Comparison of Heidelberg Retina Tomograph II and Retinal Thickness Analyzer in the Assessment of Diabetic Macular Edema

Kit Guan,1,2 Chris Hudson,1,2,5 and John G. Flanagan1,2,5

PURPOSE. To compare the within-session variability of the Macular Edema Module of the Heidelberg Retinal Tomograph II (HRT II; Heidelberg Engineering, Heidelberg, Germany) and the Retinal Thickness Analyzer (RTA, Talia Technology Ltd., Neve-IlIan, Israel) in patients with diabetes and non-diabetic subjects and to determine the agreement of both instruments to clinical observation.

METHODS. Seventeen patients with diabetic macular edema (DME) and 17 non-diabetic subjects were examined. Three scans of the posterior pole were acquired for each volunteer with both the HRT II and the RTA. The edema index and foveal average thickness were derived for a 600-µm radius circle centered on the fovea for the HRT II and RTA scans. The coefficient of variation (COV) was calculated. Clinical examination of detectable edema was performed using stereo fundus biomicroscopy and the level of agreement between each instrument and clinical observation was determined using a zonal analysis.

RESULTS. Individual COVs for the HRT II and RTA ranged from 2.3% to 24.6% (median 8.3%) and 2.1% to 46.7% (median 6.4%), respectively, in diabetic subjects and 2.0% to 37.5% (median 6.0%) and 2.3% to 14.7% (median 8.5%), respectively, in non-diabetic subjects. Clinical assessment identified edema in a total of 47 sectors in patients with DME. In comparison to clinical assessment, the HRT II gave a sensitivity of 92% and a specificity of 68% and the RTA gave a sensitivity of 57% and a specificity of 71%.

CONCLUSIONS. Both instruments have good within-session repeatability. The HRT II showed better agreement with clinical assessment than the RTA. The agreement between instruments was poor. (Invest Ophthalmol Vis Sci. 2004;45:610–616) DOI: 10.1167/iovs.03-0313

Diabetic macular edema (DME) is one of the leading causes of visual impairment among patients with diabetes.1,2 It results from fluid accumulation in the retina due to the breakdown of the blood–retinal barrier.1,4 The clinical assessment of DME uses contact lens stereoscopic biomicroscopy, which relies on the subjective recognition of thickening of the transparent retina by a clinician. It is problematic to differentiate early retinal thickening from normal variation in retinal thickness.5 Substantial differences exist between experienced retinal specialists in defining the extent and location of retinal thickening in a given patient,6 which illustrates the difficulty in assessing the location and extent of retinal edema.

Several objective techniques for the assessment of retinal edema have been developed including computed tomography, automated slit lamp biomicroscopy and optical coherence tomography (OCT). The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) is a confocal scanning laser tomograph that sequentially acquires two-dimensional, lateral (i.e., x, y plane) section images along the optical (z) axis. The distribution of reflected light intensity along the optical axis for a given pixel is described as the z-profile or confocal intensity profile. A new technique determines the signal width (at half peak height) and peak reflectance intensity of the z-profile. Studies have demonstrated a broadening of the z-profile signal width (SW) and a decrease in peak reflectance intensity (IN) in areas of edema.7 Normalization of the reflectance values reduces the variation in intensity between successive scans: Edema index = SW/IN.

An edema index can be derived for each pixel, which is sensitive to edematous changes of the retina.8 A resultant map of these edema indices gives a measure of the location and extent of retinal edema (Fig. 1).9 It should be noted that the edema index is not a measure of retinal thickness but of the optical effect of edema within the retina. The edema index methodology has been validated in diabetic retinopathy but not in other disease states. Change of the edema index has been shown to correlate with change of visual function, including logarithm of the minimum angle of resolution (logMAR) visual acuity, conventional automated static perimetry and short-wavelength automated perimetry, in patients undergoing grid laser treatment for clinically significant macular edema (CSME; Flanagan JG, Hudson C, manuscript submitted).7–9

The Retinal Thickness Analyzer (RTA, Talia Technology Ltd., Neve-IlIan, Israel) works on the principle of slit lamp biomicroscopy. It sequentially scans vertical slits across an area of the retina to generate rapidly a topographic map of retinal thickness.10,11 The reflections are captured by a black-and-white charge-coupled device (CCD) camera and stored for analysis. A bi-Lorentzian curve fitting is performed to delineate the internal limiting membrane (ILM) and retinal pigment epithelium (RPE) separation with an axial resolution of approximately 50 µm (Fig. 2).10,12 The instrument has been used extensively in the evaluation of retinal diseases including DME.13–18 The RTA has been reported to have a high level of reproducibility.12,19

Copyright © Association for Research in Vision and Ophthalmology

610
Of the techniques used to assess retinal thickness, OCT is perhaps the most established method. As described by Huang et al., OCT uses low-coherence light from a superluminescent diode coupled with a Michelson interferometer to measure optical reflections from the retina. The OCT processes 100 to 512 longitudinal A-scans to generate a cross-sectional slice of the imaged area, depending on the instrument version. By using six radial slices, it can create a topographic map of the posterior pole. The instrument in its current form provides axial resolution on the order of 10 to 17 μm. The OCT has been used in the assessment of a variety of diseases, such as macular holes, retinal edema, and nerve fiber layer thickness.

A newer version of the Heidelberg Retina Tomograph, the HRT II (Heidelberg Engineering), samples 384 × 384 pixels across a 15° × 15° field of view. The area scanned is approximately 4.5 × 4.5 mm on the retina and corresponds to a spatial resolution of 12 μm per pixel. In the central 500-μm radius circle, approximately 7100 points are sampled. The RTA samples 32 × 32 pixels across a 6 × 6-mm area. Its spatial resolution is 187 μm per pixel. In the central 500 μm radius circle,
32 points are sampled. The OCT 2000 (software version A6.1; Humphrey Systems Division, Carl Zeiss Meditec, Dublin, CA) employs six radial scans to cover a circular area with a 3000-μm radius. It samples 600 points in total, with 100 of these in the central 500-μm radius circle that results in a spatial resolution of approximately 89 μm per pixel. However, the spatial resolution of the radial-spoke methodology declines with increasing eccentricity from the center of the scan to an average of 474 μm per pixel in the periphery. This level of spatial resolution may miss lesions that are a third of a disc diameter or smaller if it falls between the scan lines, such that subtle lesions outside of the central fovea could be missed. This variable, and relatively poor, level of spatial resolution precluded our use of the OCT in the mapping of early DME (despite the obviously superior axial resolution of the OCT). The OCT 3000 recently released by Humphrey Systems (division of Carl Zeiss Meditec) increases scan resolution to 512 A-scans along a scan line and has a reported spatial resolution from 5 to 60 μm.

Both the HRT II and RTA should be examined in a clinical setting to determine their relative diagnostic test performance. An objective and repeatable method of assessing early DME would be of great benefit in monitoring the progression and treatment of the disease. The sensitivity and specificity of each instrument in the detection of DME should be established and examined with respect to the current gold standard method of stereo fundus biomicroscopy if either instrument is to be accepted for wide spread clinical use.

### Materials and Methods

#### Sample

Seventeen patients (mean age, 60 ± 7 years) with DME diagnosed in at least one eye and 17 nondiabetic subjects (mean age, 49 ± 8 years) were recruited from patients and staff of the Toronto Western Hospital (Table 1). For the patients with DME, the average duration of diabetes was 14 ± 4 years. One eye was randomly assigned to the study in all nondiabetic subjects and in those patients with DME in both eyes. The study was approved by the Research Ethics Board of the University Health Network (University of Toronto, Canada) and followed the tenets set out in the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from all participants after the nature and possible consequences of the study were explained.

#### Procedures

Each study eye underwent refraction, logMAR visual acuity (Early Treatment of Diabetic Retinopathy Study charts at 96% contrast), pupillary dilation (using 1% tropicamide), assessment of lens opacity using the Lens Opacity Classification System III (LOCS III) and stereo fundus biomicroscopy. In addition, assessment with the HRT II and RTA were performed in a randomized fashion.

#### Clinical Assessment

The clinical gold standard of stereo fundus biomicroscopy was used throughout the study. A standardized method was established to permit the quantitative comparison between clinical assessment and both imaging modalities. A 20° × 20° retinal image centered on the fovea of the study eye was acquired in each volunteer, with the HRT. A clear acetate sheet was placed over the printed retinal image, and the retinal capillary pattern of each volunteer was carefully traced. The resultant vascular trace provided no other cues that might suggest the presence of retinal edema, such as hard exudates and microaneurysms. This methodology was previously used by Hudson et al. to accurately document the area and extent of retinal edema. The location and extent of DME was documented on the vascular trace by one of six retinal specialists (WCL, RGD, MM, PTH, JL, and JC) while performing stereo fundus biomicroscopy. All assessors were masked to the results of the imaging modalities. Each vascular trace defining the location and extent of DME was divided into five sectors (central 600-μm radius circle plus four peripheral quadrants, Fig. 5). The original HRT scan was not used in the subsequent analysis.

#### HRT II: Macular Edema Module

The HRT II (Heidelberg Engineering) sequentially acquires 16 two-dimensional (that is, x, y plane) confocal section images per millimeter along the optical axis (that is, z-axis). The edema index analysis developed by Flanagan and Hudson has been incorporated within the HRT II as the Macular Edema Module (MEM). Each HRT II scan consists of 3 sequential 15° × 15° tomographic images of the retina that are averaged to display a mean topography image. The mean topography image that is subsequently analyzed has a resolution of 384 × 384 pixels. The average edema index was derived for a 600-μm radius circle centered on the fovea using the MEM software (ver. 1.0.0.4). This circle size was chosen to correspond to the same area of the Foveal Average Thickness (FAV) of the RTA. Each of the three sets of scans was divided into five sectors identical with that used for clinical assessment and areas of increased edema index were visually noted by two expert MEM assessors (JGF and CH). Assessors were masked from the subject’s clinical status. At least two of the three scans needed to
manifest evident edema for any one sector to be assigned as edematous.

Retinal Thickness Analyzer

The Retinal Thickness Analyzer (RTA; Talia Technology Ltd., Neve-Ilan, Israel) sequentially scans 16 vertical slits across a 3 × 3-mm area. Retinal thickness is calculated for 16 points along each slit, giving a single scan resolution of 256 points (16 × 16) per scan. Five overlapping scans of the posterior pole (central, superior temporal, superior nasal, inferior temporal, and inferior nasal) were performed and combined to give a total scan area of approximately 6 × 6 mm (total scan resolution of 1024 points, 32 × 32 pixels). Three sets of the five standard scans were acquired. Analysis of the topographic maps was performed using RTA software version 4.075 (Talia Technology Ltd.). The foveal average thickness (FAV) of a 600-μm radius circle was calculated for each scan. Each of the three sets of scans was divided into five sectors identical with clinical assessment, and areas of increased retinal thickness were visually noted by two expert RTA assessors (KG and CH). Assessors were masked from the clinical status of each volunteer. At least two of the three scans needed to manifest evident edema for any one sector to be assigned as edematous.

Analysis

Differences between groups were compared using a two-tailed Student’s t-test with α = 0.05. The coefficient of variation (COV = SD/mean) was calculated for the central 600-μm radius circle of both instruments. The level of agreement to clinical assessment and between each instrument was determined using a zonal analysis of the five predefined areas (Fig. 3). The zonal analysis adjusted for the fact that the area assessed using stereo fundus biomicroscopy and using the RTA was 20° × 20° compared with the area assessed using the HRT II scan which was 15° × 15°. Combining the results of patients with DME and normal subjects, the sensitivity [true positives/(true positives + false negatives)] and specificity [true negatives/(true negatives + false positives)] of each instrument with respect to clinical assessment were determined.

RESULTS

There was a significant difference in logMAR visual acuity between patients with diabetes and nondiabetic subjects (0.13 ± 0.15 vs. −0.13 ± 0.09, respectively, P < 0.001). The assessment of lens clarity using LOCS III for both groups are presented in Table 2. Patients with diabetes had significantly greater nuclear opalescence, nuclear color, and cortical cataract (P = 0.015, P = 0.049, and P = 0.001, respectively).

Both the HRT II and RTA are able to identify DME objectively. Each instrument uses distinctly different methodologies to assess the presence of edema and its effect on retinal thickening.

DISCUSSION

Both the HRT II and RTA are able to identify DME objectively. Each instrument uses distinctly different methodologies to assess the presence of edema and its effect on retinal thickening.
The HRT II analyses the optical effect of change in the profile of reflectance intensity as a function of depth attributable to retinal thickening and the concomitant reduction in retinal reflectivity most likely attributable to changes in refractive index with retinal edema. The RTA determines retinal thickness by identifying the optical separation of the ILM and RPE.

The HRT II had a higher sensitivity in detecting DME than did the RTA (92% versus 57%, respectively). The specificity was approximately the same (HRT II 68% versus RTA 71%) across the two instruments. In comparison, the OCT has a reported sensitivity and specificity in detecting CSME of 89% and 96%, respectively, within the central fovea. However, it has been shown that due to its poorer spatial resolution outside the central fovea, the OCT tends to miss subtle edema beyond 500 μm of the fovea. It should be noted that with the additional resolution of the OCT 3000, there is increased likelihood of detecting extrafoveal edema. Future studies are needed to assess the ability of the OCT 3000 in the mapping of early edema and the comparison of its diagnostic test performance to clinical assessment and other imaging modalities.

There are two possible explanations for the high sensitivity and moderate specificity of the HRT II. The first would be that its diagnostic test performance is limited by the definition of the gold standard (i.e., the additional edematous areas represent early edema undetected by the gold standard). The second explanation would be that the HRT II is identifying false positives. It is not possible in this cross-sectional study to determine which of these two possibilities determine the diagnostic test performance of the HRT II. However, it is unlikely that the HRT II would have such a high sensitivity along with the moderate specificity, if it were identifying so many false positives. This is further supported by the observation that most of the false positives were from the diabetic subjects—that is, on the whole, the technique does not suggest that there is edema within the normal group (8/85 possible sectors). Prospective studies are ongoing that will enable us to investigate this issue.

Concerning the RTA, which has poor sensitivity and moderate specificity, its diagnostic test performance bears little similarity to the clinical gold standard. The poor sensitivity of the RTA may be explained by the dependence of the instrument on clear media and a minimum 4-mm dilated pupil, not always easy to achieve in patients with diabetes. The curve-fitting algorithms used by the RTA can erroneously identify areas of apparent edema that actually represent artifact from blurred or distorted images (Fig. 5). Neubauer et al. used both the OCT and the RTA to assess foveal thickness in subjects with DME and in nondiabetic subjects. They found that the RTA, in some cases, showed high retinal thicknesses in patients without clinically detectable retinal thickening when compared with OCT. This was attributed to slit images with blurred edges, and it resulted in a high interpatient COV of 33%. Our results with the RTA are further supported by the poor correlations found in two other studies comparing it with OCT and clinical assessment.

The level of agreement between the HRT II and RTA is poor, especially in patients with DME. This is to be expected considering the instruments’ respective diagnostic test performances and given that they measure different aspects of DME.

This study used six retinal specialists to determine clinically evident edema, the standard by which we judged the diagnostic test performance of the instruments. Consequently, the definition of the location and extent of retinal edema is introduced by a single assessor.

Table 3. Sectors of Agreement between HRT II and RTA Compared with Clinical Assessment and Each Other in Patients with DME and Nondiabetic Subjects

<table>
<thead>
<tr>
<th>DME</th>
<th>Nondiabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edema Detected</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
</tr>
<tr>
<td>Clinical</td>
<td>45/47</td>
</tr>
<tr>
<td>HRT</td>
<td>—</td>
</tr>
</tbody>
</table>

Numbers in italic represent sectors of agreement between the outcome measures. Numbers in bold represent the gold standard. In the first row, clinical assessment is the gold standard and in the second row, HRT is taken as the gold standard to facilitate easier comparison between HRT II and RTA.
The median COV of approximately 7% for both instruments in the central 600-μm radius circle centered on the fovea was good. For the HRT II, this compares favorably with previously published literature that found the COV for the edema index to be approximately 14% to 22% in normal subjects using a prototype system.7-9 Investigators in prior studies have reported the COV for the FAV of the RTA to be approximately 5% to 6% for normal subjects and patients with diabetes, which is comparable to our study.10,11 In comparison, the OCT has an average COV of 6% in normal subjects and 8% in diabetics.32 Our study found a large range of individual COVs for DME subjects from 2.3% to 24.6% for the HRT II and 2.1% to 46.7% for the RTA, reflecting intersubject variation. This intersubject variation was also shown with OCT with a range of COVs in individual subjects reported from 3% to 30% in the central macula.22,30,31 Localized differences in the variability of retinal thickness measurements, particularly in areas of changing topography, have been noted previously for the HRT II, RTA, and OCT.30,52,53 At the time of this writing, new software versions for the RTA (ver. 4.10) and the HRT II (ver. 1.2.0) were being released. It is expected that, like the OCT, newer algorithms will continue to improve the variability of measurements gained with these instruments.

There was a significant age difference between patients with diabetes and nondiabetic subjects (mean age, 60 ± 7 years vs. 49 ± 8 years, respectively), but the comparison of the two instruments with clinical assessment was consistent across both groups. This age difference may cause differences in tear film quality and media clarity between the study groups, affecting the quality of the scans taken by both instruments. The LOCS III assessment of lens clarity is clearly poorer in patients with DME. Patients with established DME tend to have poorer glycemic control,4,34-36 which has been associated with reduced lens clarity.57,58 In summary, both instruments had low variability of results within 600 μm of the fovea. The HRT II showed better agreement with clinical assessment than the RTA. The agreement between instruments was poor.

Acknowledgments

The authors thank the Mustafa Rawji and Tien Wong of the Multi-Disciplinary Laboratory for Research of Sight-Threatening Diabetic Retinopathy for their support and advice and ophthalmologists Wai-Ching Lam, Robert G. Devenyi, Mark Mandelcorn, Patricia T. Harvey, Jeffrey Lim, and Jordan Cheskes of the Toronto Western Hospital for the assessment of DME.

References


