• Clinical Research •

Impact of intraocular pressure fluctuations on progression of normal tension glaucoma

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Abstract

• **AIM:** To investigate short- and long-term intraocular pressure (IOP) fluctuations and further ocular and demographic parameters as predictors for normal tension glaucoma (NTG) progression.

• **METHODS:** This retrospective, longitudinal cohort study included 137 eyes of 75 patients with NTG, defined by glaucomatous optic disc or visual field defect with normal IOP (<21 mm Hg), independently from therapy regimen. IOP fluctuation, mean, and maximum were inspected with a mean follow-up of 38mo [standard deviation (SD) 18mo]. Inclusion criteria were the performance of minimum two 48-hour profiles including perimetry, Heidelberg retina tomograph (HRT) imaging, and optic disc photographs. The impact of IOP parameters, myopia, sex, cup-to-disc-ratio, and visual field results on progression of NTG were analyzed using Cox regression models. A sub-group analysis with results from optical coherence tomography (OCT) was performed.

• **RESULTS:** IOP fluctuations, average, and maximum were not risk factors for progression in NTG patients, although maximum IOP at the initial IOP profile was higher in eyes with progression than in eyes without progression (P=0.054). The 46/137 (33.5%) eyes progressed over the follow-up period. Overall progression (at least three progression confirmations) occurred in 28/137 eyes (20.4%). Most progressions were detected by perimetry (36/46). Long-term IOP mean over all pressure profiles was 12.8 mm Hg (SD 1.3 mm Hg); IOP fluctuation was 1.4 mm Hg (SD 0.8 mm Hg). The progression-free five-year rate was 58.2% (SD 6.5%).

• **CONCLUSION:** Short- and long-term IOP fluctuations do not result in progression of NTG. As functional changes are most likely to happen, NTG should be monitored with visual field testing more often than with other devices.

• **KEYWORDS:** intraocular pressure; intraocular pressure fluctuation; glaucoma progression; visual field; optical; optical coherence tomography

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INTRODUCTION

Intraocular pressure (IOP) is described as a dynamic value with diurnal amplitude up to 5 mm Hg in healthy subjects[1-2]. The data on circadian fluctuation (amplitude between the maximum and minimum IOP readings) of normal tension glaucoma (NTG) are controversial, and range from being lower (2 to 4 mm Hg) or comparable to healthy subjects[1,3], or even higher[4]. Little is known on IOP fluctuation values calculated as "standard deviation" (SD) which is less sensitive to outliers and therefore more useful[5]. Eyes with NTG may show a larger circadian IOP fluctuation (defined as SD) compared to normal eyes (3.9 *vs* 3.0 mm Hg, P=0.040, n=46)[6].

We have learned from multicenter randomized clinical trials [Advanced Glaucoma Intervention Study (AGIS), Collaborative Initial Glaucoma Treatment Study (CITGS), Collaborative Normal Tension Glaucoma Study (CNTGS)] that mean IOP is a significant risk factor for progression in NTG[7], while IOP fluctuation is not consistently a proven risk factor for development of visual field defects in preperimetric NTG[8]. But several studies indicate that long-term IOP fluctuation is associated with progression of glaucomatous visual field loss in general[9-14]. Furthermore, that large IOP fluctuation is a risk factor for glaucoma progression even or especially at a low IOP level[11,15], specifically in normal-tension glaucoma[16-17]. Finally, the role of short- and long-term IOP fluctuation in NTG progression is controversial.

In the Early Manifest Glaucoma Trial (EMGT), and partly in the above-mentioned multicenter studies[7] further parameters beyond IOP, such as age, mean deviation, and optic disc hemorrhage are risk factors for progression.

The aim of this retrospective longitudinal cohort study is to investigate the role of short and long-term IOP fluctuation and further parameters in a large NTG cohort undergoing 48-hour IOP profile, independently from therapy regimen, regarding progression. We hypothesize that NTG progression is determined by the SD within the first pressure profile (defined as the short-term IOP fluctuation), and SD over each of the available pressure profiles (defined as the long-term IOP fluctuation).

SUBJECTS AND METHODS

Ethical Approval The study follows the Tenets of the Declaration of Helsinki. No formal approval from the Medical Ethical Committee of the State Chamber of Medicine of Rhineland Palatinate in Mainz, Germany was required according to their statute, because of the retrospective study design. All patients gave informed consent about data collection and analysis.

Seventy-five NTG patients of glaucoma patients treated in our clinic were enrolled in this retrospective longitudinal cohort study. Inclusion criteria were: 1) diagnosis of NTG (glaucomatous optic disc, or glaucomatous visual field defect, with normal IOP<21mm Hg) acquired from the first IOP profile (diagnosis taken from the records and from at least 3 IOP measurements), irrespective of the condition of the fellow eye; 2) having more than one 48-hour phasing of IOP during the day and an IOP measurement at night in supine position (with a time-difference between both IOP profiles of a minimum of 6mo); 3) more than three visual field examinations, Heidelberg retina tomograph (HRT) analyses and optic disc photographs per eye available. Both eyes were evaluated individually. The adjustment of anti-glaucomatous treatment was admissible. Basically, although not presented in this study, in case of unmet target IOP, medical treatment was intensified. We excluded patients with ocular hypertension, pseudoexfoliative syndrome/glaucoma, pigment dispersions syndrome/glaucoma, juvenile glaucoma, and myopia of more than -6 D. Lens status was not considered in this study. We also excluded investigations with bad quality findings in visual field analyses (fixation loss, false positive/negative rate of ≥30%) or HRT SD≥50 μm]. We considered 137 eyes of 75 patients with NTG, independently from therapy regimen.

The following methods, especially the device settings, had been used in a similar way in a previously published study[18].

The 48-hour IOP Profiles Goldmann applanation tonometry was used during diurnal and the handheld Perkins applanation tonometer (both Haag-Streit Diagnostics Holding AG, Switzerland) for the night time measurements in supine position. During the 48-hour profiles IOP was measured twice at 8:00 *a.m.*, 2:00 *p.m.*, 6:00 *p.m.*, 9:00 *p.m.*, and 12:00 *a.m*. The overnight IOPs were measured in supine position. Ten IOP readings in each IOP profile (5 timepoints per day; each profile lasted two days) were analyzed. We computed IOP fluctuation, maximum, and mean. By defining the IOP fluctuation as SD, it represents a robust value, by taking into account the number of readings, and it is less affected by outliers compared to range[5]. The amount of short-term IOP fluctuation was calculated by the SD within the first pressure profile, and long-term IOP fluctuation was calculated by the SD of the mean over each of the available pressure profiles.

Diagnostic Devices Either an Octopus 101 unit (Haag-Streit Int. AG, Switzerland), or a Humphrey Field Analyzer (HFA) II 750i (Carl Zeiss Meditec AG, Germany) was used for the visual field. The programs used were 30-degree Octopus G1, HFA 24-2 SITA-Standard, or HFA 30-2 SITA-Standard. Always the same unit and program were used for one patient.

To inspect the optic nerve head three-dimensionally, HRT III (Heidelberg Engineering GmbH, Germany) was performed.

All patients received mydriatic fundus photographs of the optic disc by a Carl Zeiss fundus camera (type FF450 plus iR).

Optical coherence tomography (OCT) imaging (Spectralis OCT, Heidelberg Engineering GmbH, Germany) to measure the peripapillary retinal nerve fibre layer (RNFL) was performed in some but not all patients. The evaluated OCT data was utilized for a sub-group analysis (n=38 eyes), if at least two OCTs per eye were available. Segmentation of RNFL and its thickness determination were facilitated by Heidelberg Eye Explorer (HEYEX, version 1.9.14.0). Quality control of all segmented peripapillary OCT scans were carried out manually by a board-certified ophthalmologist (Hopf S), and the results were revised by a glaucoma specialist (Hoffmann EM). There was no disagreement between the graders in the subgroup-analysis, and no decentered scan, but two eyes were excluded for segmentation errors.

Definition of Normal Tension Glaucoma Progression The evaluation of progression as reproducible deterioration (at least one confirmation) in visual field (based on 2 baseline and 2 further visual field examinations), HRT, or optic disc photographs was performed by two graders: one inexperienced examiner (Schwantuschke D), trained on a data set of 20 visual fields, photographs, and HRT each, and an experienced examiner (glaucoma specialist, Hoffmann EM). Both graders classified progression into “suspect” progression (progression confirmed once), “possible” progression (progression confirmed twice), and “confirmed” progression (at least three confirmations, on the basis of 6 visual fields). In case of discrepancies, the experienced evaluator decided on the rating.

Visual field progression was defined as: reduction in sensitivity on the pattern deviation plot, either in at least one test point location with $P<0.5\%$, or in more than one test point location with $P<1\%$, or in at least three test point locations with $P<5\%$. The upper and lower rows of the physiologic blind spot were factored out of the assessment[18]. Analyzing of the visual fields with regard to the formation of clustered points and longitudinal comparing of the mean defect/deviation were applied[19].

To evaluate structural progression of rim thinning in the HRT III, we analyzed the stereometric parameters and the topographic change analysis (TCA). Changes between single scans from follow ups to baseline were detected in the superpixel analysis in a test-retest approach. Repeated deviation confirmation was flagged as "depression" in the report.

On the stereophotographs of the optic disc, progression was to be interpreted as either diffuse or localized neuroretinal rim loss, or change of the position of the vessels at the optic disc, or development of a notch/pit, optic disc hemorrhage, or incident pallor (diffuse or localized).

For the subgroup-analysis of the OCT data, the eyes were classified as having OCT progression, if peripapillary RNFL thickness exhibited a significant trend for thinning (negative slope) over time.

Statistical Analysis We used Statistical Package for Social Sciences (SPSS) for the analysis. Data analysis included descriptive statistics, and analysis of risk factors of patients' general characteristics at baseline using Chi-square test and exact Fischer test. For each general variable and for each investigated IOP parameter [mean, fluctuation, and maximum of the first IOP profile (short-term) and of all available IOP profiles (long-term)], we used univariate Cox-regression to evaluate their contribution to NTG progression. Multivariate cox-regression models tested five risk factors (age, sex, myopia of more than -3 D but no more than -6 D, mean defect/deviation of more than 3.98 dB in the first visual field, and cup-to-disc-ratio ≥0.7 by HRT at baseline) and one short-term and long-term IOP parameter (fluctuation, maximum, or mean). To determine the progression-free time and ratio, we used a Kaplan-Meier analysis. We adjusted for dependency between eyes of patient. The IOP parameters of patients with progression was compared with those without progression using a Mann-Whitney *U* tests.

RESULTS

Data of 137 eyes of 75 NTG patients (63.5% female) with a mean age of 63.3y (range 28-82y) were analyzed. The evaluation of NTG progression was based on 528 48-hour IOP profiles, 1129 visual fields, 564 HRT measurements, 621 optic disc photographs, and 148 OCTs with reliable quality. Table 1 displays the characteristics of the study population.

Table 1 Characteristics of the NTG study population

Variable	NTG study population
No. of subjects (*n*)	137 eyes of 75 patients
Female/male (%)	63.5/36.5
Age (y, mean±SD)	63.3±11.0
Baseline IOP (mm Hg, mean±SD)	13.3±2.7
Follow-up period (mo, mean±SD)	37.6±18.0
Progression (by visual fields or HRT or optic disc photographs) (*n*; %)	46; 33.6
Confirmed progression (at least three confirmations, 6 visual fields) (*n*; %)	28; 20.4 (6.5% confirmed progression per year)

NTG: Normal tension glaucoma.

Overall progression occurred in 46 included eyes (this corresponds to a progression rate of 33.6%) with at least one single confirmation ("suspect" progression) within a follow-up period of 37.6mo in average (SD 18). The total rate of confirmed progression (≥3 confirmations) was 20.4% (28/137).

Risk Factors for Normal Tension Glaucoma Progression None of the investigated general characteristics at baseline (sex, myopia, glaucoma in family history, central corneal thickness ≤520 μm, mean defect/deviation ≥3.98 dB, cup-to-disc-ratio ≥0.7 in the HRT, migraine, arterial hyper- and hypotension, and autoimmune disease) were significantly more frequent in the progression group than in the group without progression (Chi-square test/exact Fischer test). Circulatory disorders (peripheral vascular diseases) were more frequent in eyes without progression, but the total number was too low to draw conclusions

Myopia (HR 0.484; 95%CI: 0.2-1.0; $P=0.063$) and age were identified as risk factors for NTG progression in the univariate Cox-regression of the time independent variables [sex, age, central corneal thickness, myopia (SE more than -3 D), arterial hypertension, vascular disorder, migraine, mean defect/deviation (≥3.98 dB), cup-to-disc-ratio ≥0.7 per 0.1]. The risk for progression rose about 4% per year of life (HR 1.036; 95%CI: 1.01-1.07; $P=0.016$; Table 2). The hazard ratios (HR) of the time dependent IOP parameters showed values above 1 for all parameters (Table 3), but without significant *P*-values.

Univariate Cox-regression analyses showing the HR for time independent variables as relative risks for progression with the corresponding 95%CI and *P*-values.

Multivariate Cox-regression analysis revealed that none of the investigated parameters were predictive of NTG progression (Table 4). Age and myopia were not risk factors for progression in these models.

Diagnostic Devices and Progression-Free Interval Visual field progression was identified in 73.9% (36 of 46 cases). Less frequently, HRT (30.4%, 15 cases) and optic disc photographs (19.6%, 8 cases) detected progression (Figure 1). The optic disc OCT data based sub-group analysis with a

Table 2 Univariate Cox-regression for NTG progression (general characteristics) *n*=137

NTG	HR	95%CI	*P*
Sex (female)	1.318	0.720-2.412	0.371
Age	1.036	1.007-1.065	0.016
Myopia	0.484	0.225-1.040	0.063
Family history for glaucoma	0.573	0.255-1.286	0.177
Arterial hypertension	1.141	0.613-2.125	0.677
Circulatory disorder	0.212	0.065-0.688	0.010
Migraine	0.766	0.269-2.182	0.617
Central corneal thickness <520 μm	1.067	0.590-1.930	0.830
Mean deviation (dB) at baseline	1.035	0.977-1.097	0.237
Cup-to-disc-ratio at baseline	3.038	0.664-13.900	0.152

NTG: Normal tension glaucoma.

Table 3 Univariate Cox-regression for NTG progression (IOP parameters) *n*=137

NTG	HR	95%CI	*P*
Short-term mean	1.026	0.876-1.201	0.753
Short-term fluctuation	1.081	0.766-1.525	0.657
Short-term maximum	1.011	0.912-1.121	0.833
Long-term mean	1.026	0.876-1.201	0.753
Long-term fluctuation	1.026	0.876-1.201	0.753
Long-term maximum	1.011	0.912-1.121	0.833

NTG: Normal tension glaucoma.

Table 4 Multivariate Cox-regression analysis *n*=137

NTG	HR	95%CI	*P*
Mean			
Age	1.027	0.993-1.062	0.125
Sex (female)	0.972	0.506-1.784	0.933
Myopia	0.455	0.161-1.353	0.139
Mean deviation (dB)	1.066	1.001-1.135	0.047
Cup-to-disc-ratio	3.530	0.598-20.839	0.164
Short-term mean	1.217	0.916-1.618	0.175
Long-term mean	0.923	0.659-1.292	0.639
Fluctuation			
Age	1.027	0.997-1.063	0.120
Sex (female)	1.080	0.573-2.033	0.813
Myopia	0.638	0.248-1.638	0.350
Mean deviation (dB)	1.062	0.996-1.133	0.067
Cup-to-disc-ratio	4.573	0.818-25.572	0.083
Short-term fluctuation	1.057	0.752-1.485	0.751
Long-term fluctuation	0.983	0.628-1.539	0.940
Maximum			
Age	1.027	0.992-1.063	0.136
Sex (female)	1.068	0.567-2.009	0.839
Myopia	0.571	0.221-1.474	0.247
Mean deviation (dB)	1.064	0.997-1.135	0.062
Cup-to-disc-ratio	3.989	0.694-22.919	0.121
Short-term maximum	1.090	0.944-1.259	0.242
Long-term maximum	0.946	0.814-1.100	0.473

NTG: Normal tension glaucoma.

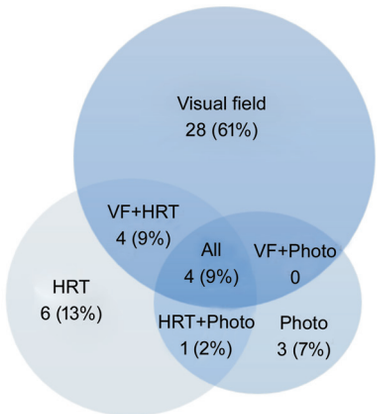

Figure 1 Venn diagram of the diagnostic device for progression detection VF: Visual field; HRT: Heidelberg retinal tomography.

response rate of 26.3% (*n*=36/137 eyes) revealed progressive reduction (negative slope) in peripapillary RNFL thickness over time in 8 out of 36 eyes (22.2%), using one confirmation for progression definition; 28/36 (77.7%) remained stable. Out of the 8 progressed eyes, 5 eyes exhibited progression by OCT alone, and not by HRT.

The interval without progression was 60mo (95%CI: 60, 65) in average. The 5-year persistence ratio without progression was 58.2% (SD 6.5), and 75% were progression-free during 43mo. The 5-year persistence ratio without visual field progression was 67.7% (SD 5.8).

IOP Measurements in the Study Population The progression eyes showed a higher average IOP, maximum IOP (*P*=0.054) and IOP fluctuation at the initial visit and these results could not be proved in the long-term analysis (Table 5).

DISCUSSION

The role of IOP parameters, especially fluctuation, and further demographic and ocular factors on NTG progression was investigated in this retrospective longitudinal study. The main results were that neither the scope of IOP fluctuation over short and long periods, nor other potential ocular, demographic, and health factors we investigated, were predictors for NTG progression.

The literature is controversial on the role of short- and long-term IOP fluctuation. While Kim *et al*[17] found no effect of short-term fluctuation on progression in NTG, the use of a time-adjusted model revealed long-term fluctuation being a risk factor. Data from the Advanced Glaucoma Intervention Study showed that long-term IOP fluctuation in patients with low mean IOP was associated with visual field progression[11]. Another study showed that long-term IOP fluctuation is associated with NTG progression[20]. Fast-progressors had larger IOP fluctuations (defined as SD) than slow-progressors. In contrast, our data showed, that neither short-term nor long-term IOP fluctuation had impact on progression. The progression *vs* no progression groups differed slightly within

Table 5 IOP profile parameters in NTG *n*=137, mm Hg

NTG	Progression (*n*=46)	No progression (*n*=91)	*P*
Short-term IOP profile			
Mean±SD	13.5±1.7	13.2±1.6	0.447
Maximum±SD	17.5±2.6	16.7±2.4	0.054
Fluctuation±SD (within the first pressure profile)	2.4±0.9	2.2±0.8	0.123
Long-term IOP profile			
Mean±SD	12.7±1.6	12.8±1.2	0.771
Maximum±SD	18.9±2.9	18.5±2.6	0.416
Fluctuation±SD (over each pressure profile)	1.5±0.9	1.4±0.7	0.949

SD: Standard deviation; NTG: Normal tension glaucoma.

the short-term interval (2.4 *vs* 2.2 mm Hg), but not in the long-term IOP parameters.

Sawada *et al*[8] reported short-term IOP mean but not IOP fluctuation to be strongly associated with visual field defect development in 130 eyes over 5y with preperimetric NTG. Interestingly, in our NTG cohort, IOP mean was not a risk factor for progression.

IOP fluctuation may change after glaucoma surgery such as trabeculectomy[21-22]. Despite lowering IOP surgically to 10 mm Hg, long-term IOP fluctuations (above 2 mm Hg) may be associated with visual field progression. This was shown by Hong *et al*[21] reporting this phenomenon after triple procedures (including cataract surgery and trabeculectomy). Our results on short-term IOP fluctuations were above 2 mm Hg, and below it in the long-term perspective. Moon *et al*[3] investigated 24-hour IOP measurements of NTG with different optic disc phenotypes. They found differences in their range (peak minus trough), which was 4 *vs* 2 mm Hg in the focal ischemic group *vs* myopic glaucomatous group (*P*=0.013). Progression data were not investigated.

In our study, baseline maximum IOP was higher in patients with progression than without progression (*P*=0.054), but not significant in the regression models. Similarly, a greater diurnal IOP at baseline was associated with greater probability of disease progression in low-teens NTG (<12 mm Hg) in a recent study by Baek *et al*[16].

Although we could not find an impact of myopia on progression in NTG respecting the fluctuation we measured, Lee *et al*[23] reported that in myopic NTG eyes, IOP fluctuation was associated with progression, while it was not in their non-myopic cohort with NTG.

We found "confirmed" progression in 20.4% (28/137) within 38mo of follow-up (6.5% per year). This is slightly higher than in a recent study from Baek *et al*[16] reporting that pretreated NTG eyes (with IOP below 12 mm Hg) showed progression in 36 patients (35%) during an average of 8.7y (4.1% per year). Sung *et al*[24] found a progression rate of 28% in NTG during 6y of follow-up (4.7% per year). Data from the preceding CNTGS showed comparable results with 12% (8/66) progression in treated NTG eyes and 27% (21/79) in untreated eyes within 7y[25]. Visual field testing is basically the device for determine progression by which other instruments are measured. Perimetry detects progression at a greater rate, than HRT or OCT, likewise in our cohort, especially in eyes with advanced NTG[26].

This study was based on a large dataset with a high number of examinations, similar to those in large multicenter studies. By targeting one type of glaucoma makes our study more valuable than studies including all types of glaucoma. Yet, several limitations need to be discussed in this retrospective study. The study underlies a selection bias, as not all patients with NTG receive 48-hour IOP phasing several times. Since IOP fluctuation was measured every 4h in the present study, the time between the measurements is not represented in the data. Contact lens sensors measuring continuous variables of IOP might provide more accurate data on fluctuation. The device Triggerfish™ uses the change in corneal curvature as a measure of change in IOP. However, up to now, the Triggerfish contact lens does not provide IOP data but particular units that might reflect IOP values and its usefulness has to be considered in further studies[27-29].

In addition, our clinical cohort was heterogeneous regarding the spectrum and adjustment of anti-glaucomatous therapy. Since this study has been designed as a real-life study, no restrictions regarding medical therapy modification to prevent further progression was allowed. Blood pressure measurements over 24h were not available, and OCT was not obtainable for each patient at the recruitment phase, which affects the total rate of progression. The grading of progression was without masking, and performed by two graders, without individual test-retest procedure or inter-observer reliability testing.

The scope of IOP fluctuation, mean, and maximum we studied regardless therapy regimen did not have a significant impact on NTG progression in our study. Appropriate glaucoma treatment pursuant to the outcomes of frequently performed pressure profiles and close controls (every three months) might

have contributed to low fluctuations. Our analysis of risk factors revealed that none of the investigated demographic, general health and ocular parameters were associated with NTG progression. Low fluctuations in this study have pointed to pressure control, eventually facilitated by the close follow-ups. As functional changes were most likely, NTG should be monitored with visual field testing more often than with other devices (HRT, OCT, optic disc photograph). We would endorse a long-term study to consider therapy status and vascular glaucoma aspects besides IOP parameters in NTG.

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