \rightarrow n = 1572 \]

Keywords “Heidelberg Retina Tomograph or scanning laser ophthalmoscopy or optic nerve head topography or optic disc topography” added: \[ n = 96 \]
\[ \rightarrow n = 17 \]

Included based on language (English): \[ n = 79 \]
\[ \rightarrow n = 19 \]

Included based on title: \[ n = 60 \]
\[ \rightarrow n = 17 \]

Included based on abstract: \[ n = 43 \]
\[ \rightarrow n = 3 \]

Included based on article: \[ n = 40 \]

Review of the references of the 40 accepted articles and the Cochrane database

\[ \leftarrow n = 16 \]

56 articles dated 1994 – 2010 accepted based on literature search

Figure 1. Flow chart summarising the literature search.
2.2 Glaucoma

Glaucoma is a progressive neuropathy of the optic nerve. It causes degeneration of ganglion cell axons resulting in defects in the retinal nerve fibre layer (RNFL) and characteristic changes in the optic nerve head (ONH). The corresponding functional damage can be detected in the visual fields (Quigley et al. 1982, Airaksinen et al. 1985).

2.2.1 Epidemiology, risk factors and consequences of glaucoma


The estimated prevalence of open-angle glaucoma is 0.2–1.0% in people between 40 and 50 years of age in a predominantly Caucasian population. The prevalence increases with age, being 2–10% in a population over 80 years (Tielsch et al. 1991, Mitchell et al. 1996, Reidy et al. 1998).

In 2010 there are approximately 61 million people suffering from glaucoma worldwide, 8.4 million of them bilaterally blind (Quigley & Broman 2006). In Finland, there are 80000 patients treated for glaucoma. It is the second most common cause of visual impairment in the elderly after macular degeneration (Finnish Register of Visual Impairment 2008). The visual impairment due to glaucoma is irreversible.

In addition to visual deterioration, glaucoma also imposes an economical burden on both the patient and society. Expenses arise from treatment, follow-up and visual disability due to glaucoma (Vaahtoranta-Lehtonen et al. 2007). The severity of glaucomatous damage correlates to the increased overall cost of illness (Fiscella et al. 2009).
2.2.2 Course and management of glaucoma

The course of open-angle glaucoma is typically a slowly progressing one (Tuulonen et al. 2003). There is progression of glaucomatous damage despite treatment (Migdal et al. 1994, AGIS Investigators 2000). With treatment the visual impairment due to glaucoma can be delayed by several years. It has been estimated to take a mean time of 23 years without treatment and 35 years with treatment for glaucomatous damage to progress from mild visual field damage to at least unilateral blindness (Burr et al. 2007). The estimate is based on randomised controlled trials of treatment vs. non-treatment. However, the rate of progression varies between patients (Airaksinen et al. 1992, Collaborative Normal Tension Glaucoma Study Group 1998a, 1998b, Heijl et al. 2002).

Risk factors for glaucomatous progression include exfoliation, age, bilaterality of glaucoma, thin central corneal thickness, optic disc haemorrhages, high IOP at baseline and follow-up and advanced glaucomatous damage at baseline (Airaksinen et al. 1981, Leske et al. 2003, Chauhan et al. 2008). Fluctuation of IOP may also increase the risk of progression (Asrani et al. 2000, Caprioli & Coleman 2008), although no correlation was found in the Early Manifest Glaucoma Trial (Bengtsson & Heijl 2005).

Currently, the only effective treatment for glaucoma is to lower IOP (Tuulonen et al. 2003, Burr et al. 2007). The onset of glaucoma is prevented or delayed by IOP reducing treatment in patients with ocular hypertension (Kass et al. 2002). The progression of glaucomatous damage is also delayed by treatment in both patients with normal tension glaucoma (Collaborative Normal Tension Glaucoma Study Group 1998a, 1998b) and patients with high initial IOP (AGIS Investigators 2000, Leske et al. 2003, Maier et al. 2005).

IOP can be reduced with medication, laser treatment or surgery. The IOP reduction is greatest with surgical treatment (AGIS Investigators 1998, Lichter et al. 2001, Burr et al. 2004). In patients with high initial IOP, it is superior to medical and laser treatment in reducing visual field progression (Migdal et al. 1994). Cataract surgery also modestly lowers IOP (Pohjalainen et al. 2001), and the effect is sustained for several years (Falck et al. 2009).

2.3 Diagnosis of glaucomatous damage

There are several different diagnostic criteria for glaucoma in the scientific literature. The diagnosis is based on the evaluation of the ONH, RNFL and visual fields. A
meticulous clinical examination including IOP measurements, biomicroscopy and
gonioscopy is needed to differentiate between different types of glaucoma. Even
in recent diagnostic studies, there is variation in the definition of glaucomatous
damage (Burr et al. 2007).

Albrecht von Graefe reported in 1855 that glaucoma may cause excavation
of the ONH (von Graefe 1855). Since then, the morphology of the ONH has
been examined using several methods. The clinical evaluation of the ONH
may be done using direct ophthalmoscopy, binocular ophthalmoscopy or ONH
photography (Jonas et al. 1999). Direct ophthalmoscopy has the disadvantage
of missing stereopsis. With ophthalmoscopy, no permanent record is left if the
appearance of the ONH is not drawn by the examiner. Both ophthalmoscopy and
the evaluation of ONH photographs are subjective methods and as such subject to
high variation even between expert observers (Lichter 1976, Varma et al. 1992).
Several classification systems for glaucomatous ONH damage have been proposed
2006). A quantitative analysis of ONH topography can be achieved with scanning
laser ophthalmoscopy.

The RNFL can be evaluated using green light on ophthalmoscopy. Documentation of the RNFL is achieved with high-resolution black-and-white
RNFL photography using a green or blue filter (Airaksinen & Nieminen 1985).
The interpretation of the images is subjective, but semiquantitative scoring of
the defects has been presented (Airaksinen et al. 1984, Quigley et al. 1993). A
quantitative analysis of the thickness of the RNFL can be obtained with scanning
laser polarimetry or optical coherence tomography (OCT).

Visual field testing can be performed using static or kinetic perimetry. In static
perimetry the visual object is stationary and in kinetic perimetry it is moving. In
static perimetry the sensitivity threshold for seeing is determined for each point of
measure in a test grid. Partly due to the pattern of glaucomatous visual field defects,
kinetic perimetry may be of less value in the diagnostics of glaucoma (Heijl et al.

In frequency doubling perimetry rapidly flickering stimuli are presented in the
visual field. Due to frequency doubling illusion, twice as many bars as actually exist
are seen in a normal field. A higher contrast level has to be used in the abnormal
regions of the visual field for the illusion to occur (Cello et al. 2000).

Standardised automated perimetry (SAP) is considered the current reference
standard for detecting glaucomatous visual field defects (Foster et al. 2002,
Tuulonen et al. 2003). The two most commonly used instruments are the Humphrey
and Octopus perimeters. Static perimetry is performed to the central visual field, usually limited to the 24-degree or 30-degree area, with test points 6 degrees apart. The reference standard is white-on-white perimetry (white testpoints on a white background), but in short-wavelength automated perimetry blue testpoints on a yellow background are used. Short-wavelength automated perimetry measures the blue cone system of the visual pathway and may detect very early loss of sensitivity in the visual fields (Johnsson et al. 1993). However, it is more difficult and time-consuming and has a higher test-retest variability compared to white-on-white perimetry (Blumenthal et al. 2003, Burr et al. 2007).

2.3.1 Stereoscopic optic nerve head photography

Stereoscopic ONH photography has been shown to be effective in evaluating glaucomatous changes (Airaksinen et al. 1984, Quigley et al. 1992). It is a well-established documentation of basic clinical examination that has remained unchanged for decades. The validity of the method has been verified in large randomised controlled clinical trials such as the Ocular Hypertension Treatment Study (OHTS), the European Glaucoma Prevention Study (EGPS) and the Early Manifest Glaucoma Trial (EMGT) (Gordon & Kass 1999, Leske et al. 1999, Miglior et al. 2002b). These studies show that by standardising the evaluation of stereoscopic ONH photographs, it can be performed in a reproducible manner (Zeyen et al. 2003, Parrish et al. 2005).

The stereoscopic ONH photographs are obtained in either a simultaneous or a sequential manner. In simultaneous stereophotography a camera with a beam-splitting prism may be used to capture the images with a fixed relative angle (Donaldson et al. 1980). The advantage of a fixed stereobasis is the reproducibility of the stereo-effect and the stereometric measurements. With sequential photography the stereo-effect is achieved by lateral shift of a normal fundus camera with a built-in stopper keeping the relative angle constant.

In order to see the three-dimensional appearance of the ONH, both images in a stereo pair are viewed simultaneously. This may be achieved by convergent or divergent view of adjacent images with the right and the left eye fixating on different images. Other methods include flicker glasses rapidly alternating the image between the eyes (Morgan et al. 2005) and a stereoviewer, a method also used with stereo slides (Armaly 1969, Reus et al. 2010).

Stereoscopic ONH photography is a qualitative method and there is variability in the detection of glaucomatous damage and the detection of progression using
Figure 2. Stereoscopic ONH photographs taken ten years apart. Progression of the glaucomatous damage can be seen in the superior and inferior quadrants.

photography (Tuulonen et al. 2003). In a recent study, general ophthalmologists from countries around Europe evaluated a set of ONH photographs of glaucoma patients and healthy controls. The study showed moderate accuracy (80.5%) for detecting glaucoma. The average intra-observer agreement was good ($\kappa = 0.7$). The ophthalmologists participating from Finland showed the greatest specificity (93.2%) but low sensitivity (69.3%) for detecting glaucomatous damage (Reus et al. 2010).
The inter-observer variability in assessing stereoscopic ONH photographs tends to be larger than intra-observer variability (Tielsch et al. 1988, Varma et al. 1992, Zeyen et al. 2003). The inter-observer agreement for detecting progression may be improved by training (Zeyen et al. 2007). However, there is considerable inter-observer variability in evaluating progression even among glaucoma experts (Azuara-Blanco et al. 2003, Jampel et al. 2009). In the EGPS, observers evaluating progression were experienced ophthalmologists masked for the temporal sequence of the stereo photographs. The inter-observer agreement of the first evaluations of the observers was moderate, with kappa-values ranging from 0.45 to 0.60 (Zeyen et al. 2003). Knowledge of the temporal sequence has been shown to influence the determination of progression. In a setting where three observers evaluated a set of stereo photographs for progression with a knowledge of the chronology, the kappa values were 0.68 +/- 0.05. When the same set was evaluated masked for sequence, the kappa values were 0.30 +/- 0.05 (Altangerel et al. 2005).

Both colour photographs and black-and-white photographs may be used in stereoscopic ONH photography. There is evidence suggesting that with black-and-white photographs both intra-observer and inter-observer agreement of progression may be higher (Zeyen et al. 2009). A variety of methods have been presented for standardising the evaluation of stereoscopic ONH photographs in order to diminish the variability of assessments (Henderer et al. 2003, Medeiros et al. 2005, DeLeon-Ortega et al. 2006). The masked evaluation of stereoscopic ONH photographs by glaucoma specialists is still considered the reference standard for ONH evaluation (Lin et al. 2007).

### 2.3.2 Heidelberg Retina Tomograph

The Heidelberg Retina Tomograph (HRT) is a confocal scanning laser imaging device, which uses a 670 nm diode laser to measure the topography of the ONH and the adjacent RNFL (Zinser et al. 1989). The device scans a 15° angle of the retinal surface in vertical and horizontal directions in equidistant focal planes. Each plane consists of a 384 x 384 pixel array with a lateral resolution of 10 μm. The number of scanned focal planes depends on the maximum depth of the cup from the highest point on the rim. There are from 16 up to 64 focal planes scanned depending on the depth of the cup. The stack of scanned planes is aligned and reassembled and the depth of the maximal reflectance intensity of each pixel is calculated to form a three-dimensional topography image.
The device automatically performs three scans, and the mean of the three scanned images is used as the final topography image. The standard deviation of the three scanned height measurements of each pixel is calculated. The mean of these standard deviations is the topography standard deviation (TSD). If the three scanned images are uniform, the TSD is low and the quality of the topography image is high.

There have been three commercially available generations of Heidelberg Retina Tomograph. The original HRT is also referred to as HRT I or HRT classic. The device relies heavily on operator input. In addition to the 15º scan, also 10º or 20º scans can be taken with HRT I. The resolution of the 10º scan is the same as in HRT II. The lateral resolution is 10 to 20 μm/pixel and longitudinal resolution is 62 to 128 μm/plane. The image acquisition time for HRT I is around 1.4 seconds (Fingeret 2005).

Compared to its predecessor, HRT II has more automated features, such as averaging of the scans, serial scans, fine focus and scan depth. The operator is still required to manually draw the contour line defining disc margin onto the topography image (Fingeret 2005). The imaging head and the light source are different in HRT I and HRT II. The images of HRT I cannot be analysed with HRT II software.

The HRT 3 introduced several changes in the imaging software (Strouthidis & Garway-Heath 2008). The imaging head is the same for HRT II and HRT 3, making these two generations of the device backwards compatible. The HRT 3 software is also able to analyse HRT I images, but since the images are acquired with different types of imaging heads, the results of HRT I and HRT 3 are not comparable as such. Compared to HRT II a slight scaling error was corrected and the drawing of the contour line was automatised (Strouthidis & Garway-Heath 2008). Also larger and ethnicity-specific, as yet unpublished, normative databases and improvements in the image alignment algorithms were introduced. The size of the imaging hardware was reduced so that HRT 3 is portable. The lateral image resolution of HRT II and HRT 3 is 10 μm/pixel and longitudinal resolution is 62 μm/plane. The image acquisition time is typically 1.0 seconds (Fingeret 2005).

Improvements in the image alignment technique have been introduced during the continuous development of HRT. A subpixel-based image alignment algorithm improved image quality and detection of glaucomatous damage using a stereometric parameter measuring cup shape (Burk & Rendon 2001). The image alignment algorithm introduced in HRT 3 software is based on a landmarking technique used in face recognition (Capel 2004). It has been reported to decrease pixel-to-pixel variability, and marginally improve the repeatability of stereometric measures compared to HRT II (Bergin et al. 2008).
2.3.2.1 Reference plane definition

To quantify stereometric rim and cup parameters in ONH topography, a reference plane is defined (Burk et al. 1990). The reference plane is parallel to the retinal surface. It needs to be stable so that the parameters change only when true structural changes in the ONH occur (Breusegem et al. 2008). Within the disc margin, the retinal surface located above the reference plane is defined as rim and below the reference level as cup. The reference plane used in HRT I is referred to as the 320 reference plane. It is set 320 μm posterior to a reference ring located in the image periphery.

With the introduction of HRT II, the reference plane definition was changed. In HRT II and HRT 3, the reference plane lies 50 μm posterior to the temporal disc margin. It is fixed upon the most stable part of the disc margin, which is on the papillomacular bundle 4º to 10º below the horizontal meridian (Burk et al. 2000). This reference plane definition is referred to as the standard reference plane.

The 320 reference plane and the standard reference plane were compared with an individually determined reference level fixed on the ring of Eschnig (Tuulonen et al. 1994) and a reference level fixed on mean height of the 1º disc margin above the horizontal meridian (Airaksinen 1994). The standard reference plane gave the most reliable results for the diagnosis of glaucoma (Vihanninjoki et al. 2002). However, the thickness of the papillomacular bundle may be decreased due to glaucoma. This may cause underestimation of glaucomatous damage by the standard reference plane (Chen et al. 2001).

Another reference plane definition is based on measurements of RNFL thickness using the OCT (Park & Caprioli 2002). It may improve the diagnosis of early glaucomatous damage in eyes with tilted discs. An experimental reference plane that always lies beneath the contour line has been presented. It is based on the mean height of the contour line and the lowest 5% of these height values (Tan & Hitchings 2003). This reference plane definition showed the best agreement with subjective rim area estimates from topography images (Tan et al. 2004b).

There may be increased variability in rim area measurements with the standard reference plane compared to the 320 reference plane (Strouthidis et al. 2005b). The residual standard deviation from a regression slope of rim area measurements obtained from patients with progressing glaucomatous damage was highest with the standard reference plane (Poli et al. 2008). Hence, while the standard reference plane may be superior in diagnosing glaucomatous damage, the 320 reference plane may be more stable and have higher repeatability of rim area measurements during follow-up.
The Moorfields reference plane uses the definition of the standard reference plane in the baseline images. During follow-up the height difference of the standard reference plane from the reference ring used in 320 reference plane is kept constant (Poli et al. 2008). The Moorfields reference plane and the 320 reference plane have shown better repeatability of rim area measurements compared to the standard reference plane (Asaoka et al. 2009). The correlation of rim area change with identified visual field progression was higher with the Moorfields reference plane compared to the 320 reference plane (Asaoka et al. 2009).

Figure 3. A three-dimensional HRT image of the ONH. The margin of the ONH is defined by the contour line. The cross-sectional image below demonstrates the position of the standard reference plane. The reference plane is needed to distinguish between cup and rim.
2.3.2.2 **Stereometric optic nerve head parameters**

To quantify the measurements of the ONH topography, various stereometric parameters are calculated (Burk et al. 1990). The disc area is defined as the area within a contour line (Figure 3). The contour line is transferred from the baseline image to the follow-up images, keeping the disc area constant. The modulation of the contour line in the temporal to superior and temporal to inferior octants as well as the maximal elevation, depression and height variation along the contour line are calculated. In addition, the mean thickness and the cross-sectional area of the RFNL along the contour line are given.

A reference plane is defined to distinguish between cup and rim (Figure 3). The topography within the contour line and above the reference plane is defined as rim and below the reference plane as cup (Burk et al. 1990). The mean height of the reference plane from the peripapillary retinal surface is calculated. The mean and maximum depth of the cup is measured. The area and volume of the cup and rim are calculated as well as cup:disc and rim:disc area ratios. The cup:disc ratios in the vertical and horizontal directions are given.

The cup shape measure is the third moment of the frequency distribution of the depth values within the disc margin. It is obtained by dividing the square of the third moment of the distribution by the third power of the second moment. It may have values between -1 and 1 (Burk et al. 1990, Zinser et al. 1990). The value is typically negative in normal eyes with small shallow cups and frequently small depth values. It is less negative or positive in deep cups with steep slopes and frequently high depth values (Uchida et al. 1996).

\[
\text{Cup shape measure} = \frac{[\Sigma (X_i - X)^3/n]^2}{[\Sigma (X_i - X)^2/n]^3}
\]

where \( X \) is the mean depth, \( X_i \) is depth of each pixel, and \( n \) is the number of pixels within the disc margin.

Before the introduction of HRT 3, the inter-operator difference in drawing the contour line could affect the stereometric ONH parameters. However, the agreement on the stereometric parameters between masked observers drawing the contour line has been shown to be good (Hatch et al. 1999). In fact, the image-acquisition-induced variability of the parameters has been reported to be higher than the operator-induced variability (Miglior et al. 2002a). There is a difference in
the parameters calculated with different generations of the device. The parameters calculated using HRT 3 are smaller than those calculated with HRT II, due to a corrected scaling error (Gabriele et al. 2008).

The stereometric ONH parameters have been used for diagnosing glaucomatous damage (Wollstein et al. 1998). The cup shape measure has shown high diagnostic precision for glaucomatous damage (Mikelberg et al. 1995, Uchida et al. 1996, Vihanninjoki et al. 2000, Kiriyama et al. 2003). It has also been reported to be the stereometric parameter with the best correlation with glaucomatous progression in the visual fields (Harju & Vest 2001, Philippin et al. 2006). The cup shape measure is independent of the reference plane.

Rim area is a stereometric ONH parameter that can be used in the detection of both glaucomatous damage and progression (Iester et al. 1997a, Lan et al. 2003, Tan & Hitchings 2004a, Strouthidis et al. 2006, Fayers et al. 2007). It is a reference plane-dependent parameter and subject to variability due to the fluctuation of the reference height (Tan et al. 2003). However, the variability of the rim area has been reported to be smaller than the variability of the cup shape measure (Jampel et al. 2006). Small rim area has been shown to be among the most predictive parameters for future development of glaucoma in ocular hypertension, along with mean contour height and mean cup depth (Zangwill et al. 2005). Both rim area and the cup shape measure have shown high correlation with glaucomatous damage in the visual fields (Iester et al. 1997a). Global and sectoral rim area measurements have been shown to correlate with visual field indices (Lan et al. 2003).

The cup:disc area ratio and the vertical cup:disc ratio are both among the parameters with relatively high accuracy for diagnosing glaucoma (DeLeon-Ortega et al. 2006, Ferreras et al. 2008, Bozcurt et al. 2010). An advantage of rim area and cup:disc ratio parameters is that they are familiar to clinicians. The vertical cup:disc ratio can also be estimated with ophthalmoscopy and stereoscopic ONH photography. The photographic evaluation and HRT measurement of the cup:disc area ratio may be used interchangeably in the risk analysis of the OHTS (Medeiros et al. 2007). Both rim area and cup:disc area ratio have shown statistically significant change before confirmed visual field changes in ocular hypertensives converting to glaucoma (Kamal et al. 1999).

et al. 2008). The discrimination between glaucoma patients and controls is not as good in other populations compared with the original population the functions are derived from (Ford et al. 2003, Ferreras et al. 2008).

### Table 1. The linear discriminant functions for diagnosing glaucoma with stereometric ONH parameters.

<table>
<thead>
<tr>
<th>Study</th>
<th>Linear discriminant function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikelberg et al. 1995</td>
<td></td>
</tr>
</tbody>
</table>
-13.079 × (cup shape measure + (0.001981 × (50 - age))) + (10.99 × volume above the reference plane) - (7.245 × height variation along contour line) - 2.662 |
| Iester et al. 1997c  | (10.068 × inferior area below reference) - (7.018 × inferior effective area) + (4.181 × nasal mean height contour) - (2.081 × superior peak height contour) + (6.094 × cup shape measure) - (11.048 × rim volume) + 1.828 |
| Bathija et al. 1998  | (-4.37 × cup shape measure) - (5.57 × height variation along contour line) + (11.78 × mean retinal nerve fibre layer thickness) + (1.85 × rim area) - 3.722803 |
| Burk et al. 1999     | (4.197 × contour line height difference temporal - temporal superior) + (5.642 × contour line height difference temporal - temporal inferior) - (3.885 × temporal superior cup shape measure) - 0.974 |
| Mardin et al. 1999   | (0.3 × rim area) + (3.7 × rim volume) + (4.3 × retinal nerve fibre layer) - (3.7 × cup shape) - (3.1 × cup volume) - (0.9 × cup area) - 2.77 |
| Ferreras et al. 2008 | (9.41 × cup shape measure) - (8.00 × contour line modulation temporal-superior) - (4.07 × rim area) + 8.23 |

#### 2.3.2.3 Moorfields regression analysis

Moorfields regression analysis (MRA) is a method for detecting glaucomatous damage with the HRT. The MRA analyses the regression of the logarithm of the global and six sectoral rim areas to the matching disc areas and compares the results to a normative database (Wollstein et al. 1998). It defines these areas as normal, borderline and outside normal limits based on the 95% and 99.9% confidence intervals. The method accurately discriminates between healthy controls and early glaucoma patients diagnosed using stereoscopic ONH photography (Wollstein et al. 1998) or visual fields (Ford et al. 2003, Miglior et al. 2003).

The diagnostic specificity of the method is decreased by increasing size of the ONH in a non-glaucomatous population (Hawker et al. 2006). The diagnostic accuracy of MRA has been reported to be similar to stereoscopic ONH photographs.
As a screening method for glaucomatous damage, it has been reported superior to standardised automated perimetry and frequency doubling perimetry (Robin et al. 2005). It has shown potential to be a valid screening method also in high-risk populations (Harasymowycz et al. 2005). In the OHTS the development of glaucomatous damage was increased when baseline MRA showed at least one sector outside normal limits (Zangwill et al. 2005). However, the positive predictive value was low.

2.3.2.4 Glaucoma probability score

The glaucoma probability score (GPS) provides an automated interpretation of ONH topography. It is based on a three-dimensional model of a normal and a glaucomatous ONH. The model is constructed by combining the horizontal and vertical curvature of the RNFL with the steepness, size and depth of the cup (Swindale et al. 2000). The analysis is performed both globally and in six sectors. The outcome is determined by the sector with the highest probability score for glaucoma (Coops et al. 2006). The values range from 0 to 1 and represent the probability of glaucomatous damage. Values between 0.28 and 0.64 are considered borderline (Coops et al. 2006). The method is independent of the contour line and the reference plane, which reduces the sources of variability. The reproducibility of GPS is high, but an increase in variability is seen related to age, diminished image quality and diagnosis of glaucoma (Taibbi et al. 2009).

The diagnostic accuracy of GPS is comparable to MRA (Coops et al. 2006, Burgansky-Eliash et al. 2007, Ferreras et al. 2007, Reddy et al. 2009). The sensitivity is reported to be higher, but the specificity lower with GPS (Harizman et al. 2006, Zangwill et al. 2007). Based on likelihood ratios, an abnormal MRA is most likely to confirm the presence of a glaucomatous disc, while a normal GPS is most likely to confirm a normal disc (Zangwill et al. 2007). Both methods have been reported to have higher sensitivity related to increasing disc size (Zangwill et al. 2007). With very large discs the diagnostic accuracy of the methods decreases (Hoesl et al. 2009). High GPS values have been shown to predict which glaucoma suspects develop glaucomatous changes in the visual fields and the ONH (Alencar et al. 2008). The linear regression of GPS scores may be used for determining glaucomatous progression with high specificity, especially in the region of values representing low probability of glaucoma (GPS < 0.30) and very high probability of glaucoma (GPS > 0.78) (Strouthidis et al. 2010).
2.3.2.5 Topographic change analysis

The topographic change analysis (TCA) is a method for detecting glaucomatous progression. It estimates the probability that a difference in surface height occurs between baseline and follow-up images by chance alone. The analysis is performed in 4 x 4 pixel clusters called superpixels. The baseline for the comparison is constructed from two or preferably three images. Progression is identified when change becomes larger than measurement variability (Chauhan et al. 2000). The method takes into account local variability. In areas of high variability, a large height change is needed to reach significance. TCA is independent of the contour line and the reference plane (Chauhan et al. 2001).

The volume and area of a cluster of changing adjacent superpixels is calculated. The sensitivity and specificity of different TCA cluster area and volume parameters for progression detected with photography and visual fields has been evaluated (Bowd et al. 2009). The specificity was low for apparently non-progressing eyes. The agreement between stereoscopic ONH photographs and the TCA on detecting progression has been reported to be only fair (Kourkoutas et al. 2007).

2.3.2.6 Statistical image mapping and proper orthogonal decomposition

Statistical image mapping (SIM) is an analysis of the topographic height of each pixel compared with a statistical image generated by permutations of the measurements of pixel height (Patterson et al. 2005). It analyses the significance level of change at each pixel using only the patient’s own imaging data. In addition to the single pixel change analysis, the significance of the size of the changing cluster is also calculated. In a simulation model data set SIM showed better diagnostic precision for change than TCA (Patterson et al. 2005). The performance of the two methods was similar when compared in a real patient data set, but the sensitivity for progression found with stereoscopic ONH photographs was poor (O’Leary et al. 2008).

A new framework using a proper orthogonal decomposition (POD) method for detecting glaucomatous changes in ONH topography has been introduced. The mathematical method constructs a baseline subspace that contains all possible topographies, using observed baseline variability. The follow-up topographies are compared with the topographies in the baseline subspace for structural and geometrical similarity. If the baseline subspace accurately describes the follow-up topography, change is considered minimal (Balasubramanian et al. 2009). When applied to a clinical data set POD was slightly better in differentiating between progressing and
non-progressing glaucomatous ONH when compared to TCA. The difference between the methods was not statistically significant (Balasubramanian et al. 2010). POD and SIM are not available in HRT software.

2.3.2.7 Measurement variability of the Heidelberg Retina Tomograph

The HRT has been reported to image ONH topography in a reproducible manner (Mikelberg et al. 1993, Rohrschneider et al. 1994, Verdonck et al. 2002). The test-retest variability of measurements is highest along the cup border. The variability increases with age and is higher in glaucoma patients compared to healthy controls (Chauhan et al. 1994). The variability of topography measurements and stereometric ONH parameters influence the detection of glaucomatous damage and especially the detection of glaucomatous progression (Artes & Chauhan 2005, Strouthidis & Garway-Heath 2008).

There are several factors that influence variability. The scan resolution is limited by the optical properties of the eye. The scanning laser passes through the tear film, cornea, anterior chamber, lens and vitreous. All these media produce aberrations degrading the obtained topography image (Artal et al. 2001). Misalignment of the patient and the scanner (Orgul et al. 1996) and movement of the eye or head during image acquisition contribute to measurement noise. Changes in the distance between the eye and the scanner cause magnification changes (Tan et al. 2004a). Cataract and pupil size may influence the obtained image (Zangwill et al. 1997). Variability due to cardiac cycle (Chauhan & McCormick 1995) and menstrual cycle (Yucel et al. 2005) has been related to changes in ocular blood flow.

Time separation between imaging does not seem to affect measurement variability (Chauhan & MacDonald 1995). The long-term fluctuation of stereometric ONH parameters has been estimated to be similar to standardised automated perimetry (SAP) (Funk & Mueller 2003). In a longitudinal study, the relative variability and progression detection rate of rim area change with HRT was similar to the pattern standard deviation of SAP (Jampel et al. 2006).

Changes in IOP and cerebrospinal fluid pressure may alter ONH topography (Parrow et al. 1992, Morgan et al. 2002). The changes in ONH topography related to IOP changes mostly occur with marked IOP changes after glaucoma surgery (Irak et al. 1996, Lesk et al. 1999), but there may be changes after medical treatment of IOP as well (Bowd et al. 2000). IOP-reducing medication may cause an increase in rim area. This effect has been reported to last at least a year (Tan & Hitchings 2004b). The decrease in cupping due to treatment has been identified as a
protective factor against glaucomatous progression (Harju et al. 2008). However, no significant change in the stereometric ONH parameters or with TCA was identified in a group of glaucoma patients in whom IOP was elevated by discontinuing topical medication (Nicolela et al. 2006).

Poor visual acuity, age and high astigmatism have been reported to increase the variability of stereometric parameters (Sihota et al. 2002). Strouthidis and co-workers have concluded that different factors affecting image quality, including lens opacification, age and astigmatism could be appropriately summarised by the topography standard deviation (TSD) (Strouthidis et al. 2005a). Image quality shows consistent influence on the variability of the stereometric ONH parameters (Strouthidis et al. 2005a). Follow-up rates may be adjusted according to image quality and different rates of rim area loss (Owen et al. 2006). The threshold of significant change may be adjusted according to image quality (Fayers et al. 2007). The increasing severity of glaucomatous damage has been reported to decrease the repeatability of rim area. In the same study, the variability of vertical cup:disc ratio was not affected by the severity of the disease (DeLeon et al. 2007).

There is inter-observer variability in drawing the contour line (Wollstein et al. 1998). The placement of the contour line also affects the reference height of the standard reference plane. The contour line is automatically transferred from the baseline image to the follow-up images by the software. A major source of variability of the stereometric ONH parameters is the inter-test variability of the reference height (Tan et al. 2003, Strouthidis et al. 2005a, Breusegem et al. 2008, Lin et al. 2009). Improving the stability of the reference plane would decrease variability of the reference plane-dependent parameters. Repetitive testing and short inter-test intervals may improve change detection despite variability (Weinreb et al. 1993, Owen et al. 2006).

2.3.3 Retinal nerve fibre layer photography

The retinal nerve fibre layer (RNFL) may be visualised with red-free or green light, which does not penetrate the RNFL and is reflected by the superficial layers of the retina (Behrendt & Wilson 1965). RNFL photographs can be obtained with a wide-angle fundus camera using a blue or green exciter filter with high-contrast film (Airaksinen & Nieminen 1985). Currently, the images are captured digitally and may undergo image-processing to improve RNFL visibility and contrast (Tuulonen et al. 2000, Hwang et al. 2006). The RNFL bundles are seen as silvery striations, and with meticulous examination of the images, both localised and diffuse defects may
be detected (Tuulonen & Airaksinen 1991). The visibility of the RNFL is improved by a large pupil, relatively dark and evenly distributed fundus pigmentation and clear optical media (Teesalu & Airaksinen 1998). Especially yellow-brown coloration of the ageing lens decreases the quality of RNFL images (Siik et al. 1997).

Figure 4. Progression of superior and inferior retinal nerve fibre layer defects detected with RNFL photography. The corresponding changes in the optic nerve head can be seen in Figure 2. The changes in the RNFL are substantially more prominent.
RNFL photography has been reported to be an effective diagnostic screening method for glaucoma (Quigley et al. 1980, Airaksinen et al. 1984, Wang et al. 1994, Niessen et al. 1997). Abnormal RNFL changes may also appear in other conditions affecting the optic nerve (Hoyt 1976) as well as in eyes considered normal (Airaksinen et al. 1984). The specificity for glaucomatous damage has been estimated to be from 83% to 97% (Quigley et al. 1980, Airaksinen et al. 1984, Wang et al. 1994). There are several reports of RNFL damage, detected with photography, preceding both visual field and ONH damage (Airaksinen & Alanko 1983, Sommer et al. 1991a, Tuulonen et al. 1993, Zeyen & Caprioli 1993, Quigley et al. 1994, Katz et al. 1997). There are no reports of a defect, once documented with RNFL photography, diminishing or disappearing.

The RNFL thickness measurements with OCT and scanning laser polarimetry are subject to variability (Iacono et al. 2006, Vizzeri et al. 2009a). A strong spatial correlation between diminished RNFL thickness measurements and localised defects in RNFL photography has been reported (Hwang et al. 2006). However, only 60 to 80% of localised defects found with RNFL photography could be identified using OCT, scanning laser polarimetry or HRT (Windisch et al. 2009). RNFL and ONH photography every one to two years together with visual field examinations every year has been recommended in the Finnish evidence-based guideline for open-angle glaucoma to reach a very good level in glaucoma follow-up (Tuulonen et al. 2003).

### 2.3.4 Scanning laser polarimetry

The RNFL thickness can be measured using scanning laser polarimetry. The most commonly used instrument is the GDx. The device uses a polarised laser beam that passes through the RNFL, which is a birefringent structure. A phase shift that correlates with RNFL thickness is measured from the reflected light (Sehi et al. 2007). The anterior segment of the eye also has birefringent properties that have to be compensated for. Originally this compensation was fixed, but the current generations of the device use variable cornea compensation (VCC) or enhanced cornea compensation (ECC) that allow for the compensation to be eye-specific. The individual compensation has improved the ability to detect glaucomatous damage (Brusini et al. 2005).

Unreliable measurements using scanning laser polarimetry may be caused by media opacities, ocular surface diseases, peripapillary atrophy and prior refractive surgery (Hoh et al. 1998). Especially GDx-VCC has a problem with atypical birefringence patterns, caused by an attempted compensation of poor signal-to-noise ratio by the device (Bagga et al. 2005). In case an atypical birefringence
pattern appears, the results of the scan are severely altered and do not match the expected retardation distribution based on RNFL anatomy.

The diagnostic accuracy of the GDx has been reported to be high, with areas under the ROC curve of the best parameters above 0.90 (Essock et al. 2005, Mai et al. 2007). A guided progression analysis method has been developed for the GDx. The sensitivity for glaucomatous progression detected with visual fields and ONH photography was only 50% (Alencar et al. 2010).

2.3.5 **Optical coherence tomography**

The optical coherence tomography (OCT) is an imaging technique based on low-coherence interferometry. It measures the time delay difference between the light reflected from the retinal layers and a reference light (Huang et al. 1991). The method provides cross-sectional images of ocular structures and is used to quantify RNFL thickness. The axial resolution of time-domain OCT is around 10 μm (Schumann et al. 1995). OCT scans are affected by eye movements, media opacities and poor signal-to-noise ratio. Time-domain OCT has been used in most published studies. The recent introduction of spectral-domain OCT has made image acquisition faster, which improves resolution and reduces artefacts due to eye movement.

The diagnostic accuracy for detecting glaucomatous damage with time domain OCT is relatively good. The areas under the ROC curve of the best RNFL parameters have been reported to vary from 0.79 to 0.91 when detecting glaucomatous damage that has been verified in the visual fields (Hong et al. 2007, Parikh et al. 2007, Pueyo et al. 2007). Progression rates have been reported to be higher when using OCT compared to visual fields (Wollstein et al. 2005).

2.3.6 **Standardised automated perimetry**

Standardised automated perimetry is considered the reference standard for detecting the presence and progression of glaucomatous visual field defects (Foster et al. 2002, Tuulonen et al. 2003). The definition of a glaucomatous visual field defect varies, even between major clinical trials (AGIS Investigators 1994, Schulzer 1994, Leske et al. 1999, Musch et al. 1999, Miglieri et al. 2002b, Vesti et al. 2003, Keltner et al. 2005). There are features considered typical for a glaucomatous defect. These include a depression in adjacent test points or a severe depression of one point, localised nature of the defect, a difference across the horizontal meridian and reproducibility of the defect (AGIS Investigators 1994, Schulzer 1994, Leske et al. 1999, Musch et al. 1999, Miglieri et al. 2002, Keltner et al. 2005).
There is also variation in the definition of glaucomatous progression (Schulzer 1994, AGIS Investigators 1998, Chauhan et al. 1999, Musch et al. 1999, Heijl et al. 2002, Vesti et al. 2003). Substantial differences in progression rates using different methods have been reported (Vesti et al. 2003). Variability of the visual fields increases progression rates of some methods while decreasing progression rates of others (Vesti et al. 2003). A glaucoma progression analysis (GPA), based on the criteria developed for the EMGT, has been introduced for the Humphrey perimeter (Heijl et al. 2003). The GPA software considers the random variability of visual field analyses from two baseline fields and identifies progressive visual field loss exceeding the normal level of test-retest variability. The software identifies test points with a significant level of change from baseline.

2.4 Diagnosing glaucoma with the Heidelberg Retina Tomograph

The quality of reporting diagnostic studies using the HRT is suboptimal (Shunmugam & Azuara-Blanco 2006). For example, more than 90% of the studies did not report how many of the participants who fulfilled the inclusion criteria did or did not undergo HRT examination or the test used as the reference standard (Shunmugam & Azuara-Blanco 2006).

The methods to detect glaucomatous ONH damage using the HRT include the sectoral and global stereometric ONH parameters, the linear discriminant functions calculated from these parameters, MRA and GPS. The sensitivity and specificity for glaucoma varies depending on the study population, the definition of glaucoma and the diagnostic method. The sensitivity for glaucoma has been reported to vary from 56% to 81% when calculated at 80% specificity; from 39% to 75% at 90% specificity and from 38% to 67% at 95% specificity, when using predetermined methods of analysing glaucomatous damage with HRT (Ford et al. 2003, Medeiros et al. 2004, Zangwill et al. 2007, Ferreras et al. 2008, Hoesl et al. 2009).

A bagging classification tree approach using stereometric parameters has shown 82% sensitivity at 89% specificity (Mardin et al. 2003). A method using the mean contour height at 36 sectors of the ONH has shown 86% specificity at 90% sensitivity (Zangwill et al. 2004). The results of these studies have not been confirmed in independent populations. The discrimination between glaucoma patients and controls has been reported to be lower in independent populations compared to original studies describing the diagnostic methods (Ford et al. 2003).

The diagnostic studies are affected by the varying definition of glaucoma (Miglior et al. 2005) and the classification of glaucoma suspects as either glaucomatous or
healthy (Miglior et al. 2003). The diagnostic accuracy of the HRT is affected by the size of the ONH. The sensitivity tends to be lower and the specificity higher with small discs (Ford et al. 2003). The diagnostic accuracy is decreased by unusually small and very large discs (Iester et al. 1997b, Hoesl et al. 2009).

The diagnostic accuracy of the HRT has been reported similar to OCT, GDx and expert evaluation of stereoscopic ONH photographs (Greaney et al. 2002, Medeiros et al. 2004, DeLeon-Ortega et al. 2006, Badala et al. 2007, Reus et al. 2007). Using a combination of RNFL and ONH topography measurements has been shown to improve the sensitivity to 91% at a specificity of 96% (Badala et al. 2007). However, the results were not calculated using predefined diagnostic criteria and they have not been confirmed in independent populations.

2.5 Detecting glaucomatous progression with the Heidelberg Retina Tomograph

There are several studies evaluating the ability of the HRT to detect glaucomatous progression. However, there is a lack of both a golden standard for progression and a generally agreed method of detecting progression using the HRT. TCA is a method designed for detecting progression, but the statistically significant number, area and volume of changing adjacent superpixels is not clear. As a result, several definitions for progression have been used (Table 2). A cluster of at least 20 depressing superpixels confirmed by three follow-up exams has been used based on the work of Chauhan and co-workers (Chauhan et al. 2001). It is based on empirical data and the statistical and clinical significance of this definition for progression is not known.

The reference standards used in the studies assessing the accuracy of HRT to detect progression include different visual field criteria, expert evaluation of stereoscopic ONH photographs or both (Table 2). The concordance between methods for detecting progression is quite low (Table 2). There may be several reasons for this discrepancy. In the presence of advanced glaucomatous damage in the visual fields or the ONH, progression within the remaining capacity for change may not reach the criteria of significant change (Hudson et al. 2007). Progression in the visual fields may be covered by learning effect (Hudson et al. 2007). The measurement variability of the methods may differ or there may be temporal dissociation between measurable progression (Strouthidis & Garway-Heath 2008). There are reports of structural changes detected with HRT that are followed by functional changes in the visual fields (Kamal et al. 1999, Chauhan et al. 2009b). The correlation between the changes in the visual fields and structural glaucomatous progression, evaluated with photography, has been reported to be only 35% on average (Tuulonen et al. 2003).
Table 2. Studies evaluating the detection of glaucomatous progression using HRT with predefined criteria for progression.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population (n)</th>
<th>Reference standard</th>
<th>HRT Criteria for progression</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chauhan et al. 2001</td>
<td>Glaucoma (77)</td>
<td>SAP (4 locations)</td>
<td>I TCA (20 superpixels)</td>
<td>88%</td>
<td>40%</td>
<td>5.5 years</td>
</tr>
<tr>
<td>Nicolela et al. 2003</td>
<td>Glaucoma (48)</td>
<td>SAP (3 locations)</td>
<td>I TCA (20 superpixels)</td>
<td>74%</td>
<td>32%</td>
<td>6.5 years</td>
</tr>
<tr>
<td>Artes &amp; Chauhan 2005</td>
<td>Glaucoma (84)</td>
<td>SAP (1 location)</td>
<td>I TCA (6% of disc area)</td>
<td>57%</td>
<td>69%</td>
<td>7.4 years</td>
</tr>
<tr>
<td>Artes &amp; Chauhan 2005</td>
<td>Glaucoma (84)</td>
<td>SAP (3 locations)</td>
<td>I TCA (18% of disc area)</td>
<td>27%</td>
<td>86%</td>
<td>7.4 years</td>
</tr>
<tr>
<td>Strouthidis et al. 2006</td>
<td>Ocular hypertension (198)</td>
<td>SAP (1 location)</td>
<td>I Sectoral rim area regression (high variability)</td>
<td>37%</td>
<td>69%</td>
<td>6.0 years</td>
</tr>
<tr>
<td>Strouthidis et al. 2006</td>
<td>Ocular hypertension (198)</td>
<td>SAP (1 location, confirmed x3)</td>
<td>I Sectoral rim area regression (low variability)</td>
<td>18%</td>
<td>89%</td>
<td>6.0 years</td>
</tr>
<tr>
<td>Philippin et al. 2006</td>
<td>Ocular hypertension (109)</td>
<td>SAP (2 locations or MD change)</td>
<td>I Cup shape measure regression</td>
<td>44%</td>
<td>59%</td>
<td>10 years</td>
</tr>
<tr>
<td>Philippin et al. 2006</td>
<td>Ocular hypertension (109)</td>
<td>SAP (2 locations or MD change)</td>
<td>I Rim area regression</td>
<td>22%</td>
<td>67%</td>
<td>10 years</td>
</tr>
<tr>
<td>Kourkoutas et al. 2007</td>
<td>Glaucoma (54)</td>
<td>ONH stereo-photographs</td>
<td>II TCA (20 superpixels)</td>
<td>70%</td>
<td>64%</td>
<td>2.6 years</td>
</tr>
<tr>
<td>Bowd et al. 2009</td>
<td>Healthy / Glaucoma (267)</td>
<td>SAP and/or photographs</td>
<td>II TCA (area ≥ 0.036 mm²)</td>
<td>78%</td>
<td>80%</td>
<td>3.9 years</td>
</tr>
<tr>
<td>Vizzeri et al. 2009b</td>
<td>Glaucoma and suspect (237)</td>
<td>ONH stereo-photographs</td>
<td>II TCA (evaluation by experienced observers)</td>
<td>50%</td>
<td>85%</td>
<td>4.6 years</td>
</tr>
<tr>
<td>Vizzeri et al. 2009b</td>
<td>Glaucoma and suspect (237)</td>
<td>ONH stereo-photographs</td>
<td>II Trend analysis of stereometric parameters</td>
<td>13%</td>
<td>89%</td>
<td>4.6 years</td>
</tr>
<tr>
<td>Vizzeri et al. 2009b</td>
<td>Glaucoma and suspect (237)</td>
<td>ONH stereo-photographs</td>
<td>II MRA (evaluation by experienced observers)</td>
<td>31%</td>
<td>89%</td>
<td>4.6 years</td>
</tr>
<tr>
<td>Strouthidis et al. 2010</td>
<td>Ocular hypertension (198)</td>
<td>SAP (1 location)</td>
<td>I GPS (positive regression slope)</td>
<td>31%</td>
<td>92%</td>
<td>6.0 years</td>
</tr>
</tbody>
</table>

The sensitivity and specificity values are presented in a summary receiver operating characteristics plot (Figure 5).

HRT = Heidelberg Retina Tomograph, SAP = Standardised Automated Perimetry, MD = Mean Deviation, TCA = Topographic Change Analysis, MRA = Moorfields Regression analysis, GPS = Glaucoma Probability Score
There is relatively poor concordance between progression detected with stereoscopic ONH photography and HRT (Table 2). Agreement on assessments within a method as well as measurement variability affects the evaluation of progression (Strouthidis & Garway-Heath 2008). It has been suggested that the evaluation of ONH using HRT and the stereoscopic ONH photographs assess different aspects of ONH change (O’Leary et al. 2008, Vizzeri et al. 2009b). It has been reported that the HRT using TCA performs at least as well as experts evaluating ONH photographs in determining progression (Chauhan et al. 2009a).

Figure 5. The summary receiver operating characteristics plot for the detection of glaucomatous progression using HRT. The sensitivities and specificities are reported in studies using predefined criteria for progression (Table 2). The reference standards for progression include standardised automated perimetry (black diamonds), stereoscopic ONH photography (black circles) or both (black triangle).
Aims of the research

The purpose of the present study was to assess the stereometric optic nerve head parameters of the HRT in the follow-up of glaucoma. The objective was to determine how the change in the stereometric parameters correlates to glaucomatous progression (I, II) and the factors that may affect the correlation with progression (III, IV). More specifically, the aims of the research were:

1. to investigate how change in the stereometric ONH parameters correlates to the small topographic changes associated with progression of the RNFL defects (I)
2. to assess the accuracy of the stereometric ONH parameters for detecting glaucomatous progression found with stereoscopic ONH photography (II)
3. to evaluate the factors affecting the sensitivity and specificity of the stereometric parameters to glaucomatous progression in ONH photographs (III)
4. to determine whether exercise affects the stereometric parameters representing ONH topography (IV)
4 Subjects and methods

4.1 Subjects

The data collection for the retrospective case-control study (I) was performed in the following manner. From the subjects monitored at Oulu University Hospital Glaucoma Clinic, we selected those who had had at least three consecutive yearly examinations with the HRT and successful RNFL photography at each visit. Patients with a fundus disease that disturbed the interpretation of RNFL photographs as well as subjects with unsuccessful HRT examinations or without open-angle glaucoma were excluded. Progression of the RNFL defect was identified in 34 eyes of 29 patients. 34 non-progressive eyes matched for age and diagnosis were selected to serve as controls (Table 3).

<table>
<thead>
<tr>
<th>Table 3. Demographic details (I).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes with progression</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Number of eyes (% right)</td>
</tr>
<tr>
<td>Diagnosis (poag/ntg/pex)*</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
</tr>
<tr>
<td>Mean time between first and third visits (years)</td>
</tr>
<tr>
<td>Number of patients (% male)</td>
</tr>
</tbody>
</table>

*poag = primary open-angle glaucoma, ntg = normal tension glaucoma, pex = glaucoma with pseudo-exfoliation

Mean age and mean time between visits are calculated for eyes.

For the retrospective follow-up study (II, III) all eyes with at least 18 months of follow-up with HRT and stereoscopic ONH photographs were reviewed. A total of 1030 eyes of 532 patients met the initial follow-up criteria. The photographs were approved for image quality by three masked evaluators. The HRT images had topography standard deviations (TSD) of < 36 μm; the TSD values could not vary more than 10 μm between visits, and image alignment was to be perfect. Figure 6 presents the flow chart summarising study exclusion.

Progression in the stereoscopic ONH photographs was assessed by three glaucoma specialists in a masked fashion. A two-out-of-three agreement was used for progression and three-out-of-three agreement for non-progression. 476 eyes of 342 patients were included in the final analysis. The demographic details are given in Table 4.
1030 eyes of 532 patients with more than 18 months of follow-up with stereoscopic ONH photographs and the HRT

- low quality HRT images in 181 eyes (TSD > 35 μm)

849 eyes

- change in HRT image quality in 160 eyes (ΔTSD > 10 μm)

689 eyes

- error in HRT image alignment in 79 eyes

610 eyes

- low quality of stereoscopic ONH photographs in 55 eyes

555 eyes included in the analysis of inter-observer agreement

- only 1 out of 3 observers reported progression in 79 eyes

476 eyes of 342 patients included in the final analysis

Figure 6. Flow chart summarising study exclusion (II).
Table 4. Demographic details (II).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), years</td>
<td>62 (13–86)</td>
</tr>
<tr>
<td>Mean follow-up (range), months</td>
<td>28 (18–56)</td>
</tr>
<tr>
<td>Mean disc area (range), mm²</td>
<td>2.4 (1.2–4.7)</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>147:195</td>
</tr>
<tr>
<td>Laterality (right-to-left)</td>
<td>249:227</td>
</tr>
</tbody>
</table>

35 healthy volunteers with no systemic or ocular disorders were recruited for the prospective study (IV). Subjects between 18 and 40 years of age with spherical equivalents between -7 and +5 diopters in the study eye (right eye) were accepted. 5 subjects did not achieve the predetermined 30 mmHg increase in systolic blood pressure during exercise and were excluded. The demographic details are given in Table 5.

Table 5. Demographic details (IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), years</td>
<td>27 (20–36)</td>
</tr>
<tr>
<td>Mean spherical equivalent (range), diopters</td>
<td>- 1.4 (-6.0 – +4.5)</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>12:18</td>
</tr>
<tr>
<td>Disc area (range), mm²</td>
<td>1.91 (1.26–2.75)</td>
</tr>
<tr>
<td>Cup:disc area ratio (range)</td>
<td>0.15 (0.00–0.37)</td>
</tr>
</tbody>
</table>

4.2 Stereoscopic ONH photography

The stereoscopic ONH photographs were obtained with a Canon CF-60 UVi funduscamera with a Canon EOS 1 D MK II, 8 Mpixel Digital SLR CMOS camera (Canon Inc, Tokyo, Japan). The patients’ pupils were dilated for the photography. The stereo-effect was obtained by lateral shift of the camera. The photographs are digital black-and-white images in stereo-pairs. When both pictures of a pair are viewed simultaneously, a three-dimensional image of the ONH can be seen.

4.3 Scanning laser ophthalmoscopy

The Heidelberg Retina Tomograph II with software version 1.6 was used to obtain three-dimensional topographic images of the ONH. A contour line was drawn at the inner edge of the scleral ring on the first image, and it transferred automatically onto the next images. All contour lines were drawn by an experienced photographer.
trained for this purpose. The stereometric ONH parameters are calculated from the topographic image. In the prospective study (IV), software version 3.0 was used to recalculate stereometric ONH parameters and the drawing of the contour lines was performed automatically by the software.

4.4 Retinal nerve fibre layer photography

The RNFL photographs were taken with a monochromatic blue interference filter (495 nm). The present technique is refined from a well-documented technique (Airaksinen & Nieminen 1985, Tuulonen et al. 2000) used in our glaucoma clinic for more than two decades. The RNFL photographs are digital images acquired with a Canon CF-60 UVi fundus camera with a Canon EOS 1 D MK II, 8-Mpixel Digital SLR CMOS camera (Canon Inc., Tokyo, Japan) using Neacapture software (Neagen Oy, Oulu, Finland) and processed with Adobe Photoshop CS (Adobe Systems Inc., San Jose, CA, USA). The RNFL photographs were taken and processed by three photographers, each with more than 10 years of experience in fundus photography in our clinic.

4.5 Examinations during exercise

In the prospective study (IV), the HRT examinations and the measurements of heart rate, blood pressure and IOP were obtained twice before exercise (baseline and pre-exercise). The ONH imaging took place during the measuring of blood pressure, in the short period between systolic and diastolic pressure measurements. IOP was measured using the Goldmann applanation tonometer. Exercise was carried out using an exercise bike with an adjustable workload. Heart rate and blood pressure were monitored. After an increase of at least 30 mmHg in systolic blood pressure was achieved, the examinations were performed for the third time (mid-exercise). Exercise was then discontinued and the subject was monitored until blood pressure normalised. The examinations were subsequently repeated (post-exercise).

4.6 Statistical analysis

Sensitivity for progression is defined as the proportion of eyes with progression in the reference standard (RNFL or ONH photography) that have a positive test. If the change in the parameter or linear discriminant function value is above the cut-off value, the test is positive. Specificity is defined as the proportion of eyes
with no progression in the reference standard that have a negative test. A plot of sensitivity versus one minus specificity (a receiver operating characteristic curve) is used to determine the quality of a diagnostic test. The areas under the receiver operating characteristic (ROC) curve were compared using MedCalc, Version 11.2 (MedCalc Software, Mariakerke, Belgium) when calculating the effect of image quality on the ROC curves for detecting glaucomatous progression (Results 5.5). A detailed description of the other statistical methods used can be found in the original publications (I–IV).

4.7 Ethical considerations

Approval for all studies was obtained in accordance to the guideline of the Ethical Committee of the Northern Ostrobothnia Hospital District. In the prospective study (IV), all subjects signed an informed consent form explaining the study protocol. The studies followed the tenets of the Declaration of Helsinki.
5 Results

5.1 Correlation of the change in the stereometric parameters with progression of the RNFL defects (I)

The change in only one stereometric ONH parameter, the cup shape measure, showed a statistically significant (p = 0.049) correlation with the progression of the RNFL defect. A change of 0.015 in the cup shape measure had a sensitivity of 53% and specificity of 74% for progression.

The best combination of two parameters found with multiple logistic regression analysis was $\Delta \left[(-7.219 \times \text{maximum cup depth}) + (21.639 \times \text{linear cup:disc area ratio})\right]$. It showed a statistically significant correlation with progression of the RNFL defect (p = 0.009). A change of 0.1372 in the two-parameter combination value had 71% sensitivity and 74% specificity.

![Figure 7. The area under the receiver operating characteristics (ROC) curve calculated for the best three parameter combination $\left[(-7.121 \times \text{maximum cup depth}) + (-3.801 \times \text{horizontal cup:disc ratio}) + (28.091 \times \text{linear cup:disc area ratio})\right]$: 0.753; the best two parameter combination $\left[(-7.219 \times \text{maximum cup depth}) + (21.639 \times \text{linear cup:disc area ratio})\right]$: 0.724 and the cup shape measure: 0.617.](image)

The three-parameter combination with the best correlation with progression was $\Delta \left[(-7.121 \times \text{maximum cup depth}) + (-3.801 \times \text{horizontal cup:disc ratio}) + (28.091 \times \text{linear cup:disc area ratio})\right]$. The correlation with progression was statistically significant (p = 0.007). A change of 0.1602 in the three-parameter combination...
value had 77% sensitivity and 79% specificity. The ROC curves of the cup shape measure, the two-parameter and the three-parameter combination are presented in Figure 7.

5.2 Correlation of the change in the stereometric parameters with progression in stereoscopic ONH photographs (II)

The cup:disc area ratio had the best correlation with progression in stereoscopic ONH photographs ($p < 0.0005$). The cut-off value optimised for sensitivity and specificity was 0.005 for change in the cup:disc area ratio. Sensitivity was 75% and specificity 56% at the cut-off. Sensitivity was 28% at a fixed specificity of 90%.

![Figure 8. The receiver operating characteristics (ROC) curves calculated for the linear discriminant function, the cup:disc area ratio, and the vertical cup:disc ratio. The areas under the ROC curves were 0.694, 0.666 and 0.724, respectively.](image)

The parameter with the largest area under the ROC curve (0.726) was the vertical cup:disc ratio. A change of 0.007 in the vertical cup:disc ratio had a sensitivity of 80% and a specificity of 65%. Sensitivity was 22% at a fixed specificity of 90%.
The linear discriminant function with the best correlation with progression was 
\[(12.241 \times \text{cup:disc area ratio}) + (3.540 \times \text{mean cup depth}) - (2.146 \times \text{horizontal cup:disc ratio}) + (27.486 \times \text{average variability})\]. An optimised change in the linear discriminant function value was 0.34 with a sensitivity of 65% and specificity of 69%. Sensitivity was 31% at a fixed specificity of 90%. With the cut-off at 90% specificity, the kappa value for inter-method agreement was 0.211 with stereoscopic ONH photography. This indicates only fair agreement. The results are summarised in Figures 8 and 9.
5.3 Factors affecting the sensitivity and specificity of the stereometric parameters to glaucomatous progression in ONH photographs (III)

The factors having the most significant effect on the sensitivity and specificity of the stereometric ONH parameters were the reference height difference and the mean topography standard deviation (TSD), indicating image quality. These two factors combined accounted for 21% of the increase in misjudging progression ($r^2$) when calculated for the cup:disc area ratio. The change in the TSD and age also showed a consistent, but variably significant influence on all parameters tested. The sensitivity and specificity improved when there was little change in the reference height, the image quality was good and stable, and the patients were younger.

The sensitivity and specificity of the vertical cup:disc ratio was improved by a large disc area and high baseline cup:disc area ratio. The rim area showed a better sensitivity and specificity for progression with a small disc area and low baseline cup:disc area ratio. Gender, the laterality of the eye, the diagnosis of glaucoma, and the duration of follow-up had no statistically significant effect. The results are summarised in Table 6.

5.4 The effect of exercise on the stereometric ONH parameters (IV)

Exercise was associated with an increase in variance in 17 of the 18 stereometric ONH parameters. The increase in variance was statistically significant in eight parameters including rim area, cup:disc area ratio and cup shape measure. There was no statistically significant change in image quality.
Table 6. Correlation coefficients and statistical significance of factors analysed for affecting the sensitivity and specificity of stereometric ONH parameters.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Stereometric ONH parameter</th>
<th>Statistical method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vertical cup:disc ratio</td>
<td></td>
</tr>
<tr>
<td>Change in reference height</td>
<td>( .296^{**} )</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td></td>
<td>(&lt; .0005 )</td>
<td>p-value</td>
</tr>
<tr>
<td>Mean TSD</td>
<td>( .268^{**} )</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td></td>
<td>(&lt; .0005 )</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>( .187^{*} )</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>Disc area</td>
<td>(- .217^{**} )</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>Baseline cup:disc area ratio</td>
<td>(- .232^{**} )</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>Baseline rim area</td>
<td>( .017 )</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>Time between visits</td>
<td>( .088 )</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Mann – Whitney U</td>
</tr>
<tr>
<td>Laterality (right/left)</td>
<td></td>
<td>Mann – Whitney U</td>
</tr>
<tr>
<td>Diagnosis of glaucoma</td>
<td></td>
<td>Kruskal – Wallis</td>
</tr>
</tbody>
</table>
| TSD, topography standard deviation (TSD)**, Correlation is statistically significant. P-value \( \leq 0.01 \). P-value \( \leq 0.05 \).
Table 7. The variance of the change (×10³) from baseline of the stereometric ONH parameters before and during exercise. The statistical significance of the change in variance is calculated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variance of change before exercise (pre-exercise – baseline)</th>
<th>Variance of change during exercise (mid-exercise – baseline)</th>
<th>Statistical significance (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cup area</td>
<td>0.510</td>
<td>1.294</td>
<td>0.0080*</td>
</tr>
<tr>
<td>Rim area</td>
<td>0.510</td>
<td>1.294</td>
<td>0.0080*</td>
</tr>
<tr>
<td>Cup:disc area ratio</td>
<td>0.0930</td>
<td>0.243</td>
<td>0.0066*</td>
</tr>
<tr>
<td>Rim:disc area ratio</td>
<td>0.0930</td>
<td>0.243</td>
<td>0.0066*</td>
</tr>
<tr>
<td>Cup volume†</td>
<td>0.0369</td>
<td>0.0323</td>
<td>0.36</td>
</tr>
<tr>
<td>Rim volume</td>
<td>0.983</td>
<td>2.373</td>
<td>0.011*</td>
</tr>
<tr>
<td>Mean cup depth</td>
<td>0.109</td>
<td>0.201</td>
<td>0.027*</td>
</tr>
<tr>
<td>Maximum cup depth</td>
<td>0.637</td>
<td>1.389</td>
<td>0.020*</td>
</tr>
<tr>
<td>Height variation contour</td>
<td>1.059</td>
<td>1.744</td>
<td>0.086</td>
</tr>
<tr>
<td>Cup shape measure</td>
<td>0.303</td>
<td>0.910</td>
<td>0.0024*</td>
</tr>
<tr>
<td>Mean RNFL thickness</td>
<td>0.398</td>
<td>0.576</td>
<td>0.16</td>
</tr>
<tr>
<td>RNFL cross sectional area</td>
<td>9.598</td>
<td>13.715</td>
<td>0.17</td>
</tr>
<tr>
<td>Horizontal cup:disc ratio</td>
<td>1.350</td>
<td>2.251</td>
<td>0.091</td>
</tr>
<tr>
<td>Vertical cup:disc ratio</td>
<td>0.451</td>
<td>0.759</td>
<td>0.087</td>
</tr>
<tr>
<td>Maximum contour elevation</td>
<td>0.370</td>
<td>0.548</td>
<td>0.12</td>
</tr>
<tr>
<td>Maximum contour depression</td>
<td>0.528</td>
<td>0.648</td>
<td>0.30</td>
</tr>
<tr>
<td>CLM temporal-superior</td>
<td>0.377</td>
<td>0.642</td>
<td>0.080</td>
</tr>
<tr>
<td>CLM temporal-inferior</td>
<td>0.460</td>
<td>0.575</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*The change is statistically significant (p < 0.05). † There was decrease in the variance in one parameter. The decrease was not statistically significant.

IOP decreased and blood pressure increased during exercise, resulting in an increase in mean ocular perfusion pressure. The absolute change in rim area, cup area and rim volume showed a statistically significant correlation with change in mean ocular perfusion pressure. The results are summarised in Tables 7 and 8.
Table 8. The correlation between the change in mean ocular perfusion pressure and the stereometric ONH parameters with statistically significant increase in variance. The statistical significance of the correlation is calculated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pearson correlation</th>
<th>Statistical significance (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cup area</td>
<td>0.194</td>
<td>0.033*</td>
</tr>
<tr>
<td>Rim area</td>
<td>0.194</td>
<td>0.033*</td>
</tr>
<tr>
<td>Cup:disc area ratio</td>
<td>0.172</td>
<td>0.052</td>
</tr>
<tr>
<td>Rim:disc area ratio</td>
<td>0.172</td>
<td>0.052</td>
</tr>
<tr>
<td>Rim volume</td>
<td>0.202</td>
<td>0.028*</td>
</tr>
<tr>
<td>Mean cup depth</td>
<td>0.014</td>
<td>0.447</td>
</tr>
<tr>
<td>Maximum cup depth</td>
<td>0.128</td>
<td>0.114</td>
</tr>
<tr>
<td>Cup shape measure</td>
<td>0.071</td>
<td>0.253</td>
</tr>
</tbody>
</table>

The correlation is calculated for absolute changes from baseline before, during and after exercise.

*The change is statistically significant (p < 0.05).

5.5 The effect of image quality on agreement for detecting glaucomatous progression

The eyes in the retrospective follow-up study (II) were divided into three subgroups based on the mean image quality of the HRT examinations. The ROC curves of three stereometric parameters (cup:disc area ratio, rim area and cup volume) were compared between the three subgroups. With better image quality, there was a considerable improvement in the areas under the ROC curve calculated for progression detected with stereoscopic ONH photographs (Figure 10). The areas under the ROC curves of each parameter were compared between images of different quality (A and C). The difference was statistically significant for cup volume with a p-value of 0.016.

With excellent image quality, the area under the ROC curve was best for the change in cup volume. A cut-off value of 0.030 mm$^3$ was determined for cup volume based on the ROC curve. With this cut-off sensitivity was 86% and specificity 90% for progression in stereoscopic ONH photographs. The inter-method agreement (kappa) for progression detected with photographs was 0.501. The inter-observer agreement between the masked evaluators of the stereoscopic ONH photographs for progression was moderate, with kappa values ranging from 0.403 to 0.510.
Figure 10. The effect of image quality on the receiver operating characteristics (ROC) curves for detecting glaucomatous progression in stereoscopic ONH photographs.

A. Excellent image quality, mean topography standard deviation (TSD) < 11 μm (n = 75). The area under the ROC curve for rim area is 0.773, for cup:disc area ratio 0.784 and for cup volume 0.861.

B. Very good image quality, 11 μm ≤ TSD ≤ 16 μm (n = 232). The area under the ROC curve for rim area is 0.712, for cup:disc area ratio 0.725 and for cup volume 0.703.

C. From very good to acceptable image quality, 16 μm < TSD ≤ 34 μm (n = 169). The area under the ROC curve for rim area is 0.537, for cup:disc area ratio 0.548 and for cup volume 0.560.
6 Discussion

6.1 Linear discriminant functions

When diagnosing glaucomatous damage with HRT, it is more accurate to use a combination of the stereometric parameters rather than just one parameter (Mikelberg et al. 1995, Ferreras et al. 2008). The correlation with progression in the RNFL was also improved by a linear discriminant function combining several parameters. (I)

The linear discriminant function \[(-7.121 \times \text{maximum cup depth}) + (-3.801 \times \text{horizontal cup:disc ratio}) + (28.091 \times \text{linear cup:disc area ratio})\] had the highest sensitivity (77%) and specificity (79%) for glaucomatous progression in RNFL photographs. (I) The linear discriminant function \[(12.241 \times \text{cup:disc area ratio}) + (3.540 \times \text{mean cup depth}) - (2.146 \times \text{horizontal cup:disc ratio}) + (27.486 \times \text{average variability})\] had the best correlation with progression in stereoscopic ONH photographs (II). It has been suggested that the parameters, which provide good sensitivity and specificity in recognising the presence or absence of glaucomatous damage, may be different from those recognising progression of the disease (Anderson et al. 2000). The parameters improving diagnostic precision in several of the reported LDFs include the cup shape measure, rim area, rim volume, the height of the contour line, and the height variation along the contour line (Table 1). The parameters in the LDFs recognising progression are different from those recognising the presence or absence of glaucoma.

The enlargement of the cup:disc area ratio is a classic sign of glaucomatous damage. Increase in the cup:disc ratio in the vertical direction was highly correlated with progression in stereoscopic ONH photographs. Both LDFs calculated for detecting progression (I, II) included a cup:disc area ratio parameter with a large positive coefficient and a horizontal cup:disc ratio parameter with a small negative coefficient. This further implies that if one focuses on the cupping occurring away from the horizontal plane, it enhances the correlation with progression, regardless of the reference standard used. This may partly be explained by the fact that the nasal area and the papillomacular bundles located temporally are the last parts of the ONH that are affected by glaucomatous damage (Quigley et al. 1982, Caprioli 1989).
6.2 Correlation between the stereometric ONH parameters with progression in RNFL photographs (I)

The glaucomatous changes in the ONH anatomy result from the loss of ganglion cell axons, which is typically first seen in the retinal nerve fibre layer (Airaksinen & Alanko 1983, Sommer et al. 1991a). However, it is yet to be established whether the changes in the ONH are measurable at the stage when the loss of axons first becomes visible in the RNFL. Only one stereometric ONH parameter, the cup shape measure, showed a barely statistically significant ($p = 0.049$) correlation with progression detected with RNFL photography. Reaching statistical significance is affected by limited sample size. There may also be temporal dissociation in measurable progression between methods. The small changes in topography may become undetectable due to variability in the stereometric parameters, especially when analysing an event of progression, instead of performing trend analysis.

6.3 Correlation between the stereometric parameters with progression in ONH photographs (II)

The progression in the stereoscopic ONH photographs had a 2-out-of-3 agreement criterion and for non-progression a 3-out-of-3 criterion. Both the stereoscopic photographs and the HRT measure change in the ONH. There is no potential time delay in measurable progression between the methods as is the case when comparing changes in the ONH and the RNFL.

Despite strict inclusion criteria for image quality and alignment excluding 46% of the original study population, there was a considerable lack in concordance between the two methods (Figure 9). The change in most parameters had a statistically significant correlation with progression. Reaching statistical significance is improved by the fairly large sample size. However, the sensitivity and specificity values of the parameters leave much to be desired, as can be seen from the ROC curves (Figure 8).

6.4 Factors affecting the sensitivity and specificity to progression in ONH photographs (III)

The factors that influence the short-term variability of the stereometric parameters include inter-test reference height difference, image quality, lens opacification, age, poor visual acuity and astigmatism (Sihota et al. 2002, Strouthidis et al. 2005a,
Breusegem et al. 2008). Strouthidis and co-workers concluded that different factors affecting image quality, including lens opacification, age and astigmatism could be appropriately summarised by topography standard deviation (Strouthidis et al. 2005a).

The factors affecting the sensitivity and specificity of the stereometric ONH parameters to glaucomatous progression in stereoscopic ONH photographs are essentially the same as those factors related to short-term variation of the parameters (Strouthidis et al. 2005a). This suggests that improving the methods of controlling the variability of the stereometric parameters would improve the agreement between stereometric ONH parameters of the HRT and stereoscopic ONH photographs for progression.

The rim area showed better sensitivity and specificity for progression with a small disc area and low baseline cup:disc area ratio. The sensitivity and specificity of the vertical cup:disc ratio was improved by a large disc area and high baseline cup:disc area ratio. This is in concordance with the results of DeLeon-Ortega and co-workers. They found that rim area variability increases with disease severity, but the variability of the vertical cup:disc ratio remains stable, even at stages of severe glaucomatous visual field loss (DeLeon-Ortega et al. 2007). Therefore it may be optimal to follow the change of different parameters depending on the size of the ONH and the stage of glaucomatous damage.

### 6.5 Variability of ONH topography during exercise (IV)

Changes during the cardiac cycle as well as changes in IOP may result in variation of ONH topography (Chauhan & McCormick 1995, Azuara-Blanco et al. 1998). There may be a change in vessel position and calibre during a cardiac cycle, but also a forward and backward shift of the ONH, independent of the vessels (Chauhan & McCormick 1995). Blood pressure is increased and IOP is decreased during exercise, resulting in increase in mean ocular perfusion pressure. Study IV shows some association between increasing variability in ONH topography and exercise-induced increase in mean ocular perfusion pressure.

The exercise-induced decrease in IOP is also seen in the elderly (Erä et al. 1993), a major age group in glaucoma follow-up. Climbing stairs or walking to the office may be physically demanding for the elderly. ONH imaging should be done after a sufficient time to rest, in order to avoid increased variance in the stereometric ONH parameters.
6.6 Comparison of methods for detecting glaucomatous progression using the HRT

Studies evaluating the detection of glaucomatous progression with the HRT use different analysis methods and different cut-off values to define progression (Table 2). One of the methods used is the regression of certain stereometric parameters such as rim area. This is a trend analysis, which requires more HRT examinations than an event analysis, but is less affected by variation. The detection rates for progression using trend analysis and event analysis are different (Fayers et al. 2007). A trend analysis is the method of choice for detecting progression when the examinations are performed at fairly short intervals. However, short intervals may not be possible with limited resources and a high number of glaucoma patients. In the Finnish evidence-based guideline for open-angle glaucoma, a good level of follow-up included ONH or RNFL imaging every two years (Tuulonen et al. 2003). With such intervals, an event analysis for determining progression would be preferable.

The topographic change analysis (TCA) is regarded as an event analysis, but it requires three or preferably four examinations with the HRT. The method identifies the location and the direction, but not the statistical significance of change. Several different definitions of progression using the TCA have been reported (Table 2). A possible method to diminish the effect of variability on results is repetitive imaging on each visit (Weinreb et al. 1993). This would also allow the use of TCA for detecting change between each visit.

The accuracy for detecting progression in the present study (I, II) is similar to other studies (Figure 11, Figure 12). As expected, the correlation between methods appears to be higher in studies using ONH photography as a reference standard compared to visual fields (Figure 5). The mean follow-up time of the present study was two years and one month (I) and two years and four months (II). Two years is the recommended time between imaging in the Finnish evidence-based guideline (Tuulonen et al. 2003). However, the relatively short follow-up time is a limitation of the present study compared to other published studies. (Table 2).
Figure 11. A summary receiver operating characteristics plot for the detection of glaucomatous progression using HRT, with the sensitivity and specificity values of single stereometric ONH parameters for progression. The results of the present study are displayed with open symbols and the results of other studies (Table 2) with black symbols. Progression in RNFL photographs (I) is the reference standard for the change in cup shape measure (open diamond). Progression in the stereoscopic ONH photographs (II) is the reference standard for the change in cup:disc area ratio (open square) and vertical cup:disc ratio (open triangle). In addition to sensitivity and specificity at the optimised cut-off, sensitivities at 90% specificity are also plotted. The sensitivity and specificity values of studies using the regression of single stereometric parameters to detect progression are displayed for comparison. The reference standards include progression in the visual fields (black diamonds) or the stereoscopic ONH photographs (black circle).
In the present study progression was analysed by calculating change in the stereometric ONH parameters between two points in time (I, II). It is an event analysis and relates to the clinician’s question ‘has there been progression in the ONH since the last visit’. As an event analysis it is very sensitive to variation of the stereometric parameters and to factors inducing variability such as decrease in image quality (Figure 10). Regardless of the reference standard and the method used for analysing progression with the HRT, high concordance between methods to detect progression has not been reported (Table 2).

Figure 12. A summary receiver operating characteristics plot for the detection of glaucomatous progression with HRT using stereoscopic ONH photographs as a reference. The results of the present study are displayed with open symbols and the results of other studies (Table 2) with black symbols. The optimised sensitivity and specificity values of the cup:disc area ratio (open square) and vertical cup:disc ratio (open triangle) for progression are given. Sensitivities at 90% specificity are also displayed (II). The studies detecting ONH progression with the HRT, using stereoscopic ONH photographs, with (black triangle) and without visual fields (black circles), as a reference standard are plotted for comparison.
6.7 **Significance of change**

Even if the change detected with an imaging method reaches statistical significance, the clinical significance of the change remains unknown. There are no studies demonstrating the efficacy of a treatment strategy based on imaging alone. Whether the change is clinically significant and warrants change in treatment is still decided by the clinician treating glaucoma. The subsequent treatment may depend on the severity and prior course of the disease, IOP, age and life expectancy of the patient and the safety and efficacy of the remaining treatment options (Tuulonen *et al.* 2003, European Glaucoma Society 2008).

Even when using the best LDFs in the present study, with sensitivity and specificity values close to 80%, more than one fifth of the patients showing no progression in ONH photographs would be classified as progressors and more than one fifth of the patients with progression in ONH photographs would be classified as stable. When detecting progression the specificity of the diagnostic test should be high in order to avoid overtreatment and subjecting stable patients to the inconvenience and risks related to additional medication or surgery. When screening for glaucoma, the specificity of the diagnostic test should be more than 96% in order for the screening to be cost-effective (Vahtoranta-Lehtonen *et al.* 2007). Also during follow-up, specificities below 90% are of limited value. In the present study, sensitivities at 90% specificity were below 50%, thus identifying less than half of the real progressors. Combining the results of the ONH, RNFL and visual fields improves the accuracy of detecting glaucomatous damage (Tuulonen *et al.* 2003, Badala *et al.* 2007, Strouthidis & Garway-Heath 2008, Zhu *et al.* 2009). Even if the clinical decisions are based on several methods for detecting progression (Figure 13), the results are still subjectively interpreted by the clinician treating glaucoma.

6.8 **Detection of glaucomatous progression**

There is no golden standard for detecting glaucomatous progression. Progression may be identified at different times during follow-up in the ONH, RNFL and visual fields. There is both a temporal dissociation and a difference in detection rates using different methods of analysis (Vesti 2003, Fayers *et al.* 2007). Figure 13 summarises some of the methods used for detecting glaucomatous progression.
Reducing the variability of the stereometric parameters improves the accuracy of detecting progression. Repetitive imaging and allowing sufficient time to rest before the HRT examination diminishes variability. Image quality should be the best possible, and mydriatics and artificial tears should be used if necessary. When images of different quality were compared, the correlation of the change in the stereometric parameters with progression in stereoscopic ONH photographs was considerably improved with images of excellent quality. With excellent image quality, the inter-method agreement for cup volume was at the same level as the inter-observer agreement between the evaluators of the stereoscopic ONH photographs.
photographs. This would challenge the view that evaluation of ONH using the HRT and the stereoscopic ONH photographs assesses different aspects of ONH change (O’Leary et al. 2008, Vizzeri et al. 2009b). However, images of excellent quality cannot be obtained from all patients. In the retrospective follow-up study (II) only 8% had mean TSD values below 11 μm, indicating excellent quality.

The detection of glaucomatous damage or progression should not rely on any single method (Tuulonen et al. 2003, Badala et al. 2007, Strouthidis & Garway-Heath 2008). There may be a considerable temporal dissociation in progression detected in the ONH, RNFL and the visual fields. Confirming progression may require repeated examinations (Tuulonen et al. 2003, Owen et al. 2006). Examining the RNFL, ONH and the visual fields on each follow-up visit improves diagnostic precision and allows implementing the 2-out-of-3 rule for progression (Tuulonen et al. 2003). The change in the stereometric parameters provides useful information on ONH topography, especially with excellent image quality. Based on the results of the current study the stereometric ONH parameters that should be used in follow-up include cup:disc area ratio, vertical cup:disc ratio, rim area, cup volume and cup shape measure. Especially when treating patients with advanced glaucomatous damage or large ONHs, change in the vertical cup:disc ratio should be monitored. With small ONHs and early stages of glaucomatous damage, change in the rim area should receive special attention. However, the evaluation of glaucomatous progression in the ONH should not rely solely on the stereometric parameters of the HRT.
7 Conclusions

1. The change in only one out of 23 stereometric ONH parameters, the cup shape measure, showed a statistically significant correlation with the progression of the RNFL defect. An optimised change in the best three-parameter combination had 77% sensitivity and 79% specificity for progression.

2. The parameter with the best correlation with progression in stereoscopic ONH photography was the cup:disc area ratio. The sensitivity of the cup:disc area ratio was 28% at 90% specificity. The parameter with the largest area under the ROC curve (0.726) was the vertical cup:disc ratio with a sensitivity of 22% at a specificity of 90%. The sensitivity of a linear discriminant function \[(12.241 \times \text{cup:disc area ratio}) + (3.540 \times \text{mean cup depth}) - (2.146 \times \text{horizontal cup:disc ratio}) + (27.486 \times \text{average variability})\] was 31% at a specificity of 90%. With the cut-off at 90% specificity, the kappa value for inter-method agreement was 0.211 with stereoscopic ONH photography, indicating only fair inter-method agreement.

3. The factors having the most significant effect on the sensitivity and specificity of the stereometric ONH parameters were the reference height difference and the mean topography standard deviation (TSD) indicating image quality. The change in the TSD and age also showed a consistent, but variably significant influence on all parameters tested.

4. Exercise was associated with an increase in variance in 17 of the 18 stereometric ONH parameters. The increase in variance was statistically significant in eight parameters including rim area, cup:disc area ratio and cup shape measure.
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STEREOMETRIC PARAMETERS OF THE HEIDELBERG RETINA TOMOGRAPH IN THE FOLLOW-UP OF GLAUCOMA

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