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## Challenges of diagnosing glaucoma in myopic eyes

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# *Chapter 10*

## **Summary, Discussion, and Future Perspectives**

## **General summary and overview of the main findings**

Myopia is a prevalent condition in the world and a major risk factor for glaucoma. However, diagnosing glaucoma in myopic subjects is difficult, since myopic eyes often display anatomical changes of the optic disc and retina and visual field changes that mimic glaucoma. Thus, understanding of the characteristics and determinants of the anatomical structures relevant to glaucoma in myopia is of great importance for glaucoma assessment. This thesis addresses the issue “challenges in diagnosing glaucoma in myopic eyes”. For this purpose, I investigated the characteristics and determinants of RNFB trajectories, RNFL thickness profile, and macular inner retinal layers in myopic eyes. Furthermore, I studied the glaucoma diagnostic classifications of both the peripapillary RNFL and macular inner retinal layers in myopic eyes by using OCT devices.

In **Chapter 2**, I investigated the relationship between the retinal vessel course and the RNFB trajectories as described by a mathematical model in Caucasian eyes. In this study, I found that the retinal blood vessel topography explains a significant part of the distribution of the RNFL bundle trajectories in the human retina. In **Chapter 3**, the characteristics of the RNFB trajectories in Chinese myopic eyes were determined by using the previously published mathematical model based on Caucasian eyes. In this study, I found that the RNFB trajectories of Chinese eyes with low or moderate myopia are similar to that of Caucasians. For high myopia, the trajectories in superior hemifield are similar to that of Caucasians; in the inferior hemifield they follow a different pattern. Axial length, vessel topography, and optic disc size and torsion are associated with the variability of the trajectories.

**Chapter 4** determines the applicability of the ISNT rules for the retinal nerve fiber layer thickness and the neuroretinal rim area in healthy myopic eyes. In healthy myopic subjects, 88 and 37% of the eyes did not comply with the ISNT rule if applied to the RNFL thickness and the rim area as measured with OCT and HRT, respectively. Thus, the ISNT rule and its variants have a limited useability

in diagnosing glaucoma in myopic subjects. In **Chapter 5**, characteristics and determinants of the peripapillary retinal nerve fiber layer thickness profile of healthy myopic eyes were evaluated. In this study, the location of the peak of the RNFL thickness profile at the 3.46 mm OCT measurement circle was analyzed separately in the superior hemiretina and inferior hemiretina. I found that the RNFL thickness profile in myopic eyes is determined by different ocular parameters in the superior and inferior hemiretina. Of all the determinants, the artery angle appeared to be the most prominent predictor of the variability of the RNFL thickness profile, for both hemiretinae. In **Chapter 6**, characteristic patterns of OCT abnormalities in the RNFL thickness deviation map was evaluated in both healthy myopic eyes and glaucomatous eyes. The main finding was that the location of the color-coded region in the RNFL thickness deviation map relative to the major temporal retinal vessels offers a simple and valuable clue for differentiating between false-positive and glaucoma in myopic eyes.

**Chapter 7, Chapter 8, and Chapter 9** address the relationship between the disc fovea distance (DFD) and several macular thickness parameters as measured with OCT. In **Chapter 7**, I found that a greater DFD was significantly associated with increasing myopia and - independently - with a lower macular thickness. In the study described in **Chapter 8**, the influence of DFD on thickness measurements of individual macular intraretinal layers was evaluated by using an automated segmentation software package based on the Iowa algorithm. A thinner nerve fiber layer (NFL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL), and a lower total macular thickness were significantly associated with a greater DFD, independent of other covariates. Finally, in **Chapter 9** the effect of DFD on the glaucoma diagnostic classifications based on the macular inner retinal layer thicknesses was evaluated by using the OCT built-in software. A greater DFD was associated with a higher percentage of abnormal diagnostic classification in the OCT maps of the mRNFL, GCIPL, and GCC.

**Discussion, potential applications, and future perspectives**

## **Retinal vessel topography and RNFB trajectories/pRNFL thickness profile in myopic eyes**

In the current thesis, I found that the retinal vessel topography was the most prominent predictor of the variability of the RNFB trajectories (Chapters 2 and 3) and the pRNFL thickness profile (Chapter 5). Furthermore, I found that the positions of the major retinal arteries correlated significantly with an abnormal diagnostic classification (based on the built-in normative database) of pRNFL thickness measurements in healthy myopic eyes (Chapter 6). Currently, as the normative database of available OCT instruments only considers the influence of age on the pRNFL thickness, a specific normative database considering the retinal vessel topography is suggested to be incorporated in the OCT devices to improve the glaucoma diagnostic performance. As the pRNFL thickness profile is widely used in most of the commercial OCT instruments, the intersections of the major superotemporal artery and the major inferotemporal artery with the OCT measurement circle can be used as a surrogate measure of the retinal vessel topography.

By investigating the relationship between the retinal vasculature and the location of color-coded regions (abnormally thin regions) in the RNFL deviation map in both healthy myopic subjects and glaucoma patients (Chapter 6), I found that evaluation of the location of the color-coded regions relative to the major temporal retinal vessels can significantly improve the glaucoma diagnostic performance in myopic eyes (large increase in specificity without loss of sensitivity). Further research is warranted to evaluate the diagnostic performance of combined parameters (combination of our vessel location criterion with OCT measurements including pRNFL and GCIPL thicknesses) in myopia. Previously, hypodense regions (holes) in the RNFL on OCT scans have been reported to be located along the retinal blood vessels in glaucoma suspects and patients (Xin et al., 2011; Hood et al., 2016). In the current thesis, I confirmed the important role of retinal vessel topography on RNFL profile and RNFB trajectories. It would be

interesting to evaluate the relationship between retinal vessel topography and the location of early glaucomatous RNFL damage. As most of the glaucoma subjects in the current thesis had moderate to severe glaucoma, future research is needed to evaluate the diagnostic performance of the suggested approaches in early glaucoma in the myopic population.

### **Characteristics and variability of the myopic RNFB trajectories/pRNFL thickness profile in the superior and inferior hemiretina**

In the current thesis, I evaluated the characteristics of the RNFB trajectories (Chapter 3) and the peripapillary RNFL thickness profile (Chapter 4) in healthy myopic eyes, in both the superior and inferior hemiretina. Consistent with previous studies (Leung et al., 2012; Denniss et al., 2012; Jansonius et al., 2012; Lamparter et al., 2013; Yamashita et al., 2017), we found that axial length was significantly associated with the RNFB trajectories and the peripapillary RNFL profile, but only in inferior hemiretina. Although the reason why axial length affects the RNFL thickness profile/the RNFB trajectories more pronounce in the inferior hemiretina remains to be uncovered, our findings may have clinical implications. Previously, asymmetry of visual field defects was reported in normal tension glaucoma subjects (Park et al., 2017), with deeper defects in the superior paracentral area (that is, in the inferior hemiretina) than in the inferior paracentral area. In another study, Park et al. (2012) investigated the relationship between disc torsion and visual field defects in 166 normal-tension glaucoma patients with myopia. Again, superior visual field defects were more prevalent than inferior visual field defects in myopic normal tension glaucoma subjects (Park et al., 2012). In Emmetropic caucasians studied in a population-based setting, no superior/inferior asymmetry was found in the incidence of glaucomatous visual field defects (Springelkamp et al., 2017). Clearly, these associations are not fully understood and should be explored further in future studies to better understand the relationship between myopia, RNFB trajectories/pRNFL thickness profile (especially in the inferior hemiretina), and glaucoma.

Recently, the nature of macular damage in glaucoma was investigated and a schematic model for relating structural glaucomatous damage of the macula to visual field defects was proposed (Hood et al., 2012; Hood et al., 2013). According to their model of macular damage, most of the inferior region of the macula projects to the macular vulnerability zone (MVZ), a region that is particularly susceptible to glaucomatous damage. As we found that axial length correlated significantly with the inferior RNFB trajectories/pRNFL thickness profile in the current thesis, it would be interesting to evaluate the inferior MVZ in myopic eyes in future studies.

Previously, individual structure function mapping has been evaluated (Denniss et al., 2014; Ballae Ganeshrao et al., 2015; McKendrick et al., 2017; Alluwimi et al., 2018). It has been reported that anatomically customized mapping shifts the map markedly in approximately 12% of the general population in the nasal step region (McKendrick et al., 2017). Consistent with previous study (Denniss et al., 2012; Jansonius et al., 2012; Lamparter et al., 2013), I found significant variability of RNFB trajectories in the current Chinese myopic population. Further research is needed to evaluate how individual structure- function mapping could improve glaucoma diagnosis in myopia.

### **DFD and variability of macular structure**

I found that a larger DFD was independently associated with a thinner overall macular thickness and the thicknesses of macular inner retinal layers (Chapters 7 and 8). I speculate that the posterior fundus in eyes with a greater DFD is stretched, which may cause the observed thinning of the macular intraretinal layers. As I showed, this occurs independent of the effect of axial length. Although the underlying mechanism between DFD and macular thickness is not fully understood, the current results have potential clinical significance in the evaluation of glaucoma and various macular diseases. I further evaluated the clinical significance of DFD by studying the glaucoma diagnostic classification

based on the macular inner retinal layers in healthy subjects. A greater DFD was found to be independently associated with a false-positive classification (Chapter 9). On the basis of these findings, I suggest that the current OCT instruments should integrate the DFD measurement in the normative database. Currently, it is easy to define the fovea and optic disc center for most of the available OCT devices. Thus, it is easy to incorporate the DFD measurement in the OCT instruments, based on the coordinates of the fovea and the optic disc center.

## **Conclusions**

I found significant variability of RNFB trajectories, peripapillary RNFL profile, and macular inner retinal layers in healthy myopic eyes. Of all the determinants, the retinal vessel topography appears to be the most prominent predictor for the variability of the pRNFL thickness profile and the RNFB trajectories, for both hemiretinae. I further found that the location of the color-coded region in the RNFL thickness deviation map relative to the major temporal retinal vessels offers a simple and valuable clue for differentiating between false-positive and glaucoma in myopic eyes. Regarding the macular measurements, this study is the first study that reports that a greater DFD was significantly associated with thinner macular inner retinal layers. The studies that formed the basis of my thesis suggest that OCT instruments should integrate the retinal vessel topography and the DFD in the normative database to improve the glaucoma diagnostic performance. As this is essentially a software update, it could be integrated in the currently available devices.

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