Enhanced Pressure in the Central Retinal Vein Decreases the Perfusion Pressure in the Prelaminar Region of the Optic Nerve Head

Richard Stodtmeister,[1] Sylvana Ventzke,[1] Eberhard Spoerl,[1] Andreas G. Boehm,[1,2] Naim Terai,[1] Michael Haustein,[1] and Lutz E. Pillunat[1]

[1]University Hospital Carl Gustav Carus Dresden, Technical University Dresden, Dresden, Germany
[2]Department of Ophthalmology, Elblandklinikum Radebeul, Radebeul, Germany

Correspondence: Richard Stodtmeister, University Hospital Carl Gustav Carus Dresden, Technical University Dresden, 01304 Dresden, Germany; stodtmeister@t-online.de.

Submitted: July 17, 2012
Accepted: April 28, 2013

Citation: Stodtmeister R, Ventzke S, Spoerl E, et al. Enhanced pressure in the central retinal vein decreases the perfusion pressure in the prelaminar region of the optic nerve head. *Invest Ophthalmol Vis Sci*. 2013;54:4698–4704. DOI:10.1167/iovs.12-10607

Purpose. The pressure in the central retinal vein (CRVP) has been shown to be higher in glaucoma patients than in controls. Until now, these measurements have been performed in arbitrary units or in units of ophthalmodynamometric force. In our study, a contact lens dynamometer, calibrated in mm Hg, was used to calculate the retinal perfusion pressure.

Methods. A total of 27 patients with primary open angle glaucoma (POAG) and 27 healthy control subjects were included in the study. The IOP measurement included Goldmann applanation tonometry, whereas the pressure enhancement measurement consisted of contact lens dynamometry.

Results. The pressures are given in mm Hg, and are expressed as the mean ± SD for the control subjects versus the POAG patients: IOP 14.4 ± 2.7 vs. 15.4 ± 2.9, systolic blood pressure 141 ± 20.1 vs. 153 ± 16.5 ($P = 0.013$), central retinal vein threshold pressure (CRVTP) 11.9 ± 3.8 vs. 16.8 ± 5.0, CRVP 15.0 ± 2.7 vs. 17.9 ± 4.2, and retinal perfusion pressure (PPret) standard 84 ± 12.2 vs. 94 ± 9.1 and new 83 ± 12.2 vs. 91 ± 9.6. The differences in PPret between using the new versus the standard method are 0.55 ± 1.33 vs. −2.5 ± 3.89 ($P = 0.041$ and $P = 0.002$, respectively). The PPret was at least 5.0 mm Hg lower in 5 of the 27 POAG patients when the new calculation method was used.

Conclusions. The perfusion pressure in the retina and prelaminar region of the optic nerve head (ONH) may be lower than expected because the CRVP may be higher. The pressure measurement in the central retinal vein may be a step toward a better understanding of ONH pathophysiology.

Keywords: perfusion pressure, glaucoma, optic nerve head, central retinal vein, ophthalmodynamometry

The ocular perfusion pressure (OPP) has been identified as an important risk factor in the development and progression of glaucoma.[1] OPP measurement comprises the retinal as well as choroidal perfusion pressure (PPchor). A low perfusion pressure (PP) together with an insufficient autoregulation may lead to an unstable ocular perfusion, and thereby to ischemia of the optic nerve fibers and reperfusion damage.[2] Until now, OPP has been defined widely as the difference between the mean arterial pressure (MAP) and the IOP: (OPP = MAP − IOP) under the assumption that IOP equals the venous pressure within the eye.[3] However, the central retinal vein pressure (CRVP) should not necessarily be included in all cases because the pressure in the vessel or its major branches may exceed the IOP to a clinically relevant degree.[4] To our knowledge, this possibility has not been considered fully in clinical practice until now. The reason for this may be that the pressure in the central retinal vein (CRV) has been given in relative units[5] or in ophthalmodynamometric force (ODF).[6] In our study, we measured the pressure in the CRV in the standard pressure unit: mm Hg. This approach allows the calculation of the retinal perfusion pressure (PPret), which is crucial in the pathogenesis of optic nerve fiber damage in glaucoma.

In our study, we used a contact lens dynamometer (CLD), which has been approved by the United States Food and Drug Administration (FDA). The IOP increase that results by pushing the instrument onto the eye is given in mm Hg. Thus, we could obtain the PPret in mm Hg by adding the actual IOP and the pressure increase by the CLD. The measurements were performed in healthy subjects and in patients with primary open angle glaucoma (POAG). The PP results using this new procedure were compared to the results obtained by previously recommended methods.[7]

Methods

Definitions

CRVP is the pressure in the CRV in the uninfluenced eye. If the CRV pulsates spontaneously, this pressure is equal or slightly higher than the uninfluenced (actual) IOP. If the CRV shows no spontaneous pulsation, this pressure equals the CRV threshold pressure (CRVTP, see below).

CRVTP is the pressure in the CRV under the artificially induced rise of IOP at which the CRV starts pulsation. Two

initial positions are possible for CRVTP measurement: (1) Spontaneous venous pulsation (SVP) present: The IOP is decreased by oculopression until no CRV pulsation is seen. During the first minutes after oculopression, the IOP rises by approximately 1 mm Hg/min.[8] The CRV is observed continuously. As soon as the CRV pulsates, the IOP is measured. This is the CRVTP. (2) Absent SVP: The IOP is increased artificially and continuously by CLD. When the CRV starts pulsation, the pressure increase induced by CLD (ΔP) is read off the instrument and added to the preexisting IOP. The sum equals the CRVTP and CRVP.

The MAP generally is the diastolic pressure (Pdiast) + 1/3(systolic pressure [Psyst] − Pdiast).

OPP is the ocular PP under the assumption that the venous pressure within the eye is equal in the retina and in the choroid. This assumption doesn't hold at CRVP > IOP at absent SVP. OPP is the mean arterial pressure in the ophthalmic artery (MAPoph) − IOP.

Systolic (Psca syst) or diastolic (Psca diast) blood pressure (BP) in the subclavian artery (sca) was determined by the cuff method at the upper arm.[9]

Patients and Subjects

In this prospective clinical investigation, 27 healthy volunteers and 27 patients with POAG (Table 1) were included. Each subject signed an informed consent form before entering the study. The study was performed in accordance with the Declaration of Helsinki, and was approved by the institutional ethics committee of the Medical Department of the University of Dresden.

Criteria for Patient and Subject Selection

The following exclusion criteria were used: spherical equivalent <|5| diopters (D), conjunctivitis, keratitis, uveitis, retinal detachment, corneal scars, penetrating injuries or surgery, opaque media, reduced cooperation, circumference of the upper arm < 24 cm or > 41 cm, and right sided heart failure.

POAG was diagnosed when two of the three following signs were present: Optic nerve head (ONH) damage typical in glaucoma patients, visual field damage typical in glaucoma patients, IOP > 21 mm Hg.

Eligible subjects based on the exclusion criteria who did not have primary open angle glaucoma were regarded as healthy in the context of this study. The presence of diseases in both groups is given in Table 2.

Examination Procedure

Both eyes were examined. One drop of proxymetacain (Proparacain POS 0.5%; Ursapharm Arzneimittel GmbH, Saarbrücken, Germany) was administered as a topical anesthetic to each eye, and central corneal thickness (CCT) was measured by ultrasound pachymetry (IOPac CCT-Pachymeter; Heidelberg Engineering GmbH, Heidelberg, Germany). Subsequently, the pupils were dilated with one drop of tropicamide (Mydrum; Chauvin Ankerpharm, Rudolstadt, Germany) ophthalmic solution.

When mydriasis was achieved, SVP was judged by ophthalmoscopy with a 78 D (Volk Optical, Inc., Mentor, OH) lens at the slit-lamp. In case the CRV didn't pulsate within the margins of the optic disc, but the CRV itself (or one of its branches) did pulsate outside the optic disc, this was noted and entered in the database.

Classification of CRV Pulsation

CRV pulsation was classified into four categories: (1) SVP that clearly is visible, (2) SVP visible after inspection during three cardiac cycles (if no pulsation has been detected observation was extended to three breathing cycles), (3) no SVP but excitable by gentle placement of a finger to the eye, and (4) No SVP.

Tonometry

After administering one drop of oxybuprocaine-HCl with fluorescein (Thilorbin; Alcon Laboratories, Elkridge, MD) into each eye, applanation tonometry was performed (Haag-Streit Diagnostics, Koeniz, Switzerland), and the IOP measurement was adjusted later based on CCT according to the method of Kohlhaas et al.[10]

Table 1. Description of the Two Patient Groups

Right Eyes	Controls	POAG	α:*P*
n	27	27	
Sex, M/F	7/20	7/20	1.000
Age, y	68 ± 10.4	69 ± 8.7	0.580
IOP, Goldmann applanation tonometry	14.4 ± 2.7	15.4 ± 2.9	0.191
IOP, dynamic contour tonometry	16.3 ± 2.8	16.9 ± 3.3	0.475
OPA, ocular pulse amplitude	2.8 ± 0.9	2.6 ± 0.79	0.373
CCT, μm	537 ± 30	521 ± 31	0.076
Psca syst, mm Hg, before CLD	141 ± 20.1	153 ± 16.5	0.013
Psca diast, mm Hg, before CLD	79 ± 9.0	87 ± 7.4	0.001
MAPsca, mm Hg, before CLD	100 ± 11.2	109 ± 8.1	0.001
Psca syst, mm Hg, during CLD	139 ± 20.0	155 ± 17.1	0.003
Psca diast, mm Hg, during CLD	77 ± 10.2	86 ± 8.0	0.001
MAPsca mean, mm Hg, during CLD	98 ± 11.5	109 ± 8.9	0.001
CRVTP, mm Hg	11.9 ± 3.8	16.8 ± 5.0	0.000
CRVP, mm Hg	15.0 ± 2.7	17.9 ± 4.2	0.003
OPP, standard method	84 ± 12.2	94 ± 9.1	0.001
PPret, new method	83 ± 12.2	91 ± 9.6	0.008
Difference PPret, new – standard method	−0.55 ± 1.33	–	0.041
Difference PPret, new – standard method	–	−2.5 ± 3.89	0.002

MAPsca, mean subclavian arterial pressure.

Table 2. General Diseases in the Glaucoma Patients and in Controls

	χ^2	Controls	POAG
Peripheral vascular disease	0.31	1	0
Chronic ischemic heart disease	0.38	5	6
Systemic arterial hypertension	0.38	17	20
Arterial hypotension	0.68	2	3
Hypercholesterolemia	0.55	9	7
Sleep apnea	0.15	0	2
Diabetes mellitus type 1 or 2	1.00	5	5

Systemic Arterial BP Measurement

The BP was measured automatically (M5 Professional; Omron, Mannheim, Germany) 1 minute before placement of the CLD and during CLD. The instrument consists of a cuff for the upper arm, and a central unit containing the automatic pressure control and an oscillation detector. The measurement process is started by pressing a button and runs automatically, giving the BP and the heart frequency.

Absent SVP: CRVTP Measurement

CLD Instrument: According to the Description by the Manufacturer. The FDA-approved CLD (Meditron GmbH, Voelklingen, Germany) consists "of a three-mirror Goldmann lens on the rear side of which a ring-shaped attachment containing several precision sensors is affixed. The sensors continuously measure the force that the ophthalmologist exerts on the eye by means of the contact lens. The CLD is connected by a thin flexible cable with a central unit which has approximately the size of a handheld calculator." The ΔP is read off a liquid crystal display in mm Hg. The calibration of the conversion of applied force to ΔP has been shown by Morgan et al.[11] They state: "Linearity between induced IOP and ODF is strong. . .." Their calibration is in good accordance with that one given in the manual of the CLD manufacturer.

CLD Measurement Procedure.[12] One drop of proxymetacaine (Proparakain POS 0.5%; Ursapharm Arzneimittel GmbH), used as a topical anesthetic, was administered before placing the CLD onto the eyes. Hypromellose (Methocel 2%; CIBA Vision, Duluth, GA) was used as the contact fluid.

The subjects were in a sitting position, and the chin and forehead were placed on the rest of the slit-lamp (Haag-Streit Diagnostics), which was set at a 16-fold magnification. The CLD was started according to the routine described in the manual. Correction for corneal thickness was not necessarily integrated in CLD measurement.

After placing the CLD on the eye, the ONH was brought into sight. The compressive force was increased until the first venous pulsation was detected, and the measurement value was fixed and read. The compressive force was released, and this process was repeated for another three times. The first measurement cycle was performed to obtain a feeling of the compressive force on the fingertips, and the pressure value was not included into the database because the first measurement value often substantially differed from the following values. The arithmetic mean of the last three values of ΔP was used for the calculation of CRVP at the time of measurement.

If SVP was present, pressure was applied to the closed upper lid by two fingers for 5 minutes. If the retinal vein still was pulsating after the first 5 minutes, oculopression was applied for another 5 minutes. Afterwards the CRV was observed by ophthalmoscopy during the subsequent rise of IOP. The IOP at which the first pulsation was seen was noted as the CRVTP.

Statistics. Statistical evaluation was performed using SPSS 17.0 software (SPSS GmbH Software, Munich, Germany). The sample size in each group was 27 for the conditions: two-sided test, SD 3.7 mm Hg, clinically relevant difference 2.0 mm Hg, $\alpha = 0.05$, power 80%.

Results

The description of the two patient groups is given in Table 1. The age of the glaucoma patients was slightly higher than that of the control subjects. The results of the right eyes did not differ significantly from those of the left eyes. Therefore, only the results of the right eyes are shown. The third CLD reading maximally differed from the first one by 0.7 mm Hg with one outlier of 2.4 mm Hg. The mean coefficient of variation in these measurements was 2.8%. The BPs before and during the dynamometric measurement and PPret were statistically significantly higher in the glaucoma patients than in the control subjects. Table 2 shows the frequency of general diseases in both groups. They did not differ significantly according to the χ^2 test. In all cases venous pulsation was observed on the disc if present. There was no spontaneous

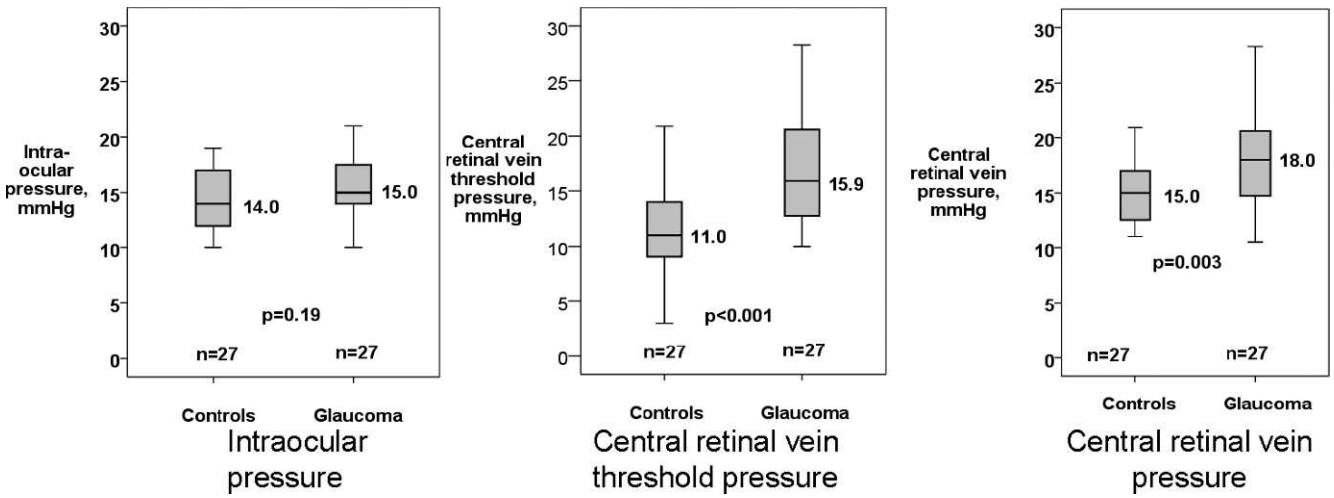

Figure 1. Box plots (*Min*, *Q1*, *Median*, *Q3*, *Max*) of IOP, CRVTP, and CRVP in the right eyes of the controls and in the glaucoma patients. *Ordinate*: pressure, mm Hg.

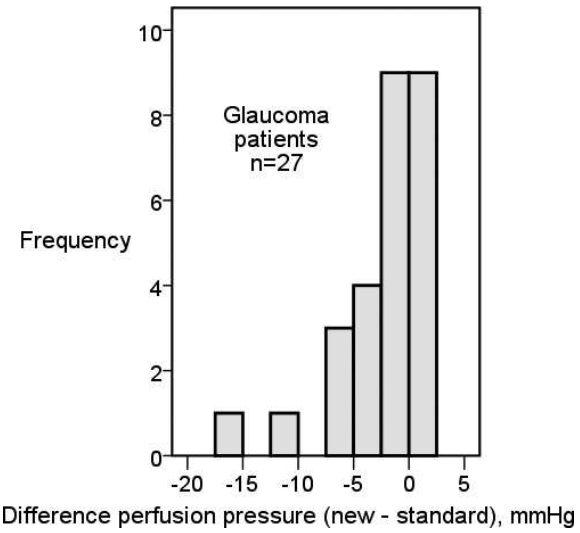

FIGURE 2. Frequency distribution of the difference in PPret entering the IOP in the formula versus entering the CRVP. A negative value means that the PP is lower by entering the pressure in the CRV.

pulsation in 17 of 27 glaucoma patients and in 1 of 27 control subjects. This difference was statistically highly significant (Pearson χ^2 test: $P < 0.001$). Figure 1 shows that the median IOP was slightly higher by 1 mm Hg in the glaucoma group. The median of the CRVTP was higher in the glaucoma group by 4.9 mm Hg. The CRVP differed in the median by 2.9 mm Hg. Figure 2 shows that in 5 of 27 glaucoma patients, the PPret was lower by at least 5.0 mm Hg if it was calculated according to the new formula. An association of the CRVP with the visual field mean defect or the cup-to-disk area ratio (Heidelberg Retina Tomograph III; Heidelberg Engineering GmbH) was not found.

DISCUSSION

A special nomenclature was used in our study because three basins of circulation had to be discriminated: the systemic, retinal, and choroidal. In medicine, the BP is the abbreviation of the systemic arterial BP measured by the cuff method at the upper arm.[9] From the physiologic point of view, it is the pressure in the sca close to its origin.[13] In our study we must abbreviate "systemic" and "systolic." To avoid confusion of these two pressures, we abbreviated the systemic arterial BP by its point of measurement (the sca). The retina and the choroid have a different arterial supply and a different venous drainage. The pressure (P) in the retinal arteries is approximately 10 mm Hg[14] higher than in ciliary arteries, which can be measured by oculooscillodynamography (OODG),[15] which is similar to the ocular pneumoplethysmography.[16] It increases the IOP by suction cups, and records the ocular pulse amplitude (OPA) due to the arterial inflow during the slow decrease of IOP. We can't measure, however, the choroidal arterial P by CLD. Therefore, we have to assume in arterial P: retinal P (Pret) = choroidal P (Pchor). The difference in venous P in the retina and in choroid is evident to every clinician in the extreme condition of central retinal vein occlusion (CRVO) in which the choroidal circulation may function unobstructed. As shown by Meyer-Schwickerath et al.,[12] the CRVP can be measured by ophthalmodynamometry (ODM) and may be higher than the IOP. Consequently, the PPret may be different from the PPchor because the venous pressure (Pven) is a codeterminator of the PP according to the formula: PP = MAP − Pven. The ophthalmic artery pressure (Poph) usually is calculated as 2/3Psca (Psca syst, Psca diast, MAP). The Poph can be measured by ODM, most conveniently by CLD.[17] These abbreviations and definitions described in this report may help to clarify new differentiations of PPs, which are made feasible by the measurement of the CRVP by CLD.

An association has been shown between the glaucomatous optic nerve damage and the ODM force that is required to elicit a pulsation of the CRV.[6] It is the force by which the contact area of the ODM is pushed to the eye inducing an increase in the preexisting (actual) IOP. The results obtained by Morgan et al.[4] may lead to the following clinically important interpretations: (1) The CRVP may be significantly higher than the IOP in glaucoma patients. (2) The PPret would be lower than assumed in these cases. (3) Consequently, the perfusion pressure in the prelaminar layer of the optic disc also would be lower because the anatomic structure is drained by the CRV as shown by Hayreh.[18] (4) The retina and prelaminar layer of the optic disc belong to the same venous basin.

The pulsation of the retinal vein on or near the optic disc generally was not regarded as being an important phenomenon until now because the origin of this pulsation has not been explained convincingly in the literature. However, in the German congress proceedings of 1925, Baurmann[19] showed through experimentation how the SVP is generated, and Meyer-Schwickerath et al. wrote a manual describing the measurement technique.[12] The CRV or its branches may pulsate spontaneously on or near the optic disc when the IOP is higher than the threshold pressure that elicits a pulsation. This behavior can be explained by the properties of a Starling resistor,[20] which is a collapsible tube[21] passing a container with a rigid wall. The extensibility of the ocular walls can be neglected in the pressure range and conditions considered here. If there is no spontaneous retinal venous pulsation, an artificial increase may elicit a pulsation.[12] Kain et al. hypothesized that the ICP pressure pulsation may be influential in the origin of the CRV pulsation, admitting that further work is needed to determine whether the ICP amplitude is greater than the IOP amplitude in most people.[22] Westlake et al. cannulated retinal veins in pigs and observed negative transmural pressures on the optic disc.[23] They concluded that their results are compatible with the Starling resistor theory of venous outflow from the eye. According to Conrad in such a system continuous flow may be converted to a pulsating flow.[21] Hence, the results of Westlake et al. may support the view that there must not be an influence of ICP pulsation in the origin of the CRV pulsation. Holt assumed the flow through collapsible tubes to be a special case of the Bernoullis theorem.[24] In this view, no further assumptions have to be made like in other theories.[22,25,26]

Golzan et al. showed, by recordings of spontaneously pulsating veins, that the amplitude of the SVP increases with the IOP,[27] and Donnelly et al.[28] demonstrated that the frequency of the SVP is dependent from the OPA recorded by the dynamic contour tonometer.[29] In our results both parameters didn't differ significantly between both groups (Table 1). Therefore, we didn't assume that clinically significant differences of PP may be due to differences in the spontaneous IOP or OPA values.

In measuring the CRVTP, the threshold criterion was the first detectable pulsation of the CRV in our study. By this definition the influence of changes in the OPA[27] may be minimized. In the decision whether there is an SVP or not, the absence was stated only when no pulsation was seen during three breathing cycles. By this procedure, the faintest pulsation should have been detectable. Three single measurements were performed with the CLD in each eye. The maximal difference between the measurements was 2.4 mm Hg. The examiner

couldn't see the figures on the display before fixing them. Thus, she was blinded in this respect. Jonas reported a mean coefficient of variation in the CLD measurement of the CRVTP of 16.3% in a single eye.[30] In our results, the mean coefficient was 2.8%. Jonas measured the CRVTP 10 times in a second step after the CLD measurement of Poph. This might explain the differences.

Our patients were under IOP lowering therapy. Stopping it would have resulted in a higher IOP. That, in turn, could have resulted in a higher frequency of spontaneous pulsation of the CRV.[31] The CRVP, however, as measured by our methods wouldn't have been different.

In absent SVP, the IOP is decreased by oculopression and the CRVP is determined by tonometry when the following IOP rise of 1 mm Hg/min[32] reaches or exceeds the CRVTP.

An artificial IOP increase is achieved by applying force to the eye, and the simplest way to do this is pushing a finger to the eye. An artificial IOP increase has been measured quantitatively using ODM instruments, such as the one invented by Sisler[33] and used by Morgan et al.[6] It is a general principle in ODM that the pressure increase induced by the instrument must be added to the preexisting (actual) IOP to determine the artificially enhanced pressure at the time of measurement. For this purpose, the actual IOP and ΔP must be given in the same physical units. In our study mm Hg was used. This requirement has not been fulfilled by the method described by Morgan et al., in which ΔP is given as force in grams,[34] or by the method of Jonas,[5] in which it is given in arbitrary units. The "same unit requirement" can be fulfilled by biophysical calibration allowing the conversion of force to pressure, which is a common principle in medicine, such as in applanation tonometry.[35,36] Morgan et al. have done such a calibration of the CLD.[11] They state: "Linearity between induced IOP and ODF is strong. . . ." Their calibration is in good accordance with that one given in the manual of the CLD manufacturer. An estimation by which order of magnitude the CRVP may be higher than the IOP couldn't be derived from data in the literature. Therefore, our study was conducted.

In planning the study, we considered the possibility of a tonographic effect. Preliminary examinations showed a decrease of IOP by maximally 2 mm Hg if present. Due to this relatively small effect, we didn't expect a considerable influence. We measured the IOP after the examination, but we were able to perform applanation tonometry in a small number of patients only because of the changes of the corneal surface by the CLD process. In these cases, the half rings were not as sharp as usual. Therefore, the measurement values must be judged very critically. Because of these doubts, we did not correct for a possible tonographic effect. In case it would have influenced our results the calculated perfusion pressures would have been shifted to lower values.

The maximal difference of 0.7 mm Hg (with one outlier of 2.4 mm Hg) between the first and the third CLD value might indicate the accuracy of the CLD method and hints that a possible tonographic effect may be insignificant.

The MAPoph was calculated from Psca syst and Psca diast. We didn't measure the systolic (Poph syst) and diastolic (Poph diast) ophthalmic artery pressures by CLD, which is possible,[17] because this measurement would have disturbed the judgment of the tonographic effect during Pven measurement, Pven being our target parameter.

In CLD, the pressure in the eye and in the orbit is increased whereby the oculocardiac reflex may be provoked. As indicated by Ulrich,[13] a reduction or an increase of the systemic BP may occur. He also observed these changes in younger patients and especially by applying ophthalmodynamography (ODG),[13] by which the intraocular pressure as well as the pressure in the whole orbit is enhanced up to 140 mm Hg. The pressures in our method were considerably lower. Young patients were not included in our study. In the calculations of the PPret, we used the BP values taken during the CLD measurement. The examiner started the automatic BP measurement by pressing the start button after the attachment of the CLD instrument. In this experimental setup, it was the method of choice in obtaining a simultaneous measurement of the CRVP and BP. In our study the BP values didn't differ significantly before or during CLD measurement.

The driving force of circulation is the PP, whereby it is assumed that the Pven in the eye equals the IOP. However, this assumption for the CRVP should not be made absolute any longer because it is higher in eyes in which SVP is absent. In these cases, we must assume that there are two perfusion pressures in the eye: one in the uveal tract and one in the retina, including the prelaminar layer of the ONH.[18] The uveal tract and retina have separate circulations, which is obvious, for example, in CRVO where the drainage of the retina is obstructed while the drainage via the vortex veins functions. Therefore, these two circulations may have different PPs, too.

The arithmetic mean of the perfusion pressures in our glaucoma patients was 94 mm Hg according to the standard method and 91 mm Hg according to the new method. The mean difference was 2.5 mm Hg. Despite statistical significance ($P = 0.002$) the clinical relevance is negligible. The comparison of groups by arithmetical means is one way of data analysis. The analysis of differences and their distribution, however, is a method that reflects the changes in single cases. Such an analysis is shown in Figure 2. It presents information that may be regarded as clinically interesting: We saw no SVP in 17 of our 27 glaucoma patients. In these cases it may be concluded that the CRVP is higher than the IOP. This is a qualitative information that gives no hint by which amount the CRVP may be higher and, vice versa, the perfusion pressure may be lower than assumed until now. The quantitative information is given in Figure 2. In 5 cases, the PPret was lower by 5 mm Hg and more. This implies that in approximately one-third of the 17 patients without a SVP the PP was lower than assumed, to a degree regarded as clinically important in IOP assessment. From the hemodynamic point of view, an increase in IOP of 5 mm Hg has the same effect as an increase of CRVP of 5 mm Hg. Therefore, the measurement of the CRVP may give additional information in the diagnosis of POAG.

There are different possible reasons why the CRVP may be increased, including an increased intracranial pressure (ICP)[37,38]; a circumscribed increase of the pressure in the liquor around the optic nerve[39–41]; a low ICP[42,43] being responsible for a high pressure gradient across the optic disc,[44] which may reduce the lateral cut of the CRV and thereby increase the CRV outflow resistance; a high pressure in the jugular veins; and a high pressure in the orbit.[45] In case signs and symptoms of other diseases may be excluded, the most probable reason for an increased CRVP in POAG patients may be an increased outflow resistance.

In our POAG patients the BP and CRVP were higher than in the control subjects. The question must be raised whether there may be an association. In cases of malignant hypertension, hypertensive encephalopathy with brain edema[46] is described. It may be hypothesized that smaller increases in BP in the order of magnitude as in our patients may increase the ICP, and thereby the CRVP, without causing papilledema.

A limitation of our study may be the small sample size. It was calculated for a power of 80% at a significance level of 0.05. The CRVTP and CRVP, as well as the calculated perfusion pressures differed between the POAG patients and controls at an α-error below the chosen level. Therefore, it seemed to be

unethical to examine more patients and controls than initially planned.

The mean IOP in the glaucoma group studied was only 1.0 mm Hg higher than in the control group, and the difference was statistically not significant (Table 1). By using the standard method for the calculation of the OPP it could be assumed that this parameter would be practically equal in patients and controls at a given BP. By using the new method, however, a significantly smaller PPret is calculated that may endanger the optic nerve fibers.

The frequency of the diagnosis "arterial hypertension" (17 in the control subjects and 20 in the glaucoma group) was not significantly different between both groups (Table 2). In spite of this similarity, the arithmetic mean of the measured BPs at the time of our examination was higher in our glaucoma patients than in the control subjects. This is the reason why the arithmetic mean of the PPret was higher in our glaucoma patients than in our control subjects. A probable source for the high values may be seen in the "white coat effect" in BP measurement.[9] The target variable of our study was the CRVP, which presently is not known to be dependent from the arterial BP. Hence, we didn't exclude the glaucoma patients with a high BP from our study.

The main result of our study is that the PPret may be lower in POAG, reaching a clinically relevant degree. The CRVP can be determined. However, the cause of a pressure enhancement may remain unknown. In case an high CRVP is measured, clinical signs of an enhanced ICP[38] should be evaluated.

In conclusion, implementing the CRVP in the assessment of ONH pathophysiology may resolve some controversies[47] and contribute to the understanding of optic nerve fiber damage.

Acknowledgments

Presented in part as a poster at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, May 2011.

The authors alone are responsible for the content and writing of this paper.

Disclosure: **R. Stodtmeister**, None; **S. Ventzke**, None; **E. Spoerl**, None; **A.G. Boehm**, None; **N. Terai**, None; **M. Haustein**, None; **L.E. Pillunat**, None

References

1. Costa VP, Arcieri ES, Harris A. Blood pressure and glaucoma. *Br J Ophthalmol*. 2009;93:1276–1282.
2. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res*. 2002;21:359–393.
3. Costa VP, Jimenez-Roman J, Carrasco FG, Lupinacci A, Harris A. Twenty-four-hour ocular perfusion pressure in primary open-angle glaucoma. *Br J Ophthalmol*. 2010;94:1291–1294.
4. Balaratnasingam C, Morgan WH, Hazelton ML, et al. Value of retinal vein pulsation characteristics in predicting increased optic disc excavation. *Br J Ophthalmol*. 2007;91:441–444.
5. Jonas JB. Central retinal artery and vein collapse pressure in eyes with chronic open angle glaucoma. *Br J Ophthalmol*. 2003;87:949–951.
6. Morgan WH, Hazelton ML, Balaratnasingamm C, et al. The association between retinal vein ophthalmodynamometric force change and optic disc excavation. *Br J Ophthalmol*. 2009;93:594–596.
7. Kiel JW. *The Ocular Circulation*. Bonita Springs, FL: Morgan & Claypool Life Sciences; 2011:1–69.
8. Ulrich C, Ulrich WD. *OPT - Okulo-Pressions-Tonometrie zur Bestimmung der Abfluleichtigkeit und Kammerwasserbildung des Auges*. Leipzig, Germany: VEB Georg Thieme; 1987.
9. Kaplan NM. *Kaplan's Clinical Hypertension*, 9th ed. Philadelphia, PA: J. B. Lippincott-Williams & Wilkins; 2006.
10. Kohlhaas M, Boehm AG, Spoerl E, Pursten A, Grein HJ, Pillunat LE. Effect of central corneal thickness, corneal curvature, and axial length on applanation tonometry. *Arch Ophthalmol*. 2006;124:471–476.
11. Morgan WH, Cringle SJ, Kang MH, et al. Optimizing the calibration and interpretation of dynamic ocular force measurements. *Graefes Arch Clin Exp Ophthalmol*. 2010; 248:401–407.
12. Meyer-Schwickerath R, Stodtmeister R, Hartmann K. Non-invasive determination of intracranial pressure. Physiological basis and practical procedure. *Klin Monatsbl Augenheilkd*. 2004;221:1007–1011.
13. Ulrich WD. *Grundlagen und Methodik der Ophthalmodynamometrie, Ophthalmodynamographie, Temporalisdynamographie*. Leipzig, Germany: VEB Georg Thieme; 1976.
14. Stodtmeister R, Kästner R, Pillunat LE. Saugnapfmethoden. In: Straub W, Kroll P, Küchle HJ, eds. *Augenärztliche Untersuchungsmethoden*, 1st ed. Stuttgart, Germany: Ferdinand Enke; 1995:436–461.
15. Ulrich WD, Ulrich C. Okulooszillodynamographie, ein neues Verfahren zur Bestimmung des Ophthalmikablutdruckes und zur okularen Pulskurvenanalyse [Oculo-oscillodynamography, a new procedure for the determination of ophthalmic artery blood pressure and ocular pulse curve analysis]. *Klin Monatsbl Augenheilkd*. 1985;186:385–388.
16. Gee W. Ocular pneumoplethysmography (OPG-Gee). In: Kempczinski RR, Yao JST, eds. *Practical Noninvasive Vascular Diagnosis*. Chicago, IL: Year Book Medical Publishers; 1982:167–180.
17. Stodtmeister R, Oppitz T, Spoerl E, Haustein M, Boehm AG. Contact lens dynamometry: the influence of age. *Invest Ophthalmol Vis Sci*. 2010;51:6620–6624.
18. Hayreh SS. The blood supply of the optic nerve head and the evaluation of it — myth and reality. *Prog Retin Eye Res*. 2001; 20:563–593.
19. Baurmann M. Ueber die Entstehung und klinische Bedeutung des Netzhautvenenpulses. *Verh Dtsch Ophthalmol Ges*. 1925; 45:53–59.
20. Knowlton FP, Starling EH. The influence of variations in temperature and blood-pressure on the performance of the isolated mammalian heart. *J Physiol*. 1912;44:208–219.
21. Conrad WA. Pressure-flow relationships in collapsible tubes. *IEEE Trans Biomed Eng*. 1969;16:284–295.
22. Kain S, Morgan WH, Yu DY. New observations concerning the nature of central retinal vein pulsation. *Br J Ophthalmol*. 2010;94:854–857.
23. Westlake WH, Morgan WH, Yu DY. A pilot study of in vivo venous pressures in the pig retinal circulation. *Clin Experiment Ophthalmol*. 2001;29:167–170.
24. Holt JP. Flow through collapsible tubes and through in situ veins. *IEEE Trans Biomed Eng*. 1969;16:274–283.
25. Jacks AS, Miller NR. Spontaneous retinal venous pulsation: aetiology and significance. *J Neurol Neurosurg Psychiatry*. 2003;74:7–9.
26. Levine DN. Spontaneous pulsation of the retinal veins. *Microvasc Res*. 1998;56:154–165.
27. Golzan SM, Graham SL, Leaney J, Avolio A. Dynamic association between intraocular pressure and spontaneous pulsations of retinal veins. *Curr Eye Res*. 2011;36:53–59.
28. Donnelly SJ, Subramanian PS. Relationship of intraocular pulse pressure and spontaneous venous pulsations. *Am J Ophthalmol*. 2009;147:51–55.
29. Kanngiesser HE, Kniestedt C, Robert YC. Dynamic contour tonometry: presentation of a new tonometer. *J Glaucoma*. 2005;14:344–350.

30. Jonas JB. Reproducibility of ophthalmodynamometric measurements of central retinal artery and vein collapse pressure. *Br J Ophthalmol*. 2003;87:577–579.
31. Seo JH, Kim TW, Weinreb RN, Kim YA, Kim M. Relationship of intraocular pressure and frequency of spontaneous retinal venous pulsation in primary open-angle glaucoma. *Ophthalmology*. 2012;119:2254–2260.
32. Ulrich WD, Ulrich C, Neunhoffer E, Fuhrmann P. Okulo-Pressions-Tonometrie (OPT)—ein neues tonographisches Verfahren zur Glaukomdiagnostik [Oculopression tonometry (OPT): a new tonographic procedure in the diagnosis of glaucoma]. *Klin Monatsbl Augenheilkd*. 1987;190:109–113.
33. Sisler HA. Optical-corneal pressure ophthalmodynamometer. *Am J Ophthalmol*. 1972;74:987–988.
34. Morgan WH, Balaratnasingam C, Hazelton ML, House PH, Cringle SJ, Yu DY. The force required to induce hemivein pulsation is associated with the site of maximum field loss in glaucoma. *Invest Ophthalmol Vis Sci*. 2005;46:1307–1312.
35. Goldmann H, Schmidt T. Weiterer Beitrag zur Applanationstonometrie. *Ophthalmologica*. 1961;141:441–456.
36. Goldmann H, Schmidt T. Über Applanationstonometrie. *Ophthalmologica*. 1957;134:221–242.
37. Firsching R, Schutze M, Motschmann M, Behrens-Baumann W, Meyer-Schwickerath R. Non-invasive measurement of intracranial pressure. *Lancet*. 1998;351:523–524.
38. Meyer-Schwickerath R, Kleinwachter T, Firsching R, Papenfuss HD. Central retinal venous outflow pressure. *Graefes Arch Clin Exp Ophthalmol*. 1995;233:783–788.
39. Killer HE, Jaggi GP, Flammer J, Miller NR, Huber AR, Mironov A. Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional? *Brain*. 2007;130:514–520.
40. Jaggi GP, Mironov A, Huber AR, Killer HE. Optic nerve compartment syndrome in a patient with optic nerve sheath meningioma. *Eur J Ophthalmol*. 2007;17:454–458.
41. Killer HE, Mironov A, Flammer J. Optic neuritis with marked distension of the optic nerve sheath due to local fluid congestion. *Br J Ophthalmol*. 2003;87:249.
42. Ren R, Jonas JB, Tian G, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. *Ophthalmology*. 2010;117:259–266.
43. Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. *Ophthalmology*. 2008;115:763–768.
44. Morgan WH, Yu DY, Alder VA, et al. The correlation between cerebrospinal fluid pressure and retrolaminar tissue pressure. *Invest Ophthalmol Vis Sci*. 1998;39:1419–1428.
45. Hartmann K, Meyer-Schwickerath R. Measurement of venous outflow pressure in the central retinal vein to evaluate intraorbital pressure in Graves' ophthalmopathy: a preliminary report. *Strabismus*. 2000;8:187–193.
46. Iencean SM, Ciurea AV. Intracranial hypertension: classification and patterns of evolution. *J Med Life*. 2008;1:101–107.
47. Hayreh SS. Cerebrospinal fluid pressure and glaucomatous optic disc cupping. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:721–724.

Investigative Ophthalmology & Visual Science