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Retinal vessel reaction to short-term IOP elevation in ocular hypertensive and glaucoma patients

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PURPOSE. *Regulation of ocular blood flow might be impaired in glaucoma patients. We compared the reaction of retinal vessels to a short-term increase of intraocular pressure (IOP), using a retinal vessel analyzer (RVA), in normal volunteers, ocular hypertensive patients (OH) and primary open angle glaucoma patients (POAG).*
METHODS. *Ten healthy subjects (56 ± 8 years, IOP 13.7 ± 1.6 mmHg), 10 OH patients (55 ± 12 years, IOD 23.4 ± 4.1 mmHg) and 11 POAG patients (60 ± 11 years, IOP 23.3 ± 1.95 mmHg) were evaluated. Arterial and venous retinal vessel diameter was measured continuously before, during and after raising IOP to suprasystolic values by the suction cup method, described as ocular oscillo-dynamography.*
RESULTS. *The change in vessel diameter after the IOP rise differed in its temporal sequence and in absolute values depending on the group examined. In the retinal branch veins the reduction of vessel diameter during the IOP rise was significantly different in POAG (0% ± 6.7) and volunteers (-6.7% ± 8.5; p = 0.06) and in POAG and OH (-6.7% ± 7.0; p = 0.04). At 70-130 sec after IOP increase a dilatation occurred, again differing significantly in POAG (+5.8% ± 3.9) and volunteers (+9.7% ± 4.3; p = 0.03). Systemic blood pressure did not show any significant differences between groups or during the course of the examination.*
DISCUSSION. *At short-term rise in IOP leads to less retinal vessel reaction in POAG patients than in volunteers and OH. This might be due to impaired autoregulation to ocular perfusion changes in POAG patients. (Eur J Ophthalmol 2001; 11: 338-44)*

KEY WORDS. *Retinal vessel diameter, Rise of intraocular pressure, Primary open-angle glaucoma, Ocular hypertension, Autoregulation of retinal blood flow*

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INTRODUCTION

Vascular factors seem to play an important role in the pathophysiology of primary open-angle glaucoma (POAG) (1-4). Clinical studies demonstrate a relationship between systemic blood pressure drops at night and POAG (5, 6) and progression of the disease (7, 8). This is an indicator that the regulatory potential to balance changes in ocular perfusion pressure is impaired in glaucoma. Ocular perfusion pressure can be temporarily reduced by a short-term artificial increase of IOP. This can be done by different methods: scleral indentation by a spring mechanism (ophthalmodynamometer) (9), corneal indentation by an automatic sensor tonometer (10) or by an episcleral suction cup (11-13). We found the suction cup method caused the least disturbance of optical parameters when examining retinal vessel diameters dur-

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ing and immediately after an articial IOP increase. The Retinal Vessel Analyzer (RVA®) allows a continuous on-line assessment of branch retinal arteries and veins in different conditions (14-18). The instrument is especially valuable for assessing vessel diameter changes in response to stimuli, and their temporal dynamic behavior.

The present study examined whether a short-term, strong artificial IOP increase caused different reactions in the retinal arteries and veins of glaucoma patients, patients with ocular hypertension and normal volunteers.

METHODS

We evaluated the retinal vessel diameter changes in response to a short-term increase of IOP caused by a suction cup in ten normal volunteers, ten ocular hypertensives (OH) and 11 primary open-angle glaucoma (POAG) patients currently without therapy. One eye was studied in each subject. In normals and in patients with similar findings in both eyes the study eye was randomised by date of birth (even date = right eye, odd date = left eye). In OH subjects the eye with the highest IOP was chosen and in POAG patients the eye with the more advanced disease or higher IOP. The groups did not vary significantly with regard to age (normals 56 ± 8 years, OH 55 ± 12 years, POAG 60 ± 11 years). Inclusion criteria were age ≥ 18 years for all groups. Ocular hypertensives were defined as IOP repeatedly > 22 mmHg and no glaucomatous changes of optic disc and visual field. POAG was defined as IOP >21 mmHg, glaucomatous visual field changes and/or glaucomatous optic changes. Eyes in the latter group were either untreated or underwent a four-week wash-out with topical medication. Exclusion criteria were opacification of optic media, visual acuity below 20/40, astigmatism > 1.0 dpt, myopia >7.0 D, previous eye surgery or ocular trauma, contact lens wear within the last 24 hours, acute infectious disease, cardiac disease stages III and IV (NYHA), anticoagulation by coumarin or heparin-like substances, known concomitant disease with a life expectancy of less than three years, pregnancy or lactation.

Before enrollment an extensive clinical ophthalmological examination was performed, encompassing assessment of visual acuity, objective refraction, keratometry, automated perimetry (Octopus 101 program G2), slit lamp biomicroscopy, applanation tonometry and fundoscopy. During the unilateral pupil dilatation with tropicamide an oxygen-permeable hard contact lens with a refraction of ± 0 D was fitted to the study eye. Vessels were assessed with the RVA®. Intraocular pressure was raised by applying a suction cup using the Oculo-Oscillo-Dynamography device (OODG), according to Ulrich (13), following the automated examination routine.

The eye to be examined was anesthesized with oxybuprocain eye drops. The measurement protocol consisted of measuring the vessel diameter for 2 minutes without any stimulus. Then the suction cup (diameter 11 mm) was applied to the temporal side of the eye and the OODG routine started. This device produces a vacuum, which is transmitted by the suction cup to the globe, raising IOP. The rise automatically increases to suprasystolic values and then decreases slowly. The phase of suprasystolic IOP lasts 45 sec. Subsequently the retinal vessel reaction is monitored for 10 minutes.

During the whole examination period an ECG is recorded and systemic blood pressure is taken every minute. Mean systemic arterial blood pressure is calculated ($RR_{mean} = RR_{diast} + 1/3\ [RR_{sys}\text{-}RR_{diast}]$).

After each examination patients were given a questionnaire asking about discomfort during the examination (1=non discomfort, 5 = severe pain) and acceptance as a diagnostic procedure in ophthalmology (yes/probably/no).

We evaluated a venous and arterial segment approximately 1.5 mm long (Fig. 1). Within the measurement window each vessel segment is scanned 25 times/sec. The vessel edges, axis of vessel and its diameter are automatically calculated by the instrument. A mean vessel diameter was calculated from the mean value of each 10-sec portion. Because of the wide variation of vessel diameters between individuals the mean diameter resulting from baseline measurements before application of the stimulus was defined as 100%, and changes were then correlated to the baseline value. Examinations yielding a standard deviation of more than 5% for arterial measurements and 1.5% for venous measurements during the 2 minutes of baseline assessment were regarded as unusable and excluded from further analysis.

For statistical purposes means were calculated for

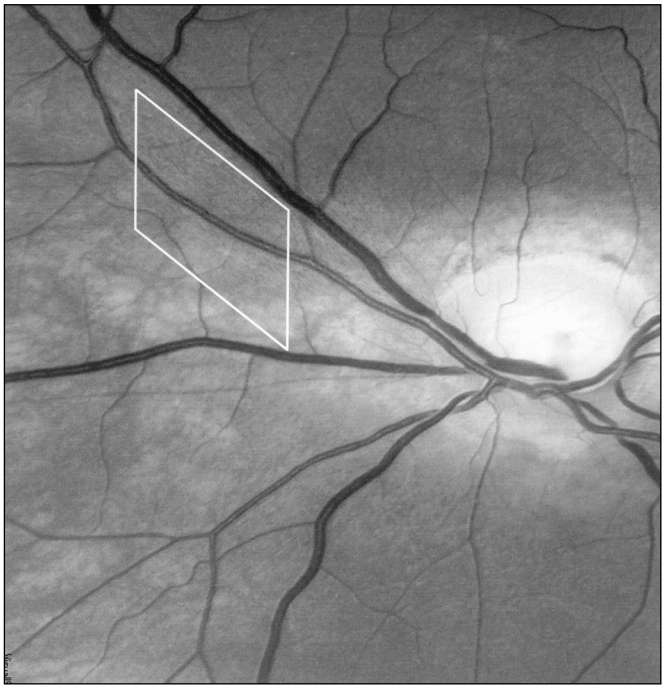

Fig. 1 - *Image of ocular fundus displaying the RVA measurement window capturing an arterial vessel segment.*

time segments (1.5 min., Fig. 2) and compared in the three groups. Each time segment had a corresponding systemic blood pressure value. Analysis of variance for repeat measurements was used, and the Mann-Whitney U-test and Wilcoxon test as non-parametric tests, because of the small number of cases at the level of significance of $p<0.05$.

The study design was approved by the ethics committee of the Medical Association of Thuringia and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All study subjects gave their informed consent prior to inclusion in the study.

RESULTS

Intraocular pressure (IOP)

IOP before and after the test protocol are set out in Figure 2. Significant differences were found between normals and POAG patients and between normals and OH patients. In all three groups there was a slight but significant reduction in IOP due to the oculopressive effect of the OODG after the IOP provocation period.

Mean systemic blood pressure

Systemic blood pressure did not vary significantly between groups at the beginning of the examination and did not change significantly during the whole period (data not shown).

Vessel reaction

Figures 2 and 3 show the reactions of arteries and veins in the three groups. In addition Figure 2 displays the absolute change in IOP regardless of oculopressive effect and the time segments used for the statistical tests. Baseline was assessed during the first two minutes. The first time frame (phase 1) shows the vessel diameter during the short-term increase in IOP. After cessation of suction the vessels dilate and second time frame (phase 2) captures the maximal dilation. Phases 3 and 4 indicate the cessation of the vessel reaction. Analysis of variance of repeated measurements showed significant differences in the mean vessel diameters at the various phases for arteries in the OH group ($p<0.03$) and for veins in all groups ($p<0.001$).

Analyzing the curves during the IOP the arteries of the normal group show less reduction in diameter than at baseline. In the OH and POAG groups dilation can already be seen starting in phase 1 (Fig. 4). These changes were not significant within groups because of widely varying individual responses. Venous diameters changed much less than arterial diameters. This was true for both inter- and intraindividual values. During the IOP rise a significant reduction in venous diameter was observed in normals and OH patients ($p<0.02$ for each group, Fig. 5). POAG patients showed no significant change from baseline. The change of diameter within phase 1 differentiates the POAG group (0% ± 6.7) from normals (-6.7% ± 8.5; $p = 0.06$) and from the OH group (-6.7% ± 7.0; $p = 0.04$). After cessation of suction, a dilatation of the arteries and veins was observed in all groups compared to baseline. During the rest of the examination period the values slowly returned to baseline. A comparison between groups found no significant differences in the amplitude of the arterial reaction in any time frame. Veins dilated less in phase 2 (70-130 sec) in the POAG group (+5.8% ± 3.9) than normals (+9.7% ± 4.3; $p = 0.03$) but during the follow-up all venous diameters returned to baseline (phases 3 and 4).

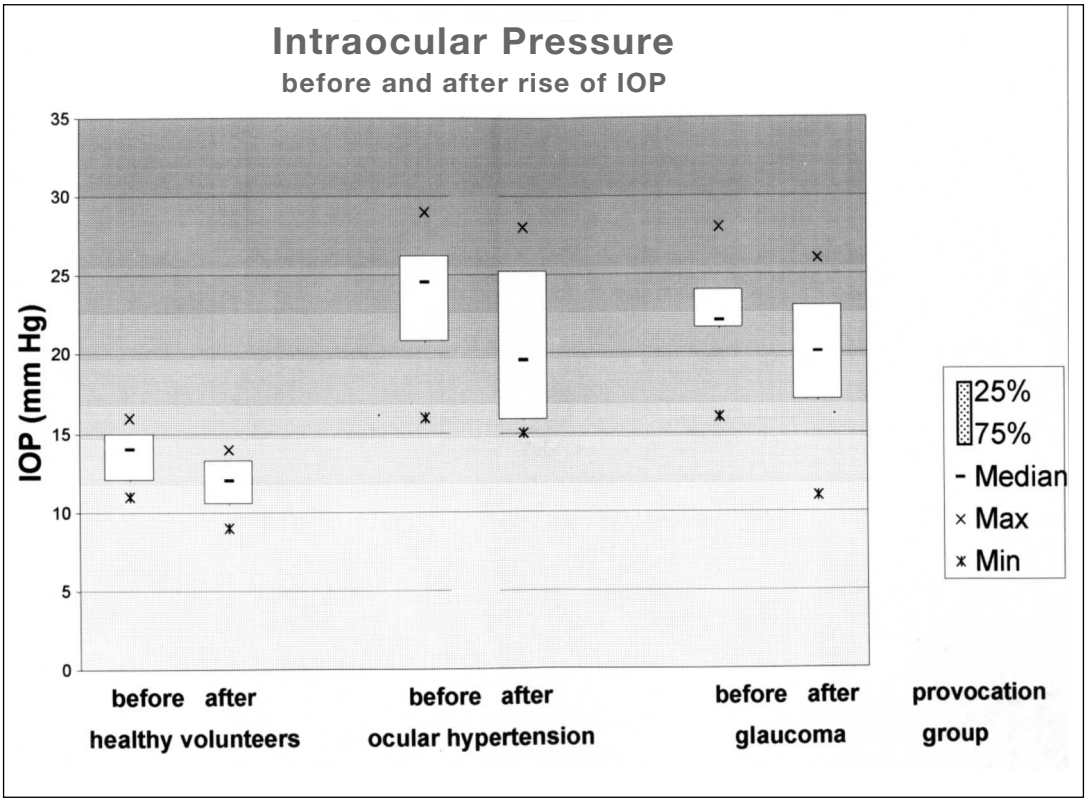

Fig. 2 - *Intraocular pressure before and after IOP provocation.*

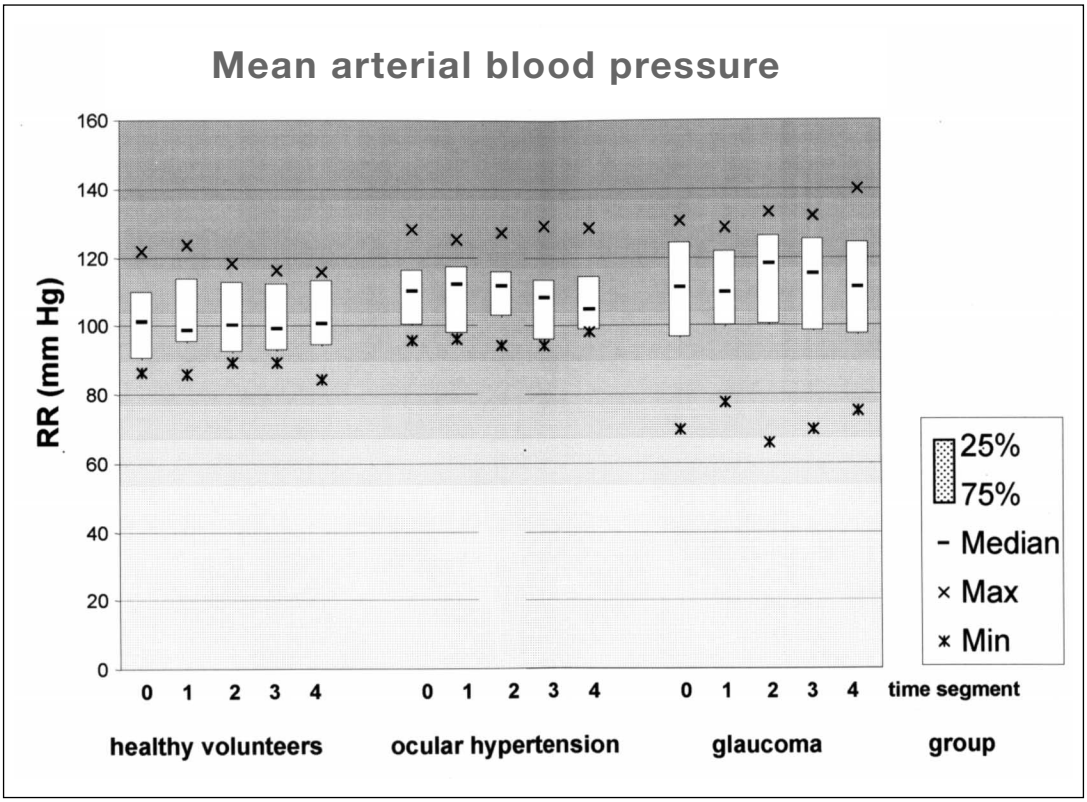

Fig. 3 - *Mean arterial blood pressure during the examination.*

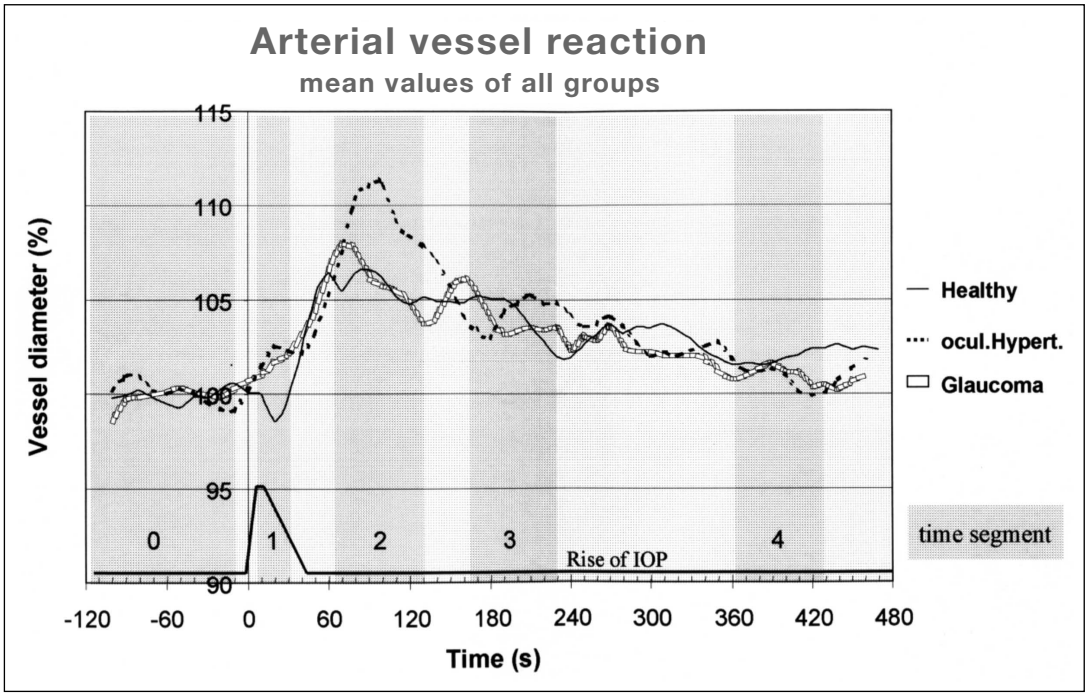

Fig. 4 - *Arterial reaction to IOP provocation.*

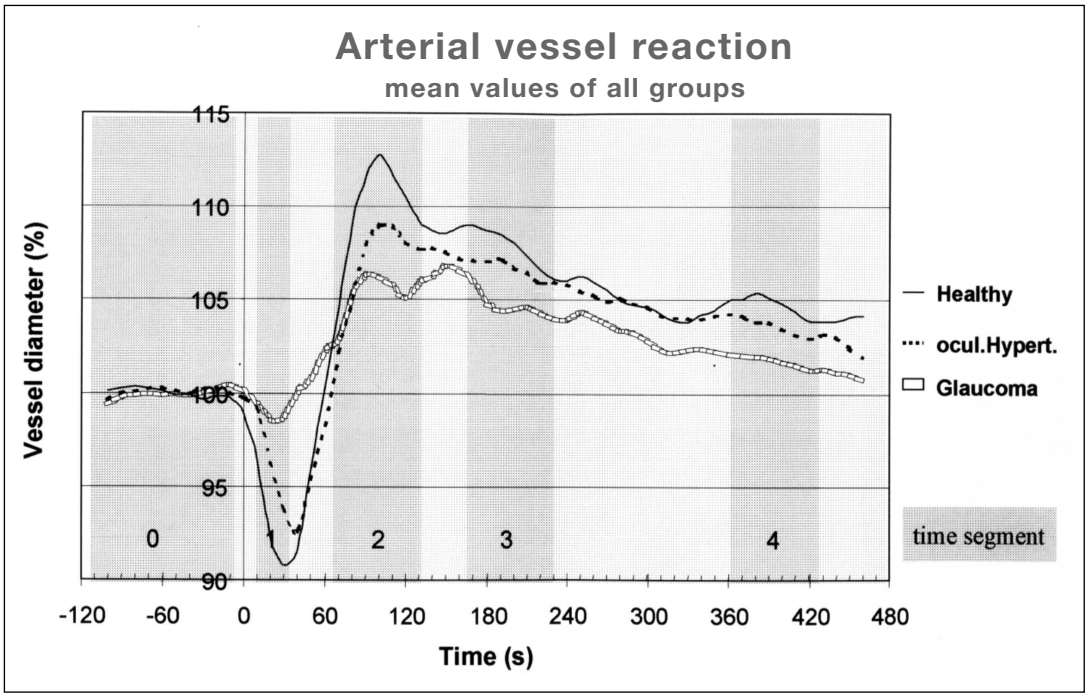

Fig. 5 - *Venous reaction to IOP provocation.*

Acceptance

All patients rated the examination set-up as acceptable (mean 1.9; max. rating 3). All eyes examined showed transient redness and slight conjunctival swelling in the area of suction cup application. All those examined said they would accept the method for diagnosis of severe ocular disease, e.g. glaucoma.

DISCUSSION

The on-line measurement of retinal vessel behavior by the RVA produces a continuous recording of the vessel diameter during the measuring period. Analyzing these curves is useful to detect trends and tendencies. Statistical analysis such as ANOVA or the Wilcoxon test needs mean values for a long period (90 sec). This reduces the number of values and the statistical power. To gain maximum information from this study one must look at the curves together with the mean values. Previous studies investigated retinal autoregulation after an artificial decrease (19) or during an artificial increase of IOP (20, 21) by a suction cup. The changes of IOP were only moderate, to establish the limits of retinal autoregulation. We used a strong short-term increase induced by the OODG to examine the reaction of retinal vessels caused by hypoperfusion, and we expected different reactions in the different groups.

Some POAG patients showed the beginning of arterial dilatation as soon as the suction cup was applied to the globe, with a small vacuum inducing a moderate IOP rise. Due to individual differences in the initial suction phase (lid and globe movements, blinking) and the resulting minor differences in the temporal reactions at the beginning of the IOP rising phase, this reaction cannot be evaluated individually or even as a group effect.

During the short suprasystolic IOP rise some arteries in some eyes collapsed and were no longer measurable by the RVA. These diameters were included as "missing values" in the calculation of mean vessel diameters even though they represent extreme cases of short-term vessel diameter reduction. During the computer-generated equal phase of IOP rise (phase 1) the mean arterial vessel diameter in POAG and OH patients did not show any reduction compared to baseline values. This was in contrast to the normal group. The venous vessel changes in phase 1 was much less obvious in POAG patients than in normals or OH patients. Possibly the difference in reaction indicates a lower retinal oxygen supply in POAG.

Immediately at the beginning of the insult to perfusion (IOP rise) vascular counterregulation is observed. The automatic examination protocol of the OODG with its inherently short IOP rise to suprasystolic values might not be the ideal stimulus. A more appropriate stimulus might possibly induce in a slower rise with longer lasting IOP provocation without reaching suprasystolic values.

The reactive phase after cessation of the short IOP increase involved vasodilation with a subsequent slow return to baseline values. This reaction is not caused by the pressure of the suction cup. Low IOP with the same systemic blood pressure values caused an increased perfusion pressure. This should be counterbalanced theoretically by ocular autoregulation, leading to vasoconstriction. However we found vasodilation in all groups. The maximal venous dilation was significantly less in the POAG group than in normals, the venous reaction being obviously retarded in POAG. We assume that POAG patients need a longer time to counterregulate the change in perfusion pressure.

Evaluation of dynamic reactions allows an assessment of the regulatory potential of different vessel segments. In this respect the behavior of arterial and venous segments proved intersting. We assume that different segments achieve different regulatory goals and functions. Less maximum dilation may also require less counterregulation as the oxygen supply in the dependent tissue is sufficient. A lower maximum of dilation in combination with a slower decrease of the dilating action is however a sign of longer-standing hypoxia. Those prolonged tissue hypoxia times may disturb the metabolism, causing irreversible damage.

The POAG group was also noteworthy because of the most widely differing individual reactions and slope changes of all three groups. This indicates the heterogeneity of the POAG group as regards their vascular reaction to identical perfusion pressure changes. Variability in POAG patients' reactions to stimuli has already been observed with other methods such as vasospastic responses to cold temperature stimuli (22) and the differentiation into carbogen responders and non-responders by means of CO_2-inhalation (23).

Our measurements of retinal vessel reactions to a short-term increase in IOP confirm that POAG patients have an impaired ability to cope with ocular perfusion pressure changes. Further examinations, especially with a moderate IOP increase, should cast further light on the pathomechanism of POAG damage, increasing our diagnostic precision and possibly enhancing our understanding of the therapeutic principles and options.

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