

Quantitative Three-Dimensional Imaging of the Posterior Segment with the Heidelberg Retina Tomograph

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1 Introduction



Figure 1

The Heidelberg Retina Tomograph (figure 1) is a confocal laser scanning system designed for acquisition and analysis of three-dimensional images of the posterior segment. It enables the quantitative assessment of the topography of ocular structures and the precise follow-up of topographic changes.

2 Confocal laser scanning imaging of the fundus

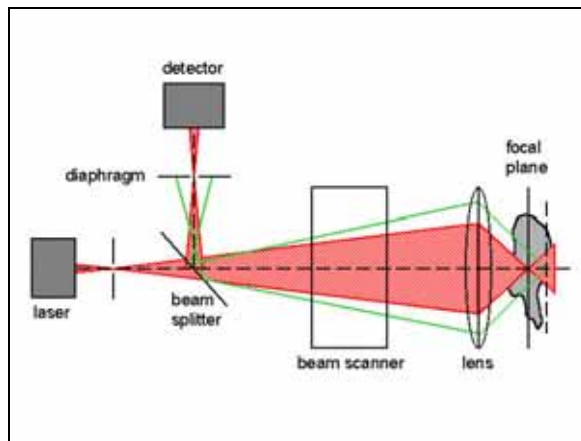


Figure 2

In a laser scanning system, a laser is used as a light source (figure 2). The laser beam is focused to one point of the examined object. The light reflected from that point goes the same way back through the optics, is separated from the incident laser beam, and deflected to a detector. This allows to measure the reflected light only at one individual point of the object. In order to produce a two-dimensional image, the illuminating laser beam is deflected periodically in two dimensions perpendicular to the optical axis using scanning mirrors. Therefore, the object is scanned point by point sequentially in two dimensions.

In a confocal optical system as shown in figure 2, a small diaphragm is placed in front of the detector at a location which is optically conjugated to the focal plane of the illuminating system. The effect of this confocal pinhole is as follows: such light reflected from the object at the focal plane is focused to the pinhole, can pass it and is detected. However, light reflected from layers of the three-dimensional object above or below the focal plane is not focused to the pinhole, and only a small fraction of it can pass the pinhole and is detected. Therefore, the out-of-focus light is highly suppressed with the suppression increasing rapidly with the distance from the focal plane. In consequence, a confocal laser scanning system has a high optical resolution not only perpendicular, but also parallel to the optical axis, that means into depth. A two-dimensional image acquired at the focal plane therefore carries only information of the object layer located at or near the focal plane. It can be considered as an optical section of the three-dimensional object at the focal plane.

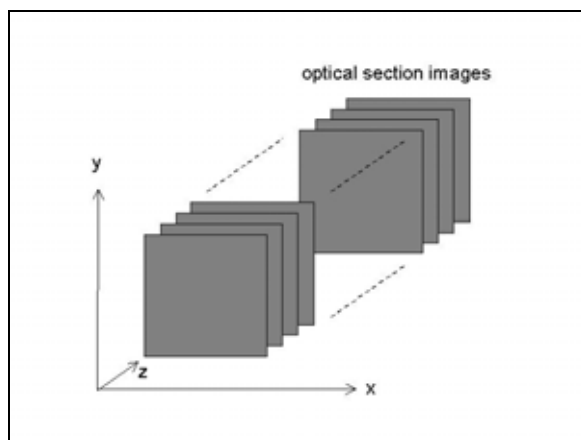


Figure 3

The confocal laser scanning system, therefore, enables real three-dimensional imaging. A two-dimensional image is an optical section at the focal plane and when we move the focal plane and acquire images at different depth locations, we receive a series of optical section images, which forms a layer-by-layer three-dimensional image of the three-dimensional object (figure 3). This procedure is known as laser scanning tomography.

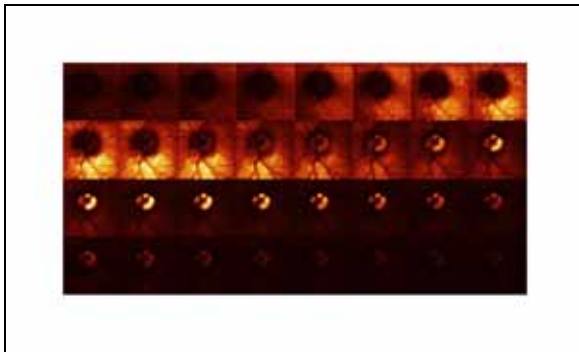


Figure 4

Figure 4 shows an example of a layer-by-layer three-dimensional image of an optic nerve head. This series consists of 32 confocal section images all at different focal planes. The field of view in this example is 15° . The series starts with the focal plane located in the vitreous. The whole image appears dark, because all structures are out of focus. As the focal plane is moved posteriorly, the retina becomes bright and appears brightest when the focal plane is located at its surface. When the focal plane is moved more posteriorly, the retina gets out of focus and becomes dark. Instead, the bottom of the cup becomes bright. When the focal plane is moved beyond the bottom of the cup, the whole image appears dark again. The total extend of this image series into depth, this is the distance between the first and the last image, is 2.5 mm. That means the focal plane distance between each two subsequent images is about $80\ \mu\text{m}$.

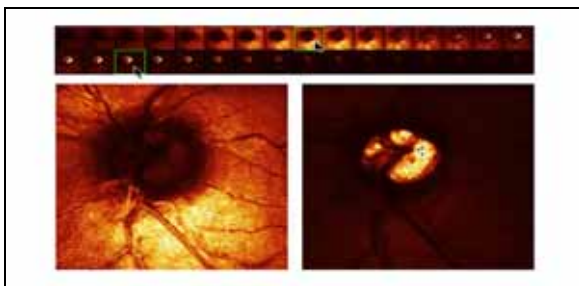


Figure 5

In figure 5, two individual section images out of the series of 32 images in figure 4 are displayed in full scale. In the left image in figure 5, the focal plane was located at the retinal surface. The retina appears bright, whereas the cup is dark. In right hand image, where the focal plane is located about 0.8 mm more posteriorly, the contrast is reversed: The retina is now dark, and the bottom of the cup appears bright. This gives a good impression of the three-dimensional information contained in such a confocal image series.

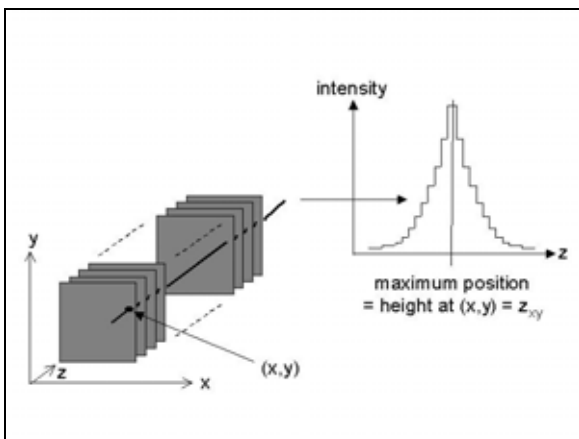


Figure 6

The layered three-dimensional image is used to compute the topography of the light reflecting surface (figure 6): For each location (x,y) in the section image planes, the series contains the distribution of the reflected light intensity along the optical axis, the z -axis. This intensity distribution is called a confocal z -profile. The confocal z -profile is a symmetric distribution with a maximum at the location of the light reflecting surface. Because of the confocal suppression, the measured intensity drops rapidly with increasing distance from the surface's position. Therefore, by determination of the position of the profile maximum, we are able to determine the location of the light reflecting surface along the z axis, that is its height.

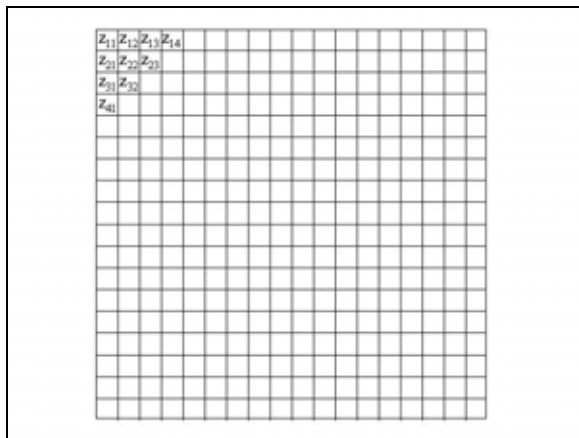


Figure 7

When this calculation is performed at all locations in the section image planes, the result is a matrix of 256 x 256 or more than 65,000 independent height measurements (figure 7), each with a reproducibility of about 10 to 20 microns.

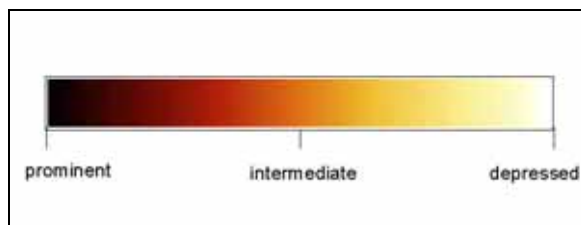


Figure 8

In order to visualize the matrix of height measurements, it is displayed as an image. This is achieved by translating each specific height into a specific color according to a color scale with dark colors representing prominent structures and light colors representing depressed structures (figure 8).

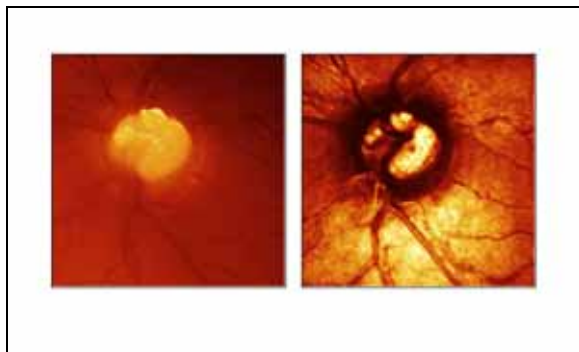


Figure 9

The result is a color coded topography image shown in figure 9 (left). The optic nerve head appears bright because it is excavated; the elevated retinal surface appears dark. With the information in the topography image, we can quantify the three-dimensional properties of the examined structure. The right side of figure 9 shows an image which is the sum of the 32 section images. It shows the reflectance at each point, comparable to a fundus photo. The reflectance image is originally black/white since we are

using a monochromatic laser. It is displayed here in pseudo colors for better visualization.

The most important technical features of the Heidelberg Retina Tomograph are as follows: Two-dimensional optical section images are acquired within 32 milliseconds and with a repetition rate of 20 Hz. The images are digitized in frames of 256 x 256 picture elements. The size of the field of view can be set to 10° x 10°, 15° x 15°, or 20° x 20°. A three-dimensional image is acquired as a series of 32 equally spaced two-dimensional optical section images. The total acquisition time is 1.6 seconds. The light source is a diode laser with a wavelength of 670 nm. Pupil dilation is not required to acquire the images; only 1 mm pupil diameter is usually sufficient to acquire high quality images. Topography images are computed from the acquired three-dimensional images, consisting of 256 x 256 individual height measurements which are absolutely scaled for the individual eye and have a reproducibility of the height measurements of approximately 10 to 20 microns.

3 Analysis of topography images

The general application of the Heidelberg Retina Tomograph is the quantitative assessment of the retinal topography and the quantification of topographic changes. Examples are the description of the glaucomatous optic nerve head, the analysis of macular holes and macular edema, and the analysis of nerve fiber layer defects. The following concentrates on the application of the Heidelberg Retina Tomograph in glaucoma management. Glaucoma is a loss of nerve fibers and subsequent loss of visual field. The loss of nerve fibers causes changes in the three-dimensional topography of the optic nerve head which are believed to precede measurable visual field defects by years.

The goal of the topographic analysis of the optic nerve head is either a quantitative description of its current state with the goal of a classification - e.g. normal or not normal - or to compare more than one topography image in order to follow up topographic changes and to quantify progression of glaucoma.

There are basically two ways to assess the current state of the optic nerve topography: interactive measurements and the parametric description, that is the determination of a set of stereometric parameters. The following examples demonstrate the interactive measurements.

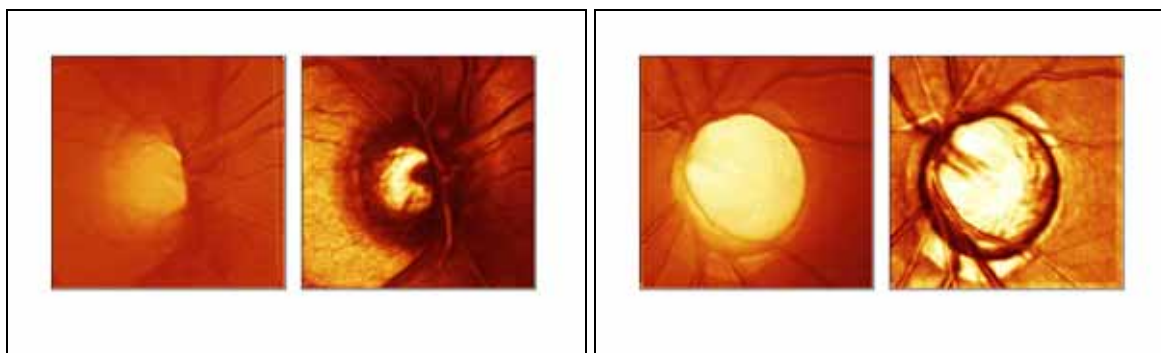


Figure 10 a (left); b (right)

Figure 10a and 10b show the topography images (left) and the reflectance images (right) of a normal optic nerve head (figure 10a) and of a glaucomatous optic nerve head (figure 10b). In the color coded topography images, bright colors code depressed structures while dark colors code elevated structures. The size of the field of view in both examinations is 10° . The highly different size and shape of the cups is obvious. The cup appears much bigger and deeper in the glaucomatous eye.

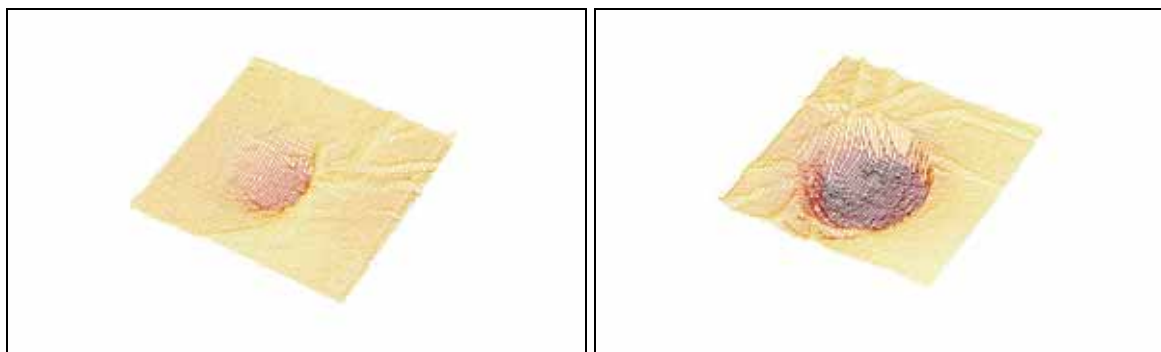


Figure 11 a (left); b (right)

The topography images can also be displayed as pseudo 3D images (figure 11). These images clearly show the difference in the cup shape of the normal (figure 11a) and the glaucomatous eye (figure (11b)). The glaucomatous cup is much deeper and shows higher slopes along the margins.

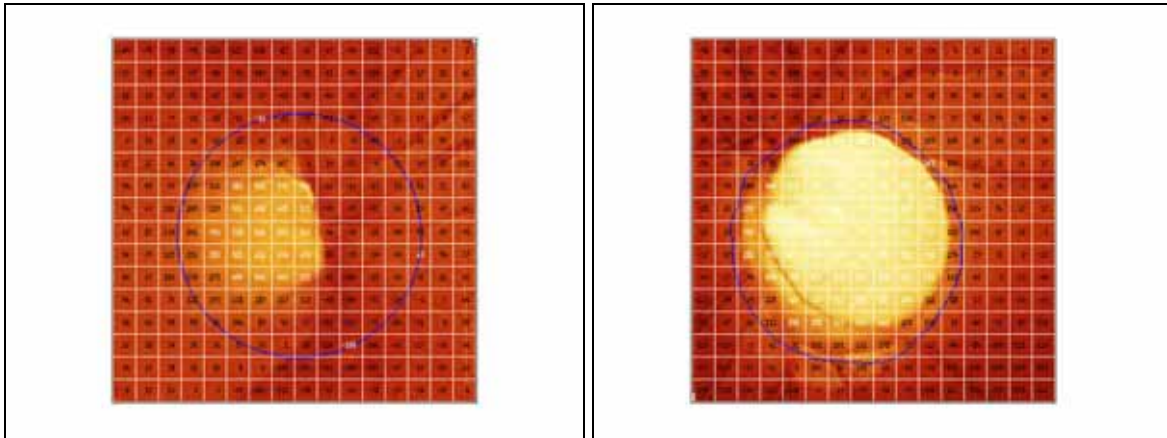


Figure 12

In the so-called topographic maps (figure 12), each number is the mean surface height in an array of 16 x 16 pixels in microns. Obviously, the glaucomatous optic nerve (figure 12b) is much deeper than the normal one (figure 12a).

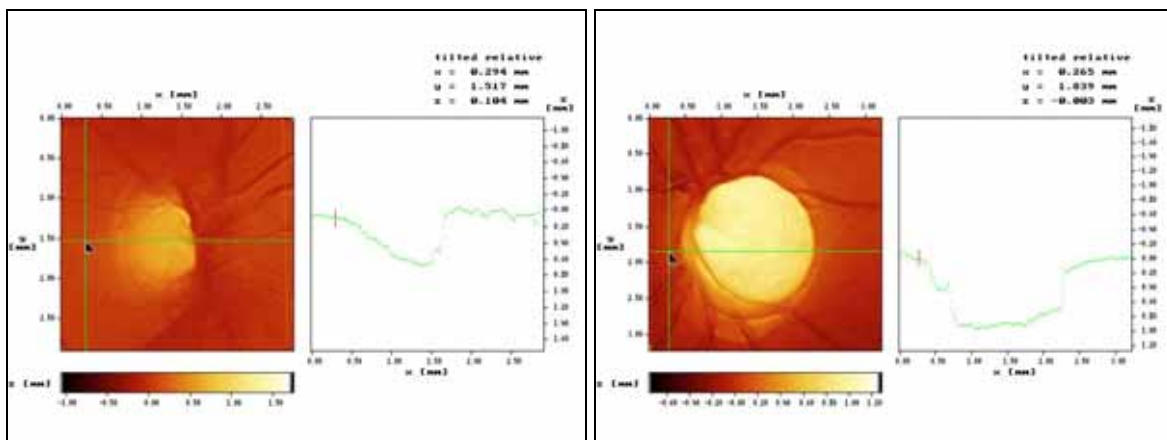


Figure 13

In figure 13, horizontal cross sections of the topography images of the normal (figure 13a) and the glaucomatous optic nerve head (figure 13b) are shown. The green diagrams on the right hand side show the variations of the measured surface height along the horizontal lines superimposed on the topography images. The normal eye shows a regular shape of the cross section through the cup with a low slope on the temporal side and a higher slope nasally. The cross section through the glaucomatous optic nerve head appears quite different; there is a high slope temporally and nasally, the cup is deep and there is a wide and flat bottom. The three numbers - top right - are the three-dimensional coordinates of the cursor cross. If the cursor is moved around, we can do very easy interactive measurements of distances, height differences, etc.

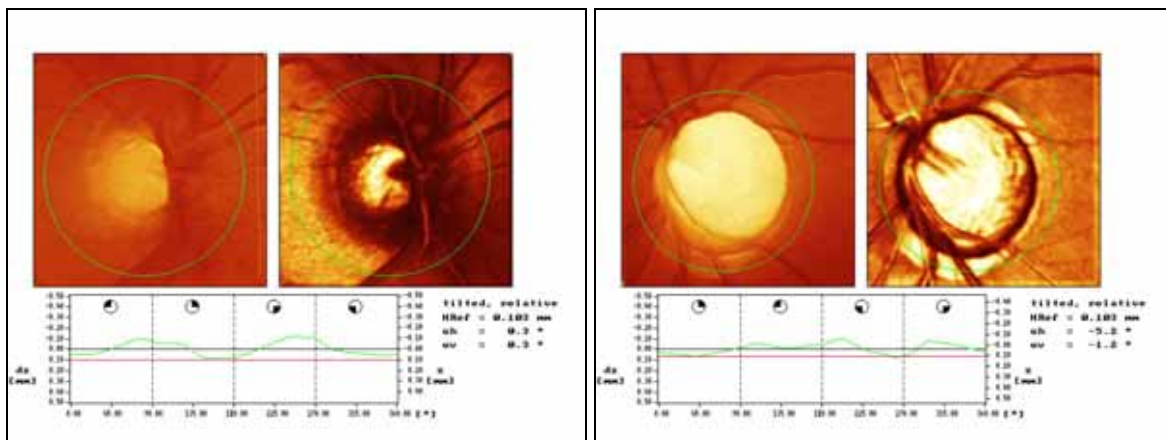


Figure 14

In figure 14, circles of 2.5 mm diameter are placed around the optic nerve heads. The green diagrams (bottom) show the variation in height of the peripapillary retinal surface along these circles. The diagrams start temporally and extend to superior, nasal, inferior, and temporal again. In the normal eye (figure 14a), the typical so-called double hump structure is visible. There are two maxima superiorly and inferiorly at the locations where the nerve fiber layer is thickest. These two maxima are missing in the glaucoma eye (figure 14b). There is only little height variation of the retinal surface. This eye has an almost complete loss of the visual field.

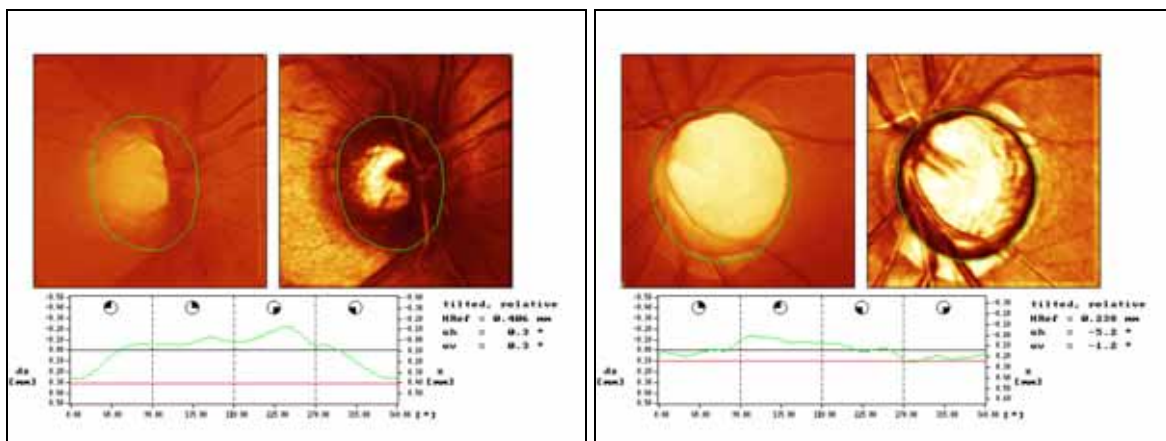


Figure 15

Of special importance in topographic evaluation of an optic nerve head is the stereometric analysis. To perform stereometric measurements, a contour line is drawn around the disk margin. The structure enclosed by that contour line is then analyzed three-dimensionally (figure 15a: normal eye; figure 15b: glaucomatous eye).

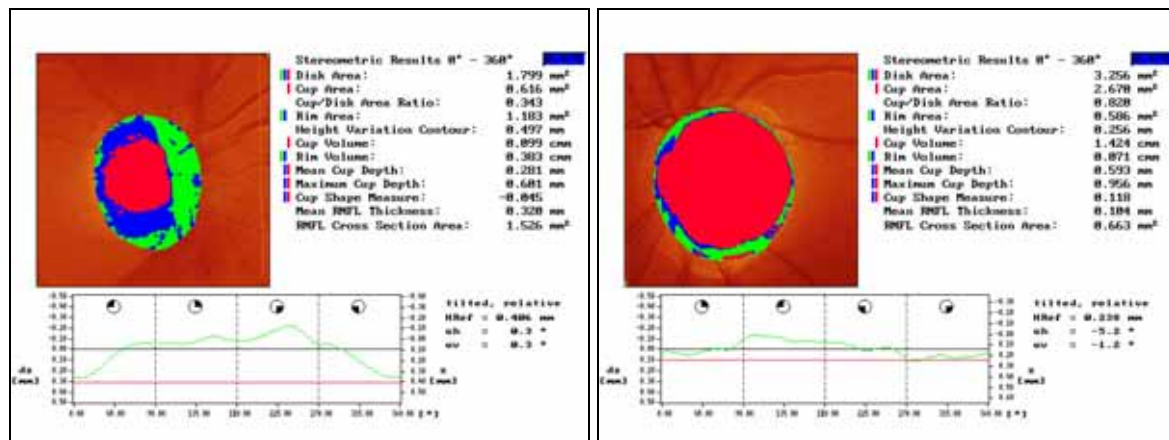


Figure 16

The result of this analysis is a set of stereometric parameters (figure 16). The most important parameters are disk area, cup and rim area, cup and rim volume, mean and maximum cup depth, a measure for the three-dimensional shape of the cup, and for the mean thickness of the retinal nerve fiber layer along the contour line. Figure 16a and 16b show the result of the stereometric analysis of the normal and the glaucomatous optic nerve head, respectively. The cup of the optic nerve head is displayed in red color, the rim is displayed in blue and green colors. Again, the green curve indicates the height variation of the retinal surface along the contour line, whereas the red line indicates the location of the reference plane used to differentiate between cup and rim. The distance between the reference plane and the retinal surface is used to measure the mean thickness of the retinal nerve fiber layer.

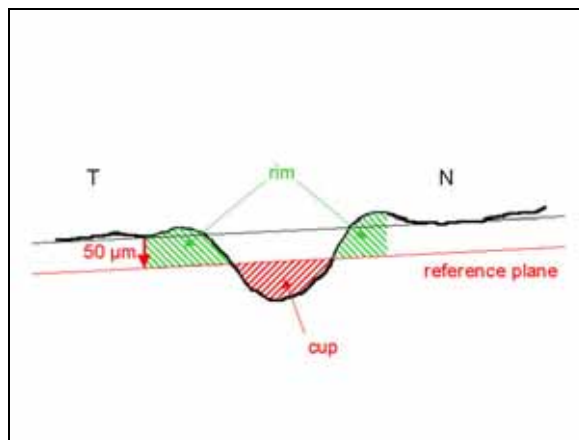


Figure 17

For this kind of measurements, it is very important how the reference plane is defined. The Heidelberg Retina Tomograph operation software automatically defines a reference plane for each individual eye as indicated in figure 17. The yellow line represents a cross section through an optic nerve head. The reference plane is defined parallel to the peripapillary retinal surface and is located 50 microns posteriorly of the retinal surface at the papillo-macular bundle. The reason for this definition is that during development of glaucoma the nerve fibers at the papillo-macular bundle remain intact longest and the nerve fiber layer thickness at that location is approximately 50 microns. We can therefore assume to have a stable reference plane located just beneath the nerve fiber layer. All structures located below the reference plane are considered to be cup, all structures located above the reference plane and within the contour line are considered to be rim.

The reproducibility of the stereometric parameters was evaluated in different clinical studies including normal and glaucomatous eyes. The typical coefficients of variation for area, volume and depth measurements turned out to be about 5 %.

4 Using stereometric parameters: detecting glaucoma

Different methods have been used in clinical studies for detecting an abnormal optic nerve head using the stereometric parameters: The analysis of individual stereometric parameters; multivariate analysis techniques that use combinations of stereometric parameters; and the ranked sector distribution analysis leading to a graphical presentation of the configuration of an individual optic nerve head in its relation to normal eyes. When we consider individual stereometric parameters, it turns out that most of the parameters change significantly with deteriorating visual field. Examples are rim and cup volume, the shape of the cup, and the retinal surface height variation around the disk.

Reinhard Burk and coworkers in Heidelberg studied the stereometric parameters in several hundred eyes that they classified according to the visual field into groups of normal eyes and of eyes with early, moderate and advanced glaucomatous damage. They found that most of the stereometric parameters provided by the Heidelberg Retina Tomograph change significantly with progression of glaucoma; the standard errors of the means in the visual field groups are very small, and the means differ significantly between groups. The parameters are useful, therefore, to follow the progression of the disease. But the physiologic variability of the optic nerve head configuration is high and so are the standard deviations of the parameter values. The distributions of the parameter values of the different groups overlap each other. Hence, it is difficult - except in advanced cases - to classify an individual eye as being normal or glaucomatous based on individual stereometric parameters.

More advanced methods for the classification of an individual eye into a normal or a glaucoma group are provided by two approaches: the multivariate analysis and the analysis of ranked sector distribution curves. Multivariate analysis studies of the Heidelberg Retina Tomograph stereometric parameters that take into account not individual but combinations of parameters were performed by Airaksinen and coworkers, Burk and coworkers, and Mikelberg and coworkers. They all found that the three parameters cup shape measure, rim volume and retinal surface height variation along the disk contour are - as a group and in this order - the most important parameters to differentiate between a normal and a glaucomatous optic nerve head.

Discriminant function (Ophthalmology 1997;104:545-8)

$$F = a * (CSM+a_0) + b * RV + c * CHV + d$$

a = -13.079	b = 10.990
c = -7.245	d = -2.662
a ₀ = 0.001981*(50-age)	

Figure 18

and coworkers found that the detection of early glaucomatous damage is possible with a sensitivity of 87% and a specificity of 84%.

Mikelberg and coworkers (Ophthalmology 1997;104:545-548) computed a discriminant function based on this analysis. They tested normal eyes against eyes with early visual field defects. The discriminant function is a linear combination of the three parameters cup shape measure, rim volume and contour line height variation (figure 18). An eye is classified as being normal if the discriminant function value F is positive; it is classified as glaucomatous if F is negative. With this approach, Mikelberg

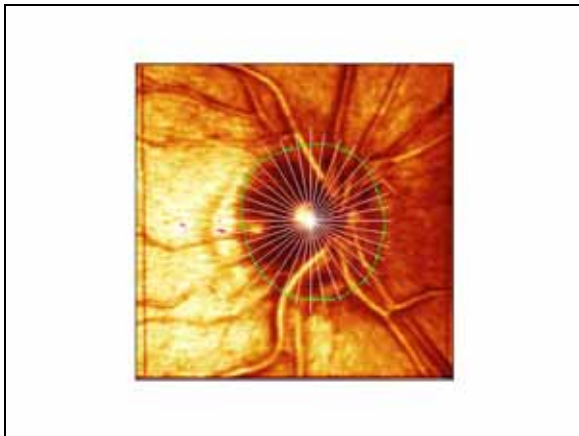


Figure 19

An other approach in using the Heidelberg Retina Tomograph to detect glaucomatous optic nerve heads is the analysis of the so-called ranked sector distribution curves. Here, the idea is to subdivide the optic nerve head into 36 sectors (figure 19), each 10° wide, to compute the stereometric parameter values in each segment, and to sort these 36 values in descending order. The result is a graphical representation of the optic nerve head configuration similar to the Bebie curves used in perimetry (figure 20). From a population of normal eyes, we can compute normal RSD curves. They are shown in figure 20 as the 5th and 95th percentile curves. That means only 5% of normal eyes show RSD curves lying below the normal 5th percentile or above the normal 95th percentile curve. To test a specific eye, its RSD curve is simply plotted together with the normal RSD curves.

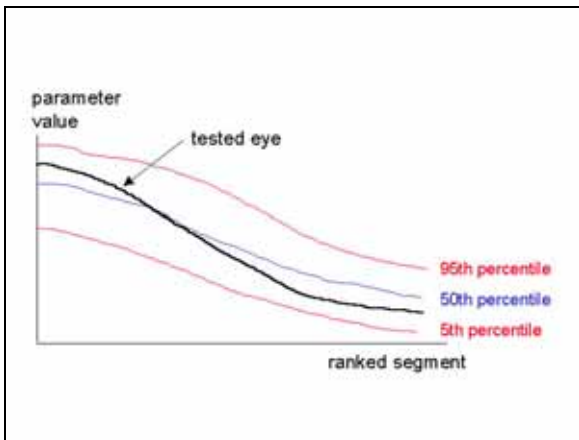


Figure 20

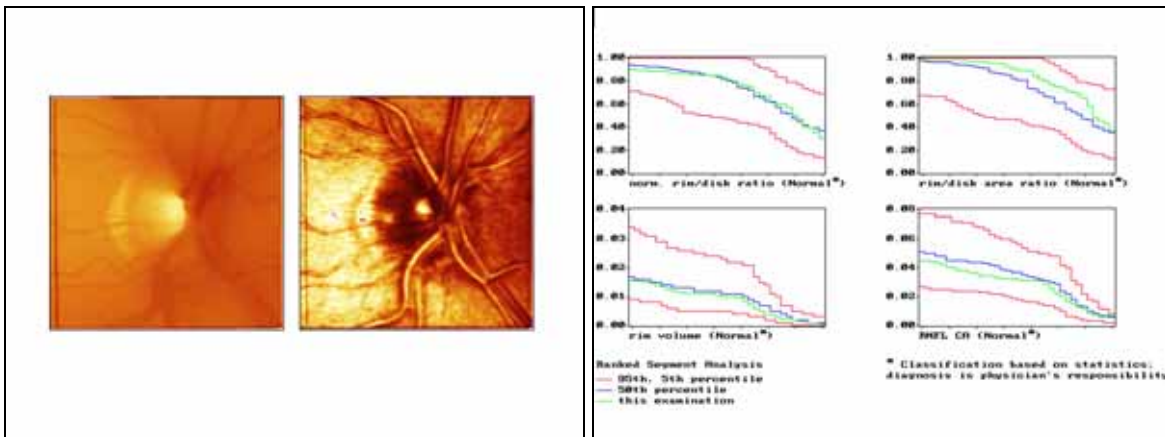


Figure 21

Figure 21 shows an example of a RSD curve computed with the HRT. This is a normal eye. The red curves are the normal 5th and 95th percentiles, the blue curves are the 50th percentiles. The green line is the RSD curve of the tested eye. It falls indeed right into the middle of the normative curves.

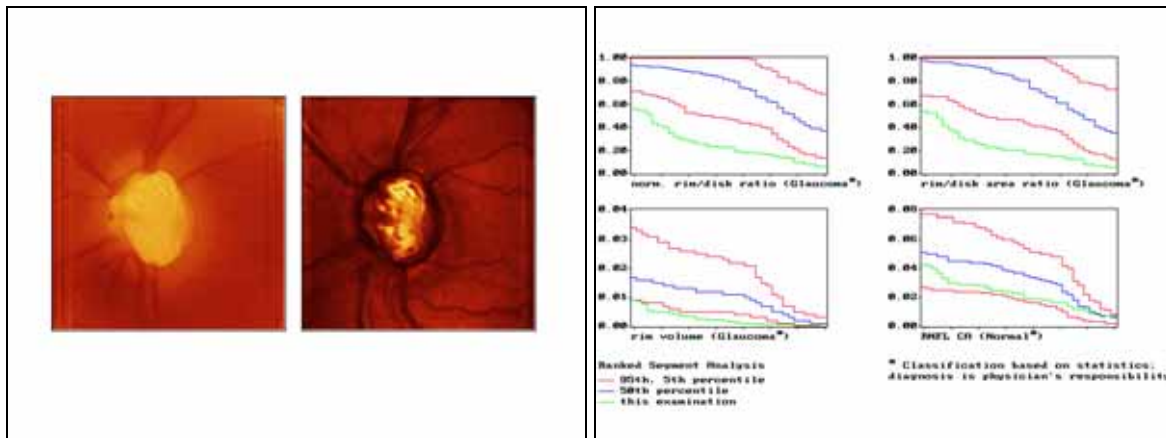


Figure 22

An eye with glaucomatous damage is shown in figure 22. The RSD curves are far outside the 5th percentile of normal eyes. This eye can therefore be classified as being glaucomatous with an error probability of less than 5%.

5 Follow-up of topographic change and glaucomatous progression

Besides the classification of an eye, it is also important to be able to follow-up topographic changes, especially to detect progression in glaucoma. Different methods have been proposed and are used in the HRT software today. The parametric description of the optic nerve head as discussed before can be used for follow-up as well, of course. Alternative methods are the computation and analysis of topographic difference images and of change probability maps.

When the stereometric parameters are used to detect changes, it is of course essential that always the same contour line is used. Therefore, the procedure is as follows: A contour line is defined for the baseline exam and the baseline stereometric parameters are computed. The defined contour line is then transferred to the follow-up exam and automatically placed at the same position. During transfer, the software normalizes baseline and follow-up exam to correct for translation, rotation, magnification and perspective. The stereometric parameters are then re-computed for the follow-up exam and compared to the baseline result. As discussed earlier, the typical coefficients of variation of the stereometric parameters are about 5%. We also know that there are significant differences in the parameter values - much higher than 5% - between normal eyes and eyes with glaucomatous damage; so, this is a useful approach.

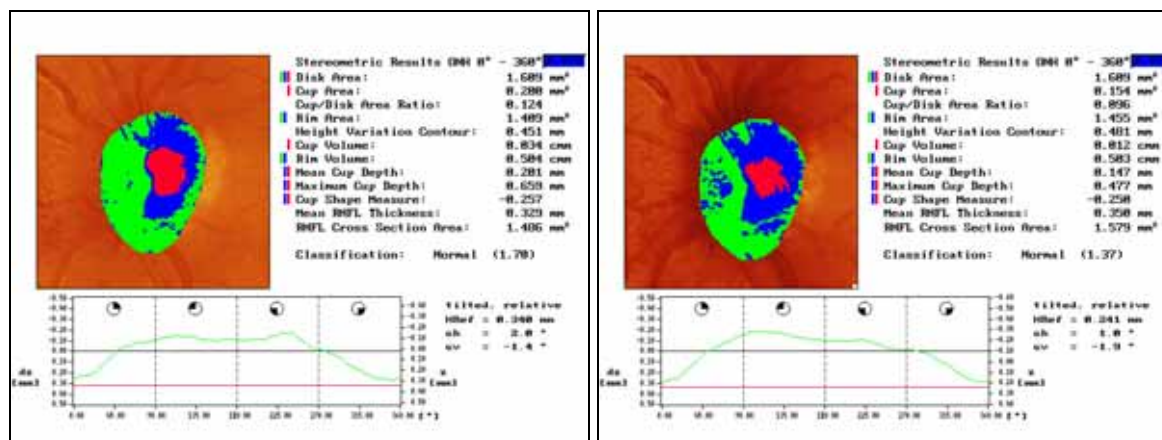


Figure 23

Figure 23 shows an example of the follow-up of topographic changes with stereometric parameters. This patient was examined with an intra-ocular pressure of 50 mmHg (figure 23a) and a pressure of 15 mmHg (figure 23b). The contour has been drawn for the baseline examination and then transferred to the follow-up exam. Consequently, the disk area is identical in both exams. Interestingly, the rim volume and the retinal nerve fiber layer thickness remained almost constant, while the cup volume and the cup depth decreased due to the anterior movement of the lamina cribrosa.

A second method to quantify topographic changes is the computation of topographic difference images. It enables to analyze local height changes. The procedure is as follows: Sets of three images are acquired during the baseline exam and the follow-up exam. From the sets of images, the mean topography images and the standard deviation images are computed for both the baseline and the follow-up exam. The two mean topography images are then normalized to each other and subtracted. The result is a topographic difference image that is used to quantify local height changes. The standard deviation images computed together with the mean topographies give the reproducibility of the examinations at each point of the images. It is used to test the significance of a detected local height change at any pixel.

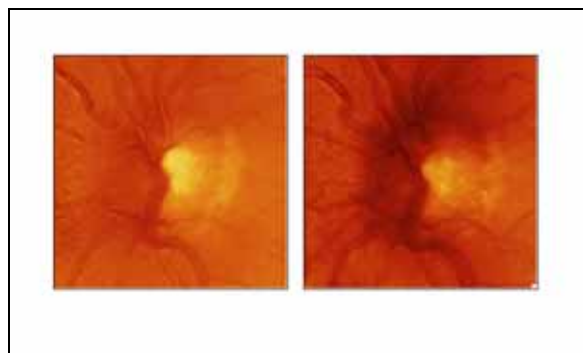


Figure 24

The following is an example of a change analysis with topographic difference images. Figure 24 shows two optic nerve head topography images acquired at different intra-ocular pressures. At the baseline examination (left) this eye had an intra-ocular pressure of 50 mmHg. In the follow-up exam after surgery (right) the IOP was only 15 mmHg. It is obvious from the topography images, that the optic nerve head appears darker in the follow-up exam, that means the optic nerve head is more elevated at the lower pressure.

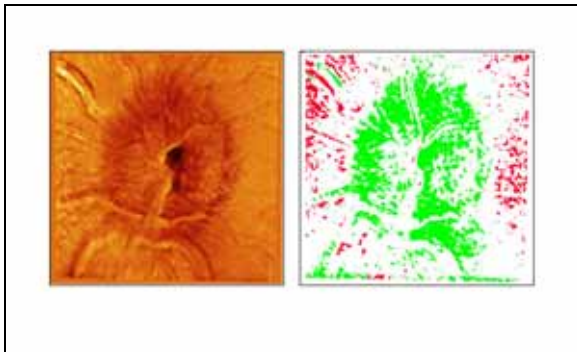


Figure 25

Figure 25 shows the topographic difference image for these examinations. As darker the difference image, as more elevated the follow-up examination is compared to the baseline examination. Bright locations in the difference image show more depression in the follow-up examination compared to the baseline examination. On the right, the significance marker image which is the result of a t-test using the height change and the local standard deviation of the measurements at each pixel. All portions of the image with significantly higher elevation in the follow-up exam are displayed in green color. Obviously, the whole optic nerve head moved anteriorly. The biggest height change of about 300 microns was observed at the bottom of the cup.

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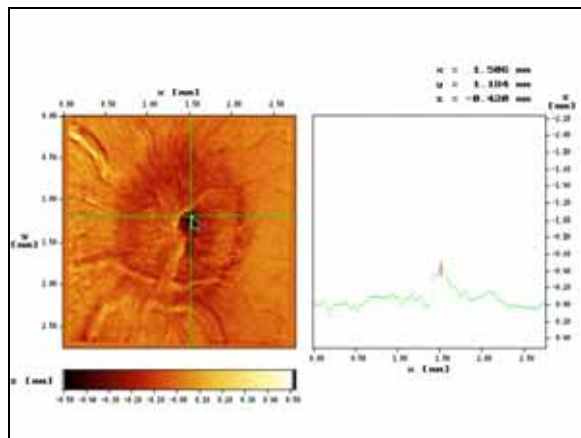


Figure 26

A horizontal cross section through the topographic difference image is shown in figure 26. From that we can measure that the highest anterior movement occurred at the bottom of the cup and is more than 300 microns. However, the whole optic disk moved anteriorly.

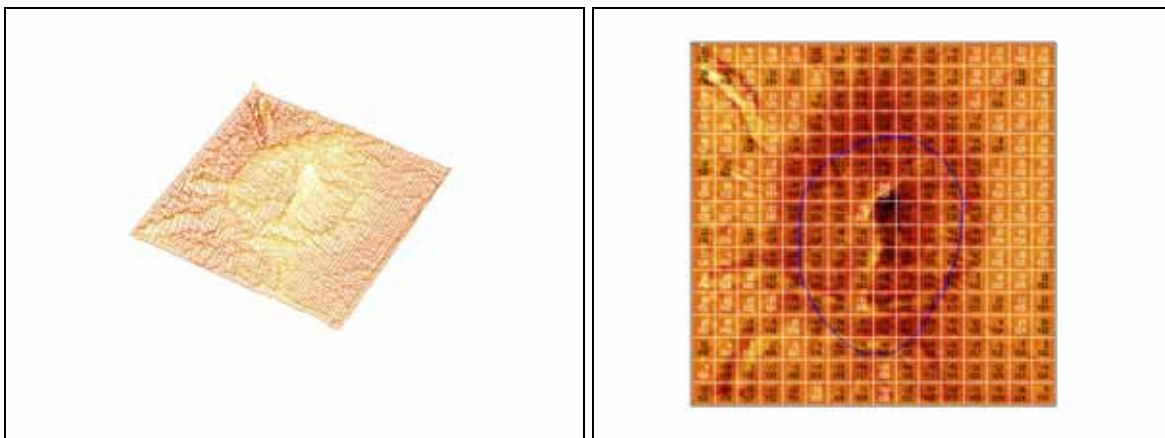


Figure 27

Figure 27 a and b display a pseudo-3D representation of the difference image and the topographic difference map, respectively. Each number in the difference map shows the average height change in an array of 16 x 16 pixels in microns, plus and minus the local reproducibility.

A new approach to analyze progression in glaucoma - the probability map analysis - was proposed by Dr. Chauhan and coworkers in Halifax. This method is as follows: Three images are acquired during the baseline and during the follow-up exam. The six images are aligned and normalized to each other. Then in each image clusters of 4 by 4 adjacent height measurements or pixels are combined to so-called superpixels. That means for each superpixel we have 48 baseline height measurements and 48 follow-up height measurements. Then the variability of the 48 baseline measurements is compared to the combined variability of the 96 baseline and follow-up measurements at each superpixel with an F-test.

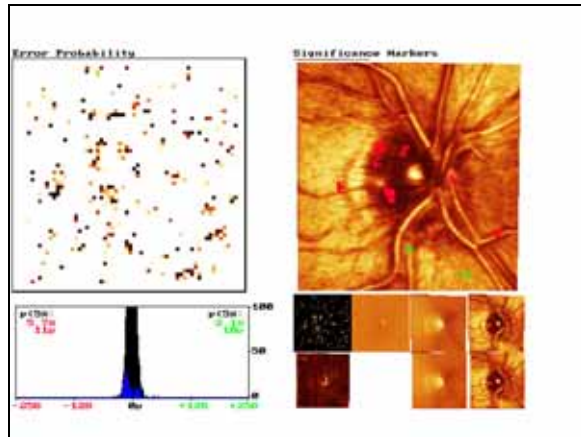


Figure 28

The resulting probability maps are displayed color coded. Superpixels with no significant change are displayed white; at the dark superpixels, the surface height changed significantly with an error probability of less than 5%. In the example in figure 28, a normal eye was examined; baseline and follow-up exam were performed during the same day. Obviously, this probability map is rather clean, with about 5% of the superpixels randomly spread over the entire image exhibiting significant change. This is what one expects as the noise if there is no change at all. The significance marker image on the right in figure 28 shows locations of significant topographic change.

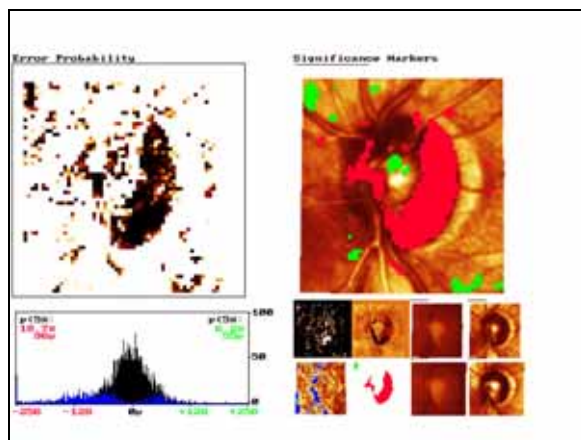


Figure 29

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Figure 29 shows the probability map analysis of a glaucoma patient with 5 years between baseline and follow-up examination. The visual field remained stable during the 5 years, but the optic nerve head topography obviously deteriorated, as the cup became wider and deeper. The red markers on the right of figure 29 indicate glaucomatous progression in most part of the neuroretinal rim.

6 Other applications

The quantification of glaucomatous change and progression shown previously is a typical example for the clinical application of the Heidelberg Retina Tomograph. However, the clinical use of this instrument is much broader. In general, it can be used in all cases where topographic changes at the posterior segment must be quantified. Examples are the analysis of the

retinal topography, the evaluation of macular holes and edema, and the detection and quantification of nerve fiber layer defects.

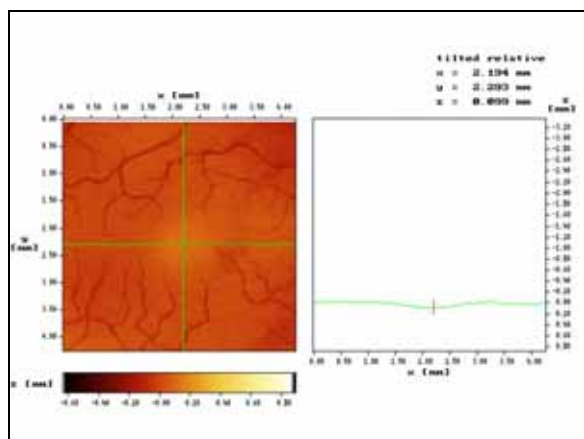


Figure 30

Figure 30 shows the topography image obtained from the examination of a normal macula, and a horizontal cross section showing the variation of the retinal surface height through the fovea. The highest elevations obviously occur in about 1 mm distance from the fovea, the locations where there is highest density of nerve fibers. This elevation is only about 20 microns but can be clearly shown in this examination.

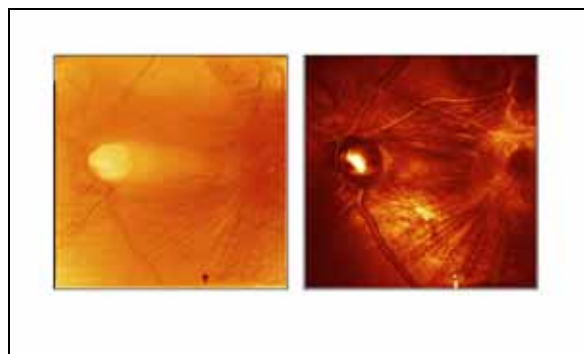


Figure 31

Figure 31 shows a case of macular pucker with a pseudo hole. Topography image (left) and reflectance image (right) are shown.

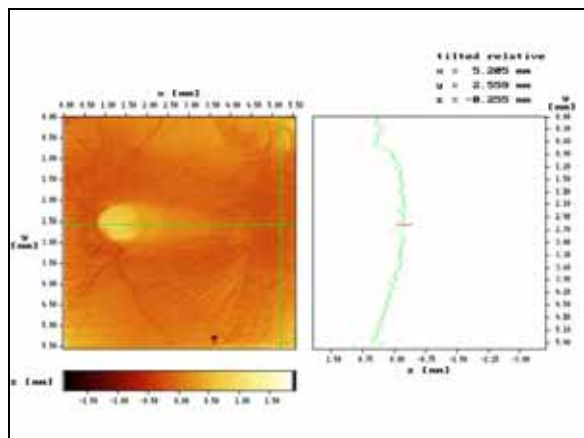


Figure 32

A vertical cross section through the hole is displayed in figure 32. Obviously, there is no depression, that means there is a membrane above the hole.

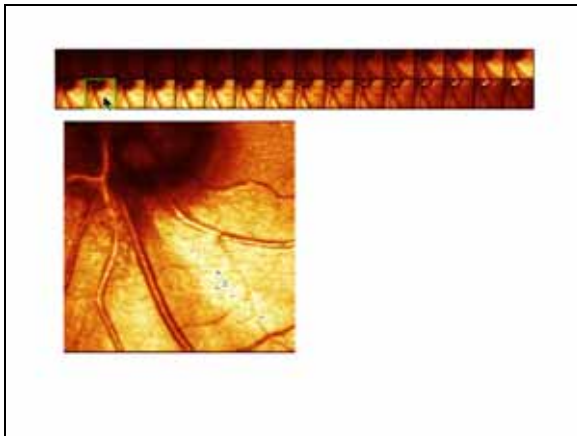


Figure 33

Figure 33 shows a series of optical section images of an eye with a nerve layer bundle defect. The bundle defect is easily visible by the decreased reflectance. One of the images - with the focal plane located at the retinal surface - is shown in full scale on the right slide. The extent of the nerve fiber layer defect is clearly visible.

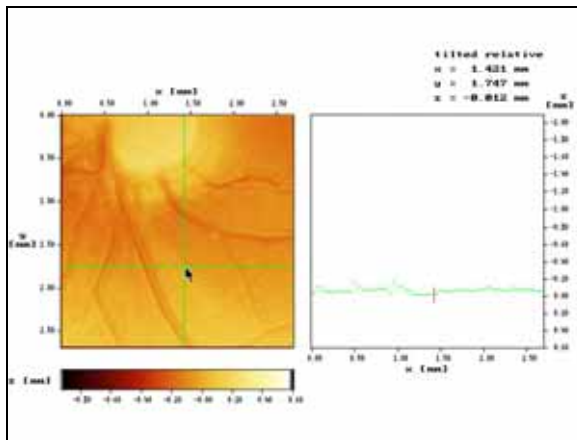


Figure 34

The topography image computed from this image series is shown in figure 34, together with horizontal cross sections through the nerve fiber layer defect at about 1 mm distance from the disk. The nerve fiber layer defect obviously causes a depression of the retinal surface height. The depression is about 50 microns near the disk margin and about 20 microns in 1 mm distance from the disk.

7 Conclusions

In conclusion, the Heidelberg Retina Tomograph enables quantitative imaging of the posterior segment. The system allows the acquisition of two- and three-dimensional images and we can perform a three-dimensional topographic analysis of the retinal structures. In particular, laser scanning tomography as realized in the HRT allows us to quantitatively assess the optic nerve head topography. There are promising approaches for the classification of individual eyes to support the diagnosis of glaucoma, and for the quantification of progression of glaucomatous damage.