Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Individualized Significance of 24-Hour Intraocular Pressure Curves for Therapeutic Decisions in Primary Chronic Open-Angle Glaucoma Patients

This article was published in the following Dove Press journal:
Clinical Ophthalmology

Mael Lever[1]
Jan Darius Unterlauft[2]
Christian Halfwassen[1]
Nikolaos E Bechrakis[1]
Anke Manthey[1]
Michael RR Böhm[1]

[1]Department of Ophthalmology, University Hospital Essen, Essen, Germany; [2]Department of Ophthalmology, University Hospital Leipzig, Leipzig, Germany

Purpose: Diagnostic 24-hour intraocular pressure curves (IPC) are well established in the management of glaucoma. However, objective criteria for the IPC indication are lacking. The aim of this study was to evaluate the impact of individual patient characteristics and glaucoma-related parameters on therapy decisions after IPC and thus examine their relevance for glaucoma management.

Patients and Methods: Retrospective analysis of adult primary open-angle glaucoma (POAG) patients who underwent an IPC (≥6 IOP measurements in 24 hours). The main exclusion criterion was previous IOP-lowering surgery. IPC-dependent (eg, mean and peak IOP) and IPC-independent parameters (eg, perimetry, RNFL thickness) were analyzed in relation to the therapeutic decision after IPC. Further, these parameters were compared in patient subgroups based on age, glaucoma stage, or therapy intensity.

Results: A total of 101 eyes of 101 patients were included. In general, mean and peak IOP were elevated in patients with a therapeutic change after IPC. These subjects presented differences of IPC-independent parameters (eg, IOP at admission, RNFL thickness, glaucoma stage). Regression analysis results suggested a predictive role of IPC-independent parameters for IPC therapeutic decisions. In subgroups of patients of older age or advanced glaucoma, IPC-independent parameters did not correlate with therapeutic decisions after IPC.

Conclusion: These results support the relevance of IPC in the therapeutic management of POAG. Moreover, the study promotes a personalized classification of patients using selected glaucoma characteristics to objectivize their individual benefit from IPC. Further prospective studies are needed to verify the utility of these parameters and IPC in the management of glaucoma.

Keywords: glaucoma management, IOP phasing, diagnostic, antiglaucomatous therapy

Introduction

In Europe and North America, glaucoma, including its most common primary open-angle form (POAG), represents the second most frequent cause for blindness.[1] It describes a group of optic neuropathies characterized by a progressive loss of retinal ganglion cells which leads to a deterioration of visual field perception (VF) and loss of vision.[2] Although the precise pathogenesis is not clearly understood, elevated intraocular pressure (IOP) is one of the main risk factors regarding onset and progression of POAG.[3] Therefore, the primary therapeutic goal is IOP reduction by medical or surgical means.[4,5] Due to the chronicity of the disease, IOP measurements and evaluation of clinical signs of glaucoma progression (eg, deterioration of visual field perception, progression of optic

Correspondence: Mael Lever
Department of Ophthalmology, University Hospital Essen, Hufelandstr. 55, Essen 45147, Germany
Tel +49 201 723 2900
Fax +49 201 723 5917
Email mael.lever@uk-essen.de

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/OPTH.S251333

nerve head (ONH) cupping, increased thinning of the peripapillary retinal nerve fiber layer (RNFL)) are required regularly in order to adjust therapy.[6]

In addition, further IOP related parameters are associated with glaucoma progression, like long term or nictemeral IOP fluctuations.[7] In particular, for patients with a high risk of disease progression, it is crucial to detect high fluctuation or IOP peaks.[8] To assess IOP alterations and record its daily course, several methods have been developed (eg, home self-tonometry devices,[9] IOP measuring contact lenses[10]). Still, hospitalizing glaucoma patients over 24 hours for sequential IOP measurement is the most common method to provide data about nictemeral IOP variation.[11,12] Although the information gathered can be indispensable for the evaluation and therapy of glaucoma,[11] its relevance for therapeutic decisions has been discussed controversially.[14] The cost of IPC for the patient as well as for health care providers (eg, logistically, financially) account for serious limitations of the method and may partly motivate this controversy.[13] Another explanation could be that the potential benefit of IPC for glaucoma management varies individually. Moreover, objective rules for indicating a 24-hour IOP curve (IPC) are lacking.

The aim of this study was to identify glaucoma-related individual characteristics influencing the relevance of IPC for therapeutic decisions in POAG patients. Therefore, IPC derived and IPC-independent parameters were compared in relation to therapeutic decisions after IPC as well as within patient subgroups.

Patients and Methods

Study Design

Retrospective chart analysis of POAG patients admitted at the Department of Ophthalmology, University Hospital Essen between March 2015 and July 2017 to perform a 24-hour IOP curve. The study was conducted in accordance with the 1964 Declaration of Helsinki and was approved by the ethics committee of the University Hospital Essen. Inclusion criteria were diagnosis of POAG, patient's age ≥18 years, ≥6 IOP measurements in 24 hours for at least 2 days. Exclusion criteria were previously performed IOP-lowering surgical procedures, recent modifications of topical antiglaucomatous therapy (within 3 months prior to or during IPC), or the administration of systemic antiglaucomatous medication. In cases of bilateral glaucoma, the eye with the most advanced visual field (VF) defect was analyzed.

Patients and Glaucoma Diagnostics

At the day of IPC indication, a comprehensive ophthalmic examination including review of medical history, measurement of best-corrected visual acuity (BCVA), slit-lamp examination of anterior segment, fundoscopy (including evaluation of ONH linear cup-to-disc ratio, CDR), measurement of IOP (Goldmann applanation tonometry, GAT, Haag-Streit, Bern, Switzerland) adjusted to central corneal thickness (CCT; Canon TX-20P tonometer) using the Dresdener correction table,[15] and gonioscopic examination. Also, stereoscopic ONH photography, analysis of retinal nerve fiber layer (RNFL) thickness by spectral domain optical coherence tomography (SD-OCT) (SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany) and/or scanning laser polarimetry (SLP; GDx Pro ECC, Carl Zeiss Meditec, Oberkochen, Germany) were acquired. Actual RNFL thickness and its qualification as "within normal limits", "borderline", "outside normal limits" by both devices were processed. VF examination using 30–2 static automated perimetry (SAT) (Twinfield 2, OCULUS Optikgeräte, Wetzlar, Germany) was performed and only reliable VF results (fixation loss <33%, false-positive and false-negative rates <25%) were kept for further analysis. Figure 1A gives an overview of these parameters, which were qualified as IPC independent (IPCi).

IPC Modalities

On the main day of IPC, IOP measurements took place at 7 AM, 10 AM, 1 PM, 4 PM, 9 PM, and 12 PM, all using GAT in a seated position (Figure 2). Antiglaucomatous eye drops were applied by the patient or, in case of impairment, by nursing personal. Eye drop application modalities remained unchanged throughout the IPC. In any case, the eye drop application occurred strictly according to patients' individual therapy modalities. The IOP measurements obtained during IPC allowed determination of minimal and maximal IOP (IOPmin, IOPmax, respectively), IOP amplitude (IOPampl), mean IOP (IOPmean), mean daytime (IOPday) and nighttime IOP (IOPnight), presented in Figure 2. Those parameters were sorted as IPC dependent (IPCd) (Figure 1A) except for the first IOP measurement on the day of admission for IPC (IOPini), considered as IPC-independent due to its possible availability within an outpatient clinic visit.

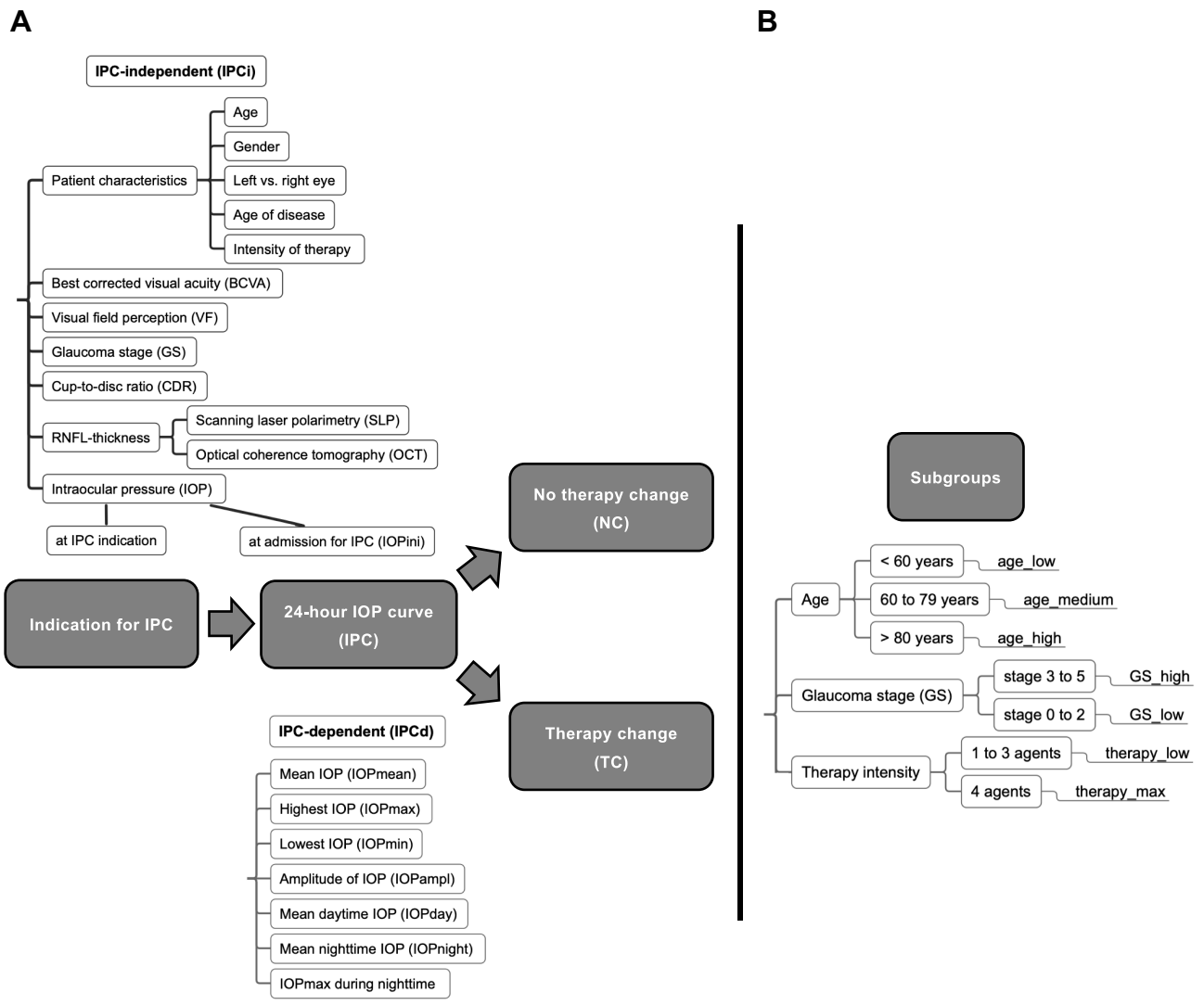

Figure 1 Study approach, and patients subgroups, glaucoma parameters and abbreviations. (**A**) An overview of all parameters analyzed in this 24-hour intraocular pressure curve (IPC) study. They are separated into IPC dependent (IPCd) and IPC independent (IPCi). (**B**) presents the subgroups created for detailed analysis, based on patients' age, therapy intensity (number of antiglaucomatous agents), and glaucoma stage.

IPC Outcome and Data Analysis

Progression of RNFL thinning by OCT and SLP, and VF deterioration were evaluated at the time of performing IPC by two consultant ophthalmologists from our department's glaucoma division independently. This data was included for further study when at least three consecutive examinations separated by 6 months were available. The presence of a decrease of peripapillary RNFL thickness was considered clinically significant when ≥5.0 µm in 24 months.[16] A progression of VF defects was stated considering alterations of the mean deviation and of the configuration of significant field defects. Finally, the individual target IOP and related therapeutic decisions were determined in accordance with the guidelines of the European Glaucoma Society. Particularly, glaucoma stage and VF perception, ONH morphology and RNFL thickness, the presence of progression, current IOP range, as well as the patients' age and quality of life were considered.[17] IPC outcome was then categorized as "no change of therapy" (NC) or "therapeutic change" (TC: escalation of topic therapy or indication for surgery).

In addition to analyzing the data from the whole cohort, we separated patients into subgroups based on age: age_low (<60 years of age); age_medium (60–80 years) and age_high (≥80 years); therapy intensity: therapy_low (1–3 antiglaucomatous substances) and therapy_max (4 substances); glaucoma stage (using the classification by Mills et al[18]): GS_low (glaucoma stage 0 to 2 corresponding to minimal, early, and moderate visual field defects)

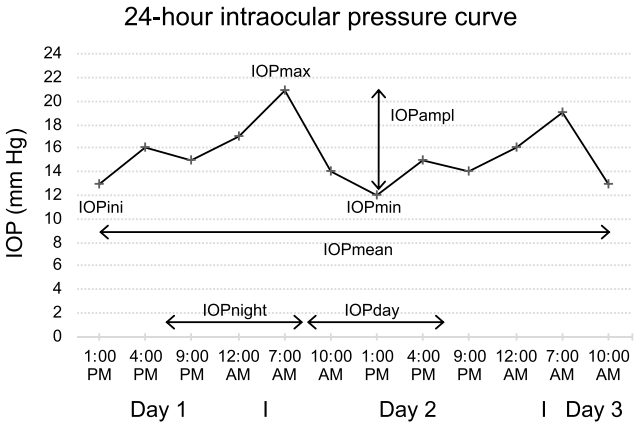

Figure 2 The 24-hour intraocular pressure curve. The figure presents an example of the 24-hour intraocular pressure curve (IPC) like it was performed for this study. Principal IPC-related parameters are also represented: IOPmean is the mean of all measured intraocular pressure (IOP) values, IOPmax is the peak IOP, IOPmin the lowest measured IOP, and IOPampl the amplitude of IOP (defined as the difference between IOPmax and IOPmin). IOPday and IOPnight are the mean IOP measured during daytime (10 AM, 1 PM, 4 PM) or during nighttime (9 PM, midnight, 7 AM), respectively. IOPini (first IOP measured on the day of admission for IPC) is considered IPC independent.

and GS_high (stage 3 to 5 corresponding to advanced, severe, and end-stage visual field defect). An overview of the subgroups considered in this study is provided in Figure 1B.

Statistical Analysis

Data was analyzed using Microsoft Excel (Microsoft, Redmond, WA, USA) and Prism 8.3 for Mac (GraphPad, La Jolla, CA, USA). Normality was examined using the D'Agostino and Pearson normality test. To compare numerical data Student's *t*-test, or Mann–Whitney *U*-test was applied, when appropriate; categorical data was analyzed using Fischer's exact test. In general, results are presented as mean ± standard deviation (SD) or median (CL: confidence level). To evaluate the correlation between the parameters and a therapeutic change, univariate and multivariate logistic regression analyses were performed. For univariate logistic regression, the presented results include the odds ratio (OR) and its 95% confidence interval (95% CI). For multivariate logistic regression, Tjur's R^2 and the p-value of the Log-likelihood test are presented. These results were compared using their respective sensitivity and specificity as well as the area under the receiver operating characteristic curve (AUC). Statistical significance was assumed for $p<0.05$.

Results

One hundred and one eyes of 101 patients out of 548 glaucoma patients were included (Table 1). The mean age of patients was 65.8±12.7 years. POAG diagnosis existed for a mean of 5.1±5.6 years before IPC. The mean follow-up after IPC was 5.8 months. The median glaucoma stage (GS) was stage 2 (CL 95.8%). Topical antiglaucomatous therapy consisted of 2.9±1.2 active substances applied over 3.7±1.6 times per day. After IPC, a change of therapy was decided in 55 (54.4%) cases.

Differences of Glaucoma Parameters Depending on IPC Outcome

Epidemiological and glaucoma-related parameters were compared between patients without a change of therapy after IPC (NC) and patients with an escalation of therapy (TC). General epidemiological and basic ophthalmological parameters, ie, gender, age, laterality, and age of therapy did not show any relationship to therapeutic decisions after IPC (NC compared to TC) (data not shown). Further, IPC-dependent parameters (IPCd, see overview in Figure 1A) were compared between both IPC outcome groups. The following IPCd were found to be different between NC and TC (Table 2A): IOPmean (NC: 13.2±2.2; TC: 15.8 ±3.0 mm Hg), IOPmax (NC: 17.0±2.7; TC: 20.8±3.8 mm Hg), IOPampl (NC: 7.3±2.1; TC: 9.3±3.3 mm Hg) ($p<0.01$ each). In TC patients, the highest IOP (IOPmax) occurred during nighttime hours in 27 cases (26.7%), which was significantly more frequent than in NC patients ($p=0.003$).

In analogy, the relation between IPC-independent parameters (IPCi) and the IPC outcome was analyzed comparing results in NC and TC. The following differences were observed (Table 2B): median GS (NC: stage 1 (CL: 97.4%); TC: stage 2 (CL: 97.0%), $p=0.0003$), IOPini (NC: 13.4±3.0; TC: 16.9±4.3 mm Hg, $p=0.0001$), median CDR (NC: 0.8 (CL: 96.9%); TC: 0.9 (CL: 96.0%); $p=0.0001$), progression of GS ($p=0.004$) and decrease of RNFL thickness ($p=0.013$).

Differences of Glaucoma Parameters in Patient Subgroups

To study the impact of individual glaucoma parameters on the IPC-related therapeutic decision in a more personalized manner, subgroups based on age, glaucoma stage, and therapy intensity (presented in Figure 1B) were analyzed separately.

IPC-Dependent Parameters

First, the relation between IPCd parameters and the therapeutic decisions after IPC was studied in each subgroup. These results are summarized in Table 3A. Age: The

Table 1 Epidemiologic and General Ophthalmologic Characteristics of Patients

General Epidemiologic Data	
Gender, Male : female (%)	41.6 : 58.4
Age, Mean±SD (y)	65.8±12.7
Eye, Right : left (%)	52.5 : 47.5
Age of disease, Mean±SD (y)	5.1±5.6
Follow-up period, Mean±SD (m)	5.7±14.5
Therapy intensity, Mean±SD (n)	2.9 ±1.2
Therapy frequency, Mean±SD (n)	3.7±1.6
BCVA, Median (CL) (LogMAR)	0.2 (95.4%)
IOPmean, Mean±SD (mm Hg)	14.6±2.9
IOPmean (raw), Mean±SD (mm Hg)	15.0±2.7
GS, Median (CL)	Stage 1 (95.4%)
CDR, Median (CL)	0.8 (95.8%)
CCT, Mean±SD (µm)	561.7±36.8

Note: The table presents the main characteristics of patients included in the study. Therapy intensity refers to the number of topical antiglaucomatous agents used by patients. Therapy frequency represents the number of eye drop applications per day.

Abbreviations: GS, glaucoma stage; CCT, central corneal thickness; CDR, cup-to-disc- ratio; IOP, intraocular pressure; IOPini, first intraocular pressure measurement at day of admission for 24-hour IOP curve; SD, standard deviation; CL, actual confidence level; y, years; m, months; mm Hg, millimeter of mercury.

relation between IPCd and IPC outcome was analyzed in age-based subgroups (patients younger than 60 years (age_low), patients aged 60 to 80 years (age_medium), and patients aged 80 years or more (age_high)). A therapeutic change was observed in age_low for 16 patients (61.3%), in age_medium in 27 cases (47.4%), and in age_high in 9 cases (69.2%). While IOPampl was different between NC and TC in all three subgroups ($p<0.05$ each), higher IOPmean and IOPmax were found for TC only in age_low and age_medium. Therapy intensity: IPCd results were then analyzed separately in patients using 1–3 antiglaucomatous agents (therapy_low) and patients with 4 antiglaucomatous agents (therapy_max). An escalation of therapy was found in 25 patients (50%) in the therapy_low subgroup compared to 42 cases (59.5%) in the therapy_max subgroup. Moreover, higher IOPmean, IOPampl, and IOPmax were found in TC compared to NC in both subgroups (each $p<0.05$). Glaucoma stage: IPCd parameters in patients with advanced glaucomatous defects (GS_high, GS 3 and above) and patients with mild to moderate defects (GS_low; GS 0 to 2) revealed the following differences in NC and TC: an escalation of therapy was decided for 38 of 78 patients (48.7%) in GS_low and for 18 of 24 patients (75%) in GS_high. In both GS_low and GS_high, higher IOPmax and IOPmean were found in TC compared to NC ($p<0.05$). Also, differences of IOPmax, IOPmean, and IOPampl in relation to the presence or absence of progression of GS, VF defects, RNFL thickness, and ONH excavation were analyzed comparatively between NC and TC patients (see Supplementary Table 1).

IPC-Independent Parameters

In analogy to analyses of IPCd parameters, the relation between IPCi parameters and the IPC outcome was analyzed distinctively using the previous subgroups (Table 3B). The main parameters are presented here. Age: Patients in age_low displayed a higher median GS ($p=0.02$), IOPini (NC: 13.2±3.2; TC: 16±3.7 mm Hg, $p=0.035$), and median CDR (NC: 0.75 (CL: 97.7%); TC: 0.8 (CL: 97.7%); $p=0.049$) in TC compared to NC. In age_medium, median GS (NC: stage 1 (CL: 95.7%); TC: stage 2 (CL: 98.1%); $p=0.003$), IOPini (NC: 13.9±2.8; TC: 17.1±4.7 mm Hg, $p=0.0052$), and median CDR (NC: 0.8 (CL: 98.1%); TC: 0.9 (CL: 97.1%); $p=0.001$) were higher in TC than NC. In age_high, IOPini was significantly higher in TC compared to NC (NC: 10.8 ±2.9; TC: 18.1±4.3 mm Hg, $p=0.0028$), whereas other IPCi parameters did not show any differences. Therapy intensity: In therapy_low, a higher median GS (NC: stage 1 (CL: 97.6%); TC: stage 2 (CL: 95.7%); $p=0.028$) and higher IOPini (NC: 13.1±3.5; TC: 16.8±5.0 mm Hg, $p=0.0053$) were found in TC compared to NC. Patients in therapy_max had a higher median GS (NC: stage 1 (CL: 95.1%); TC: stage 2 (CL: 95.7%); $p=0.0056$), IOPini (NC: 13.8±2.4; TC: 17.0 ±4.0 mm Hg; $p=0.0024$), and median CDR (NC: 0.8 (CL: 95.1%); TC: 0.9 (CL: 95.7%); $p=0.004$). Glaucoma stage: In GS_low, IOPini (NC: 13.6±3.0; TC: 17.4±4.0 mm Hg, $p=0.0053$), median GS ($p=0.02$), and median CDR (NC: 0.8 (CL: 96.2%); TC: 0.9 (CL: 95.3%); $p=0.02$) were higher in TC than NC. In GS_high the median GS was significantly higher in TC compared to NC (NC: stage 3 (CL: 96.9%); TC: stage 4 (CL: 96.9%); $p=0.04$). A more frequent decrease of RNFL thickness ($p=0.0098$) in TC compared to NC was only reported for the therapy_max subgroup (data not shown).

Correlation of IPC-Dependent and Independent Parameters with the Therapeutic Decision After IPC

Predictive factors for a therapeutic change after IPC were studied using logistic regression. In the entire cohort, IOPini (OR: 1.3; $p<0.0001$), a worsening of GS (OR: 12.7; $p=0.0016$) and a decrease of RNFL thickness (OR: 6.3; $p=0.0006$) were identified as predictive for a change

Table 2 Comparison of Glaucoma Parameters in Relation to the IPC-Related Outcome

	No Therapy Change (NC)	Therapy Change (TC)	p-value
(A) – IPC-Dependent Parameters			
Patients, n (%)	46 (45.5%)	55 (54.5%)	n/n
IOPampl, Mean±SD (mm Hg)	7.3±2.1	9.3±3.3	**<0.01**
IOPmean, Mean±SD (mm Hg)	13.2±2.2	15.8±3.0	**<0.01**
IOPmean (raw), Mean±SD (mm Hg)	13.7±2.2	16.2±2.5	**<0.01**
IOPmax, Mean±SD (mm Hg)	17.0±2.7	20.8±3.8	**<0.01**
IOPday, Mean±SD (mm Hg)	13.0±2.3	15.5±3.0	**<0.01**
IOPnight, Mean±SD (mm Hg)	13.3±2.3	16.1±3.3	**<0.01**
Highest IOP at night, n (%)	6 (22.2%)	21 (77.8%)	**<0.01**
(B) – IPC-Independent Parameters			
Age, Mean±SD (y)	65.8±10.6	65.8±14.3	1.00
Therapy intensity, Mean±SD (n)	2.8±1.2	2.9±1.3	0.67
GS, Median (CL)	1 (97.4%)	2 (97.0%)	**<0.01**
GS worse, n (%)	1 (7.1%)	13 (92.9%)	**<0.01**
BCVA, Median (CL) (LogMAR)	0.20 (97.4%)	0.20 (97.0%)	0.54
CDR, Median (CL)	0.8 (96.9%)	0.9 (96.0%)	**<0.01**
CDR progression, n (%)	9 (42.9%)	12 (57.1%)	0.78
VF deterioration, n (%)	16 (45.7%)	19 (54.3%)	0.38
RNFL progression, n (%)	7 (24.1%)	22 (75.9%)	**0.01**
IOPini, Mean±SD (mm Hg)	13.4±3.0	16.9±4.3	**<0.01**

Notes: Table 2A shows differences of IPC-dependent parameters related to the therapeutic decision after IPC. Daytime IOP measurements took place at 10 AM, 1 PM, 4 PM, nighttime measurements at 9 PM, midnight and 7 AM Raw IOPmean corresponds to the mean IOP without correction for central corneal thickness. Table 2B presents differences of IPC-independent parameters related to the therapeutic decision after IPC. Therapy intensity refers to the number (n) of topical antiglaucomatous agents used by patients.

Abbreviations: GS, glaucoma stage; BCVA, best-corrected visual acuity; CDR, cup-to-disc ratio; CL, actual confidence level; SLP, scanning laser polarimetry; IOP, intraocular pressure; IOPampl, amplitude of IOP; IOPmax, highest IOP; IOPday, mean daytime IOP; IOPnight, mean nighttime IOP; IOPini, first IOP measurement at admission for IPC; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; SD, standard deviation; VF, visual field; y, years; m, months; p-value statistically significant when p<0.05 (bold).

of therapy. Further, multivariate logistic regression using these three parameters confirmed this correlation between IPC-independent parameters and the IPC outcome (R^2=0.46; p<0.0001) (Table 4).

These observations can be differentiated more precisely using patient subgroups. With univariate regression, IOPini correlates positively with a therapy modification in age_low (OR: 1.3; p=0.033) and age_medium (OR: 1.3; p=0.0029), and in all GS- and therapy intensity-based subgroups (Table 4). Also, the progression of GS correlates positively with a therapeutic change in age_medium (OR: 6.9; p=0.048) and GS_low (OR: 16.1; p=0.0007). The decrease of RNFL thickness and the worsening of GS also correlate with a therapeutic change in the age_medium and GS_low subgroups. Multivariate logistic regression analysis confirms these results in age_medium (R^2=0.45; p=0.0006), therapy_low (R^2=0.39; p=0.0019), and GS_low (R^2=0.44; p<0.0001). The analysis of the predictive potential of these IPC independent parameters compared to selected IPC-dependent factors shows considerable fluctuations. In general, sensitivity and specificity are particularly high for the IPC-dependent parameters IOPmax and IOPmean – and to a lesser extent IOPampl – in age_high, therapy_low, and GS_high. Also, in these three subgroups, the area under the receiver operating characteristic curve (AUC) of the multivariate logistic regression is the highest (AUC: 0.97; 0.90; and 0.90, respectively), while this analysis using the mentioned IPC-independent parameters returns no correlation. In contrary, in age_medium, therapy_low, and GS_low, sensitivity and specificity of IPC-independent parameters are comparable or slightly higher than for IPC-dependent parameters and AUC is higher using the IPC-independent parameters (eg, AUC for IPCi in therapy_low is 0.87, compared to 0.73 for the IPCd) (Table 5).

Discussion

The present study analizes IPC-derived parameters and individual glaucoma characteristics to personalize the role of IPC in glaucoma management. The principal findings of this study are the following:

Table 3 Subgroup Analysis of Glaucoma Parameters in Relation to IPC Outcome

(A) – IPC-Dependent Parameters in Subgroups of Patients									
	IOPmax Mean±SD (mmHg)			**IOPmean Mean±SD (mmHg)**			**IOPampl Mean±SD (mmHg)**		
	No Change (NC)	**Therapy Change (TC)**	**p-value**	**No Change (NC)**	**Therapy Change (TC)**	**p-value**	**No Change (NC)**	**Therapy Change (TC)**	**p-value**
Age_low	17.2±2.5	19.5±3.5	**0.05**	13.3±1.8	15.5±2.9	**0.02**	7.6±2.1	8.3±2.7	0.44
Age_medium	17.1±2.9	21.8±3.9	**<0.01**	13.3±2.2	16.1±3.4	**<0.01**	7.2±2.0	10.2±3.2	**<0.01**
Age_high	15.8±2.2	20.4±3.6	**0.02**	11.7±3.2	15.7±1.5	**0.02**	7.3±2.6	9.0±4.2	0.38
Therapy_low	17.6±2.8	20.8±4.3	**<0.01**	13.6±2.0	15.8±3.3	**<0.01**	7.1±2.0	9.2±3.8	**0.02**
Therapy_max	16.4±2.6	21.4±3.3	**<0.01**	12.7±2.5	16.3±2.7	**<0.01**	7.6±2.3	9.6±2.6	**0.01**
GS_low	17.1±2.7	20.9±3.7	**<0.01**	13.3±2.1	16.0±3.0	**<0.01**	7.4±2.2	9.2±2.7	**<0.01**
GS_high	16.2±3.4	20.6±4.1	**0.03**	12.4±2.5	15.5±3.0	**0.04**	6.8±1.0	9.6±4.3	0.21
(B) – IPC-Independent Parameters in Subgroups of Patients									
	IOPini Mean±SD (mmHg)			**GS Median (CL)**			**CDR Median (CL)**		
	No Change (NC)	**Therapy Change (TC)**	**p-value**	**No Change (NC)**	**Therapy Change (TC)**	**p-value**	**No Change (NC)**	**Therapy Change (TC)**	**p-value**
Age_low	13.2±3.2	16.0±3.6	**0.04**	1 (96.1%)	1 (98.1)	**0.02**	0.75 (97.7)	0.8 (97.7%)	**0.049**
Age_medium	13.9±2.8	17.1±4.7	**<0.01**	1 (95.7%)	2 (98.1)	**<0.01**	0.8 (98.1%)	0.9 (97.1%)	**<0.01**
Age_high	10.8±2.9	18.1±4.3	**<0.01**	2 (87.5%)	2 (96.1%)	0.58	0.9 (87.5%)	1.0 (96.9%)	0.22
Therapy_low	13.1±3.5	16.6±5.0	**<0.01**	1 (97.6%)	2 (95.7%)	**0.02**	0.75 (97.7%)	0.8 (97.7%)	**0.048**
Therapy_max	13.8±2.4	17.0±4.0	**<0.01**	1 (95.1%)	2 (95.7%)	**0.01**	0.8 (95.1%)	0.9 (95.7%)	**<0.01**
GS_low	13.6±3.0	17.4±4.0	**<0.01**	1 (96.2%)	1 (95.3%)	**0.02**	0.8 (96.2%)	0.9 (95.3%)	**0.02**
GS_high	12.7±3.4	16.8±4.3	0.052	3 (96.9%)	4 (96.9%)	**0.04**	0.9 (93.8%)	1.0 (95.1%)	0.050

Notes: Table 3A shows results for representative 24-hour IOP curve-dependent parameters (IPCd): IOPmax (highest intraocular pressure), IOPmean (mean IOP), IOPampl (amplitude of IOP throughout IPC) in the subgroups of patients (age_low (up to 60 years of age); age_medium (60 to 80 years of age); age_high (older than 80 years); therapy_low (up to 3 active antiglaucomatous agents); therapy_max (4 active antiglaucomatous agents); GS_low (glaucoma stage 0 to 2); GS_high (GS 3 to 5). Table 3B shows results for representative IPC-independent parameters (IPCi) in the patient subgroups: GS, the cup-to-disc ratio of the optic nerve head (CDR), and IOPini (first intraocular pressure measurement at day of admission for 24-hour IOP curve). Statistically significant results when p<0.05 (bold).

- In general, IPC-dependent and IPC-independent parameters vary comparably in relation to the therapeutic decision after IPC.
- IPC-dependent and IPC-independent parameters correlate differently with the IPC outcome in age, glaucoma stage, and therapy intensity-based patient subgroups.
- Individual glaucoma parameters can help identify the patients for whom IPC is most valuable.

The elevation of IOP and high IOP amplitudes are the main risk factors for the development and progression of POAG.[7] Further, IOP represents the sole modifiable target for the treatment of glaucoma.[12] The examination of nycthemeral IOP variations revealed that IOP peaks occur most often outside of clinic hours, particularly at night[19] or in the early morning hours.[20] Consequently, the 24-hour monitoring of IOP eg, during IPC allows for a reliable assessment of IOP peaks and amplitude, whereas single IOP measurements seem to fail.[21,22] Also, hospitalization of patients can provide additional information about adherence to the individual therapeutic regime.[23] In this study, nightly IOP peaks have been found in 26.7% and IPC resulted in an escalation of therapy in 54% of the studied cases. Additionally, nighttime IOP was significantly higher in patients with a therapy modification. Hence, IPC and its nighttime IOP measurements allowed identifying patients with an insufficient treatment, who would have stayed unrecognized using sole daytime IOP measurements. The study's retrospective design and its main outcome measure being the IPC-related therapeutic decision, data did not allow evaluating the impact of IOP measured during IPC and subsequent therapeutic decisions on the course of the disease and a possible progression. Moreover, as both IOP-derived values and IPC-independent parameters (eg, VF, ONH morphology and RNFL thickness, patient's age) affect the target IOP, it was difficult to analyze the separate effect of each parameter on IPC-related therapeutic decisions. Also, the typical setup of IPC leads to further limitations: waking up of patients at night reduces the reliability of nighttime IOP

Table 4 Logistic Regression Analysis of Selected IPC-Independent Parameters for the IPC Outcome

	IOPini			GS Worse			Progression of RNFL Thinning			Multiple Regression	
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	R^2	p-value
Entire cohort	1.3	1.1–1.5	**<0.01**	12.7	1.6–102.8	**<0.01**	6.3	2.1–19.2	**<0.01**	0.46	**<0.0001**
Age_low	1.3	1.0–1.6	**0.03**	n/n			n/n			n/n	
Age_medium	1.3	1.1–1.5	**<0.01**	6.9	0.8–63.5	**0.05**	8.4	1.6–44.1	**<0.01**	0.45	**0.0006**
Age_high	n/n			n/n			n/n			n/n	
Therapy_low	1.3	1.1–1.5	**<0.01**	n/n			n/n			0.39	**0.0019**
Therapy_max	1.4	1.1–1.7	**<0.01**	n/n			n/n			n/n	
GS_low	1.3	1.1–1.5	**<0.01**	15.6	1.9–129.5	**<0.01**	5.8	1.7–19.3	**<0.01**	0.44	**<0.0001**
GS_high	1.4	1.0–2.0	**0.03**	n/n			n/n			n/n	

Notes: Table 4 presents the odds ratio (OR), 95% confidence interval (95% CI) and p-value (statistically significant when p<0.05; bold) of the univariate logistic regression analysis for IOPini (first intraocular pressure measurement at day of admission for 24-hour IOP curve), the presence of worsening of glaucoma stage (GS worse), and the progression of RNFL thinning (by OCT and/or SLP) in the whole cohort of patients as well as for several subgroups (age_low (up to 60 years of age); age_medium (60 to 80 years of age); age_high (older than 80); therapy_low (up to 3 active antiglaucomatous agents); therapy_max (4 active antiglaucomatous agents); GS_low (GS 0 to 2); GS_high (GS 3 to 5). R^2 and the p-value (statistically significant when <0.05, bold) of the Log-likelihood ratio test of the multivariate logistic regression analysis using all three above parameters are also presented for the entire cohort as well as for the mentioned subgroups.

measurements and the hospitalization setting is known to influence patients' adherence to therapy.[13] Other factors influencing the IOP values are that all IOP measurements (including those during the night) were performed in a seated position and that IOP values were adjusted to the CCT using the "Dresdener correction table"; target IOP for IPC decisions was defined using these corrected values. The patient's position is known to affect the measured IOP value and having the patient seating may allow a reliable IOP measurement during the day, this position may be less accurate for nighttime measurements.[24] Moreover, as a standard clinical practice, IOP is adjusted to the CCT, additional factors influencing the precision of IOP measurements (eg, corneal curvature, astigmatism, elasticity[25,26]) were not assessed in this study. Finally, several authors suggest that sequential diurnal IOP measurements provide more realistic data about IOP and therefore are more reliable for the identification of IOP peaks while being more cost-effective.[14] Despite this, the presented results corroborate previous findings promoting the relevance of IPC in the management of POAG.

Due to the known limitations of IOP measurements (eg, acquired during IPC), additional parameters like VF perception, ONH morphology and patient's quality of life should be taken into account for glaucoma management.[17] Therefore, the influence of IPC-independent parameters on IPC-related therapeutic decisions was investigated. In the present cohort, like IPC-dependent parameters, several IPC-independent parameters vary with the IPC outcome: IOPini is higher and a progression of the glaucoma stage or of RNFL thinning is more frequent in patients with a therapeutic change. In addition, logistic regression analysis shows that these parameters correlate with the IPC-derived therapeutic decisions and thus are statistically predictive for these decisions. This observation suggests that in some cases, even though the therapeutic decision after IPC is mainly based on IOP measurements, the same decision could have been made independently of those IOP measurements. This supports the importance of IPC-independent parameters in glaucoma management, which is well recognized: VF is used for the classification of glaucoma severity[27] and is also the main outcome measure for evaluating therapy efficacy;[4,28] monitoring ONH morphology (splinter hemorrhages, evolution of cupping[29]) and the loss of RNFL thickness over time (using OCT[30] or SLP[31]) help detect POAG progression. Furthermore, the assessment of the progression rate of VF defects and RNFL thinning seems to be important in the management of glaucoma.[32] In summary, the present results further support the relevance of IPC-independent parameters for justifying therapeutic changes in POAG and also raise the question about the conditions under which IPC is most valuable.

Considering the diversity of POAG patients regarding age, therapy intensity, glaucoma stage, and visual function, therapeutic decisions require an individual assessment of all available parameters. Subgroups of patients were created to analyze selected IPC-

Table 5 Comparison of the Predictive Potential of IPC-Dependent and Independent Parameters for the IPC Outcome

	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)	AUC
IPCd	**IOPmax**			**IOPmean**			**IOPampl**			**Multivariate Regression**		
Entire cohort	78	61	0.79	72	70	0.76	69	57	0.71	0.77	0.72	0.80
Age_low	74	42	0.70	78	58	0.73	100	0	0.59	67	58	0.70
Age_medium	67	77	0.83	62	83	0.74	67	80	0.80	81	77	0.85
Age_high	89	50	0.89	89	50	0.92	100	0	0.65	89	75	0.97
Therapy_low	70	76	0.71	62	69	0.68	63	66	0.70	66	69	0.73
Therapy_max	84	71	0.88	83	71	0.84	76	41	0.72	88	82	0.90
GS_low	65	78	0.80	65	75	0.76	54	78	0.72	68	75	0.79
GS_high	89	33	0.79	94	67	0.85	100	0	0.68	94	67	0.90
IPCi	**IOPini**			**GS worse**			**RNFL worse**			**Multivariate regression**		
Entire cohort	72	69	0.75	22	98	0.60	67	76	0.71	77	79	0.88
Age_low	83	33	0.73	n/n			57	70	0.64	n/n		
Age_medium	69	79	0.71	19	97	0.58	64	82	0.73	79	76	0.89
Age_high	n/n			n/n			n/n			n/n		
Therapy_low	66	69	0.73	15	97	0.56	54	68	0.61	69	89	0.87
Therapy_max	83	50	0.77	n/n			75	90	0.83	n/n		
GS_low	68	82	0.74	29	98	0.63	68	73	71	75	77	0.88
GS_high	94	50	0.78	n/n			n/n			n/n		

Note: The table shows sensitivity, specificity and area under the receiver operating characteristic curve (AUC) values of univariate and multivariate logistic regression using selected IPC-dependent (IPCd) and- independent (IPCi) parameters in the entire cohort as well as in several patient subgroups.

Abbreviations: IOPmax, peak intraocular pressure; IOPmean, mean IOP; IOPampl, amplitude of IOP; IOPini, first IOP at day of admission for IPC; GS worse, worsening of the glaucoma stage; RNFL worse, decrease of RNFL thickness in OCT and/or SLP; age_low, up to 60 years of age; age_medium, 60 to 80 years of age; age_high, older than 80; therapy_low, up to 3 active antiglaucomatous agents; therapy_max, 4 active antiglaucomatous agents; GS_low, GS 0 to 2; GS_high, GS 3 to 5.

independent and IPC-dependent parameters and characterize their relevance for IPC-related decisions in particular patient profiles. Our results show that, in patients of increased age, maximum topic antiglaucomatous therapy, or advanced glaucoma stage (subgroups age_high, therapy_max, and GS_high, respectively), therapeutic modifications are tightly associated to IPC-related parameters (eg, IOPmax, IOPmean) and less to IPC-independent ones (eg, IOPini or worsening of the glaucoma stage or RNFL thickness). This can be explained by the lower precision of some diagnostic methods in these subpopulations: CDR changes are more difficult to observe when advanced ONH morphological alterations are present; perimetry is less sensitive to detect progression in case of pronounced defects[33] and may be influenced by media opacity and cognitive capabilities present in older patients;[34] RNFL thickness measurements are well suited for progression detection in early and pre-perimetric glaucoma but less informative in advanced disease.[35] The present results should be interpreted carefully though, as patient count in both subgroups (age_high and GS_high) is relatively low. In contrast, the present analysis suggests that, in patients of younger age, lower GS, or when the antiglaucomatous therapy can be escalated, several IPC-independent parameters (ie, IOPini, the worsening of GS, and the RNFL thickness) seem to better predict the therapeutic decisions after IPC than IPC-dependent parameters. Still, some exceptions may exist. In patients with a single functioning eye, maximum topical therapy and uncertain disease progression, performing an IPC should be considered in order to maximize the diagnostic certainty when evaluating the need for a surgical procedure.[11] Taken together, the present results propose that IPC is most valuable in patients of higher age or advanced glaucoma stage as IPC-independent parameters seem less informative than those obtained by IPC. In comparison, in younger and less affected patients, the IPC-independent parameters correlate strongly with the IPC-based therapeutic decision. Therefore, IPC-independent parameters could be sufficient for the management of those POAG-affected patients; IPC seems less indispensable for these individuals.

Conclusion

The present study shows the ability of IPC to identify insufficiently treated POAG patients. However, the data also underlines the significance of IOP unrelated functional and morphologic glaucoma parameters (perimetry, peripapillary RNFL thickness) for the detection of insufficient therapy. Considering the patient's age, glaucoma stage and therapy intensity seem helpful to evaluate their personalized benefit from performing an IPC. Such an individualized IPC indication could enhance the medical and socioeconomic efficiency of glaucoma management. Larger, prospective studies are needed to investigate the detailed relevance of patient characteristics and clinical parameters for the management of glaucoma.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards with the 1964 Helsinki declaration and its later amendments. In conformity to the guidance of the ethics committee of the University Hospital Essen (approval number: 18-8537-BO), patient consent was not required for this study due to its retrospective design. Patient data for this study was processed strictly anonymously.

Acknowledgments

This study was supported by the Junior Clinician Scientist program of the University Medicine Essen Clinician Scientist Academy (UMEA) and by the Open Access Publication Fund of the University of Duisburg-Essen.

Funding

No funding was received for this research.

Disclosure

Dr Michael Böhm reports personal fees from Novartis, Travel Grant from Novartis and Santen, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Quigley H, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262–267. doi:10.1136/bjo.2005.081224
2. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet (London, England)*. 2004;363(9422):1711–1720. doi:10.1016/S0140-6736(04)16257-0
3. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study. *Arch Ophthalmol*. 2002;120(6):701. doi:10.1001/archopht.120.6.701
4. AGIS7. The advanced glaucoma intervention study (AGIS): 7. the relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol*. 2000;130(4):429–440. doi: 10.1016/S0002-9394(00)00538-9.

5. Dietlein TS, Hermann MM, Jordan JF. The medical and surgical treatment of glaucoma. *Dtsch A¨rzteblatt Int*. 2009;106(37):597–605. doi:10.3238/arztebl.2009.0597
6. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma a review. *JAMA*. 2014;311(18):1901–1911. doi:10.1001/jama.2014.3192
7. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol*. 2008;53(6):3–10. doi:10.1016/j.survophthal.2008.08.006
8. Fischer N, Weinand F, Kügler MU, Scheel S, Lorenz B. Are diurnal and nocturnal intraocular pressure measurements over 48 H justified? *Ophthalmologe*. 2013;1–5. doi:10.1007/s00347-012-2774-x
9. Wilensky JT, Gieser DK, Mori MT, Langenberg PW, Zeimer RC. Self-tonometry to manage patients with glaucoma and apparently controlled intraocular pressure. *Arch Ophthalmol*. 1987;105(8):1072–1075. doi:10.1001/archopht.1987.01060080074031
10. Twa MD, Roberts CJ, Karol HJ, Mahmoud AM, Weber PA, Small RH. Evaluation of a contact lens-embedded sensor for intraocular pressure measurement. *J Glaucoma*. 2010;19(6):382–390. doi:10.1097/IJG.0b013e3181c4ac3d
11. Hughes EH, Spry P, Diamond J. 24-Hour monitoring of intraocular pressure in glaucoma management: A retrospective review. *J Glaucoma*. 2003;12(3):232–236. doi:10.1097/00061198-200306000-00009
12. David R, Zangwill L, Briscoe D, Dagan M, Yagev R, Yassur Y. Diurnal intraocular pressure variations: an analysis of 609 diurnal curves. *Br J Ophthalmol*. 1992;76(5):280–283. doi:10.1136/bjo.76.5.280
13. Mansouri K, Weinreb RN, Medeiros FA. Is 24-hour intraocular pressure monitoring necessary in glaucoma? *Semin Ophthalmol*. 2013;28(3):157–164. doi:10.3109/08820538.2013.771201
14. Moodie J, Wilde C, Rotchford AP, Vernon SA, King AJ. 24-Hour versus daytime intraocular pressure phasing in the management of patients with treated glaucoma. *Br J Ophthalmol*. 2010;94(8):999–1002. doi:10.1136/bjo.2009.160267
15. Kohlhaas M. Effect of central corneal thickness, corneal curvature, and axial length on applanation tonometry. *Arch Ophthalmol*. 2006;124(4):471. doi:10.1001/archopht.124.4.471
16. Wessel JM, Horn FK, Tornow RP, et al. Longitudinal analysis of progression in glaucoma using spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54(5):3613–3620. doi:10.1167/iovs.12-9786
17. European Glaucoma Society. *Terminology and Guidelines for Glaucoma*. 4th ed. 2014.
18. Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. *Am J Ophthalmol*. 2006;141(1):24–30. doi:10.1016/j.ajo.2005.07.044
19. Wozniak K, Köller AU, Spörl E, Böhm AG, Pillunat LE. Intraocular pressure measurement during the day and night for glaucoma patients and normal controls using goldmann and perkins applanation tonometry. *Ophthalmologe*. 2006;103(12):1027–1031. doi:10.1007/s00347-006-1407-7
20. Jonas JB, Budde WM, Stroux A, Oberacher-Velten IM, Jünemann A. Diurnal intraocular pressure profiles and progression of chronic open-angle glaucoma. *Eye*. 2007;21(7):948–951. doi:10.1038/sj.eye.6702351
21. Realini T, Weinreb N, Wisniewski S. Short-term repeatability of diurnal intraocular pressure patterns in glaucomatous individuals. *Ophthalmol*. 2011;118(1):47–51. doi:10.1016/j.ophtha.2010.04.027
22. Mosaed S, Liu JHK, Weinreb RN. Correlation between office and peak nocturnal intraocular pressures in healthy subjects and glaucoma patients. *Am J Ophthalmol*. 2005;139(2):320–324. doi:10.1016/j.ajo.2004.09.062
23. Böhm M, Lill T, Eter N, Prokosch-Willing V. Alterations of intraocular pressure in comparison of self- and external-administered topical antiglaucomatosa during diurnal intraocular pressure measurements. *Klin Monbl Augenheilkd*. 2014;231(08):810–817. doi:10.1055/s-0034-1368639
24. Gautam N, Kaur S, Kaushik S, Raj S, Pandav SS. Postural and diurnal fluctuations in intraocular pressure across the spectrum of glaucoma. *Br J Ophthalmol*. 2015;(1):bjophthalmol-2015-306861. doi:10.1136/bjophthalmol-2015-306861
25. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. *J Cataract Refract Surg*. 2005;31(1):146–155. doi:10.1016/j.jcrs.2004.09.031
26. Damji KF, Muni RH, Munger RM. Influence of corneal variables on accuracy of intraocular pressure measurement. *J Glaucoma*. 2003;12(1):69–80. doi:10.1097/00061198-200302000-00015
27. Aulhorn E. Glaukom-Gesichtsfeld. *Ophthalmologica*. 1969;158(5–-6):469–487. doi:10.1159/000305861
28. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmol*. 2007;114(11):1965–1972. doi:10.1016/j.ophtha.2007.03.016
29. Medeiros FA, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. *Am J Ophthalmol*. 2005;139(6):1010–1018. doi:10.1016/j.ajo.2005.01.003
30. Abe RY, Gracitelli CPB, Medeiros FA. The use of spectral-domain optical coherence tomography to detect glaucoma progression. *Open Ophthalmol J*. 2015;9(1):78–88. doi:10.2174/1874364101509010078
31. Moon BG, Sung KR, Cho JW, et al. Glaucoma progression detection by retinal nerve fiber layer measurement using scanning laser polarimetry: event and trend analysis. *Korean J Ophthalmol*. 2012;26(3):174–181. doi:10.3341/kjo.2012.26.3.174
32. Medeiros FA, Zangwill LM, Bowd C, Mansouri K, Weinreb RN. The structure and function relationship in glaucoma: implications for detection of progression and measurement of rates of change. *Investig Ophthalmol Vis Sci*. 2012;53(11):6939–6946. doi:10.1167/iovs.12-10345
33. Blumenthal EZ, Sample PA, Berry CC, et al. Evaluating several sources of variability for standard and SWAP visual fields in glaucoma patients, suspects, and normals. *Ophthalmol*. 2003;110(10):1895–1902. doi:10.1016/S0161-6420(03)00541-4
34. de Moraes CG, Liebmann JM, Medeiros FA, Weinreb RN. Management of advanced glaucoma: characterization and monitoring. *Surv Ophthalmol*. 2016;61(5):597–615. doi:10.1016/j.survophthal.2016.03.006
35. Abe RY, Diniz-Filho A, Zangwill LM, et al. The relative odds of progressing by structural and functional tests in glaucoma. *Investig Ophthalmol Vis Sci*. 2016;57(9):OCT421–OCT428. doi:10.1167/iovs.15-18940