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Diurnal IOP fluctuation: not an independent risk factor for glaucomatous visual field loss in high-risk ocular hypertension.

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Title page

Title:

Diurnal IOP Fluctuation – Not an Independent Risk Factor for Glaucomatous Visual Field
Loss in High Risk Ocular Hypertension

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Abstract

Purpose: To study whether intraocular pressure (IOP) fluctuations contribute to the risk of developing glaucoma in patients with high-risk ocular hypertension.

Methods: Ninety patients included in the Malmö Ocular Hypertension Study were examined every 3 months with office hour diurnal tension curves and computerised perimetry. Patients were followed prospectively for 10 years or until glaucomatous visual field loss could be demonstrated. Post-study data was included in the analyses, extending maximum follow-up to 17 years.

Results: After 17 years 37 patients had developed glaucomatous visual field defects. When applying univariate Cox regression analyses, mean IOP of all measurements during the prospective part of the study was a significant risk factor for developing glaucoma (95% confidence interval (CI): 1.08 —1.39), while IOP fluctuations were almost significant (95% CI: 0.98—1.93). When separating effects of mean IOP level and mean IOP fluctuation using Cox multiple regression analysis, only IOP level came out as significant (95% CI: 1.09–1.38), and IOP fluctuations did not contribute to the risk (95% CI: 0.80—1.60). IOP fluctuation depended linearly on IOP level (p<0.0001), i.e. IOP fluctuation was larger in eyes with higher IOP levels

Conclusion: IOP fluctuations were not an independent risk factor for the incidence of glaucomatous visual field loss in subjects with ocular hypertension.

Introduction

Increased intraocular pressure (IOP) is a well-known risk factor for development of glaucoma

[17] and also for glaucoma progression [14]. IOP is a dynamic parameter, i.e. IOP values and

measurements fluctuate during the 24 hours. Fluctuations of IOP have been the subject of

many studies, but most describe diurnal patterns of IOP. Maslenikow [21] was one of the first

in 1904. Much later Duke Elder (1952) reported that diurnal variation seldom exceeded 5

mmHg in healthy subjects [9]. This finding was confirmed by Drance (1960), who also

showed that a majority of untreated glaucoma patients had IOP fluctuations larger than 5

mmHg [7]. At that time increased IOP fluctuations were thought of as an indicator of early

glaucoma [8, 18], although it was also known that IOP fluctuations are proportional to IOP

levels [19, 24], i.e. that patients with higher IOP also have larger IOP variation. Later, De

Vivero and co-workers (1994), could not demonstrate higher IOP variation in normal tension

glaucoma patients than in normal subjects [6]. Today reports are available, where the effects

of IOP level and IOP fluctuations as risk factors for glaucoma and glaucoma progression have

been separated. Asrani et al. reported that increased IOP fluctuations, as revealed by diurnal

tension curves using home tonometry, increased the risk for glaucoma progression [2]. Only

patients with IOP < 24 mm Hg during follow-up were included in the analysis. In a study by

Ishida and co-workers [16] results depended upon which criteria for visual field progression

that were applied. In the study by Daugeline et al 1999 [5] IOP variability was not an

independent risk factor. Both the latter studies included patients with normal tension

glaucoma only.

Effects of IOP fluctuations on visual fields have also been studied in glaucoma patients with

elevated pressures. Smith (1985) found that diurnal fluctuations were as large in patients with

elevated IOP without field loss as in glaucoma patients with field defects [25], while Bergeå

et al. (1999) [4] reported that glaucoma patients with smaller IOP variations progressed less often than those with larger variations. In a longitudinal study of patients with ocular hypertension Gonzales and co-workers (1997) reported that increased IOP variation at one baseline diurnal tension curve was a risk factor for development of glaucomatous field defects using manual perimetry [10].

A couple of studies, reporting IOP fluctuations to be an independent risk for glaucoma and glaucoma progression [2, 4] have analyzed IOP measurements obtained at different times, e.g. baseline IOP fluctuations and follow-up IOP levels, or vice versa. This approach is less than optimal to determine whether IOP fluctuations are an independent risk factor, i.e. whether they predict future risk better than the IOP level itself, e.g. mean IOP.

The alleged proof for IOP fluctuations as an independent risk factor for glaucoma or glaucoma progression is thus rather weak. Despite this, increased diurnal fluctuation is frequently referred to as an important risk factor for glaucoma progression, e.g., in printed and web based material provided by the drug industry.

Our aim was to study the effect of IOP fluctuations on the incidence of glaucomatous visual field loss in patients with ocular hypertension, who were prospectively followed with diurnal office hour tension curves and computerized perimetry every 3 months for up to 10 years, and subsequently followed for a maximum of 17 years as clinical patients. We wanted to separate the effects of IOP variations and IOP level, in order to study whether IOP fluctuations were an independent risk factor.

Subjects and Methods

The prospective study

Ninety patients with ocular hypertension were included in the prospective Malmö Ocular

Hypertension study. Detailed inclusion criteria have been published before [11, 3], but briefly

patients had to have an untreated IOP ≥ 22 mm Hg, defined as the mean of three

measurements with the Goldmann tonometer at, 8.00 11.30 and 15.30 hours, and normal

visual fields. Prior to inclusion, visual fields were tested with static threshold computerised

perimetry with the Competer perimeter [12] and with peripheral and nasal mid-peripheral

kinetic testing on the Goldmann perimeter. At least one additional risk factor was required for

inclusion: suspect disc topography or disc haemorrhage, positive family history of glaucoma,

pseudo-exfoliation or pigment dispersion syndrome, diabetes, or mean IOP of ≥27 mm Hg on

the baseline diurnal tension curve.

Patients were recruited consecutively between 1981 and 1987, and gave informed consent to

participate. The tenets of the declaration of Helsinki were followed and the study was

approved by the Ethics Committee of the Medical Faculty of Lund University.

The study was designed as a randomized, prospective, double masked trial comparing topical

timolol treatment with placebo treatment. Patients were prospectively followed every 3

months in the study for 10 years or until they reached the outcome, which was development of

reproducible glaucomatous visual field loss. Some patients also left the prospective study

because of: mean IOP ≥35 mmHg, appearance of non-glaucomatous visual field defects

caused by neurological or retinal conditions, dense cataract, adverse reactions, systemic ß-

blocker treatment, serious illness, or because they wished to withdraw. Detailed information

about attrition has been published before [11]. These patients were included in the

retrospective follow-up part.

All patients underwent diurnal Goldmann tonometry (8.00 11.30 and 15.30 hours),

computerized threshold perimetry with the Competer perimeter, disc photography and a

general eye examination at each visit every three months while being followed in the

prospective part of the study. During this part 22 patients developed visual field defects,

defined as reproducible clusters of depressed test point locations as compared to the mode

value of the test. Seven patients died and 3 were lost to follow-up.

The retrospective follow-up part

Also after leaving the prospective part of the study all living patients, but the 3 lost for follow-

up during the prospective part, were followed at our department.

For the purpose of this paper, all available post-study patient records were searched except

those of patients who had developed reproducible glaucomatous field loss, had been lost to

follow-up, or died during the prospective part of this study. Throughout the post study phase

most patients were changed from computerized threshold perimetry on the Compter perimeter

the to the 30-2 Full Threshold test of the Humphrey Field Analyzer 640 (Carl Zeiss Meditech,

Dublin, CA, USA). Thus, those patients who developed glaucoma field loss, defined as

reproducible cluster of significantly depressed points in pattern deviation probability maps

[15], during the retrospective follow-up part were examined with the Full Threshold program

of the Humphrey Field Analyzer.

IOP parameters

All IOP data included in our analyses were those collected using diurnal tension curves during the prospective part of the study. Individual levels of IOP were computed in different ways:

1. as the mean of all measurements

2. as the mean of the maximum IOP measurement of each diurnal tension curve

3. as the mean of a randomly chosen value of the three IOP values of each tension curve

Individual IOP variation was also computed in different ways:

1. as the mean of the range of each diurnal tension curve

2. as the maximum range in all tension curves

3. as the difference between the lowest and highest IOP values measured during the whole prospective part of the study

All analyses were based on patients rather than eyes. When both eyes of a patient were eligible, the first eye to reach the outcome was included in the analyses. When visual field remained normal, one eye was randomly selected.

Statistical analyses

Univariate Cox regression analyses were performed to evaluate the different parameters of IOP levels and IOP variability as risk factors for developing glaucomatous visual field defects. A multivariate Cox regression analysis was performed to evaluate the simultaneous effect of IOP fluctuations and IOP level. All Cox analyses were performed using treatment group, timolol or placebo, as a stratification variable, i.e. effects of treatment on IOP were controlled for.

Results

Fifty-two females and 38 males were included in the study. Mean age at baseline was 62

years, ranging from 48 to 79. Including post study data increased follow-up time from up to

10 years to a maximum of 17.5 years. Mean follow-up time was 8.5 years. Forty-four patients

were randomised to treatment with placebo and 46 to timolol. Thirty-seven patients developed

reproducible glaucomatous visual field defects, 18 initially randomised to timolol , and 19 to

placebo. The mean follow-up IOP was 22.7 mmHg ranging from 15.3 to 33.0, and mean IOP

fluctuations, calculated as the mean diurnal range, was 3.7 mmHg ranging from 2.0 to 8.2.

Using univariate analyses all parameters describing IOP level came out as highly significant

risk factor*s*, Table I. The risk for developing glaucoma increased with slightly more than 20%

for each mmHg of pressure. Mean IOP of all measurements showed somewhat higher risk

than mean of the maximum or of a randomly chosen IOP value from every tension curve.

Table I
Cox univariate analyses – different parameters for IOP level

Explaining variable	risk	95% confidence interval	p-value
Mean of all IOP measurements	1.226	1.08 – 1.39	0.0013
Mean of maximum IOP	1.203	1.07 – 1.36	0.0027
Mean of random IOP	1.216	1.08 – 1.38	0.0017

When analysing IOP fluctuations using univariate models, the mean of the daily range came

out as an almost significant risk factor (p=0.063), Table II. The highest daily range and the

highest total range was not associated with any increase of risk.

Table II
Cox univariate analyses – different parameters for IOP variability

Explaining variable	risk	95% confidence interval	p-value
Mean of daily range	1.379	0.98 – 1.93	0.063
Maximum of all daily ranges	1.039	0.91 – 1.19	0.577
Range between minimum and maximum IOP of all measurements	1.021	0.95 – 1.09	0.56

When applying a multivariate analysis including both IOP level and IOP fluctuations, only

mean IOP came out as a significant risk. Thus, the effect of IOP fluctuations was non-

significant (p=0.49), when separated from IOP level using multivariate analysis, Table III.

Table III
Cox multivariate analysis – IOP level and IOP variability

Covariates	risk	95% confidence interval	p-value
Mean of all IOP of all measurements	1,209	1.09-1.38	0.005
Mean of daily range	1.13	0.80-1.60	0.49

Discussion

In this group of patients with high risk ocular hypertension, IOP fluctuations were not an

independent risk factor for glaucoma development. Mean IOP was a strong and highly

significant risk factor both in uni- and in multi- variate analyses, while IOP fluctuations were

almost significant but only when IOP level not was taken into account. These results could be

explained by the dependence of IOP fluctuations on IOP level; IOP fluctuations increased

with 0.17 mmHg for each mm increase in IOP level (linear regression analysis p<0.0001).

Thus, IOP fluctuations were proportional to mean IOP, Fig.1.
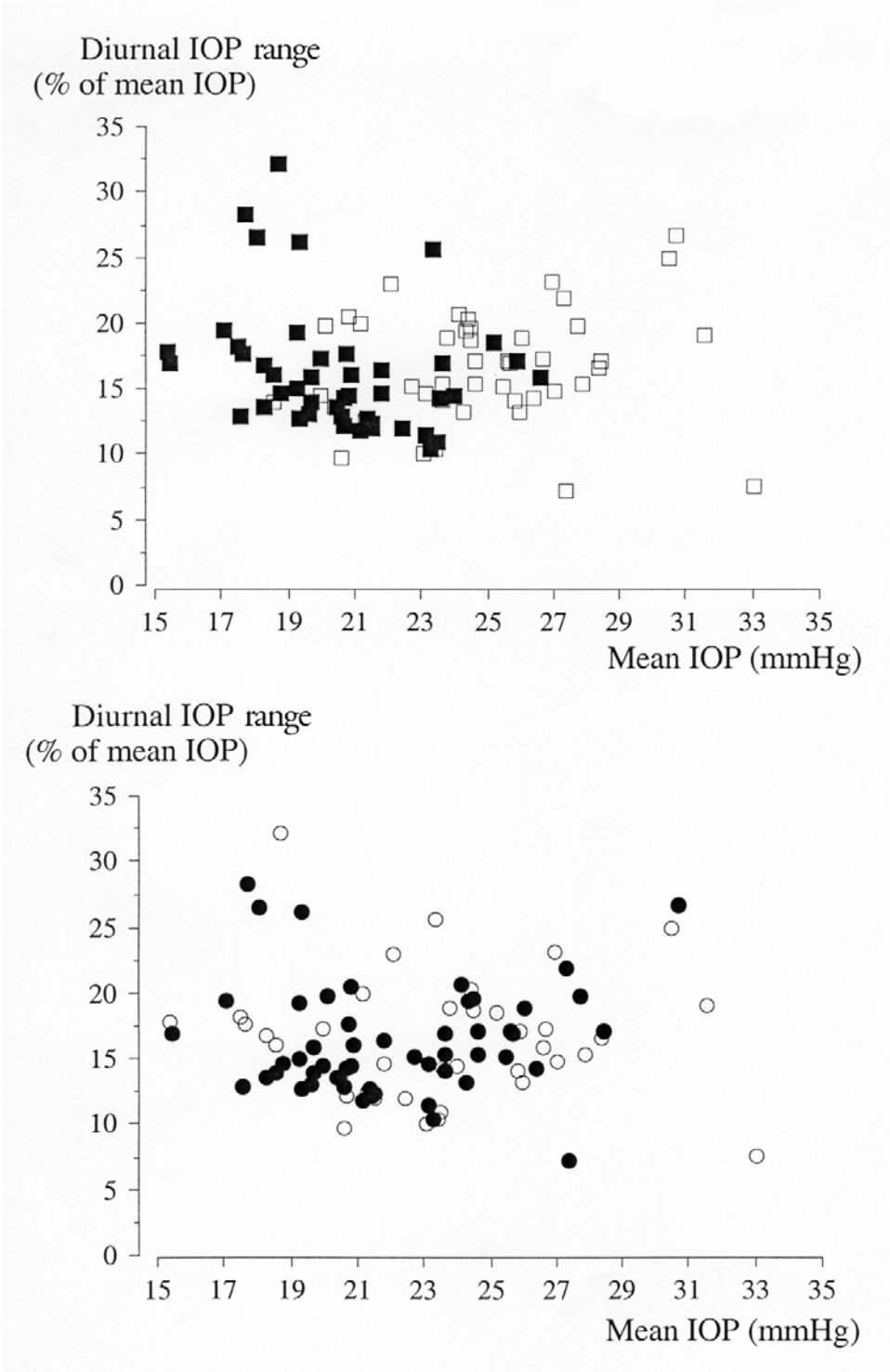
Fig.1 IOP fluctuations as percentages of mean IOP. Fluctuations relative to IOP level are of similar magnitude all over the range of mean IOP values. Top: filled symbols indicate timolol treated patients; open symbols indicate placebo treated patients. Mean IOP was lower in the timolol group, but fluctuations were similar among timolol and placebo treated patients. Bottom: filled symbols indicate patient who developed glaucomatous field defects; open

symbols indicate patients with no visual field defects after 17 years of follow-up. IOP

fluctuations were similar in the two groups.

Gonzales and co-workers [10] found that IOP fluctuations were a significant risk factor for

glaucomatous visual field defects in patients with ocular hypertension. They compared

development of field loss in two groups of patients: one with IOP fluctuations > 5mmHg and

another with such fluctuations ≤5 mmHg at a baseline tension curve. Thus, the importance of

IOP level was not considered at all. Our univariate analysis also suggested that increased IOP

fluctuations may be a risk factor, but when taking IOP level into account IOP fluctuations lost

importance totally.

Most studies have looked at IOP fluctuations as a risk factor for progression of glaucomatous

visual field loss. Such progression may be more difficult to estimate than onset of

glaucomatous damage because of the much larger perimetric test-retest variability in diseased

eyes as compared to normal ones. Different criteria for field progression could then yield

different study results. Thus, Ishida and co-workers found that increased IOP fluctuations was

a risk for visual field progression when defining progression as pointwise deterioration of

threshold values, but not when defining progression as deterioration of the global Mean

Deviation values [16].

In our study all patients were tested with the threshold program of the computerized static

Competer perimeter during the prospective phase. During the clinical follow-up the patients

switched to the 30-2 Full Threshold program of the Humphrey Field Analyzer (Carl Zeiss

Meditech Inc, Dublin, Calif). This means that the patients who developed glaucoma during

the prospective part were diagnosed using a different instrument than those who developed

reproducible field loss during the retrospective follow-up part. We do not believe, however, that there were any important differences between the two instruments in their ability to identify repeatable glaucomatous field loss. Some early studies reported similar sensitivities and specificities between the Competer and the Octopus perimeters (Haag-Streit AG Switzerland), and between the Octopus and Humphrey Field Analyzer perimeters [13,22].

Asrani et al found that IOP fluctuations, as measured with self tonometry at home, was a significant risk factor for progression independent of IOP level [2]. This report has often been cited as the proof for variability as a risk factor for glaucoma progression. Others have pointed out, however, that the Asrani study lacked well-defined criteria for visual field glaucoma progression, and also doubts have been raised about patients' ability to perform the self tonometry making the significance of the results less reliable [26]. Further, the analysis was limited to patients with normal or only slightly increased IOP. More than 60% of the subjects originally included were excluded from the analysis because they showed IOP > 24mmHg once or more during the 5 year follow-up. The conclusions of Asrani and co-worker's study could therefore not be considered as relevant for the large majority of clinical glaucoma patients having increased IOP. The patients included in Asrani's study were quite different from the ones included our study. We included patients with increased IOP only, while such patients were excluded from the analyses in Asrani's study, hence, there is little similarity between patients analysed in the present study and their paper.

In the study by Bergeå et al. also multivariate analyses including several different IOP parameters were performed [4]. Prior to the risk analyses they carried out principal component analysis to avoid multicollinearity, i.e to avoid highly inter-correlated explanatory variables in the same model. This resulted in a number of multivariate regression models

including different IOP parameters. Two of them included IOP range, calculated in the same way as our "mean of daily range". In these two regression models IOP range was combined with: untreated baseline IOP, and with IOP change, i.e. treatment effect calculated as the difference between untreated baseline IOP and mean of treated follow-up IOP. Effects of follow-up IOP level and follow-up IOP fluctuations were not simultaneously tested in the same model. Thus, this study neither showed, nor disapprove, that IOP fluctuations were a risk factor for glaucoma progression independent of IOP level.

A recent paper by Nouri-Mahdavi and co-workers [23] reports that IOP fluctuations, calculated as the standard deviation of single IOP measurements measured at different days during the follow-up of the Advanced Glaucoma Intervention Study and analysed using multivariate technique, was a significant risk factor for visual field deterioration. Surprisingly, and in contrast with an earlier AGIS report [1], mean IOP did not increase risk for field worsening.

While the apparent differences between our results and several studies discussed above, most likely depend on whether both IOP level and IOP variability have been independently analysed in a multivariate way. We should point out that we measured IOP during office hours only. More measurements outside office hours would of course improve estimates of fluctuations, but retention was also important. It is not likely that patients would have stayed for 10 years in the prospective part of the study if we had asked them to come for measurements more than three times per day every three months. Bergeå also measured office hour curves 3 times per day[4], while the patients included in Asrani and co-workers' study [2] measured their own pressure 5 times a day, from early morning to bedtime. In this context it could be of interest to mention a more recent study by Liu and co-workers [20], where IOP

was measured every 2 hours during a 24-hour period in patients with untreated glaucoma and in age-matched healthy subjects. They found that diurnal IOP was higher in the glaucoma eyes, but that the diurnal to nocturnal IOP range was larger in the healthy eyes. This result could be interpreted as high diurnal IOP is a risk for glaucoma, but not large IOP fluctuation.

In summary in the present study IOP fluctuations were not an independent risk factor for the incidence of glaucomatous visual field loss.

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