

# Analysis of Risk Factors for Long-Term Glaucomatous Damage Development

## Analyse der Risikofaktoren für die langfristige Glaukomschadenprogression

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**Key words**

- predictors
- glaucoma
- progression

**Schlüsselwörter**

- Prädiktoren
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**Abstract**


**Purpose:** The aim of this study was to analyze predictors of long-term glaucoma progression.

**Patients and Methods:** We followed 17 primary open angle glaucoma patients (POAG) and 25 ocular hypertensives (OHT) over three years, with regular follow-up examinations of both eyes every 6 months. Glaucoma damage was quantified by optical coherence tomography (retinal nerve fiber layer – OCT RNFL) and by perimetry. Corneal and hand temperature (infrared thermometer), corneal hysteresis, pachymetry and ocular pulse amplitude (OPA) readings were taken at baseline, and applanation intraocular pressure and retinal vessel analysis recordings were made at baseline and follow-up visits. Forward-stepwise multiple regression analysis was performed.

**Results:** With OCT-RNFL progression as the dependent variable, the model selected initial diagnosis (OHT less probable of progressing), baseline RNFL thickness, retinal arterial and venous diameter and arterial flicker response as significant damage predictors. For visual field damage progression, these were: corneal temperature, OPA, initial diagnosis and venous flicker response (all  $p < 0.05$ ).

**Conclusion:** Initial damage and vascular factors are strong predictors of future glaucoma progression.

**Zusammenfassung**


**Hintergrund:** Analyse der Prädiktoren des Glaukomschadens.

**Methoden und Patienten:** Primäröffenwinkelglaukom-Patienten (17) und okulären Hypertoniker (25) wurden über 3 Jahre alle 6 Monate untersucht. Glaukomschaden wurde mittels Optischer Kohärenztomografie und Perimetrie erfasst. Dazu wurden auch die Hornhaut- und Handtemperatur (Infrarotthermometrie), korneale Hysterese, Pachymetrie und okuläre Pulsamplitude (OPA) bei der ersten Untersuchung dokumentiert, und die Augendruckmessungen und die retinale Gefäßaufnahmen am Anfang und im Verlauf durchgeführt. Als statistische Methode wurde die schrittweise Regressionsanalyse angewendet.

**Ergebnisse:** Die Ausgangsdicke der Nervenfaserenschicht, initiale Diagnose, arterieller und venöser Gefäßdurchmesser und die arterielle Antwort aufs geflickerte Licht waren die ausgewählten signifikanten Prädiktoren des glaukomatösen Nervenfasernverlustes. Für die Gesichtsfeldschadenprogression waren dies die Hornhauttemperatur, OPA, initiale Diagnose und venöse Antwort aufs geflickerte Licht (alle  $p < 0.05$ ).

**Schlussfolgerung:** Trotz Initialschäden und die vaskulären Faktoren sind wichtige Glaukomshadenprädiktoren.

**Introduction**


Glaucoma is one of the major causes of blindness worldwide [1]. The disease is characterized by increased optic disc cupping, irreversible loss of retinal ganglion cells and their axons and by consequent typical visual field losses. If left untreated, disease is progressive. For over a century, increased intraocular pressure was seen not only as a major risk factor, but as a definition of disease

itself. It is in the last two decades, faced with entities such as normal-tension glaucoma and ocular hypertension, that the attention of researchers shifted to other risk factors, most notably flawed ocular perfusion [2]. Measuring ocular blood flow in order to define limits between normality and disease has however proven to be quite a difficult task. Each measuring technique delivers at best only an information for a given vascular bed [3], and we still do not know which one is of relevance.

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**Bibliography**

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vance. To make matters worse, glaucoma is a slowly progressive disease. It takes quite a long time to establish damage progression with certainty, which makes prospective type of glaucoma studies cumbersome. However, in the face of irreversible nature of the damage, waiting is a luxury patients and their clinicians cannot really afford. From the researchers' point of view, prospective studies are clearly superior to cross-sectional studies in identifying risk factors for a disease, and in particular for its progression. Identification and early detection of these risk factors and, if possible, their treatment can help manage the condition and prevent vision loss. The purpose of this present study was to analyze these predictors in a prospective manner. After taking baseline readings of presumed risk factors, we followed 17 primary open angle glaucoma (POAG) and 25 ocular hypertensive (OHT) patients over three years, with 6-monthly examination intervals of both eyes.

## Patients and Methods

### ▼ Patients

Patients with the diagnosis of primary open angle glaucoma (POAG) and ocular hypertension (OHT) were consecutively recruited for the study from the glaucoma consultations at the University Eye Clinic Basel.

Tenets of the Declaration of Helsinki were followed. After approval by the ethical committee, we obtained informed consent from our subjects. Both groups of patients who met study criteria underwent baseline study examinations. The systemic and topical therapy applied, if present at the time of baseline examination, was continued or adjusted if so deemed appropriate by the treating physician. Patients during the course of the study who for any reason had their therapy changed prior to visit 5 (24 months, arbitrarily set) were in this study design excluded from the analysis (in our cohort, none); damage parameters of those patients with therapy change between this time and study conclusion were carried forward (4 OHT and 1 POAG).

POAG was diagnosed based on glaucomatous optic disc cupping and matching glaucomatous visual field defects in both eyes [4]. Progression rate prior to entering the study, as well as the specific level of glaucomatous damage at the time of recruitment, were not a selection criterion. Intraocular pressure (IOP) was neither exclusion nor inclusion criterion for POAG diagnosis; however, measurements on at least three occasions with or without therapy in both eyes of OHT patients through their pre-study recorded history had to be 21 mmHg or higher. OHT patients did not exhibit any relevant glaucomatous optic disc cupping and/or glaucomatous visual field defects at the time of recruitment. Diabetes mellitus, untreated or unstable essential hypertension, untreated or unstable hypercholesterolemia [5], drug or alcohol abuse, history of eye surgery except uneventful cataract operation, high ametropia (spherical equivalent  $< -5$  diopters or  $> +3$  diopters), astigmatism above 2 diopters, any form of closed angle glaucoma and secondary open angle glaucoma were exclusion criteria. Smokers were excluded as well [6–8]. Both eyes entered the study with the appropriate diagnosis. As there was no available a priori power analysis for parameters analyzed in this study, the number of study subjects was set arbitrarily. Subjects who met all the above mentioned criteria at recruitment and throughout the study were included in the final analysis.

## Methods

Baseline intraocular pressure was obtained as a daily profile by means of Goldmann applanation tonometry, at 8:00 AM, 11:00 AM and 4:00 PM. The mean IOP was calculated in mmHg, as well as the standard deviation/coefficient of variation for the readings (in %), as a measure of diurnal IOP variability. IOP was then measured at every visit.

Blood pressure (BP) readings were taken oscillometrically, and mean blood pressure (diastolic plus  $\frac{1}{3}$  of the systolic–diastolic BP difference).

Central corneal thickness was measured by an ultrasound pachymeter.

Superficial tissue temperature was measured by infrared thermometry (THI-500 non-contact infrared thermometer, Tasco Japan, Osaka) on the cornea [9] in degrees °C, and in distal skin – temperature readings were obtained on the dorsal and palmar side of the 4th finger, and averaged between the two. These measurements served as possible estimates of perfusion in the eye and a measure of peripheral vasospasticity, as shown earlier [10–13].

Ocular pulse amplitude was obtained with Pascal® Dynamic Contour Tonometer (Ziemer Ophthalmic Systems AG, Port, Switzerland) [14], and expressed in mmHg as the difference between the systolic and diastolic IOP.

Corneal hysteresis as a measure of ocular biomechanical properties was recorded at baseline examination by Ocular Response Analyser (Reichert Inc., NY, USA) [15].

Retinal vessels were analyzed by means of Retinal Vessel Analyzer [16,17]. Details on this device were published previously [18,19]. Because experience shows that the recording data quality is best at temporal inferior quadrant, average diameter of a chosen segment of retinal artery and vein in this quadrant was continuously recorded with the RVA device. An average baseline diameter (in micrometers) of arteries and veins as well as vessel response to flicker light (expressed as a change to baseline in percents of baseline of the averaged maximal dilation diameter during the last second of each of the three flicker periods) entered the analysis.

Blood pressure readings, central corneal thickness (five of OHT patients had readings over 600 micrometers), corneal and hand temperature, OPA, corneal hysteresis and RVA readings were recorded at baseline visit. Applanation tonometry was performed and OCT and VF readings were recorded at every visit.

Damage parameters were divided in functional (visual field) and structural (peripapillary retinal nerve fiber layer thickness, RNFLT, was chosen for this purpose). Visual field was measured by automatic perimetry with Octopus (Interzeag, Schlieren, Switzerland), and the visual field mean defect (VFMD) was the parameter of interest. RNFLT was measured by ocular coherence tomography (Stratus OCT, Carl Zeiss Meditec, Germany), as a measure of morphological glaucomatous damage. Readings were taken in both eyes at baseline and afterwards every six months for the three years study duration. The damage progression was quantitatively defined as a beta-coefficient of the regression slope, with time on the x-axis and VFMD, respectively RNFLT, on the y-axis. Worsening was hence reflected in the positive slope of the VFMD-time regression line, and in the negative slope of RNFLT-time regression line, respectively.

## Data analysis

Forward stepwise multiple regression models were applied, with the intention of putting together known risk ("rounding up the

usual suspects") and identifying those with significant predictive value for the progression of structural and functional glaucomatous damage. Both POAG and OHT groups were analyzed together in both models described below, with a group affiliation as one of the independent variables.

RNFL and VFMD slopes, being a measure of progression, constituted the dependent variable in each of the two models, respectively. Independent variables were for both models the same: age, baseline diagnosis (POAG or OHT), corneal hysteresis, central corneal thickness, IOP at baseline, its daily variability and mean of follow-up values, ocular pulse amplitude, corneal temperature, distal finger skin temperature, baseline retinal artery and vein diameter, baseline flicker response of retinal arteries and veins, and level of damage at baseline examination (RNFLT, VFMD).

This essentially exploratory type of analysis selects in a stepwise manner parameters that contributes the most of the new information to the model, explaining the remaining variability of the dependent parameter, in this case the progression slope of structural (RNFLT) and functional (VFMD) damage, while correcting for the correlation with the parameters already in the model. The selecting process stops when none of the remaining parameters reaches the pre-selected F-to-enter, in this case standard 1.0. Parameters found to be significant each explain part of the variability of the analyzed dependent parameter, and this contribution of information is independent from other parameters in the model.

## Results



We followed 42 patients during the full study period.

The average age of POAG patients was  $60.4 \pm 9$  years, and that of OHT patients was  $62.9 \pm 9$  years (*p*-value between groups 0.87). Gender distribution male/female was 11/6 and 15/10 in the POAG and the OHT group, respectively. Analyzed parameters are reported descriptively in **Table 1**.

Topical therapy distribution in the POAG/OHT group after the first study visit was respectively: prostaglandin analogon alone 4/1, beta-blocker alone 2/2, combination beta-blocker and carbonic anhydrase inhibitor 5/2, other combinations 3/3, no topical therapy 3/17. Relevant systemic therapy was distributed in the following manner: statines 3/3, combination ACE-inhibitor plus diuretics 2/2, beta-blocker 0/1, magnesium 3/2, antiaggregation therapy 1/4 (several patients had two or more of the mentioned medications, the majority did not have relevant systemic therapy).

In the model with the structural damage progression (slope of RNFL thickness during the study duration), following parameter reached F-to-enter = 1 in the following sequence: central corneal thickness, diagnosis (POAG/OHT), baseline RNFL thickness, baseline retinal venous and arterial vessel diameter, arterial vessel response to flicker light, ocular pulse amplitude and distal skin temperature. With these parameters in the model, *R* was *R* = 0.67 (meaning that 46% of the RNFL slope variability was explained by these parameters), *p* = 0.0003. However, not all of these parameters contributed significantly to the model. Significant parameters are reported in **Table 2**, and discussed in the Discussion section.

In the model with functional damage progression (slope of visual field MD during the study duration), the following parameters reached F-to-enter = 1 in the following sequence: baseline RNFL thickness, corneal temperature, baseline retinal venous vessel

**Table 1** Descriptive reporting of analyzed parameters in both groups, mean  $\pm$  SD (42 patients).

Parameter	POAG	OHT
Baseline RNFLT (micrometers)	$80.7 \pm 13.8$	$91.8 \pm 12.1$
Baseline visual field MD (dB)	$1.7 \pm 2.6$	$0.15 \pm 1.26$
Baseline mean IOP (mmHg)	$16.5 \pm 4.6$	$20.9 \pm 4.2$
IOP variability (coefficient of variation in %)	$10.8 \pm 6.7$	$12.1 \pm 8.2$
Ocular pulse amplitude (mmHg)	$2.59 \pm 1.12$	$3.23 \pm 0.98$
Central corneal thickness (micrometers)	$535 \pm 53$	$558 \pm 57$
Corneal hysteresis (mmHg)	$8.8 \pm 1.5$	$8.9 \pm 2.1$
Corneal temperature (°C)	$34.7 \pm 0.7$	$34.2 \pm 1.2$
Distal skin temperature (°C)	$31.6 \pm 3.0$	$30.6 \pm 3.2$
Mean blood pressure (mmHg)	$98.2 \pm 19.3$	$108.8 \pm 14.0$
Baseline retinal arterial diameter (micrometers)	$109 \pm 10$	$108 \pm 11$
Baseline retinal venous diameter (micrometers)	$142 \pm 13$	$137 \pm 14$
Baseline arterial response to flicker light (in % of baseline)	$2.15 \pm 2.14$	$2.20 \pm 2.13$
Baseline venous response to flicker light (in % of baseline)	$3.25 \pm 1.68$	$2.83 \pm 1.46$

**Table 2** Structural damage progression model, partial correlation coefficients of the parameters selected by the model as significant contributors and their corresponding *p*-values (42 patients).

Parameter	Partial correlation coefficient	p-value
Diagnosis (POAG/OHT)	0.40	0.006
Baseline RNFLT	-0.47	0.0009
Baseline retinal venous diameter	-0.45	0.0016
Baseline retinal arterial diameter	0.45	0.0015
Baseline arterial response to flicker light	0.33	0.024

**Table 3** Functional damage progression model, partial correlation coefficients of the parameters selected by the model as significant contributors and their corresponding *p*-values.

Parameter	Partial correlation coefficient	p-value
Diagnosis (POAG/OHT)	-0.34	0.02
Ocular pulse amplitude	0.41	0.004
Corneal temperature	0.46	0.0013
Baseline venous response to flicker light	-0.34	0.022

diameter, ocular pulse amplitude, diagnosis (POAG/OHT), distal skin temperature, venous and arterial vessel response to flicker light and baseline retinal arterial vessel diameter. With these parameters in the model, *R* was *R* = 0.68 (meaning that 47% of the RNFL slope variability was explained by these parameters), *p* = 0.0003. However, not all of these parameters contributed significantly to the model. Significant parameters are reported in **Table 3**, and discussed in the Discussion section.

While baseline visual field MD and RNFL thickness were correlated with each other (*p* = 0.04), the two modalities of damage progression over three years, the slope of RNFL thickness and of visual field MD, did not correlate whatsoever with each other (*p* = 0.90). Functional damage progression was more strongly pronounced in the POAG than in the OHT group, whereas in the OHT group, VF MD remained practically stable (VF MD slope was 0.099/-0.03, *p* = 0.036; positive means here higher Octopus VF

MD and hence worsening). Structural damage progression was present in both groups but pronounced borderline stronger in the POAG than in the OHT group (RNFL thickness slope was  $-0.93/-0.43$ ,  $p=0.078$ ; negative means here thinner RNFL and hence worsening).

## Discussion

In the present prospective observational study we recorded the parameters related to the intraocular pressure, blood perfusion and ocular biomechanical properties at baseline and then followed glaucoma damage progression for three years in POAG and OHT patients without changing their ocular and systemic therapy. Forward stepwise multiple regression analysis performed separately in two models, one for the structural and the other for the functional damage, identified different parameters showing significant association with the progression.

Baseline RNFL thickness was weakly negatively correlated with visual field mean defect. The degree of damage progression during the next three years of follow-up showed no correlation between the structural and functional damage modality. Although two sides of the same coin, morphological and functional glaucoma damage components are not identical. It is known that structure-function relationship in glaucoma is complex and non-linear [20, 21]. Correlation between the structure, here defined as a thickness of retinal ganglion cell axons, on one side and their function, reflected in visual field sensitivity, on the other side, is generally weak at best [22]. It takes a certain range of glaucoma damage progression for this correlation to rise above the statistical noise, and three years study period is obviously not long enough for a chronic disease like glaucoma to produce such damage range. In addition, a relatively low level of baseline visual field and RNFL damage reveals an inclusion of either early or low-aggressive glaucoma in our study cohort. Moreover, patients that had to undergo early therapy change were excluded from the final analysis, which lead to the exclusion of more aggressive forms of glaucoma from the study and ultimately to further narrowing of the damage range.

It is therefore not surprising that parameters selected in the two models differed, a finding similar to the recently published cross-sectional study despite its different design [23].

The baseline diagnosis was clearly selected as significant in both models. Obviously we do not know for how long IOP had already been increased in a given OHT patient prior to the study recruitment. Nevertheless, OHT patients have distinctly lower progression levels, as there was a more pronounced tendency for damage progression in both modalities in the POAG group. This finding fits well with the results in the literature [24].

Given this fact and the fact that OHT patients per definition have thicker RNFL, it is surprising that thicker baseline RNFL was associated with a stronger thinning in the follow-up. One possible explanation is that the higher starting point mathematically produces a somewhat steeper slope of the RNFL thickness across time.

Being a tertiary referral centre specialized in ocular vascular disorders, it is likely that our cohort of POAG patients is shifted towards "normal"-tension glaucoma patients, and that mechanisms other than IOP might have played a role.

Thinner baseline diameter of the retinal arteries is associated with the stronger RNFL thinning. Similar observation was made in the cross-sectional study [23]. In contrast to the latter, where

it remained unclear whether thinner arteries are causal or a consequence of less tissue-less demand phenomenon, in the present study thinner arteries can indeed indicate a retinal vascular dysregulation and its prognostic value for the glaucoma damage. It can however be in part a result of "less demand phenomenon". Higher baseline retinal vein diameter was also selected in the RNFL slope model. Retinal veins with their thin walls are directly embedded in the peripapillary RNFL, and individual anatomical variability can influence analysis in a cross-sectional study design. In the present prospective study design, however, such an argument is not valid, as here we deal with a prognostic value of the parameter. A study which was published recently confirmed lower retinal vein pulsation amplitudes in glaucoma [25]. One possible explanation is that the intraluminal retinal venous pressure is higher in glaucoma due to disturbed venous outflow, be it because of the active functional wall dysregulation [2] or be it because of the passive pressure gradients [26].

Retinal vessel response to flicker light is reduced in glaucoma patients [27, 28]. Retinal vessel flicker response obviously also has a certain prognostic value for glaucoma damage progression. It is at present not clear why the RNFL slope model favoured the arterial response and the visual field MD slope model favoured the venous response. However, once one of the two has been selected, the other could hardly offer a significant new contribution, as these two responses are relatively correlated with each other. The higher the ocular pulse amplitude, the stronger the visual field damage progression. There was a tendency towards recruiting POAG patients with normal-range IOP in our cohort (IOP was not a selection criteria, and we are a tertiary glaucoma referral center with a focus on vascular aspects), and indeed higher OPA was observed in normal-tension glaucoma patients [29]. However, the relationship between OPA and glaucomatous damage is complex [30, 31], and the interpretation of this particular finding remains challenging.

The same holds true also for corneal temperature. Corneal temperature is indeed related to the ocular blood flow [10], this association is however weak at best. Many factors, not the last being the influence of insufficient tear film and dry eyes [32, 33], may have played a role in visual field testing performance of in particular topically treated glaucoma patients.

This study was not designed to specifically analyze an influence of IOP on glaucoma progression, ample literature already exists on that subject [34, 35]. Although given a similar starting position as the parameters describing ocular or at least retinal perfusion, no parameter related to IOP was included in either model. This interesting observation by no means implies a direct comparison of the importance of IOP versus vascular risk factors in favour of the latter, but it does underscore a relevant prognostic value of at least some vascular parameters in glaucoma.

The major limitation of our study is the small number of patients included in the cohort, and a modest follow-up time. As some patients were newly diagnosed when they entered the study, we do not have any information about the progression rate prior to their inclusion. Moreover data on cardiovascular conditions and possible sleep-apnoea during the follow-up were not available. Progression rates were on the average low, and mostly or only in the POAG group. Censoring the patients with therapy change, in particular due to inadequate IOP control, might have introduced the bias and lead to underrepresentation of IOP as a risk factor for progression; the therapy change however occurred only in one POAG and in 4 OHT patients.

In conclusion, different parameters, mostly vascular, may have a predictive value for the two damage modalities in glaucoma. Whether their timely manipulation could lead to a more favourable course of disease remains to be elucidated in future interventional studies.

### Conflict of Interest



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### References

- 1 Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care* 2013; 19 (5 Suppl.): S67–S75
- 2 Flammer J, Orgul S, Costa VP et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002; 21: 359–393
- 3 Harris A, Kagemann L, Ehrlich R et al. Measuring and interpreting ocular blood flow and metabolism in glaucoma. *Can J Ophthalmol* 2008; 43: 328–336
- 4 European Glaucoma Society EGS. Perimetry. In: Terminology and Guidelines for Glaucoma. Savona: Dogma; 2008: 82–87
- 5 Patel SR, Bellary S, Qin L et al. Abnormal retinal vascular function and lipid levels in a sample of healthy UK South Asians. *Br J Ophthalmol* 2011; 95: 1573–1576
- 6 Wimpissinger B, Resch H, Berisha F et al. Effects of isometric exercise on subfoveal choroidal blood flow in smokers and nonsmokers. *Invest Ophthalmol Vis Sci* 2003; 44: 4859–4863
- 7 Wimpissinger B, Resch H, Berisha F et al. Response of choroidal blood flow to carbogen breathing in smokers and non-smokers. *Br J Ophthalmol* 2004; 88: 776–781
- 8 Wimpissinger B, Resch H, Berisha F et al. Response of retinal blood flow to systemic hyperoxia in smokers and nonsmokers. *Graefes Arch Clin Exp Ophthalmol* 2005; 243: 646–652
- 9 Kocak I, Orgul S, Flammer J. Variability in the measurement of corneal temperature using a noncontact infrared thermometer. *Ophthalmologica* 1999; 213: 345–349
- 10 Gugleta K, Orgul S, Flammer J. Is corneal temperature correlated with blood-flow velocity in the ophthalmic artery? *Curr Eye Res* 1999; 19: 496–501
- 11 Galassi F, Giambene B, Corvi A et al. Evaluation of ocular surface temperature and retrobulbar haemodynamics by infrared thermography and color doppler imaging in glaucoma patients. *Br J Ophthalmol* 2007; 91: 878–881
- 12 Gardner-Medwin JM, Macdonald IA, Taylor JY et al. Seasonal differences in finger skin temperature and microvascular blood flow in healthy men and women are exaggerated in women with primary Raynaud's phenomenon. *Br J Clin Pharmacol* 2001; 52: 17–23
- 13 Gompfer B, Bromundt V, Orgul S et al. Phase relationship between skin temperature and sleep-wake rhythms in women with vascular dysregulation and controls under real-life conditions. *Chronobiol Int* 2010; 27: 1778–1796
- 14 Kaufmann C, Bachmann LM, Thiel MA. Comparison of dynamic contour tonometry with goldmann applanation tonometry. *Invest Ophthalmol Vis Sci* 2004; 45: 3118–3121
- 15 Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg* 2005; 31: 156–162
- 16 Seifertl BU, Vilser W. Retinal Vessel Analyzer (RVA)—design and function. *Biomed Tech (Berl)* 2002; 47 (Suppl. 1, Pt 2): 678–681
- 17 Vilser W, Nagel E, Lanzl I. Retinal Vessel Analysis—new possibilities. *Biomed Tech (Berl)* 2002; 47 (Suppl. 1, Pt 2): 682–685
- 18 Gugleta K, Zawinka C, Rickenbacher I et al. Analysis of retinal vasodilation after flicker light stimulation in relation to vasospastic propensity. *Invest Ophthalmol Vis Sci* 2006; 47: 4034–4041
- 19 Garhofer G, Bek T, Boehm AG et al. Use of the retinal vessel analyzer in ocular blood flow research. *Acta Ophthalmol* 2010; 88: 717–722
- 20 Schlottermann PG, De Cilla S, Greenfield DS et al. Relationship between visual field sensitivity and retinal nerve fiber layer thickness as measured by scanning laser polarimetry. *Invest Ophthalmol Vis Sci* 2004; 45: 1823–1829
- 21 Strouthidis NG, Vinciotti V, Tucker AJ et al. Structure and function in glaucoma: The relationship between a functional visual field map and an anatomic retinal map. *Invest Ophthalmol Vis Sci* 2006; 47: 5356–5362
- 22 Katsanos A, Kothiy P, Konstas AG et al. Correlation between polarimetric retinal nerve fiber layer thickness and retinal sensitivity determined with frequency-doubling technology. *Ophthalmic Surg Lasers Imaging* 2005; 36: 394–400
- 23 Gugleta K, Polunina A, Kochkorov A et al. Association between risk factors and glaucomatous damage in untreated primary open-angle glaucoma. *J Glaucoma* 2013; 22: 501–505
- 24 Gordon MO, Beiser JA, Brandt JD et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120: 714–720
- 25 Ghanem M, Gugleta K, Oettli A et al. [Analysis of retinal vein motion in glaucoma patients]. *Klin Monatsbl Augenheilkd* 2013; 230: 358–362
- 26 Morgan WH, Hazelton ML, Azar SL et al. Retinal venous pulsation in glaucoma and glaucoma suspects. *Ophthalmology* 2004; 111: 1489–1494
- 27 Gugleta K, Kochkorov A, Waldmann N et al. Dynamics of retinal vessel response to flicker light in glaucoma patients and ocular hypertensives. *Graefes Arch Clin Exp Ophthalmol* 2012; 250: 589–594
- 28 Gugleta K, Waldmann N, Polunina A et al. Retinal neurovascular coupling in patients with glaucoma and ocular hypertension and its association with the level of glaucomatous damage. *Graefes Arch Clin Exp Ophthalmol* 2013; 251: 1577–1585
- 29 Lee M, Cho EH, Lew HM et al. Relationship between ocular pulse amplitude and glaucomatous central visual field defect in normal-tension glaucoma. *J Glaucoma* 2012; 21: 596–600
- 30 Dastiridou AI, Tsironi EE, Tsilimbaris M et al. Ocular rigidity, outflow facility, ocular pulse amplitude and pulsatile ocular blood flow in open angle glaucoma; a manometric study. *Invest Ophthalmol Vis Sci* 2013; 54: 4571–4577
- 31 Kyrigopoulos M, Tzamalis A, Ntampos K et al. Decreased ocular pulse amplitude associated with functional and structural damage in open-angle glaucoma. *Eur J Ophthalmol* 2012; 22: 111–116
- 32 Fujishima H, Toda I, Yamada M et al. Corneal temperature in patients with dry eye evaluated by infrared radiation thermometry. *Br J Ophthalmol* 1996; 80: 29–32
- 33 Morgan PB, Tullo AB, Efron N. Infrared thermography of the tear film in dry eye. *Eye* 1995; 9: 615–618
- 34 Leske MC, Heijl A, Hyman L et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology* 2007; 114: 1965–1972
- 35 The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. *Am J Ophthalmol* 2000; 130: 429–440