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Inter-observer agreement for spectral- and time-domain optical coherence tomography image grading: a prospective study

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Abstract The purpose of this study was to compare inter-observer agreement of Stratus^{TM} OCT versus Spectralis^{TM} OCT image grading in patients with neovascular age-related macular degeneration (AMD). Thirty eyes with neovascular AMD were examined with Stratus^{TM} OCT and Spectralis^{TM} OCT. Four different scan protocols were used for imaging. Three observers graded the images for the presence of various pathologies. Inter-observer agreement between OCT models was assessed by calculating intra-class correlation coefficients (ICC). In Stratus^{TM} OCT highest interobserver agreement was found for subretinal fluid (ICC: 0.79), and in Spectralis^{TM} OCT for intraretinal cysts (IRC) (ICC: 0.93). Spectralis^{TM} OCT showed superior interobserver agreement for IRC and epiretinal membranes (ERM) (ICC$_{Stratus^{TM}}$: for IRC 0.61; for ERM 0.56; ICC$_{Spectralis^{TM}}$: for IRC 0.93; for ERM 0.84). Increased image resolution of Spectralis^{TM} OCT did improve the inter-observer agreement for grading intraretinal cysts and epiretinal membranes but not for other retinal changes.

Introduction

Optical coherence tomography (OCT) was introduced in 1991 as a non-invasive, cross sectional imaging technique [1]. In 1995 Time-Domain OCT (TD-OCT) was used first for imaging macular diseases with many studies published about imaging in age-related macular degeneration (AMD) [2–15]. In neovascular AMD, retinal structure can be disturbed by choroidal neovascularisation (CNV) which is frequently associated with intraretinal cysts (IRC), subretinal fluid accumulation (SRF), pigment epithelium detachments (PED), and epiretinal membranes (ERM). In addition, one can frequently observe subretinal hyper-reflective material (SHM) in OCT images that might correspond to subretinal scar tissue, haemorrhages, fibrin formation and subretinal deposition or choroidal neovascularisations.

Recently, different treatment modalities for neovascular AMD have been introduced [11, 12, 16–19]. Conventional TD-OCT plays an important role in following patients with neovascular AMD during therapy with intravitreal anti-VEGF agents such as ranibizumab or bevacizumab [16]. OCT imaging was part of main outcome measures in various clinical trials.

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This led to the creation of OCT reading centers where independent observers review OCT scans for defined pathologies and retinal thickness measurements. Data regarding OCT retinal thickness measurement reproducibility has been published previously [20–27].

Recently, improvements in OCT technology have been introduced [28, 29]. Spectral-Domain OCT (SD-OCT) provides increased resolution and scanning speed by recording the interferometric information using a Fourier-domain-spectrometric method. Axial resolution is up to five microns and imaging speed is up to 100 times faster than in conventional TD-OCT [30, 31]. In addition to radial line scans (RLS), SD-OCT can perform high-density volume scans (VS). These volume scans provide considerably more data compared to the six radial line scans of conventional TD-OCT and allow calculation of a three-dimensional map of the macula with less need for interpolation within the scanning area. Some SD-OCT devices offer averaging of multiple scan images for noise reduction and in addition a real time eye tracking for improved reproducibility of measurements. SD-OCT has been used previously to demonstrate its ability to visualize macular pathologies in patients with AMD [32–36].

One can hypothesize that higher scan resolution and greater scan coverage, i.e. higher number of B-scans, might lead to increased identification of retinal lesions in AMD and a higher interpretation agreement between different clinicians (inter-observer agreement).

Our goal was to compare the result of TD-OCT with SD-OCT in terms of grading-agreements between three independent observers. Two scan types in each OCT device were used.

Methods

Thirty eyes of 28 patients with previously diagnosed neovascular AMD were included in this prospective, comparative, observational study. Exclusion criteria were patients with severe media opacity, patients unable to undergo OCT examination, and patients with vast central subretinal hemorrhages that make OCT image interpretation impossible. OCT images had to be of good quality which was considered if all single line scans within a scan type showed a good signal with detailed retinal structure, no blinking artifacts, and no problems with the retinal thickness

measurement algorithm. The initial diagnosis of exudative AMD was established by fundus examination and fluorescein angiography. All study patients were recruited from the retina unit of the Department of Ophthalmology, University Hospital Zurich, Switzerland. All patients had previous anti-VEGF treatments with either bevacizumab or ranibizumab for their CNV and were planned for regular follow-up examinations. Study patients gave written informed consent to participate in this study, which was approved by the local ethics committee.

For OCT, Stratus[TM] OCT (Zeiss Meditec, Dublin, CA, USA, Softwareversion 4.0.7) was used for Fast Macular scan (FMS) and Cross Hair scan (CHS). FMS consists of 6 intersecting line scans in a spoke wheel-like pattern. Each line is 6 mm long and includes 128 A-scans. The CHS consists of two intersecting line scans of 6 mm length in a cross pattern. Each line scan includes 512 A-scans. Both scan protocols were chosen, because they belong to the most common used protocols in clinical routine and in ongoing clinical trials. Spectralis[TM] OCT (Heidelberg Engineering, Heidelberg, Germany, Softwareversion 5.3) was used to perform high-resolution volume scans (VS), and radial line scans (RLS). For the VS, a raster scan pattern consisting of 25 line scans was chosen for macular scanning in an area of 30 × 20°. Each line scan was averaged 25-times by the Spectralis[TM] OCT ART function. The Spectralis[TM] OCT is capable of performing more line scans per raster scan for even greater retinal coverage. However, since patients with AMD are rather old and visual acuity and fixation stability is relatively poor, scan numbers were reduced to 25 line scans in order to speed up the scanning process and to allow measurements in less than 3 min. The RLS consists of 6 intersecting line scans similar to the FMS of Stratus[TM] OCT with 512 A-scan per line and a scan length of 20°. Figure 1 shows examples of all 4 OCT scan types.

Three observers (PBK, HK, MNM) reviewed the OCT scans of all study eyes independently. All observers were specialist for treating exudative AMD and experienced OCT user, but not specifically trained grader from an OCT reading center. All 120 scans (30 eyes × 4 scan types) were presented in random order. Since the 4 scan types consisted of 6 (FMS), 2 (CHS), 6 (RLS), and 25 (VS) single line scans, a total of 1,170 single line scans were reviewed. Each observer was masked to the patient data and to the decision of the

Fig. 1 Four different OCT scan types used in a left eye with neovascular age-related macular degeneration. On the left, different scan patterns are projected on either infrared fundus images (Stratus[TM] OCT) or scanning laser ophthalmoscope fundus images (Spectralis[TM] OCT). All presented B-scan images on the *right* were performed in *horizontal* direction and focused on the fovea. *Top* fast macular scan pattern (Stratus[TM] OCT). *Second from top* Cross hair scan pattern (Stratus[TM] OCT). *Third from top*: Volume scan pattern (Spectralis[TM] OCT). *Bottom* Radial line scan pattern (Spectralis[TM] OCT). In all B-scan images one can appreciate two retinal pigment epithelium detachments and subretinal fluid accumulation
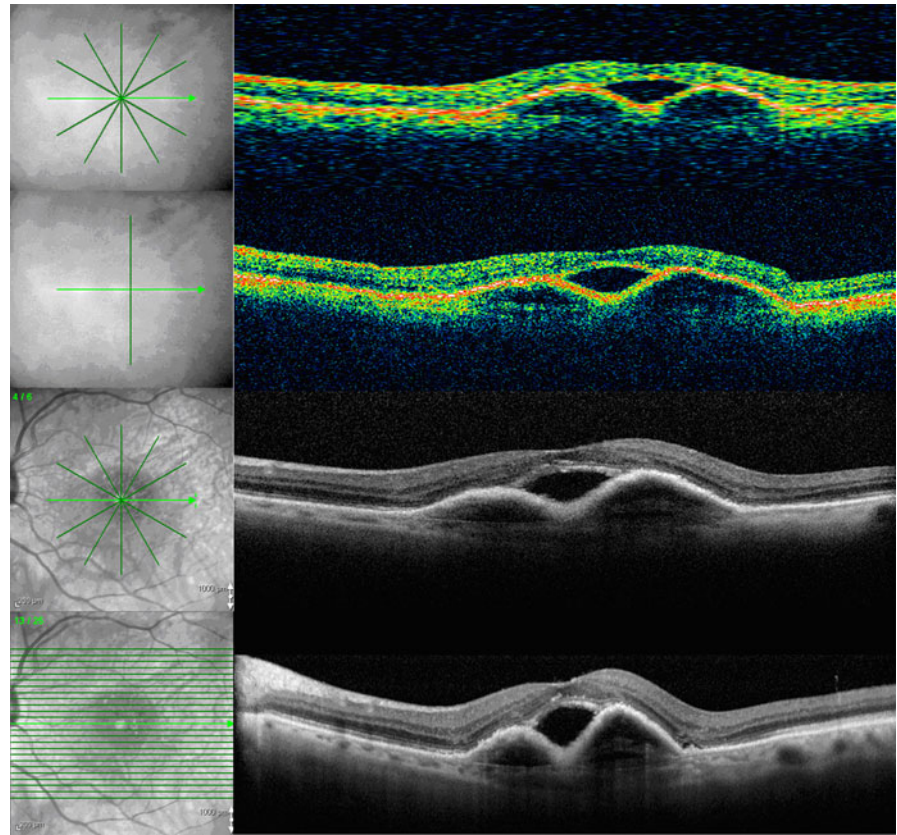
treating physician regarding re-treatment with intravitreal anti-VEGF drugs. Images were presented on a high resolution monitor.

Observers were asked to review each line scan within the scan protocol (FMS, CHS, VS, and RLS) and to give a summarized grading for each scan and eye for the absence (=0) or presence (=1) of IRC, SRF, PED, ERM, and SHM.

IRC were defined as the any noticeable presence of hypo-reflective, round or oval-shaped spaces within the neurosensory retina. SRF was defined as a hypo-reflective space between the neurosensory retina and the retinal pigment epithelium. PED was defined as any elevation (not just localized thickening of the retinal pigment epithelium such as in Drusen) of the retinal pigment epithelium layer with consecutive elevation of the neurosensory retina. ERM was defined as a highly-reflective thin layer on top of the inner limiting membrane with or without retinal wrinkling. SHM was defined as a highly-reflective signal underneath the retinal pigment epithelium with an irregular

shape, that cannot be classified as PED. SHM might be due to scar tissue, blood or neovascular material.

Intraclass correlation coefficients (ICC) were separately calculated to assess inter-observer agreement for grading morphologic pathologies within Stratus[TM] OCT (ICC$_{Stratus[TM]}$; data of FMS and CHS gradings), and within Spectralis[TM] OCT (ICC$_{Spectralis[TM]}$; data of VS and RLS gradings). Calculating ICC is a statistical procedure to determine the reproducibility (in this case inter-observer agreement) of a measurement of a variable. This correlation is based on variance components analysis and measures the homogeneity within groups relative to the total variation. The ICC is large when there is little variation within the groups compared to variation among group means. A small ICC occurs when within-group variation is large compared with between-group variability, indicating that some unknown variable has introduced non-random effects in the different groups. A linear mixed-effect model was used to calculate variance components and 95 % confidence intervals (95 % CI) for eyes, OCT devices,

and scan types. Commercial software (Stata, ver. 9.2; StataCorp, College Station, TX) was used for analysis.

Results

The mean age of the study subjects was 78 ± 6 years, with a range of 42–88 years. Eighteen patients were female. Good quality OCT scans could be performed in all 30 eyes with Stratus[TM] OCT (FMS and CHS) and Spectralis[TM] OCT (VS and RLS). Table 1 shows variance components with 95 % confidence intervals for eyes, OCT device, scan type, and the corresponding ICCs for the agreement of OCT image grading. In Stratus[TM] OCT the highest agreement was found for SRF (ICC$_{Stratus[TM]}$: 0.79). In Spectralis[TM] OCT the highest ICC was found for identification of IRC (ICC$_{Spectralis[TM]}$: 0.93). Lowest agreement was found for SHM with an ICC$_{Stratus[TM]}$ of 0.65, and an ICC$_{Spectralis[TM]}$ of 0.52. Spectralis[TM] OCT showed marked superior inter-observer agreement for IRC and ERM compared to Stratus[TM] OCT.

Discussion

In our study, Spectralis[TM] OCT showed superior inter-observer agreement for grading IRC and ERM. This suggests that increased image resolution might be beneficial for grading pathologies that are located in the vitreo-retinal interface or in the neurosensory retina. In addition, the increased retinal coverage increased the chance of finding pathologies. This might also explain the better agreement. The used SD-OCT

device was operated with 25 line scans for each raster scan although it is capable of performing more line scans if necessary. Other SD-OCT models use raster scans with up to 128 line-scans which increases retinal coverage even more. Interestingly, the improved image resolution and scan coverage of SD-OCT did not significantly improve inter-observer OCT image grading agreement for most other pathologies tested.

Lowest inter-observer agreement was found for SHM. It seems to be difficult to distinguish SHM from other pigment epithelial changes, intraretinal blood, or increased light penetration artifacts due to pigment epithelium atrophy. These findings are in agreement with previous studies of Zhang et al. [26] who tested OCT reader agreement in neovascular AMD by comparing 3 observers, who were certified by an OCT reading center. All observers used a standardized grading protocol. Two different scan protocols (FMS and 7 mm line scan) were compared and all scans were performed with the Stratus[TM] OCT. Inter-observer agreement was found to be high for 7 of 8 pathologies tested (IRC, SRF, ERM, PED, macular edema, vitreomacular interface changes, choroidal neovascularisations) ranging from 79 to 98 %. Observer agreement for pigment epithelium atrophy was significantly lower and ranged from 43 to 50 %. No significant differences were found between the two tested scan types.

Recently, Sayanagi et al. [37] compared 4 different SD-OCT models versus TD-OCT for the management of neovascular AMD. In their study, inter-observer reproducibility for OCT image grading was not tested, but they found all 4 SD-OCT models to be superior in detecting SRF, IRC, intraretinal fluid and sub-RPE fluid compared to TD-OCT. In contrast, our results

Table 1 Inter-observer agreement of OCT image grading for different pathologies

	Var. eye	95 % CI	Var. OCT type	95 % CI	Var. scantype	95 % CI	ICC Stratus[TM]	ICC Spectralis[TM]
IRC	9.68	4.1–22	1.93	0.46–7.98	0.98	0.15–6.39	0.61	0.93
SRF	7.07	2.64–18.9	3.91	1.38–11.13	5.46e-14	0	0.79	0.73
PED	5.2	2.21–12.26	0.91	0.2–4.19	2.57e-14	0	0.66	0.66
ERM	6.24	1.98–19.68	2.31	0.46–11.68	0.78	0.05–13.35	0.56	0.84
SHM	3.77	1.87–7.61	0.27	0.02–4.41	3.80e-22	0	0.65	0.52

Intraclass correlation coefficient (ICC) values are presented for Stratus[TM] OCT, and Spectralis[TM] OCT inter-observer agreement

The linear mixed model was used to calculate ICCs. ICC Stratus[TM] = Inter-observer agreement of Stratus[TM] OCT image grading in regard of given pathology

ICC Spectralis[TM] = Inter-observer agreement of Spectralis[TM] OCT image grading in regard of given pathology

Var. variance; *CI* confidence interval; *IRC* intra-retinal cyst; *SRF* sub-retinal fluid; *PED* pigment epithelium detachment; *ERM* epiretinal membrane; *SHM* subretinal hyper-reflective material

showed no differences between OCT types in grading PED and SRF. One can hypothesize that image resolution of TD-OCT seems to be sufficient to identify all PED and SRF if present in line scans.

Although the previously published data indicates a relatively good inter-observer agreement in OCT reading centers, one has to be cautious in assuming the same inter-observer agreement in daily clinical routine [26]. Usually, treating physicians are not trained by an OCT reading center and personal clinical experience is applied when deciding on re-treatment rather than a standardized OCT grading protocol. In larger clinics, the same patient is often treated by various ophthalmologists. Therefore, inter-observer variability in OCT image grading might even lead to changing treatment protocols in patients with neovascular AMD. In this study, observers were experienced OCT user but not specifically trained by an OCT reading center. This might explain the lower inter-observer agreement compared to previously published data [26].

Previously, automated quantitative subanalysis of morphologic pathologies such as PEDs and SRF has been introduced for computer assisted image grading [24, 38]. Such software systems are however not common and are mostly used for quantitative analysis. Our data indicates that most pathologies can be graded with good inter-observer agreement regardless of the used OCT device without automated sub-analysis tools. However, agreement was poor for grading SHM in both OCT devices. To our knowledge, no automated sub-analysis tool is available for identification and quantification of SHM. Since subretinal hemorrhages, choroidal neovascularisations and subretinal scar tissue appears very similar in OCT, further diagnostics will be needed to differentiate these conditions from each other.

In conclusion, our study showed relatively good inter-observer agreement for most tested pathologies for both OCT devices, except for SHM. Spectralis^{TM} OCT showed superior inter-observer agreement for IRC and ERM. This indicates that increased image resolution of SD-OCT might show structural abnormalities located in the vitreo-retinal interface or in the neurosensory retina more accurately, which facilitates image grading for these morphologic changes.

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