

# Short-term variability of systemic blood pressure and submacular choroidal blood flow in eyes of patients with primary open-angle glaucoma

Asan Kochkorov · Konstantin Gugleta ·  
Robert Katamay · Josef Flammer · Selim Orgul

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## Abstract

**Purpose** To analyse short-term variability of systemic blood pressure and choroidal blood flow in glaucoma patients, and compare them with ocular hypertensive patients and controls.

**Subjects and methods** Thirty untreated patients with primary open-angle glaucoma (POAG), 25 untreated patients with ocular hypertension (OHT) and 50 healthy controls without local therapy were included in the study. Continuous 5-minute measurements of arterial systemic blood pressure (SBP) by Finometer and choroidal blood flow (CBF) by laser Doppler flowmetry were obtained. Variability of SBP and CBF was analysed by means of coefficient of variation and analyzed in ANOVA model. Linear regression analysis was performed on parameters of morphological (nerve fiber layer thickness) and functional glaucomatous damage (visual field) on one side, and between SBP and CBF on the other side.

**Results** ANOVA model demonstrated significant differences in variability between the groups ( $p=0.003$ ); post-hoc analysis specified a significantly higher short-term variability of both the blood pressure and choroidal blood flow in POAG patients (coefficients of variation:  $3.33\% \pm 1.05\%$  and  $3.90\% \pm 2.17\%$  respectively) than in healthy controls (coefficient of variation:  $2.57\% \pm 0.80\%$  and  $2.94\% \pm 1.52\%$  respectively). No significant differences were found for OHT patients.

**Conclusions** POAG patients without local therapy demonstrate an increased short-term BP and CBF variability.

**Keywords** Glaucoma · Short-term variability · Blood pressure · Choroidal blood flow

## Introduction

Ocular perfusion pressure (OPP) is an important component in the pathogenesis of glaucomatous optic neuropathy (GON) [1]. Not only low mean ocular perfusion pressure [1–6], but also its variability play an important role in pathogenesis of GON [7–11]. Since OPP depends on intraocular pressure (IOP) and blood pressure in ocular vessels, their fluctuation could also be regarded as a risk factor for GON. Indeed, there are several studies indicating long-term and circadian IOP variability as a separate risk factor for GON [12–14]. With regard to blood pressure (BP) variability in particular, a number of studies have confirmed unstable or low BP as a factor in GON development [4, 9–11, 15, 16]. However, all observations with regard to BP refer either to so-called “night dipping” [11, 16–18] or to average low systemic BD [2, 19]. Moreover, most of the investigations dealing with ocular perfusion variability in GON patients investigated middle- and long-term ocular blood flow [8, 20–22], whereas ischemia/reperfusion damage, postulated as one of the pathogenetical mechanisms for GON [7], takes place on a shorter time scale. In line with the hypothesis that ischemia/reperfusion damage plays an important role in the pathophysiology of glaucoma, and that such damage occurs due to short-term disturbances to ocular perfusion, in our present study we analysed short-term variability of SBP and CBF in glaucoma patients, and compared them with ocular hypertensive patients and controls.

Asan Kochkorov and Konstantin Gugleta contributed equally.

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A. Kochkorov · K. Gugleta (✉) · R. Katamay · J. Flammer ·  
S. Orgul  
Ophthalmology Department, University Hospital Basel,  
Mittlerestr. 91,  
CH-4031 Basel, Switzerland  
e-mail: gugletak@uhbs.ch

## Subjects and methods

### Subjects

Consecutive primary open-angle glaucoma (POAG) patients and patients with ocular hypertension (OHT) were recruited for the study from glaucoma consultations at the University Eye Clinic Basel. The tenets of the Declaration of Helsinki were followed. After approval by the ethics committee, we obtained informed consent from our subjects. Newly diagnosed and therapy-naive POAG and OHT patients meeting study criteria underwent study examinations; patients on IOP-lowering therapy were first subjected to a 4-week wash-out phase. Healthy controls were recruited through ads in local newspapers. Subjects were screened for ocular and systemic diseases. A detailed medical and ophthalmic history was recorded, and all subjects completed an ophthalmological examination, including IOP daily profiling (IOP readings were taken at 8 a. m., 11 a.m. and 4 p.m.). POAG was diagnosed based on glaucomatous optic disc cupping (in particular, thinning of the inferior and/or superior rim, cup-to-disc ratio asymmetry of  $>0.2$ ), and based on matching glaucomatous visual field defects [23]. Native IOP was neither an exclusion nor an inclusion criterion for POAG diagnosis; hence, patients from both the “high tension” and “normal tension” side of the IOP spectrum in POAG were included. In contrast, at least two daily readings of naive IOP of  $\geq 21$  mmHg, in absence of disc or visual field damage, were required for the diagnosis of OHT. All participants with diabetes mellitus, history of essential hypertension, untreated or unstable hypercholesterolemia, drug or alcohol abuse, history of eye surgery except pseudophakia, high ametropia (spherical equivalent  $< -5$  diopters or  $> +3$  diopters), astigmatism above 2 diopters, significant cataract, pigment or PEX dispersion syndrome, history of an acute glaucoma attack, or any form of secondary glaucoma were excluded from the study. Smoking was an exclusion criterion. In the POAG group, an eye with the most advanced damage (higher mean VF defect and thinner peripapillary RNFL as demonstrated by ocular coherence tomography) was selected, in the OHT group an eye with the higher mean diurnal IOP was selected, and in healthy controls one randomly selected eye per subject entered the analysis.

### Systemic blood pressure

Blood pressure was measured by the Finometer device, version 1.21 (FMS, Finapres Medical Systems BV, Amhem, The Netherlands) [24]. This device measures non-invasively the blood pressure in the finger. As the finger arterial pressure may differ from intra-brachial pressure, pulse shape differences are removed by applying a generalized waveform

filter. Pressure level differences are corrected by a generalized level correction equation using filtered systolic and diastolic levels and by level calibration, which uses an additional return-to-flow systolic pressure measurement on the ipsilateral upper arm for an individual calibration of the reconstructed brachial pressure. It measures the brachial pressure in a traditional way, and corrects the finger pressure accordingly. The device allows continuous measurement of blood pressure, with a sampling rate of 100 per second. According to Guelen et al. [24], the calculated estimations deviate from the intra-arterially measured intra-brachial blood pressure values by  $-1.1 \pm 10.7$ ,  $-0.2 \pm 6.8$  and  $-1.5 \pm 6.6$  mmHg for the systolic, diastolic, and mean blood pressure respectively. All the measurements were arbitrarily taken on the third digit of the left hand. The device, having a sampling rate of 100 Hz, effectively estimates the mean blood pressure; hence, the parameters of BP variability refer to the mean arterial blood pressure.

### Submacular choroidal blood flow

Submacular choroidal blood flow was determined using a method based on the laser Doppler flowmetry technique. Compact laser Doppler choroidal flowmeter was applied (IRO, Sion, Switzerland) [25]. The optical system is based on a confocal arrangement. A polarised laser source ( $\lambda = 785$  nm, 100 m) is relayed with a 1:1 optical system (laser beam at the cornea: width = 1.3 mm, power = 90  $\mu$ W) and focused at the subject's retina (spot in the retinal image plane = 10–20  $\mu$ m in diameter, optical thickness of confocal layer = 300  $\mu$ m). The point laser source, the point of illumination of the fovea, and the detecting optical fibre are located in conjugated planes. The scattered light is collected by an optical system organised with six fibres arranged circularly around the central fixation point along a circle of diameter of 180  $\mu$ m (within the avascular zone of the fovea). The photocurrent from the photodetector is Fourier transformed and the haemodynamic parameters flow (more precisely, flux), volume, and velocity are processed. As for optic nerve laser Doppler flowmetry, each parameter varies linearly with respect to changes in blood flow.

The subjects fixated the red light spot within the ocular, and adjusted the focus by turning the ocular. The ocular to cornea distance was set between 1.5 and 2 cm. A constant very low level artificial room illumination was used throughout all the experiments. A stable DC during a recording was used as a criterion of proper fixation. DC represents a “direct current” expressed in volts, and it is a measure of the overall amount of light returning from the eye to the photodetector. An unstable fixation during the blood flow measurement is directly reflected in the amount of returning light, and thus in the DC level [26]. Variations of DC on the average throughout the recording of  $>10\%$

**Table 1** Demographics, age (in years) and gender distribution

	Men	Women
POAG ( <i>n</i> =30)	62.4±7.4 ( <i>n</i> =15)	58.6±8.8 ( <i>n</i> =15)
OHT ( <i>n</i> =25)	57.3±8.8 ( <i>n</i> =11)	58.2±9.1 ( <i>n</i> =14)
Healthy controls ( <i>n</i> =50)	59.5±9.4 ( <i>n</i> =27)	57.4±8.7 ( <i>n</i> =23)

were arbitrarily chosen as an exclusion criterion due to inability to fixate.

Visual field and retinal nerve fibre layer (RNFL) thickness

In addition, visual field was assessed with OCTOPUS 101 (Haag Streit International, Switzerland) and retinal nerve fiber layer thickness measured by means of Stratus OCT (Carl Zeiss Meditec, Germany). Mean peripapillary RNFL thickness was analyzed.

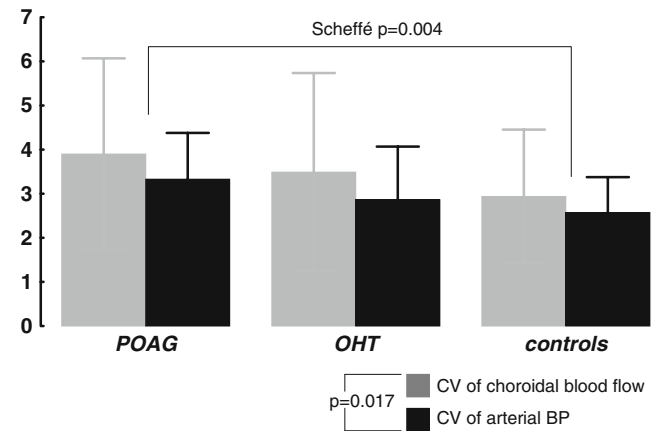
#### Experimental procedures

After evaluation of inclusion criteria, LDF measurement and BP were performed simultaneously. One eye per subject entered the analysis. Participants were instructed to abstain from a large meal, coffee, alcohol consumption (including alcohol-containing products and drugs), and physical exercise for 24 h prior to the measurements. On the day of the experiments, the subjects were seated for 30 min in the laboratory. After stabilisation of BP during the next 5 minutes, recordings of arterial blood pressure and submacular choroidal blood flow were taken. Ten times 20-second recordings, interrupted by 10-second breaks, were taken during these 5 minutes. The 20 seconds of data were arbitrarily collapsed to one mean value, producing a total of ten values during 5 minutes. Variability of these ten values, expressed as a coefficient of variation, was analyzed. This was done for the LDF parameter “Flow” as well as for the mean arterial BP estimated with Finometer.

#### Data analysis

Variability of BP and CBF was expressed as a coefficient of variation (coefficient of variation = standard deviation/mean × 100%). A two-way ANOVA model, with grouping

Coefficient of Variability - CV (%)



**Fig. 1** Short-term variability of both the blood pressure and choroidal blood flow in POAG patients, in patients with OHT and in healthy controls

(POAG vs OHT vs controls) as one, and SBP- vs CBF-variability as the second factor, was applied. Linear regression analysis was performed between parameters of morphological (RNFL thickness) and functional damage (visual field mean defect) on one side, and BP/CBF variability on the other side. Linear regression analysis was also performed between the variability of SBP and CBF in the POAG group, and between the mean IOP and the variability parameters separately in the POAG and in the OHT group.

#### Results

Thirty patients with primary open-angle glaucoma (POAG) and 25 patients with ocular hypertension (OHT) were consecutively recruited for the study. Age and gender of subjects/patients are presented in Table 1, and other relevant parameters in Table 2.

Variability parameters are presented within Table 2 and in Fig. 1. The two-way ANOVA model showed significant differences in parameter variability between the three groups ( $p=0.003$ ); post-hoc analysis with the Scheffe test revealed a significantly higher short-term variability of both the blood pressure and choroidal blood flow in POAG

**Table 2** Descriptive statistics: best-corrected visual acuity, intraocular pressure (native), mean nerve fibre layer thickness, visual field mean defect, mean blood pressure, coefficient of variability of choroidal blood flow and mean blood pressure across groups

	BVCA	IOP (mmHg)	RNFL (micrometers)	VF MD (dB)	Mean BP (mmHg)	CV CBF (%)	CV BP (%)
POAG ( <i>n</i> =30)	1.0±0.19	17.6±4.8	80.8±17.6	2.1±2.1	99.7±11.2	3.90±2.17	3.33±1.05
OHT ( <i>n</i> =25)	1.07±0.14	20.2±4.0	92.8±11.3	0.1±1.2	104.0±11.0	3.49±2.25	2.86±1.21
Healthy controls ( <i>n</i> =50)	1.07±0.10	13.7±2.7	100.3±11.9	0.7±1.6	100.8±13.2	2.94±1.52	2.57±0.80

patients than in healthy controls (Scheffé  $p=0.004$ ). In ocular hypertensives, the variability values were statistically equidistant from both the healthy controls (Scheffé  $p=0.28$ ) and POAG patients (Scheffé  $p=0.33$ ). Coefficients of variations are relative numbers, and can be directly compared: the variability of choroidal blood flow was on the average higher than the variability of arterial blood pressure across all three groups (SBP- vs CBF-variability as the second factor:  $p=0.017$ ). Within the POAG group alone, the correlation of BP and CBF variability on one side and the visual field MD, peripapillary RNFL, and mean IOP recordings on the other side was not significant (all six  $p$ -values  $>0.14$ ). Also, the two parameters of variability correlated neither with each other in the POAG group ( $r=-0.09$ ,  $p=0.65$ ) nor in all groups taken together ( $r=0.09$ ,  $p=0.35$ ). In the OHT group, mean diurnal IOP did not correlate with the CBF/BP variability ( $r=-0.09$ ,  $p=0.69$  and  $r=-0.05$ ,  $p=0.79$  respectively).

## Discussion

The concept of ischemia/reperfusion damage has been previously described [7]: the amount of free oxygen radicals increases in the reperfusion phase after ischemia [27]. The combination of increased nitric oxide and superoxide (mostly produced in the mitochondria of the axons) results in formation of a neurotoxic substance—peroxynitrate [28]. According to the ischemia/reperfusion concept of glaucomatous damage, if blood supply is constantly reduced at a moderate level, not leading to necrosis (for example, in atherosclerosis), the tissue can adapt to reduced oxygen supply. In case of severe blood supply reduction, it may lead to infarction of tissue. However, varying oxygen supply may trigger a cascade of reperfusion damage as described above. It is at present not exactly known in which range and on what time scale ischemia is most productive in causing glaucomatous damage. The analyzed duration of 5 minutes may well be too short to capture oscillations of blood flow which would be of relevance for ischemia/reperfusion damage. However, even in this arbitrarily chosen short time-frame significant differences between the groups could be observed, indicating that regulatory mechanisms both on the ocular choroidal and on the systemic blood pressure level are altered in POAG patients compared to those in healthy controls.

Variability of the two parameters—choroidal blood flow and systemic blood pressure—seems to be independent one from the other. No direct intraindividual correlation between SBP and CBF variability was observed. Variability was expressed in relative numbers, enabling direct comparison between the two, and the former had a significantly

higher range of variability than the latter. This finding indicates different and independent sets of regulatory mechanisms on the ocular and on the systemic level, and both the choroidal blood flow and the systemic BP regulation were altered in POAG patients as a group. However, the correlation between CBF/BP variability and visual field MD and peripapillary RNFL thickness was not significant. As no IOP limits were set, both the high-tension and normal-tension POAG patients were included in the glaucoma group; hence, various both IOP- and non-IOP-related pathophysiological mechanisms may have been at play in our cohort of POAG patients, which possibly precluded a statistical association between the local and systemic variability of circulation and the actual glaucomatous damage in an individual patient.

The group of OHT subjects was designed in order to analyze possible effects of the increased IOP on parameters of interest. Whereas the OHT group was statistically equidistant from both the POAG patients and healthy controls, mean untreated IOP in the OHT group was not correlated with the variability of the choroidal blood flow, suggesting a lack of effect of increased IOP on this parameter.

It is unlikely that the increased variability of choroidal blood flow was caused by unstable fixation in POAG patients. In none of the patients was the central fixation jeopardized by glaucomatous damage. Mean best-corrected visual acuity was comparable in all three groups (Table 2, ANOVA  $p>0.05$ ). No fixation deficit was observed in any of the examined subjects, as further demonstrated by the stable DC during the LDF measurements.

In conclusion, short-term variability of choroidal blood flow and systemic blood pressure are increased in POAG patients. Further longitudinal studies are necessary to elucidate possible causal relationships between the analyzed parameters, and whether manipulation and reduction of oscillation of perfusion parameters could influence course of the disease.

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