Optical coherence tomography: beware of optical illusions

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Citation for published version (APA):

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General Discussion
In this thesis factors of influence on retinal OCT images and their interpretation are studied. This chapter will discuss the following subjects:

- Optical density filter sets as model for media opacities
- Importance of image quality in OCT
- The use of OCT for diagnosis and follow-up of glaucoma
- Recent developments in OCT
- Amblyopia as a retinal disease
- Clinical impact of neurodegeneration in diabetes mellitus
- OCT; Beware of optical illusions

OPTICAL DENSITY FILTER SETS AS MODEL FOR MEDIA OPACITIES

Attenuation, scattering, and refraction

Due to the complexity of optical disturbances, in particular in cataract, we simplified the optical disturbances and approached them by using filters simulating the three main effects on the optical light path, namely pure attenuation, scattering, and refraction. It was found that loss of OCT image quality, due to disturbances in the optical media, can be fully explained by attenuation of the light in the OCT scanning spot on the retina (chapter 2). Simulating opacities in the optical system with filters has its limitations. Since disturbances in the optical media are very complex, the model described in chapter 2 approximates the effects of cataract on OCT image quality. Other potential influences on OCT signal are the reflectance of the retinal layers, head tilt and positioning of the filters (see elsewhere).

In chapter 3 the effect of cataract on OCT image quality as well as on RNFL thickness measurements was further defined. The eventual goal was to establish a relationship between the optical density of cataract and its influence on RNFL thickness measurements to correct for cataract-induced changes in these measurements. The assumption was made that the effects of a cataract in the optical light path would result in an overall attenuation of the light of the OCT scanning spot on the retina and would have comparable effects as the set of attenuation filters (Balzers). The optical density values of this attenuation filters (Balzers) are of the same order as observed in cataract patients.

Cataract-induced underestimation of RNFL thickness and the OCT-effective optical density of the cataract, calculated from the quality factor, are linearly related. Unfortunately, the predictive value based on this observed weak linear relationship was however limited. One reason could be that in actual practice, owing to nonhomogeneous distributed opacities throughout a cataractous lens, the disturbance of the light contributing to a single b-scan OCT image will be unequal. This will lead to a variable quality of the resulting b-scan, while the measured quality factor is a single mean value, in addition to the variability in the RNFL thickness measurement, which is also a single mean value. Ignoring this local variability will probably lead to a less strong
relationship between both mean values. In contrast, the artificial filters used in this study are homogeneous and will not show this variability. At present, individual correction of cataract-induced variation in OCT measurements of the RNFL not possible.

**Inter-individual difference in reflectivity**

Other components of influence on the OCT signal are differences in reflectance of the retina. In our study (chapter 4) inter-individual differences in the relationship between change in optical density and change in retinal layer thickness were found. This implies that a correction of the retinal layer thickness measurement induced by a certain loss in OCT image quality should be different for each individual. This variation appeared to be caused by inter-individual differences in reflectivity of the retinal layers. A possible correction for the influence of optical density is more complex, because the percentual decrease in layer thickness between the mIRL and pRNFL induced by filters was not equal within one individual.

Tappeiner et al. reported that in TD-OCT data of macular line scans, highly reflective peaks in the averaged A-scan reflectivity profiles decreased more than less reflective peaks, as a result of light attenuation. These results could serve as a possible explanation of the individual differences in our results. Indeed, we found that the mean initial reflectivity peak of the RPE border was higher and decreased slightly more, compared with the IPL-INL transition reflectivity peak. However, this difference was small. This relationship between the height of the other peaks in the reflectivity profile per individual and filter induced decrease was not found. So, we could not confirm the theory of Tappeiner et al. to be the explanation for the individual differences in our results. Indeed, we found that the mean initial reflectivity peak of the RPE border was higher and decreased slightly more, compared with the IPL-INL transition reflectivity peak. However, this difference was small. This relationship between the height of the other peaks in the reflectivity profile per individual and filter induced decrease was not found. So, we could not confirm the theory of Tappeiner et al. to be the explanation for the individual differences in the relation between change in optical density and percentage decrease in thickness of the pRNFL and mIRL, nor for the differences found between the percentage decrease between mIRL and pRNFL.

Van der Schoot et al. measured the attenuation coefficient for the OCT signal passing through the RNFL in different stages of glaucoma in comparison with healthy eyes. In their study they used a relative measurement to extract quantitative scattering properties. The attenuation coefficient of the RNFL decreased with increasing disease severity. Probably, individual differences in attenuation coefficient could partially explain differences in percentual decrease in layer thickness of the measured retinal layers between individuals, and between the mIRL and pRNFL within one individual.

The study by van der Schoot et al. demonstrates that besides inter-individual differences in reflectivity and attenuation of the retinal layers, the attenuation coefficient of the layers also decreases with disease progression, making a possible correction for the influence of optical density in glaucomatous eyes even more complex.

**Head Tilt and Positioning of the Filters**

The reflectivity of retinal layers, especially the inner and outer plexiform layers (centrally named Henle’s fiber layer) is altered when the OCT scan is tilted. As the
SD-OCT entrance beam moves closer to the edge of a dilated pupil the reflectivity of the Henle’s fiber layer (HFL) on that side of the fovea will be reduced whereas HFL reflectivity on the opposite side of the fovea will be increased. Despite the effort to avoid tilt of the eye relative to the scanning light of the OCT, a potential change in tilt of the eye between successive measurements cannot completely be ruled out.

Because the measurements using the filters were taken in one session and those in cataract patients in two sessions, before and after cataract surgery, a potential influence of the head tilt would have contributed mainly to higher variability in the cataract patients group.

Another possible source of variation is the positioning of the filters used in the light beam of the OCT. Accurate care was taken in positioning of the filters to avoid potential tilt of the filters. The tilt was estimated to be less than 10°. In this manner a maximum error of 2% was accepted.

**IMPORTANCE OF IMAGE QUALITY IN OCT**

Image quality is an important factor in the reliability of OCT test results, as a high-quality image ensures accurate diagnosis. For example in case of subtle subretinal and/or intraretinal fluid, retinal layer thickness differences or complete loss of certain retinal layers may occur. It is important to take into account the image quality as a parameter in scientific clinical studies using OCT.

But even with the best possible image quality erroneous conclusions can be drawn. For example: the prognostic value of an intact visible external limiting membrane, and ellipsoid zone is a topic of interest, previously considered to be the junction between the inner and outer segments of the photoreceptors (IS/OS PR), and may be a marker for visual acuity recovery in treatment of macular diseases, like exudative age-related macular degeneration, and diabetic macular edema. Absence of these structures may be a bad prognostic sign, with a minimal chance of visual acuity improvement. However, these retinal structures can also be temporarily disorganized creating their own kind of optical illusion by not being visible on an OCT image, but still being present with a potential of functional recovery.

Hardware, acquisition methods and postacquisition processing of the signal are different among SD-OCT devices. This diversity results in data incompatibility like different scanning window sizes and data formats. Due to this diversity standardization of the different image quality parameters of different devices seems to be impossible. In chapter 5 is described that equal disturbances of the OCT signal have different effects on subjective scan quality and on the image quality parameter provided by different devices. Normalizing the various signal characteristics and reducing systematic difference among SD-OCT devices is desirable.

Fortunately, research groups are successfully working on novel signal normalization methods reducing the effect of A-scan profile differences between devices. This signal
normalization method is a step forward in establishing fundamental signal compatibility among OCT devices and making image quality, analysis and measurements directly comparable. However, comparisons will still be hampered by the different effects the filters proved to have per device, as described in chapter 5.

THE USE OF OCT FOR DIAGNOSIS AND FOLLOW-UP OF GLAUCOMA

A review of the evidence to date suggests that RNFL thickness remains the dominant OCT parameter for glaucoma diagnosis and detection of progression while initial studies of macular and optic nerve head parameters have shown promising results. A decrease in OCT image quality, such as that observed in patients with cataract, may cause an underestimation of RNFL thickness measurements and will affect glaucoma diagnosis and detection of glaucoma progression using OCT. Cataract-induced underestimation of RNFL thickness and the OCT-effective optical density of the cataract are linearly related. As mentioned above, the predictive value based on this observed linear relationship was however limited.

To increase the sensitivity and specificity of disease detection intensity profile normalization methods have been developed to compensate the RNFL thickness measurements variability caused by inconsistent attenuation of the reflectivity.

An important consequence of the change in retinal layer thickness measurement induced by attenuation of the OCT signal caused by media opacities, as demonstrated in this thesis (chapters 3 and 4) is the need to perform new OCT measurements after cataract extraction in glaucoma patients to establish a new baseline value.

RECENT DEVELOPMENTS IN OCT

Since its introduction in ophthalmology OCT has become a very important imaging tool in the every day clinic. Apart from the several commercially available SD-OCT systems, prototype OCT systems have contributed to new studies in this field. These include swept-source OCT (SS-OCT) systems. SS-OCT uses broadband light sources to achieve 3μm resolution in tissue. It also uses Fourier domain analysis to measure the depth resolved reflectivity profiles. However, it employs a tunable frequency swept laser light source, which sequentially emits various frequencies in time. The interference spectrum is then measured by photodetectors instead of a spectrometer. This increases the signal quality in deep tissue by elimination of the sensitivity of a spectrometer to higher frequency modulation as with SD-OCT, thereby improving the visualization of the deeper layers, like the choroid. The scanning speed of an SS-OCT is much higher, decreasing artefacts induced by movements of the eye. Last but not least, with the longer wavelength used the influence of media opacities on SS-OCT is less as compared to TD-OCT and SD-OCT (OCT systems used in this thesis). Perhaps in the future these systems will be used more often, but for now, in
clinical practice predominantly SD-OCT systems are used, and the influence on and the interpretation of retinal SD-OCT remains an important field of research.

**AMBLYOPIA AS A RETINAL DISEASE**

OCT measured pericentral retinal thickness was used for clinical interpretation of the ganglion cell layer in amblyopic eyes. In the retina the ganglion cell layer is thickest in the pericentral area of the macula, so changes in retinal thickness due to a loss of ganglion cells are expected to be most pronounced in this area of the retina.

Previous studies have reported a correlation between retinal thickness and axial length.\(^8\)\(^-\)\(^10\) The longer the eye, the thinner the retina. For this reason; the effect of axial length must be taken into consideration in statistical analyses to obtain reliable results. However, most of the previous studies involving amblyopic retinal OCT measurements did not take into account this potential effect of axial length, which could have influenced their results.

In our study both axial length and pericentral retinal thickness show the same interrelationship between fellow eyes, for amblyopic individuals and healthy individuals alike. Surprisingly however, the relation between axial length and pericentral retinal thickness was anomalous in amblyopic children, as pericentral retinal thickness was not significantly related to the axial length, contrary to what was found in healthy children. This could point to a disturbed development of both the amblyopic and fellow eye, something that should be further investigated. This anomalous relation between AL and pericentral retinal thickness in amblyopic children has not been described previously in the literature.

Interestingly, four patients showed a very particularly deviation from the expected relation between axial length and pericentral retinal thickness. These patients had eyes of short axial length, but with a relatively thin pericentral retinal thickness, instead of the expected thicker retina. No common feature between these patients could be demonstrated to explain the relatively thin retinal thickness measurement. It could be postulated that a thin retinal thickness in these patients is caused by a different, e.g. retinal, type of amblyopia. In a recent study by Szigeti et al.\(^{11}\) subtle changes in amblyopic eyes affecting the outer nuclear layer of the fovea suggesting the possible involvement of the photoreceptors. More research is required to investigate this hypothesis.

Our study also included patients with a history of amblyopia who at the time of testing did not always have the criterion difference in visual acuity of at least two lines. We felt justified in including patients with a history of amblyopia because any retinal change that might have developed during the critical period in the amblyopic process might still be detectable later on, even if they might not be categorized as amblyopic based on visual acuity at the time of testing. Nevertheless, this might have affected our study results. No significant differences were found between transient and permanent amblyopic patients.
General discussion

CLINICAL IMPACT OF NEURODEGENERATION IN DIABETES MELLITUS

Based on the OCT findings in diabetic retinopathy, we concluded that the inner retina becomes thinner in patients with type 1 diabetes and no or minimal DR. Previous studies have shown a decrease in total retinal thickness, and our study confirms and expands these results. The loss of neural tissue agrees with previous studies showing neuroretinal functional deficits in patients with diabetes, occurring before the onset of vascular lesions, such as an abnormal mf-electroretinogram, loss of dark adaptation and of contrast sensitivity, color vision disturbances, and abnormal micro-perimetry. Retinal neurodegeneration could be the result of hyperglycemia. But there are mechanisms other than hyperglycemia in diabetes that could be the cause. The molecular mechanisms involved in retinal neurodegeneration in diabetes have previously been proposed to be complex and may include a combination of ocular factors such as increased oxidative stress, loss of neuroprotective factors, increased inflammation, glutamate excitotoxicity, and systemic factors including hyperglycemia, dyslipidemia, and insulin deficiency.

An interesting question is the clinical impact of neurodegeneration in diabetic retinopathy. Although neurodegeneration is often asymptomatic, visual functioning is hampered, and in the future we should perhaps start treatment to prevent progression of neurodegeneration in diabetes mellitus like we also treat asymptomatic patients with glaucoma. Careful and longitudinal assessment of neuroretinal degeneration in relation to vasculopathy and functional deficits may lead the way for using neuroretinal degeneration as a biomarker for early disease progression in diabetes mellitus, and as a tool to monitor the effect of therapeutic interventions.

OCT; BEWARE OF OPTICAL ILLUSIONS

Nowadays many physicians think of OCT as a flawless tool for the evaluation of retinal diseases, but prudence is called for. This thesis illustrates that optical illusions are present in OCT images and hamper their interpretation. For instance, one could mistakenly diagnose a patient with glaucoma based on a false interpretation of OCT thinning of the retinal nerve fiber layer or macular inner retinal layers. Alternatively, the OCT measurement of a patient with both glaucoma and cataract can be misinterpreted as showing progression of the glaucoma, but in reality there is progression of cataract. Different OCT devices have different optical illusions. Retinal layers visible with one OCT device may not be visible with the other, or vice versa. Even with the best possible image quality, erroneous conclusions can be drawn with respect to the potential of visual acuity recovery in the treatment of macular diseases.

Sophisticated research using OCT did unmistakably unravel many pathophysiologic changes in the retina or did shine a new light on retinal diseases. However, OCT is merely a reflection of the retina, and prone to optical illusions.
REFERENCES


